Platelet-to-Neutrophil Ratio after Intravenous Thrombolysis is Prognostic Marker for 90-days Outcome in Acute Ischemic Stroke

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Abstract

Introduction: Platelet-to-neutrophil ratio (PNR) is a new biomarker that combines platelets and neutrophil counts. A recent study suggested that the level of PNR on admission is associated with the prognosis of acute ischemic stroke (AIS) patients.

Objective: To investigate PNR value as a prognostic marker for 90-days outcomes in AIS patients after intravenous thrombolysis.

Material and Method: Data on AIS patients who received intravenous thrombolysis treatment from January 2018 to June 2021 were collected at Thammasat University Hospital. Clinical outcome indicators included early neurological deterioration (END), hemorrhagic transformation (HT), delayed neurological deterioration (DND), and poor 3-month outcome (3m-mRS ≥ 3).

Results: A total 434 patients were analyzed in this study. The age was 64.5 (53-72) years, and 249 (59.6%) were male. PNR level was identified as high (at the cut-off value or above) or low (below the cut-off value) according to receiver operating curve (ROC) analyses on each endpoint. Comparison of hemorrhagic transformation (HT) delayed neurological deterioration (DND), and poor 3-month outcome (3m-mRS ≥ 3) between patients at high and low levels for platelet-to-neutrophil ratio (PNR) showed statistical differences ($p < 0.05$).

Conclusion: PNR was independently associated with poor 3-month outcome (mRS ≥ 3), hemorrhagic transformation and delay neurological deterioration. Lower PNR can predict a worse outcome.

Keywords: Stroke, Thailand, Platelet, Neutrophil, Ratio, Outcome

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Introduction

Stroke is the second leading cause of death worldwide and also the leading cause of long-term disability. Ischemic stroke is the most common type of stroke.[1] An occurrence of acute ischemic stroke (AIS) always leads to the death of brain tissues and focal neurological deficits. The World Health Organization (WHO) estimates that every year there will be more than 15 million stroke patients worldwide, and by 2020 this will double.[2] Thailand situation in the past 5 years of the Department of Strategic and Planning, Ministry of Public Health (2013 - 2017), the number of stroke cases tends to increase every year. In 2017, there were 304,807 new cases and deaths more than 30,000 cases last year.[3] Recombinant tissue plasminogen activator (rtPA) is the only thrombolytic agent approved by the FDA for ischemic stroke therapy.[4] But, owing to the limitation of the narrow therapeutic time window (4.5 h from the onset of symptoms of ischemic stroke) and the potential risk of hemorrhagic transformation (HT), only partial patients can benefit from intravenous thrombolysis (IVT).

In the pathogenesis of AIS, platelet activation and aggregation are important. Under pathological conditions, excessive activation and aggregation of platelets may lead to thrombosis and vascular occlusion, which would result in ischemic stroke.[5] Numerous studies have demonstrated that platelet count (PLT) decreases in the circulatory system of AIS patients, whereas platelet distribution width (PDW) and mean platelet volume (MPV) increase.[6] It is known that the immune response is vital in the pathological changes of AIS. Ischemic and anoxic brain tissue promote the infiltration of peripheral blood leukocytes to the injured area and neutrophils are the first cell to be recruited into the brain after stroke, which release inflammatory mediators in the ischemic brain area, exacerbate brain damage[7] and promote the occurrence of ischemia by inducing thrombosis with different mechanisms such as interacting with platelets and coagulation factors, and releasing proteases.[8] Platelet-to-neutrophil ratio (PNR) is a new biomarker that combines platelets and neutrophil counts. Compared with single platelet counts and neutrophil counts, PNR reflects the severity of both thrombosis and inflammation, revealing the connection between the two processes. In the stroke field, a recent study suggested that the level of PNR on admission is associated with the prognosis of AIS patients.[9] In this retrospective study our aim was to demonstrate the clinical value of PNR in predicting the outcome in AIS patients treated with IVT.

