



Platelet distribution width: a novel prognostic marker in an internal medicine ward

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ABSTRACT

Background: Platelet distribution width (PDW) has demonstrated clinical significance in populations with specific disorders; its prognostic significance in internal medicine wards has not been investigated.

Methods: Demographic, clinical and laboratory data were collected prospectively for 1036 internal medicine inpatients. The primary outcome was 90-day mortality, secondary outcomes were: treatment with mechanical ventilation, prolonged hospital stay, in-hospital death, and all-cause mortality following discharge. Data were assessed according to PDW values on admission $\leq 16.7\%$ (group A) and $> 16.7\%$ (group B).

Results: Compared to group A patients ($n = 273$), group B patients ($n = 763$) were more likely to be older, admitted for cardio-cerebrovascular disorder, to present with comorbidities, to be mechanically ventilated, to have prolonged hospital stay and to die during the current hospitalization. The respective 90-day and total (median follow-up of 5 months) mortality rates were significantly higher in group B (13.2% and 16.3%) than in group A (6.6% and 9.5%), $P < 0.01$. On multivariate analysis, higher PDW values on admission predicted 90-day mortality and shortened survival (relative risks 1.58 and 1.26; 95% confidence intervals 0.89 – 2.78 and 0.97–1.64, respectively).

Conclusion: Higher PDW values on admission to internal medicine wards are associated with a more severe clinical profile and increased risk of 90-day mortality.

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Platelet distribution width; thrombocyte; hospitalization; prognosis; mortality

1. Introduction

Platelets play an important role in the processes of coagulation, inflammation, and immune response [1–3]. Platelet distribution width (PDW) reflects variability in platelet size, and is considered a marker of platelet function and activation [4].

Increased PDW values have been reported in patients with diabetes mellitus [5], cancer [6,7], and cardio-cerebrovascular and respiratory disorders [8–12]. Moreover, higher PDW levels have recently been reported to be associated with increased morbidity and mortality among patients with critical illness [11,13], coronary artery disease [14–17], cancer [18–21], pulmonary embolism [10,22], and chronic obstructive pulmonary disease [23]. Most previous studies on the clinical significance of PDW involved patients with specific disorders. Clinical characteristics and prognosis associated with increased PDW levels have not been studied in a heterogeneous population of internal medicine inpatients.

We aimed to compare demographic, clinical, and laboratory characteristics, as well as short-term

outcomes, among patients hospitalized in internal medicine wards, according to PDW values on admission.

2. Patients and methods

2.1. Study population and design

We conducted a prospective observational investigation. Figure 1 illustrates the study design. The study population comprised consecutive adult patients hospitalized in one of seven internal medicine departments of our tertiary care university hospital during February–October 2017. This department included 30 general and 5 intensive care beds. The patients were randomly admitted from the Emergency Department or transferred from other departments due to a variety of acute internal medicine conditions, including infections, cardiovascular disorders and malignant diseases. For patients who were readmitted during the study period, only the data of their first hospitalization were analyzed. Patients without complete blood count on admission were excluded from the study (Figure 1).

