Original article

Platelet distribution width is associated with 1-year all-cause mortality in the elderly population

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ABSTRACT

Purpose: The aim of this investigation was to analyze whether the following platelet indices are useful markers for functional dependence and 1-year all-cause hospitalization and mortality in the elderly population: platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), and platelet−large cell ratio (P-LCR).
Methods: The 119 participants in this study were 90 women and 29 men between the ages of 68 and 105 years who were selected from the Santa Teresa nursing home (Oviedo, Spain). We studied morbidity, sociodemographic characteristics, and functional status using the Barthel Index (BI) and Katz Index (KI) for activities of daily living.
Results: In logistic regression models adjusted for age, sex, and anti-inflammatory drug use, low levels of PDW were associated with death at 1 year. When we applied logistic regression models adjusted for morbid conditions as well as age, sex, and anti-inflammatory drug use, the PDW remained statistically significant. No relation between PLT, MPV, or P-LCR and mortality was found. No statistical associations between the platelet indices studied and functional dependence or hospitalization were observed.
Conclusion: Our data suggest that the PDW could be a predictor of 1-year mortality in the elderly population and may therefore serve as a useful tool for identifying individuals with a high risk of mortality who may benefit from preventative care or early-stage strategies.
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1. Introduction

Aging is associated with an increased risk of functional dependence, hospitalization and mortality. The age-related physiological decline is intimately associated with poor quality of life, the need for long-term care and higher healthcare costs.[1] Therefore, many recent studies have investigated the usefulness of various parameters as biomarkers for adverse clinical outcomes in the elderly.[2–5] One important focus of this field is to determine whether typical parameters of automated blood cell counters demonstrate an association with adverse outcomes in the elderly. For example, total leucocytes and some subpopulations of leucocytes have been associated with frailty.[6,7] In addition, red blood cell distribution width seems to be a good indicator of mortality in older adults.[8,9] Platelet indices have received an increasing amount of attention as potential markers for disease. Several epidemiological studies have reported platelet indices, in particular the mean platelet volume (MPV), as markers for cardiovascular disease. Elevated MPV has been proposed as a risk factor for ischemic heart disease.[10] High levels of MPV seem to be associated with acute myocardial infarction and mortality following myocardial infarction, suggesting that MPV is a potentially useful prognostic biomarker in patients with cardiovascular disease.[11] However, the current knowledge of the usefulness of platelet indices as markers for adverse clinical outcomes, such as functional dependence or hospitalization, in the elderly population is limited. The lack of data addressing this issue

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is somewhat surprising when one considers the relevant health, social, and economic implications of adverse clinical outcomes of elderly subjects and the need to identify risk factors at a stage of age-related decline that would be amenable to preventive interventions. In addition, the availability of powerful biological markers for functional dependence, hospitalization, and mortality would allow for an assessment of the efficacy of possible interventions.

To address this issue, we analyzed the association of the following platelet indices with functional dependence and 1-year all-cause hospitalization and mortality in elderly subjects: platelet count (PLT), platelet distribution width (PDW), MPV, and platelet−large cell ratio (P-LCR). The ultimate goal of this study was to identify potentially useful biological markers for clinical practice.

2. Methods

2.1. Participants

Participants were selected from the Santa Teresa nursing home (Oviedo, Spain), and all those over 65 years old were considered for the current investigation. Exclusion criteria were recent or current infection, malignant disease, malnutrition, and pharmacological interference (immunosuppressive and antineoplasic drugs and testosterone). Malnutrition was defined as a recent (at least 1 month prior to enrollment in the study) measurement of serum albumin level of less than 3 g/dL. Participants were not selected based on morbidity characteristics. The participants were recruited from November 2008 to February 2009. During 1 year of follow-up, the number of hospitalizations and the patients' vital status were reported by internal nursing home clinicians. Follow-up of the cohort was 98% complete for hospitalization reports (1-year hospitalization data for two individuals was lost) and 99% complete for mortality reports (1-year mortality data for one individual was lost). Blood was drawn from all of the participants. Initial evaluations were carried out by experienced geriatricians and included an exhaustive review of the subject's medical and pharmacological history, a physical examination, and a physical activity questionnaire. The disease status of a patient was based on an explicit diagnosis in the patient's medical history. Diseases that were considered in the current analysis were cognitive impairment, dementia, osteoporosis, hypertension, chronic obstructive pulmonary disease, osteoarthritis, depression, heart failure, ischemic heart disease, rheumatoid arthritis, hyperthyroidism, cancer, dyslipidemia, and type 2 diabetes. The diagnosis of cognitive impairment and dementia was based on the Pfeiffer test (SMPSQ) and the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), respectively.

