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Platelet to Lymphocyte Percentage Ratio Is Associated With Brachial–Ankle Pulse Wave Velocity in Hemodialysis

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Abstract: Increased arterial stiffness in patients receiving hemodialysis (HD) is highly prevalent and is associated with cardiovascular morbidity and mortality. In HD, inflammation is one of the major causes of increased arterial stiffness. Activation of platelets and decreased lymphocyte percentage (LYMPH%) may exhibit inflammation. The aim of this study is to examine the relationship between platelet to LYMPH% ratio and arterial stiffness in HD patients.

A total of 220 patients receiving HD were enrolled in this study. The brachial–ankle pulse wave velocity (baPWV) was measured using an ankle–brachial index form device. Multivariate linear regression analysis was performed to investigate the relations of the platelet to LYMPH% ratio and baPWV.

The value of the platelet to LYMPH% ratio was 59.2 ± 33.3 (10^9 cells/L/%). After multivariate stepwise analysis, diabetes (β: 163.973, $P = 0.02$), high systolic blood pressure (per 1 mm Hg, β: 9.010, $P < 0.001$), high platelet to LYMPH% ratio (per 10^9 cells/L/%, β: 3.334, $P < 0.01$), and low albumin (per 0.1 mg/dL, β: −55.912, $P < 0.001$) were independently associated with an increased baPWV. Furthermore, high white blood cells (per 10^9 cells/L, β: 3.941, $P < 0.001$), high neutrophil percentage (per 1%, β: 1.144, $P < 0.001$), and high CRP (per 1 mg/L, β: 9.161, $P = 0.03$) were independently associated with an increased platelet to LYMPH% ratio.

An increased platelet to LYMPH% ratio is associated with an increased baPWV in HD patients. An easy and inexpensive laboratory measure of platelet to LYMPH% ratio may provide an important information regarding arterial stiffness in patients with HD.

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Abbreviations: baPWV = brachial–ankle pulse wave velocity, CRP = C-reactive protein, ESRD = end-stage renal disease, HD = hemodialysis, iPTH = intact PTH, LYMPH% = lymphocyte percentage, NLR = neutrophil-to-lymphocyte, PLR = platelet-to-lymphocyte.

INTRODUCTION

Increased arterial stiffness has been reported in patients undergoing hemodialysis (HD), and this has been associated with an increased risk of cardiovascular disease.[1,2] Therefore, the careful management and evaluation of arterial stiffness in such patients is vital. Brachial–ankle pulse wave velocity (baPWV) has been used as a good marker of arterial stiffness,[3,4] and it has shown potential as an effective method to evaluate the extent of peripheral vascular damage. Inflammation has been reported to play an important role in the development of arterial stiffness in addition to the well-known risk factors including calcium/phosphate imbalance, secondary hyperparathyroidism, homocysteine, fluid overload, malnutrition, uremic toxins, oxidative stress, and insulin resistance.[5,6] Furthermore, chronic inflammation in patients with end-stage renal disease (ESRD) has been reported to be a component of malnutrition-inflammation-atherosclerosis syndrome.[7]

In recent years, some hematological parameters, such as neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), lymphocyte percentage (LYMPH%), were found to be surrogate markers of inflammation.[8–10] Furthermore, they were shown as potential markers to predict the morbidity and mortality in renal, cardiac, and different oncologic cancers.[10–13] Besides, NLR and PLR were reported to be associated with limb ischemia and arterial stiffness.[14–16] However, the relationship between hematological parameters and arterial stiffness remains unclear in patients receiving HD. Therefore, this study investigated the relationships of NLR, PLR, and platelet to LYMPH% ratio with baPWV in patients receiving HD.