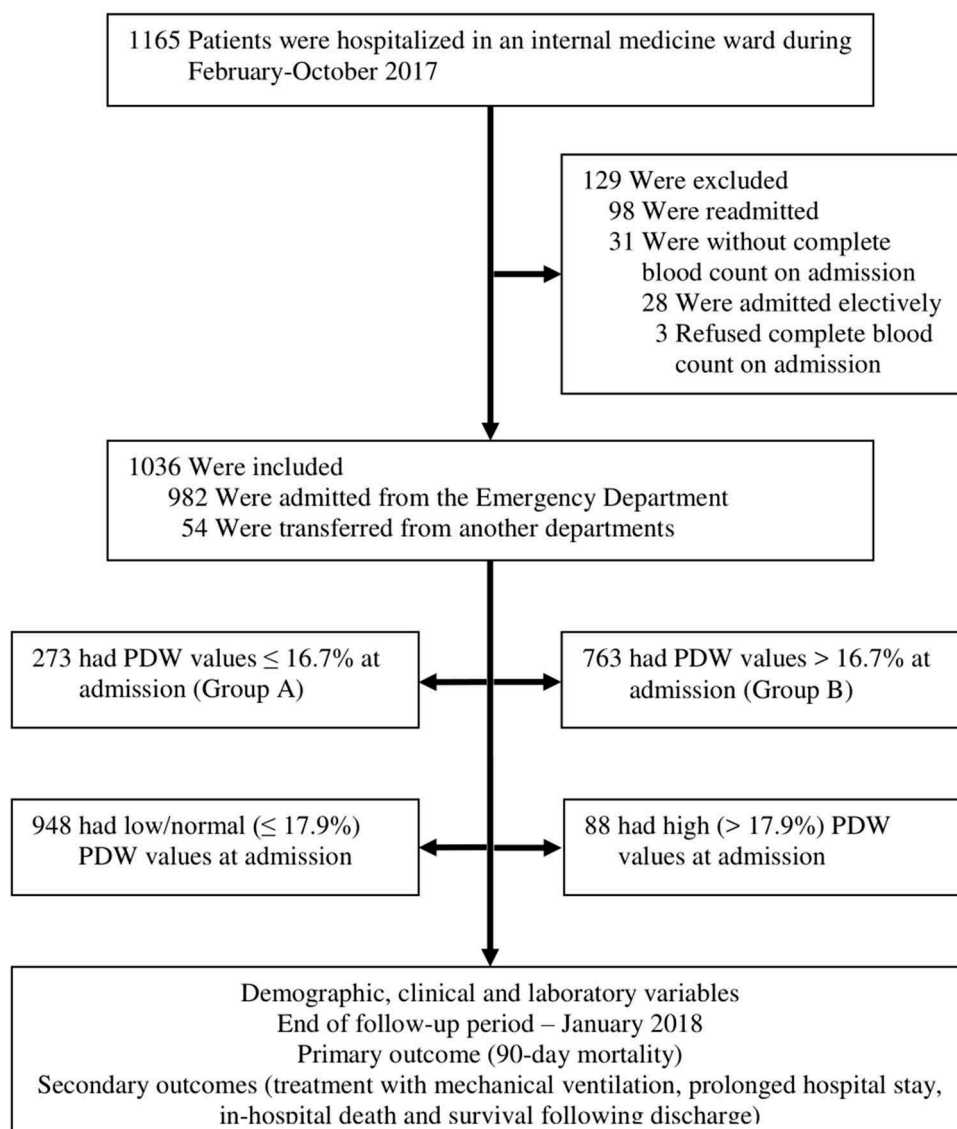


Figure 1. Flowchart presenting the study design. PDW, platelet distribution width.

For all participants, PDW and other complete blood count parameters were evaluated on hospital admission. Blood samples were drawn into ethylenediaminetetraacetic acid (EDTA) anticoagulation tubes and tested within 1 hour of collection by an automated UniCel DxH 800 hematology analyzer (Coulter® A63013-AD; Beckman Coulter, Inc., CA, USA) [24]. In our laboratory, the range of normal PDW values measured by this device is 15.1–17.9%; the respective intra- and inter-assay coefficients of variation are 0.5% and 4.2%.

The follow-up ended on January 2018. For patients who survived, pre-specified minimal and maximal follow-up durations were 3 and 12 months, respectively. The primary outcome of the study was 90-day mortality. Secondary outcomes included in-hospital outcomes (treatment with mechanical ventilation, prolonged hospital stay and death) and all-cause mortality following discharge. For analysis of the outcomes, patients were classified according to values of PDW on admission $\leq 16.7\%$ (group A) and $> 16.7\%$ (group B). The rationale of this cut-off for PDW values was based on our

preliminary statistical analysis in which this threshold was found optimal for predicting the primary outcome. The outcomes were also analyzed according to another cut-off of PDW, namely low/normal ($\leq 17.9\%$) and high ($> 17.9\%$) PDW values at admission. The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional Ethics Committee (approval number 0019-17-ASF).

2.2. Data collection

During the index hospitalization, the following data were collected from patients' charts and hospital records: demographic, clinical, and laboratory variables, and outcomes (treatment with mechanical ventilation, length of hospital stay, and in-hospital death). Following discharge, all-cause mortality rate at 90 days and vital status at the end of follow-up were recorded, based on information from the registry of the Ministry of Internal Affairs and hospital records.