The functional abilities of the subjects were assessed using the Barthel Index (BI) and Katz Index (KI).[12,13] BI is a ten-item scale with an assessment of the following activities: feeding, grooming, bathing, toilet use, dressing, walking, transfers, climbing stairs, fecal incontinence, and urinary incontinence. The highest score is 100 (independence), and the lowest score is 0 (total dependence). KI ranks the adequacy of performance of the following six functions: bathing, dressing, using the toilet, transferring, continence, and feeding. The subjects were scored using 'yes' or 'no' for independence in each of the six functions. A score of 6 indicates severe functional impairment, and a score of 0 indicates functional independence. BI and KI were assessed by nursing aides who live with the patient and can therefore objectively and effortlessly evaluate the performance of the individual. The functional status of each subject was assessed during the week prior to inclusion in the study to eliminate subjective bias caused by interrogation regarding a particular subject.

Each participant or the participant's guardian received information about the purposes and objectives of the study and signed an informed consent form. The study was approved by the Hospital Central de Asturias (Oviedo, Spain) Ethics Committee.

2.2. Blood collection

Blood samples were obtained by venipuncture following an overnight fast and 15-minute rest in the morning. All venous blood samples were obtained in the morning before 10:00 AM to preclude circadian variation. The blood samples were drawn into BD Vacutainer tubes (BD, Franklin Lakes, NJ, USA).

2.3. Biochemical analysis

Serum albumin level was analyzed by a well-standardized hematology laboratory at the Monte Naranco Hospital (Oviedo, Spain). The following platelet indices were measured using an automated hematology analyzer SYSMEX SF-3000 (GMI Inc., Ramsey, MI, USA) in the same laboratory: platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), and platelet−large cell ratio (P-LCR).

2.4. Statistical analysis

Descriptive statistics were used to characterize the study population and to describe the studied parameters at baseline. The data were expressed as frequencies (percentages) for categorical variables and the mean ± standard deviation (SD) for continuous variables. The normality of the data was analyzed using the Kolmogorov−Smirnov test.

The linear regression analysis for each measurement of physical performance (BI and KI) was fitted against each marker after adjusting for age, sex, and anti-inflammatory drug use (model 1) to account for potential confounding variables. To establish whether the association of marker levels and BI and KI were influenced by morbid conditions, sequential linear regressions were also adjusted for age, sex, anti-inflammatory drug use, and total number of diseases per subject, including diagnoses of cognitive impairment, dementia, osteoporosis, hypertension, chronic obstructive pulmonary disease, osteoarthritis, depression, heart failure, ischemic heart disease, rheumatoid arthritis, hyperthyroidism, cancer, dyslipidemia, and type 2 diabetes (model 2).

Sequential logistic regressions for at least one hospitalization compared with nonhospitalized patients during 1 year and for death *versus* survival at 1 year were performed for each of the platelet markers measured at baseline, with adjustments made for age, sex, and anti-inflammatory drug use (model 1). To establish whether the observed association of biomarker levels with 1-year hospitalization or 1-year mortality could be altered by morbid conditions, sequential logistic regressions were also adjusted for age, sex, anti-inflammatory drug use, and the total number of diseases per participant (model 2). The results were presented as an odds ratio (OR) and 95% confidence interval (CI). The area under the receiver operating characteristic (ROC) curve (AUC) of PDW models was analyzed. The Youden Index was estimated.

The statistical software package SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Differences were considered statistically significant when $p < 0.05$.

3. Results

Demographic and clinical characteristics for the sample population are shown in Table 1. The mean age of the sample population was 86 ± 7 years. The prevalence of women was 75.6%. The sample population displayed a wide range of functional statuses (BI score = 0–100; KI score = 0–6). The study included 94

Table 1
Characteristics of the sample population.

Characteristics	$n = 119$
Age (y)	86 ± 7
Female	90 (75.6)
Male	29 (24.4)
Barthel Index	67 ± 34
Katz Index	2 ± 2
Total number of medical diagnoses per patient	2 ± 1
Cognitive impairment	20 (16.8)
Dementia	12 (10.1)
Osteoporosis	27 (22.7)
Hypertension	45 (37.8)
Chronic obstructive pulmonary disease	15 (12.6)
Osteoarthritis	28 (23.5)
Depression	21 (17.6)
Heart failure	6 (5.0)
Ischemic heart disease	8 (6.7)
Rheumatoid arthritis	2 (1.7)
Hyperthyroidism	2 (1.7)
Dyslipidemia	20 (16.8)
Type 2 diabetes	18 (15.1)
Total number of medications per patient	6 ± 3
Taking steroidal anti-inflammatory drugs	3 (2.5)
Taking nonsteroidal anti-inflammatory drugs	44 (36.9)
PLT (10^3/μL)	218.10 ± 73.28
PDW (fL)	13.85 ± 2.60
MPV (fL)	11.32 ± 1.14
P-LCR (%)	35.86 ± 9.13

Data are expressed as the mean ± SD for continuous variables and as frequencies (percentages) for categorical variables.
MPV = mean platelet volume; PDW = platelet distribution width; P-LCR = platelet–large cell ratio; PLT = platelet count.

nonhospitalized participants and 23 participants with at least one hospitalization during a 1-year period (19% of subjects). The study included 99 survivors and 19 participants who died during the 1-year study (16% of subjects).