SUBJECTS AND METHODS

Study Patients and Design

We performed this study at a single dialysis clinic of a regional hospital in southern Taiwan. We enrolled all patients undergoing routine HD at our clinic except those who refused to undergo ankle-brachial index (ABI) assessments (n = 5), and those with atrial fibrillation (n = 4), amputation of both legs below the knees (n = 2), and those who were hospitalized or prescribed with antibiotics in the last 4 weeks (n = 6). In total, 220 patients (114 men and 106 women) were enrolled as the study cohort. This study was approved by the Institutional Review Board of Kaohsiung Municipal Hsiao-Kang Hospital, and all patients provided written informed consent to participate in this study.

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Hemodialysis

All of the enrolled patients received HD 3 times a week. Each session lasted for 3 to 4 hours with a dialyzer using a blood flow rate of 250 to 300 mL per minute and dialysate flow of 500 mL/min.

Assessment of baPWV

BaPWV was assessed 10 to 30 minutes before each HD session using an ABI-form device. This oscillometric device measured the blood pressure in the arms and ankles.[3,17] Occlusion and monitoring cuffs were placed tightly around the upper arm without blood access and both sides of the lower extremities in the supine position. BaPWV values were measured, and the measurement method has been reported and validated in previous studies.[3,17] The larger bilateral baPWV value was used in the analysis, with baPWV values being measured once in each patient.

Collection of Demographic, Medical, and Laboratory Data

Demographic data including age, gender, smoking status (ever vs never), and comorbidities were obtained from medical records and interviews with the patients. The body mass index was recorded as kg/m^2. Laboratory examinations were performed using fasting blood samples obtained within 1 month of enrollment with an autoanalyzer (Roche Diagnostics GmbH, D-68298 Mannheim COBAS Integra 400, Germany). Complete white blood cell count (normal range: 4.8–10.8 $\times$ 10^9 cells/L), percentage of neutrophils (normal range: 55–75%), percentage of lymphocytes (normal range: 19–49%), and platelet count (normal range: 140–500 $\times$ 10^9 cells/L) were evaluated using an automatic blood counter. The concentrations of intact PTH (iPTH) in serum and C-reactive protein (CRP) were measured using assay kits (CIS Bio International, France and Dade Behring Marburg GmbH, Germany, respectively). We used monthly values of Kt/V to assess the efficiency of dialysis determined by the Daugirdas procedure.[18]

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 for windows (SPSS Inc. Chicago). Data are expressed as percentages, mean $\pm$ standard deviation, or median (25th–75th percentile) for duration of dialysis, triglyceride, iPTH, and CRP. Multiple linear stepwise regression analysis was used to identify the factors associated with baPWV and platelet to LYMPH% ratio. Significant variables in univariate analysis were selected for multivariate analysis. A difference was considered significant if the P value was <0.05.

RESULTS

The mean age of the 220 patients was 61.0 $\pm$ 11.7 years. The mean value of baPWV was 1992.3 $\pm$ 553.1 cm/s. The values of NLR, PLR, and platelet to LYMPH% ratio were 3.0 $\pm$ 1.5, 139.1 $\pm$ 59.9, and 59.2 $\pm$ 33.3 (10^9 cells/L/%), respectively. Baseline characteristics of the study patients are shown in Table 1.