2.3. Definitions

Thrombocytopenia and thrombocytosis were defined as platelet counts below ($140 \times 10^9/l$) and above ($450 \times 10^9/l$) normal range values provided by the laboratory device manufacturer. Anemia was diagnosed according to the World Health Organization criteria: a hemoglobin concentration of <13 g/dl in men and <12 g/dl in women in any measurement during current hospitalization. Renal dysfunction was defined as any value of estimated glomerular filtration rate <60 ml/min/ $1.73m^2$ during current hospitalization, using the Modification of Diet in Renal Disease equation [25].

2.4. Statistical analysis

The data were analyzed using the Biomedical Package software program [26]. The results were expressed as means and standard deviations for quantitative data, and as numbers (percentages) for qualitative data. Pearson's correlation coefficient (r) was calculated to evaluate correlations of PDW with mean platelet volume (MPV) and with platelet count on admission. Data were compared according to PDW values on admission. Pearson's chi-square or Fisher's exact test was applied for comparisons of discrete variables. Analysis of Variance (ANOVA) was used for continuous variables. Survival curves were plotted using the Kaplan-Meier estimate. Differences between the curves were evaluated by Mantel-Cox and Breslow tests. P values ≤ 0.05 were considered statistically significant. Variables that were found to be associated with poor in-hospital outcomes and 90-day mortality on univariate analysis, were reevaluated by stepwise logistic regression analysis. The area under the curve (AUC) of the receiver operating characteristic (ROC) plots was calculated to determine the variables most significantly associated with poor prognosis. Variables that were found to be associated with shortened survival using the Kaplan-Meier method were reevaluated by the Cox proportional-hazards model, to identify those most significantly associated with mortality.

3. Results

3.1. Patient characteristics

3.1.1. The entire sample

The demographic, clinical and laboratory data of the 1036 patients who were included in the study are presented in Table 1. Groups A and B comprised 26.4% and 73.6% of the patients, respectively. Higher than normal ($>17.9\%$) PDW values on admission were found among 8.5% of patients. PDW values on admission were correlated positively with MPV values on admission ($r = 0.542$, $P < 0.001$) and inversely with platelet counts on admission ($r = -0.427$, $P < 0.001$).

3.1.2. Comparisons between groups A and B (Table 1)

Patients with PDW values on admission $>16.7\%$ were more likely to be older, admitted for cardio-cerebrovascular disorder, and to present with comorbidities than were patients with values of PDW $\leq 16.7\%$. Moreover, treatments including statins and anticoagulants were more often administered to patients from group B. In addition, the respective mean values of MPV were higher and platelet counts lower in group B than in group A.

3.2. In-hospital outcomes

Patients in group B were more often mechanically ventilated, and more likely to have prolonged hospital stay and to die during the current hospitalization than those in group A (Table 1). Patients with high ($>17.9\%$) vs. low/normal ($\leq 17.9\%$) PDW values on admission were more likely to be treated with mechanical ventilation (19.3% vs. 10.0%, $P = 0.01$) and to succumb during the current hospitalization (13.6% vs. 6.4%, $P = 0.02$). On multivariate analysis, none of the in-hospital outcomes were associated with PDW on admission.

3.3. Survival

3.3.1. Univariate analysis

The follow-up period extended up to 12 months (median 5 months). The respective 90-day and total mortality rates for the entire sample were 11.5% and 14.5%. For group B, survival was shorter ($P = 0.004$, Figure 2), and the respective 90-day and total mortality rates significantly higher: 13.2% and 16.3%, compared to 6.6% and 9.5% for group A ($P < 0.01$ for all comparisons). A high vs. low/normal level of PDW on admission was also associated with decreased survival: the respective mortality rates were 22.7% vs. 10.4% at 90 days ($P = 0.001$) and 28.4% vs. 13.2% at the end of follow-up ($P < 0.001$). Other variables associated with decreased survival in the entire cohort were: advanced age, male sex, pneumonia, anemia, diabetes mellitus, renal dysfunction, coronary artery disease, cerebrovascular disease, heart failure, chronic lung disease, malignancy, higher MPV values, and lower platelet counts.