Table 2 displays the linear regression models that were used to examine the relationship between the platelet indices and functional dependence using BI and KI as outcome measurements. In linear regressions that were adjusted by age, sex, and anti-inflammatory drug use, no association between platelet indices and BI or KI were reported. Because platelet indices have been correlated with several chronic diseases, an additional analysis was conducted to determine whether the incidence of diseases altered the relationship between platelet indices and BI or KI scores. When we applied linear regressions that were adjusted by age, sex, anti-inflammatory drug use, and morbid conditions, no statistically significant association was found.

Logistic regression models were used to examine the relationship between the platelet indices analyzed and either hospitalization or

mortality at 1 year (Table 3). In regressions adjusted by age, sex, and anti-inflammatory drug use, low levels of PDW were associated with at least one hospitalization during the study period with nearly significant differences, even after adjusting by morbid conditions. An association with 1-year mortality was observed for low levels of PDW in a model adjusted for age, sex, and anti-inflammatory drug use. Adjustment for morbid conditions retained statistical significance. A nearly significant relationship between MPV and P-LCR and 1-year mortality was found for both mortality models.

Because of the association of PDW regression models and 1-year mortality we analyzed the AUC for both models. For model 1, AUC (95% CI) was 0.706 (0.596–0.815), sensitivity was 0.895, specificity was 0.46, and the cut-off point was 0.113. For model 2, AUC (95% CI) was 0.734 (0.619–0.849), sensitivity was 0.842, specificity was 0.61, and the cut-off point was 0.152.

4. Discussion

In this study, we tested the hypothesis that platelet indices are associated with functional dependence and 1-year all-cause hospitalization and mortality in the elderly. The ultimate goal of this study was to identify potentially useful biological markers for clinical practice. Our results showed that institutionalized older subjects with lower PDW levels present a higher risk of mortality within 1 year. These results were statistically significant after adjusting for age, sex, anti-inflammatory use, and morbid conditions. It is important to point out that the AUC for both 1-year mortality models were elevated, indicating a good accuracy of the models obtained. Our findings are notable given that PDW is widely available to clinicians as part of the complete blood count and therefore incurs no additional costs.[14] Subjects with low PDW could be identified during routine hematological analysis and could possibly benefit from preventive treatment.

We obtained conflicting results from our analysis of the relationship between platelet indices and health status. MPV, PDW, and P-LCR were reported to be significantly higher in patients with diabetes compared to the control subjects. Furthermore, among patients with diabetes, the PDW was higher in those with microvascular complications.[15] MPV, PDW, and P-LCR were elevated in patients with acute myocardial infarction and unstable angina compared with stable coronary artery disease subjects and matched healthy controls with no history of heart disease.[16] However, previous studies proposed that MPV, PDW, and P-LCR were significantly lower in aortic aneurysm subjects than in age-matched healthy controls.[17] De Luca and colleagues proposed that PDW levels are not related to extent of coronary artery disease and concluded that the PDW cannot be considered as a risk factor for

Table 2
Association between platelet indices and functional dependence.

Variable	Model 1			Model 2		
	B (95% CI)	β	p	B (95% CI)	β	p
Barthel Index						
PLT (10^3/μL)	0.059 (−0.024, 0.141)	0.125	0.161	0.058 (−0.025, 0.141)	0.124	0.168
PDW (fL)	1.205 (−1.097, 3.507)	0.091	0.302	1.183 (−1.143, 3.509)	0.089	0.316
MPV (fL)	2.240 (−3.048, 7.528)	0.074	0.403	2.178 (−2.874, 7.691)	0.072	0.422
P-LCR (%)	0.255 (−0.406, 0.916)	0.067	0.446	0.247 (−0.423, 0.916)	0.065	0.467
Katz Index						
PLT (10^3/μL)	−0.003 (−0.008, 0.002)	−0.099	0.270	−0.003 (−0.008, 0.002)	−0.100	0.267
PDW (fL)	−0.078 (−0.222, 0.066)	−0.095	0.285	−0.080 (−0.225, 0.066)	−0.097	0.279
MPV (fL)	−0.164 (−0.494 0.166)	−0.087	0.328	−0.169 (−0.504, 0.165)	−0.090	0.319
P-LCR (%)	−0.020 (−0.061, 0.021)	−0.084	0.343	−0.021 (−0.062, 0.021)	−0.087	0.333

Model 1 is adjusted for age, sex, and anti-inflammatory drug use.
Model 2 is adjusted for age, sex, anti-inflammatory drug use, and morbid conditions.
β = standardized betas; B = betas; CI = confidence intervals; MPV = mean platelet volume; PDW = platelet distribution width; P-LCR = platelet–large cell ratio; PLT = platelet count.