TABLE 1. Baseline Characteristics of Study Patients

Characteristics	All Patients (n = 220)
Age (year)	61.0 $\pm$ 11.7
Male gender (%)	51.8
Duration of dialysis (years)	7.2 (2.8–12.6)
Smoking history (%)	41.6
Diabetes mellitus (%)	46.4
Hypertension (%)	53.2
Coronary artery disease (%)	13.2
Cerebrovascular disease (%)	5.9
Systolic blood pressure (mm Hg)	153.9 $\pm$ 25.7
Diastolic blood pressure (mm Hg)	80.8 $\pm$ 14.5
baPWV (cm/s)	1992.3 $\pm$ 553.1
Body mass index (kg/m^2)	23.8 $\pm$ 3.7
Laboratory parameters	
WBC ($\times$10^9 cells/L)	6.6 $\pm$ 2.2
Neutrophils (%)	63.8 $\pm$ 8.5
Lymphocytes (%)	24.4 $\pm$ 6.9
Hemoglobin (g/dL)	10.2 $\pm$ 1.4
Platelets ($\times$10^9 cells/L)	200.9 $\pm$ 70.7
Neutrophil to lymphocyte ratio	3.0 $\pm$ 1.5
Platelet to lymphocyte ratio	139.1 $\pm$ 59.9
Platelet to lymphocyte % ratio (10^9 cells/L/%)	59.2 $\pm$ 33.3
Albumin (g/dL)	3.9 $\pm$ 0.3
Fasting glucose (mg/dL)	118.4 $\pm$ 49.0
Triglyceride (mg/dL)	141.5 (97.5–214)
Total cholesterol (mg/dL)	184.7 $\pm$ 51.1
HDL-cholesterol (mg/dL)	38.5 $\pm$ 12.0
LDL-cholesterol (mg/dL)	95.4 $\pm$ 33.8
Creatinine (mg/dL)	9.9 $\pm$ 4.1
Total calcium (mg/dL)	9.1 $\pm$ 0.8
Phosphorous (mg/dL)	4.5 $\pm$ 1.0
Calcium-phosphorous product (mg^2/dL^2)	41.5 $\pm$ 9.9
Uric acid (mg/dL)	7.5 $\pm$ 1.6
iPTH (pg/mL)	419.8 (225.2–659)
CRP (mg/L)	3 (1.6–6.75)
Kt/V	1.6 $\pm$ 0.3

baPWV = brachial–ankle pulse wave velocity, CRP = C-reactive protein, HDL = high-density lipoprotein, iPTH = intact parathyroid hormone, LDL = low-density lipoprotein, WBC = white blood cell.

Numbers of missing data (n): smoking history (1), albumin (2), fasting glucose (9), triglyceride (6), total cholesterol (6), HDL-cholesterol (6), LDL-cholesterol (6), creatinine (3), total calcium (3), phosphorous (3), calcium–phosphorous product (4), uric acid (2), iPTH (12), and Kt/V (5).

Determinants of baPWV

Table 2 shows the determinants of baPWV in our study patients. In the univariate regression analysis, a high baPWV was found to be associated with old age, short duration of dialysis, diabetes mellitus (DM), hypertension, high systolic blood pressure, high diastolic pressure, high platelets, high platelet to LYMPH% ratio, low albumin, high fasting glucose, low high-density lipoprotein (HDL)-cholesterol, low total calcium, and high CRP. In the multivariate stepwise analysis, DM (β: 163.973, $P = 0.02$), high systolic blood pressure (per 1 mm Hg, β: 9.010, $P < 0.001$), high platelet to LYMPH% ratio (per 10^9 cells/L/%, β: 3.334, $P < 0.01$), and low albumin (per 0.1 mg/dL, β: -55.912, $P < 0.001$) were independently associated with an increased baPWV.

We further performed subgroup analysis after excluding 76 patients with abnormal platelet count or LYMPH%. We found