3.3.2. Multivariate analysis

On stepwise logistic regression analysis (Table 2), PDW $>16.7\%$ on admission was one of the variables that most significantly associated with increased 90-day mortality: relative risk (RR) 1.58 and 95% confidence interval (CI) 0.89 – 2.78. Figure 3 illustrates the relationship between PDW on admission and 90-day mortality. The ROC curve using a cut-off of 16.7% for PDW values demonstrates that higher PDW predicted 90-day mortality with AUC = 0.826. Reevaluation of the analysis, with PDW on admission as a continuous variable, showed

Table 1. Characteristics of patients hospitalized in an internal medicine ward.

Characteristics	Entire sample (n = 1036)	Group A PDW ≤16.7% (n = 273)	Group B PDW >16.7% (n = 763)	Difference between groups A and B P value
Age (years)	66.4 ± 18	61.7 ± 19	68.0 ± 17	<0.001
Male sex	604 (58.3%)	146 (53.5%)	458 (60.0%)	0.06
<i>Main reason for admission</i>				
Infectious/inflammatory disease	445 (43.0%)	126 (46.2%)	319 (41.8%)	0.2
Pneumonia	163 (15.7%)	41 (15.0%)	122 (16.0%)	0.8
Urinary tract infection	96 (9.3%)	26 (9.5%)	70 (9.2%)	0.9
Infected chronic lung disease	44 (4.2%)	12 (4.4%)	32 (4.2%)	0.9
Other infection*	101 (9.7%)	30 (11.0%)	71 (9.3%)	0.8
Inflammatory disorder	41 (4.0%)	17 (6.2%)	24 (3.1%)	0.2
Cardio-cerebrovascular disorder	352 (34.0%)	78 (28.6%)	274 (35.9%)	0.03
Exacerbated heart failure	90 (8.7%)	12 (4.4%)	78 (10.2%)	0.003
Acute coronary syndrome	78 (7.5%)	16 (5.9%)	62 (8.1%)	0.3
Cerebrovascular disorder	64 (6.2%)	13 (4.8%)	51 (6.7%)	0.3
Other cardiovascular disorder	120 (11.6%)	37 (13.6%)	83 (10.9%)	0.2
Other disorder**	239 (23.1%)	70 (25.6%)	169 (22.1%)	0.2
<i>Comorbid conditions</i>				
History of hypertension	647 (62.5%)	130 (47.6%)	517 (67.8%)	<0.001
Anemia during hospitalization	579 (55.9%)	158 (57.9%)	421 (55.2%)	0.2
Diabetes mellitus	402 (38.8%)	81 (29.7%)	321 (42.1%)	<0.001
Renal dysfunction during hospitalization	365 (35.2%)	65 (23.8%)	300 (39.3%)	<0.001
Coronary artery disease	332 (32.0%)	65 (23.8%)	267 (35.0%)	<0.001
Cerebrovascular disease	303 (29.2%)	67 (24.5%)	236 (30.9%)	0.05
Heart failure	220 (21.2%)	33 (12.1%)	187 (24.5%)	<0.001
Chronic lung disease	196 (18.9%)	48 (17.6%)	148 (19.4%)	0.5
Malignant disease (per history or active)	188 (18.1%)	38 (13.9%)	150 (19.7%)	0.036
<i>Treatment</i>				
Antiaggregants	411 (39.7%)	96 (35.2%)	315 (41.3%)	0.08
Statins	411 (39.7%)	86 (31.5%)	325 (42.6%)	0.001
Anticoagulants	261 (25.2%)	52 (19.0%)	209 (27.4%)	0.007
<i>Laboratory data</i>				
Serum creatinine on admission (normal 0.5–0.9 mg/dl)	1.13 ± 0.7	0.93 ± 0.5	1.20 ± 0.8	<0.001
Blood hemoglobin on admission (normal 13.0–16.2 g/dl)	12.3 ± 2	12.3 ± 2	12.3 ± 3	1.0
White blood cell count on admission (normal 4–11x10 ⁹ /l)	10.1 ± 7	10.1 ± 4	10.0 ± 7	0.9
Platelet count on admission (normal 140–450x10 ⁹ /l)	227 ± 95	283 ± 102	207 ± 84	<0.001
Thrombocytopenia on admission (<140x10 ⁹ /l)	123 (11.9%)	4 (1.5%)	119 (15.6%)	<0.001
Thrombocytosis on admission (>450x10 ⁹ /l)	31 (3.0%)	18 (6.6%)	13 (1.7%)	<0.001
Mean platelet volume on admission (normal 7.3–11.5 fl)	9.07 ± 1.1	8.3 ± 0.8	9.4 ± 1.1	<0.001
Mean PDW on admission (normal 15.1–17.9%)	17.13 ± 0.6	16.43 ± 0.3	17.39 ± 0.5	<0.001
<i>In-hospital outcomes</i>				
Mechanical ventilation	112 (10.8%)	19 (7.0%)	93 (12.2%)	0.02
Duration of hospital stay (days)	8.0 ± 10	6.6 ± 7	8.5 ± 11	0.01
Prolonged hospitalization (>7 days)	330 (31.9%)	70 (25.6%)	260 (34.1%)	0.01
Death	73 (7.0%)	10 (3.7%)	63 (8.3%)	0.01