Table 3
Associations between platelet indices and subsequent 1-year all-cause hospitalization or mortality.

Variable	Hospitalization				Mortality			
	Model 1		Model 2		Model 1		Model 2	
	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p
PLT ($*10^3$/μL)	0.998 (0.992, 1.005)	0.617	0.998 (0.991, 1.004)	0.503	1.000 (0.993, 1.007)	0.993	1.000 (0.993, 1.007)	0.987
PDW (fL)	0.811 (0.636, 1.034)	0.092	0.790 (0.611, 1.020)	0.071	0.761 (0.583, 0.993)	0.044[*]	0.761 (0.583, 0.993)	0.044[*]
MPV (fL)	0.754 (0.470, 1.209)	0.241	0.700 (0.422, 1.162)	0.168	0.638 (0.381, 1.068)	0.087	0.611 (0.360, 1.035)	0.067
P-LCR (%)	0.966 (0.910, 1.024)	0.246	0.957 (0.899, 1.019)	0.172	0.947 (0.889, 1.009)	0.095	0.942 (0.883, 1.006)	0.074

Model 1 is adjusted for age, sex, and anti-inflammatory drug use.
Model 2 is adjusted for age, sex, anti-inflammatory drug use, and morbid conditions.
[*]Statistically significant.
CI = confidence interval; MPV = mean platelet volume; OR = odds ratio; PDW = platelet distribution width; P-LCR = platelet–large cell ratio; PLT = platelet count.

coronary artery disease.[18] Moreover, while some authors reported that platelet indices could be used as potential markers of platelet activation,[19,20] others showed that platelet indices could not be used as an indicator of this phenomenon.[21] Therefore, a discrepancy between previous studies and our data is conceivable.

We cannot conclude whether the relationship between 1-year all-cause death and PDW in institutionalized elderly population is causal. Interestingly, high levels of interleukin-6 and white blood cells were negatively associated with PDW, indicating a possible relationship between inflammation and PDW.[20,22] PDW reflects the variability in platelet size. Previous data suggest a possible influence of chronic inflammation on PDW values; the data supporting this possibility include platelet size heterogeneity because of the production of factors in the bone marrow and not of their maturation during circulation,[23] the regulation of thrombopoiesis by inflammatory mediators,[24] and the association of mortality with chronic inflammation in the elderly population.[25,26] Indeed, subclinical chronic inflammation, defined by a two- to fourfold increase in the levels of circulating pro-inflammatory mediators, is an underlying biological mechanism responsible for health decline in the elderly.[27–29] This phenomenon is corroborated by recent data from our laboratory: we have shown a close association between higher levels of inflammatory parameters and 1-year mortality in the same study population as presented in this study.[8] Accordingly, the PDW might be considered as a surrogate marker of chronic inflammation rather than a direct causal factor of functional decline.

No correlation between PLT, MPV, or P-LCR and mortality was identified. Furthermore, no associations were found between the platelet indices analyzed and functional dependence or 1-year hospitalization. Prior to this study, there was a lack of data investigating an association between platelet indices and adverse clinical outcomes in the elderly population. Our findings provide additional information on platelet indices in relation to functional dependence, hospitalization, and mortality in elderly patients.

There are several noteworthy limitations to this study. First, a larger population size would have been desirable; the sample size is too small to perform adjusted stratified analyses in different clinical subgroups. Further, the sample size of this study was not large enough to test for cause-specific hospitalization and mortality. Regarding functional dependence, because of the cross-sectional characteristics of this study, we could not determine a causal explanation for the observed association between platelet indices and physical function. Finally, we cannot exclude the effect of diseases that were not recorded on subsequent outcomes, including subclinical inflammatory diseases. Based on these limitations, a cautious interpretation of these results is warranted.

We conclude that low PDW values could be a predictor of subsequent 1-year mortality in institutionalized elderly populations. The PDW may therefore provide a useful tool in translational research for identifying elderly people who have a high risk of death and may

benefit from preventive or early-stage strategies. Given these results, a more detailed investigation of this topic will be of great interest.

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