TABLE 2. Determinants of baPWV in Study Patients

Parameters	Univariate		Multivariate (Stepwise)	
	Unstandardized Coefficient β (95%CI)	*P*	Unstandardized Coefficient β (95%CI)	*P*
Age (per 1 year)	9.702 (3.526, 15.878)	< 0.01	–	–
Male vs female	103.289 (−43.484, 250.062)	0.17	–	–
Duration of dialysis (log per 1 year)	−15.442 (−27.273, −3.611)	0.01	–	–
Smoking(ever vs never)	33.752 (−115.701, 183.205)	0.66	–	–
Diabetes mellitus	363.646 (224.137, 503.155)	< 0.001	163.973 (33.479, 294.461)	0.02
Hypertension	243.305 (99.301, 387.308)	< 0.01	–	–
Coronary artery disease	97.904 (−119.446, 315.254)	0.38	–	–
Cerebrovascular disease	−170.179 (−481.746, 141.387)	0.28	–	–
Systolic blood pressure (per 1 mm Hg)	9.353 (6.761, 11.945)	< 0.001	9.010 (6.447, 11.572)	< 0.001
Diastolic blood pressure (per 1 mm Hg)	10.699 (5.817, 15.580)	< 0.001	–	–
Body mass index (kg/m^2)	−2.806 (−22.553, 16.940)	0.78	–	–
Laboratory parameters				
WBC (per 10^9 cells/L)	19.082 (−15.006, 53.171)	0.27	–	–
Neutrophils (per 1 %)	3.084 (−5.625, 11.793)	0.49	–	–
Lymphocytes (per 1 %)	−3.810 (−14.570, 6.950)	0.49	–	–
Hemoglobin (per g/dL)	11.772 (−42.376, 65.919)	0.67	–	–
Platelets (per10^9 cells/L)	1.109 (0.075, 2.144)	0.04	–	–
Neutrophil to lymphocyte ratio (per 1)	−11.031 (−60.106, 38.045)	0.66	–	–
Platelet to lymphocyte ratio (per 1)	0.433 (−0.797, 1.664)	0.49	–	–
Platelet to lymphocyte% ratio (per 10^9 cells/L/%)	2.915 (0.733, 5.097)	< 0.01	3.334 (1.252, 5.417)	< 0.01
Albumin (per 0.1 g/dL)	−47.892 (−71.707, −24.076)	< 0.001	−55.912 (−78.736, −33.088)	< 0.001
Fasting glucose (per 1 mg/dL)	1.991 (0.505, 3.477)	< 0.01	–	–
Triglyceride (log per 1 mg/dL)	−28.376 (−312.378, 255.626)	0.84	–	–
Total cholesterol (per 1 mg/dL)	−0.223 (−1.659, 1.212)	0.76	–	–
HDL-cholesterol (per 1 mg/dL)	−8.487 (−14.499, −2.475)	< 0.01	–	–
LDL-cholesterol (per 1 mg/dL)	0.567 (−1.601, 2.736)	0.61	–	–
Creatinine (per 1 mg/dL)	−14.812 (032.837, 3.213)	0.61	–	–
Total calcium (per 1 mg/dL)	−89.353 (−176.854, −1.852)	0.05	–	–
Phosphorous (per 1 mg/dL)	0.395 (−63.243, 84.032)	0.78	–	–
Calcium−phosphorous product (per 1 mg^2/dL^2)	−2.170 (−9.636, 5.296)	0.57	–	–
Uric acid (per 1 mg/dL)	−40.221 (−86.925, 6.484)	0.09	–	–
iPTH (per 1 pg/mL)	88.077 (−93.018, 269.172)	0.34	–	–
CRP (per 1 mg/L)	216.204 (55.403, 377.005)	< 0.01	–	–
Kt/V (per 1)	−46.074 (−325.031, 232.883)	0.75	–	–

Values expressed as unstandardized coefficient β and 95% confidence interval (CI). baPWV = brachial−ankle pulse wave velocity, CI = confidence interval, CRP = C-reactive protein, HDL = high-density lipoprotein, iPTH = intact parathyroid hormone, LDL = low-density lipoprotein, WBC = white blood cell.

Initial model included age, duration of dialysis, diabetes mellitus, hypertension, systolic and diastolic blood pressures, platelets, platelet to lymphocyte% ratio, albumin, fasting glucose, HDL-cholesterol, total calcium, and CRP. Forward stepwise selection included variables with entry and removal probability < 0.05.

old age (per 1 year, β: 12.680, $P < 0.01$), high systolic blood pressure (per 1 mm Hg, β: 7.554, $P = 0.02$), high platelet to LYMPH% ratio (per 10^9 cells/L/%, β: 5.545, $P < 0.01$), and low albumin (per 0.1 mg/dL, β: −38.005, $P = 0.02$) were still independently associated with an increased baPWV.