Data are presented as means ± SD or as the numbers (percentages) of presented cases. PDW, platelet distribution width. Bold entries in the table indicate a *P* value of ≤0.05. *Includes soft tissue infections, gastroenteritis, hepatitis, endocarditis, osteomyelitis, and meningitis.

**Includes non-cardiac chest pain, anemia, endocrinologic disorders, drug adverse effects or overdoses, renal disorders, active malignant diseases, and allergic reactions.

that each 1% increment of PDW was significantly associated with 90-day mortality (*P* = 0.022, RR 1.49, 95% CI 1.06–2.09, AUC = 0.825). High (>17.9%) PDW on admission was not found to be among the examined parameters to be most significantly associated with 90-day mortality.

Analysis by the Cox proportional-hazards model (Table 3) revealed that PDW as a quantitative variable was one of the variables that most significantly associated with shortened survival (*P* = 0.083, RR 1.26, 95% CI 0.97–1.64). However, PDW as a dichotomized variable (using cut-offs 16.7% and 17.9%) did not remain as one of the parameters that was most significantly associated with survival.

4. Discussion

To the best of our knowledge, this is the first study to investigate associations of PDW values on admission, with clinical characteristics and prognosis in internal medicine wards. The main novelty of our study is the associations observed, among internal medicine inpatients, of higher PDW levels with 90-day mortality and shortened survival following discharge.

Most previous studies focused on clinical correlates and prognosis associated with PDW in specific disorders. The strength of the present investigation is the detailed evaluation of demographic, clinical and laboratory characteristics associated with higher

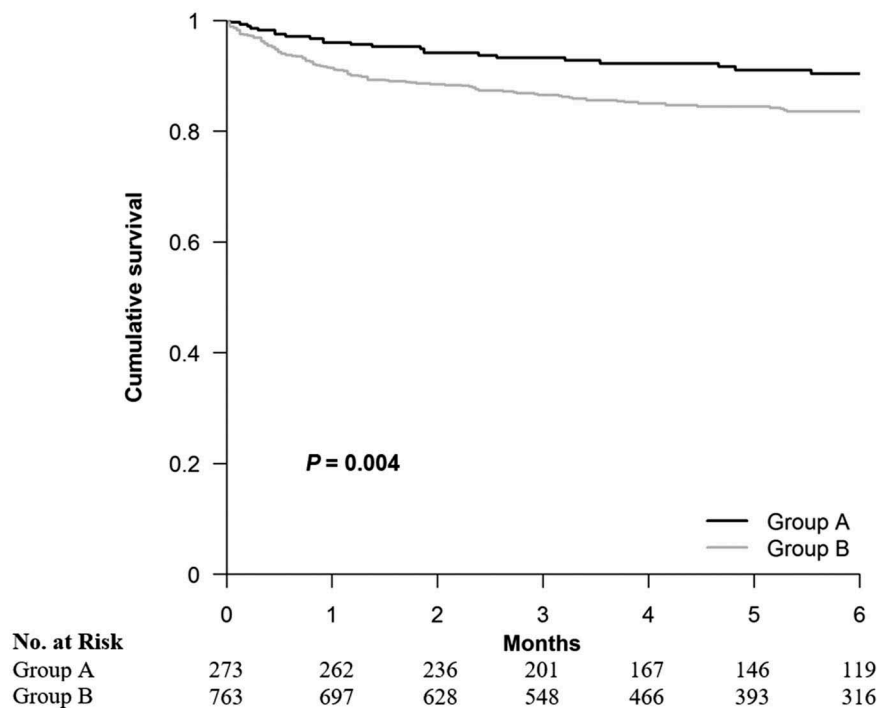


Figure 2. Kaplan-Meier estimates of survival for groups A and B. Group A- PDW values on admission $\leq 16.7\%$. Group B- PDW values on admission $> 16.7\%$. PDW, platelet distribution width.