Determinants of Platelet to LYMPH% Ratio

The determinants of platelet to LYMPH% ratio in our study patients are shown in Table 3. In the univariate regression analysis, a high platelet to LYMPH% ratio was found to be associated with DM, high white blood cells, high neutrophil percentage, low HDL-cholesterol, and high CRP. In the multivariate stepwise analysis, high white blood cells (per 10^9 cells/L, β: 3.941, $P < 0.001$), high neutrophil percentage (per 1%, β: 1.144, $P < 0.001$), and high CRP (per 1 mg/L, β: 9.161, $P = 0.03$) were independently associated with an increased platelet to LYMPH% ratio.

We further performed subgroup analysis after excluding 76 patients with abnormal platelet count or LYMPH%. We found high white blood cells (per 10^9 cells/L, β: 3.943, $P < 0.001$),

TABLE 3. Determinants of Platelet to Lymphocyte% Ratio in Study Patients

Parameters	Univariate		Multivariate (Stepwise)	
	Unstandardized Coefficient β (95%CI)	*P*	Unstandardized Coefficient β (95%CI)	*P*
Age (per 1 year)	−0.010 (−0.390, 0.371)	0.96	–	–
Male vs female	4.893 (−3.962, 13.748)	0.28	–	–
Duration of dialysis (log per 1 year)	−4.516 (−13.793, 4.761)	0.34	–	–
Smoking(ever vs never)	7.939 (−1.022 16.900)	0.08	–	–
Diabetes mellitus	11.707 (2.949, 20.466)	< 0.01	–	–
Hypertension	5.675 (−3.183, 14.534)	0.21	–	–
Coronary artery disease	4.799 (−8.300, 17.898)	0.47	–	–
Cerebrovascular disease	1.018 (−17.797, 19.833)	0.92	–	–
Systolic blood pressure (per 1 mm Hg)	0.099 (−0.074, 0.272)	0.26	–	–
Diastolic blood pressure (per 1 mm Hg)	0.166 (−0.140, 0.472)	0.29	–	–
Body mass index (kg/m^2)	0.819 (−0.365, 2.004)	0.17	–	–
Laboratory parameters				
WBC (per 10^9 cells/L)	7.423 (5.619, 9.228)	< 0.001	3.941 (1.992, 5.890)	< 0.001
Neutrophils (per 1 %)	1.734 (1.263, 2.205)	< 0.001	1.144 (0.692, 1.595)	< 0.001
Hemoglobin (per g/dL)	−0.054 (−3.317, 3.209)	0.97		–
Albumin (per 0.1 g/dL)	0.168 (−1.294, 1.630)	0.82	–	–
Fasting glucose (per 1 mg/dL)	0.057 (−0.036, 0.149)	0.23	–	–
Triglyceride (log per 1 mg/dL)	−4.303 (−20.471, 11.864)	0.60	–	–
Total cholesterol (per 1 mg/dL)	−0.069 (−0.151, 0.012)	0.09	–	–
HDL-cholesterol (per 1 mg/dL)	−0.353 (−0.698, −0.008)	0.05	–	–
LDL-cholesterol (per 1 mg/dL)	−0.019 (−0.143, 0.105)	0.76	–	–
Creatinine (per 1 mg/dL)	−0.559 (−1.631, 0.514)	0.31	–	–
Total calcium (per 1 mg/dL)	1.582 (−3.658, 6.822)	0.55	–	–
Phosphorous (per 1 mg/dL)	1.807 (−2.581, 6.194)	0.42	–	–
Calcium-phosphorous product (per 1 mg^2/dL^2)	0.174 (−0.272, 0.620)	0.44	–	–
Uric acid (per 1 mg/dL)	−0.828 (−3.660, 2.004)	0.57	–	–
iPTH (per 1 pg/mL)	−0.150 (−11.639, 11.339)	0.98	–	–
CRP (per 1 mg/L)	19.259 (9.761, 28.757)	< 0.001	9.161 (0.828, 17.495)	0.03
Kt/V (per 1)	−15.941 (−32.594, 0.712)	0.06	–	–

Values expressed as unstandardized coefficient β and 95% confidence interval (CI). baPWV = brachial–ankle pulse wave velocity, CI = confidence interval, CRP = C-reactive protein, HDL = high-density lipoprotein, iPTH = intact parathyroid hormone, LDL = low-density lipoprotein, WBC = white blood cell.