Table 2. Variables that were most significantly associated with 90-day mortality in the entire study population (stepwise logistic regression analysis).

Variable	P value	Relative risk	95% confidence interval
Malignant disease	<0.001	3.53	2.27– 5.50
Cerebrovascular disease	<0.001	2.39	1.52– 3.74
Renal dysfunction	<0.001	2.67	1.27– 3.19
Pneumonia	<0.001	2.01	1.69– 4.24
Age (for each 10 year increment)	0.002	1.32	1.10– 1.58
PDW on admission $> 16.7\%$	0.08	1.58	0.89– 2.78

PDW, platelet distribution width.

PDW values in a heterogeneous internal medicine inpatient population. We found that higher values of PDW on admission were associated with age, various cardiovascular disorders, renal dysfunction, diabetes mellitus, and cerebrovascular and malignant diseases, as well as with treatments by statins and anticoagulants. Moreover, increased PDW levels were positively correlated with MPV values and inversely correlated with platelet counts. Several of our findings concur with studies of various populations [5–12]. PDW is an indicator of heterogeneity in platelet size. Higher PDW values reflect a larger range of platelet size, which may result from increased activation, destruction and consumption of platelets [4,9,10,16]. Aging, cardiovascular disorders, cancer, and other comorbidities that were associated with higher PDW values in our study may cause progressive platelet activation. This may increase the range of platelet size, due to changes in the morphology of platelets as spherically shaped and pseudopodia-formed [4,9]. Another possible pathophysiological

mechanism for higher variability in platelet size is hypercoagulability. During thrombosis, increased platelet destruction and consumption result in declining platelet count, on one hand; and in stimulation of thrombopoiesis with enhanced release of younger larger platelets from the bone marrow into the blood circulation, on other hand [10,16]. In support of this explanation are the associations found in the current study, of higher PDW values with acute cardiovascular disorders, and with higher MPV levels and lower platelet counts.

Our most interesting finding is the demonstration of prognostic significance of higher values of PDW on admission in internal medicine wards. Higher PDW levels have recently been reported to be associated with increased morbidity and mortality in numerous clinical investigations that focused on patients with critical illness [11,13], and with specific acute and chronic disorders [10,14–23]. We observed that PDW values above the cut-off of 16.7% at admission, as well as above the normal range, were associated with an increased risk of mechanical ventilation and death during the current hospitalization, and shortened survival following discharge. However, in multivariate analysis, higher PDW value did not remain one of the variables most significantly associated with any of the in-hospital outcomes examined. Therefore, we suggest that, in our patient population, higher PDW on admission serves as a marker of the severity of acute illness and comorbidities, rather than as a predictor of poor in-hospital prognosis.

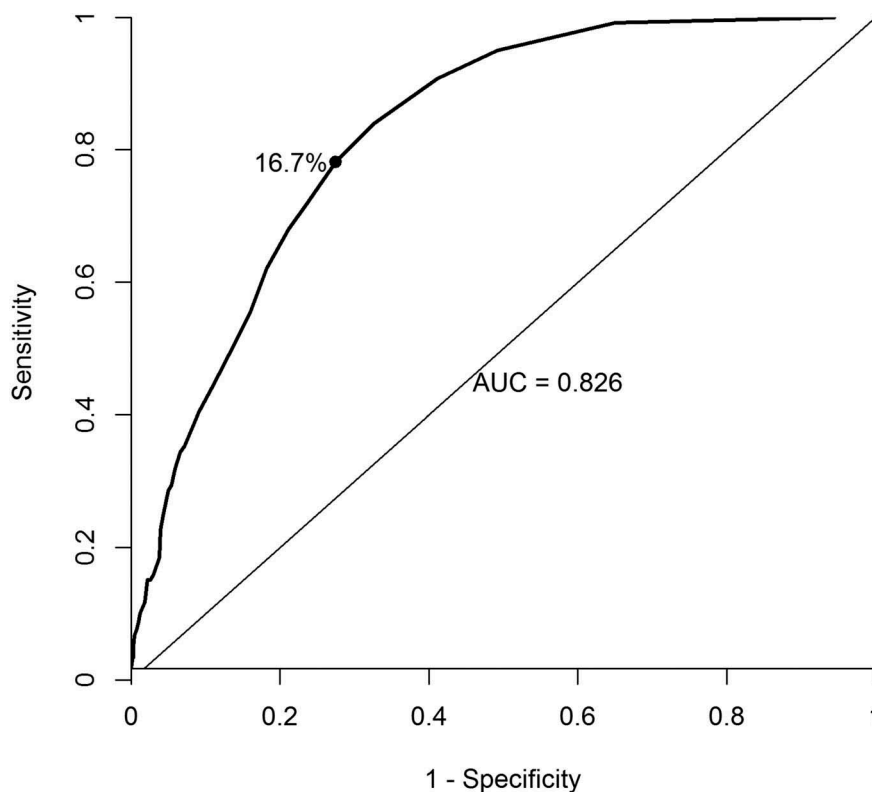


Figure 3. The receiver operating characteristic (ROC) curve for the relationship between 90-day mortality and PDW on admission using a cut-off of 16.7%. PDW, platelet distribution width. AUC, the area under the curve.

Table 3. Variables that were most significantly associated with low survival in the entire cohort (Cox proportional-hazards model).

Variable	P value	Relative risk	95% confidence interval
Age (for each 10 year increment)	<0.001	1.25	1.08– 1.44
Malignant disease	<0.001	3.04	2.17– 4.25
Cerebrovascular disease	<0.001	2.16	1.53– 3.05
Pneumonia	<0.001	2.06	1.46– 2.91
Renal dysfunction	<0.001	1.94	1.34– 2.79
PDW on admission (for each 1% increment)	0.083	1.26	0.97– 1.64

PDW, platelet distribution width.

In contrast to the lack of relationship to in-hospital outcomes, higher PDW levels at hospital admission were significantly associated with shortened survival following discharge. Moreover, a PDW value >16.7% and a 1% increment increase in PDW were associated with 90-day mortality. The pathophysiological mechanisms for a relationship of higher PDW with poor outcome following hospitalization for acute illness, yet not during hospitalization, are not clear. The increased 90-day mortality in patients with higher PDW values may be explained by their older age and a more severe clinical profile, leading to diminished host defense and impaired recovery. Another possibility is persistent increased platelet activation following discharge. PDW is considered a more specific marker of platelet function and activation than MPV, because it is not affected by single platelet distention resulting from platelet swelling

[4,14]. Greater platelet activation enhances the release of prothrombotic and vasoactive substances such as thromboxane A₂, β -thromboglobulin, P-selectin, and glycoproteins; this results in platelet hyperaggregability, endothelial dysfunction, and vasospasm [1–4,10]. These mechanisms may contribute to an increased risk of cardiovascular thrombosis and death in patients with increased PDW [10,16]. An additional explanation for an increased risk of 90-day mortality in patients with higher PDW values is increased release of chemokines, cytokines, growth factors, enzymes, and other substances from persistently activated platelets; this results in impaired immune function of platelets and other cells, as well as increased oxidative stress and apoptosis [2,3,11].

5. Limitations

Our investigation has a number of limitations. First, as a single center study, the results may not be generalizable to other populations. Second, since PDW was measured only on admission, misclassification could arise subsequent to changes in PDW during hospitalization or laboratory error. Finally, it is possible that some unaccounted confounders, such as body temperature, breathing frequency, heart rate and blood pressure, influenced the results. Strengths of our study are the relatively large sample size and the prospective design. This enabled completeness of collected data and follow-up, with precise description of the study groups.

6. Conclusions

Higher PDW values on admission at internal medicine wards are associated with older age, and more severe clinical and laboratory characteristics than lower levels of PDW. Higher PDW is associated with increased risk of 90-day mortality and shortened survival following discharge from the hospital. PDW determination is simple and inexpensive, and may be routinely measured in complete blood counts. Despite these advantages, PDW is not widely evaluated in clinical practice due to the novelty and difficulty of standardization. We suggest that PDW could serve as a novel prognostic marker in an internal medicine ward.

Disclosure statement

No potential conflict of interest was reported by the authors.

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