Initial model included diabetes mellitus, WBC, neutrophil percentage, HDL-cholesterol, and CRP. Forward stepwise selection included variables with entry and removal probability < 0.05.

high neutrophil percentage (per 1%, β: 0.527, $P = 0.04$), and high CRP (per 1 mg/L, β: 7.300, $P = 0.04$) were still independently associated with an increased platelet to LYMPH% ratio.

DISCUSSION

Complete blood counts are easy, inexpensive, and routine examinations that give the information about the blood contents: the red and white cells, the platelets, and the counts and percentages of subgroups of cells. In the present study, we evaluated the association between hematological parameters and arterial stiffness in HD patients and found that increased platelet to LYMPH% ratio was independently associated with an increased baPWV. Besides, high white blood cells, high neutrophil percentage, and high CRP were associated with an increased platelet to LYMPH% ratio.

The most critical finding of the study was that increased platelet to LYMPH% ratio was independently associated with increased arterial stiffness in patients with HD. Consistent with the result, some reports have documented the association between arterial stiffness and inflammatory markers, such as interleukin-6 and CRP.[19,20] Chronic inflammation is a component of malnutrition-inflammation-atherosclerosis syndrome, which is associated with adverse cardiovascular outcomes in ESRD.[7] Inflammation is well known to play a major role in atherosclerosis.[7] Platelets are found to be evolved in the atherogenesis via serectory proinflammatory cytokines.[21] Platelets interact with endothelial cells and leukocytes[22] and release inflammatory substances leading to adhesion and transmigration of monocytes.[23] Endothelial dysfunction and increased expression of proinflammatory cytokines could increase vascular inflammation, smooth muscle cell proliferation, and subsequently elevated arterial stiffness.[24] Hence, platelets may play an important role in the development of arterial stiffness.

The other component of the platelet to LYMPH% ratio is the LYMPH%. The LYMPH% is an important parameter in patients with advanced cancer.[10,25] A low LYMPH% is associated with an increased mortality and a short disease-free survival in advance colorectal cancer.[10,25] Patients with decreased LYMPH% may exhibit a poorer lymphocyte-

mediated immune response to malignancy, thereby increasing the risk of tumor recurrence. In the present study, the platelet to LYMPH% ratio was found to be significantly associated with inflammatory markers, such as white blood cells, neutrophil percentage, and CRP. Increased inflammation is highly link to increased arterial stiffness.[7] Therefore, a high platelet count and a low LYMPH% and thus a high platelet to LYMPH% ratio, probably reflecting a high inflammation status, may lead to an increased arterial stiffness.

Study Limitations

There were several limitations to our study. First, this study was cross-sectional, so the causal relationship and long-term clinical outcomes could not be confirmed. Future prospective studies are needed to address the issues. In addition, we used a single blood sample to calculate platelet to LYMPH% ratio, which remained unclear whether this single blood sample really reflected an elevated platelet to LYMPH% ratio. Finally, some important inflammation markers (eg, interleukein-6, interleukin 1β, and tumor necrosis factor-α) were lacking.

CONCLUSIONS

In conclusion, our results demonstrated that an increased platelet to LYMPH% ratio was independently associated an increased arterial stiffness and this ratio was also correlated with inflammation markers. Therefore, the platelet to LYMPH% ratio is a simple, relatively inexpensive, and universally available method of identifying patients with increased arterial stiffness in HD patients.

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