Materials and Methods

1. Study population

Data from this retrospective study were collected at Thammasat University Hospital. Acute ischemic stroke patients who received intravenous thrombolysis treatment from January 2018 to June 2021 were included. Inclusion criteria: [1] patients diagnosed with AIS accepted IVT (rt-PA) treatment within 4.5 hours of stroke onset according to stroke fast track criteria of Thammasat University Hospital, [2] age of 18 to 85 years. Exclusion criteria: [1] history of prior infection or surgery within 2 weeks, [2] underlying disease of malignancy, rheumatoid arthritis, connective tissue disease, [3] chronic liver disease (Child-Pugh > B), [4] chronic kidney disease (serum creatinine > 2.0 mg/dL), and [5] prior abnormalities of platelets and white blood cells. Finally, 434 patients were included in the study.

The Human Research Ethics Committee of Thammasat University (Medicine) approved this study.

2. Data Collection

Base on the clinical manisfestation and sign, an experienced clinician determined whether the patient met the clinical case description of acute stroke, and stroke severity was assessed on admission using the National Institute of Health Stroke Scale (NIHSS) score. All patients underwent emergent computerized tomography (CT) scan or magnetic resonance imaging (MRI) before IVT to rule out the possibility of hemorrhagic stroke. Baseline clinical characteristics including laboratory examination within 24 hours of admission were collected for all patients, such as complete blood count, fasting blood glucose (FBG), low-density lipoprotein (LDL). PNR was calculated according to platelet counts and neutrophil counts; and demographic information (age, gender), vascular risk factor (hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation (AF), current smoking and current drinking), past medical history (antihypertensive therapy, antiplatelet therapy and hypoglycemic therapy), the National Institute of Health Stroke Scale (NIHSS) score on admission.[10]

3. Evaluation Standard

Hypertension is defined as repeated multiple systolic blood pressure ≥ 140 on admission or a history of previous hypertension. Diabetes is defined as a history of previous diabetes or admission to hospital with diabetes mellitus and fasting plasma glucose ≥ 126 mg/dL or HbA1C ≥ 6.5%. AF is defined as the any previously known AF episode or electrocardiogram of AF recorded at the time. Hyperlipidemia is defined as a history of hyperlipidemia or admission dyslipidemia and is one of the following LDL ≥ 100 mg/dL, triglyceride (TG) ≥ 150 mg/dL.[11]

434 cases were examined with computed tomography (CT) scans or magnetic resonance imaging (MRI), according to the formula 0.5 x a x b x c (a: maximum longitudinal diameter; b: maximum transverse diameter perpendicular to a; c: 10 mm slices with infarction) to calculate the infarct volume (12). Defined as < 5 cm^3 as small infarct volume, ≥ 5 cm^3 as large infarct volume.

4. Outcomes

Four clinical outcome indicators included early neurological deterioration (END), hemorrhagic transformation (HT), delayed neurological deterioration (DND) and poor 3-month outcome. HT was defined as any visible hemorrhage on brain CT or MRI within 24 h after thrombolysis. END was defined as ≥ 4-point increase in scores on the NIHSS or dead within 24 h after intravenous thrombolysis. DND and 3-months clinical outcome were measured using modified Rankin Scale (mRS). DND defined as poor outcome group (mRS score of 3-6 at discharge date (24 h to 7 d). In 3-months clinical outcome, poor outcome was defined as an mRS score of 3-6 at discharge date (24 h to 7 d) and good outcome was defined as an mRS score of 0-2 at discharge date.

5. Statistical Analysis

Data were analyzed using the Statistical Program for Social Sciences version 22.0 (SPSS, IBM, West Grove, PA, USA). The difference between the 2 groups was tested using the Mann-Whitney U-test for nonparametrically distributed variables. The differences between categorical variables were determined using the χ^2 test. Median with IQR and percentage were used to describe the distribution of continuous and categorical variables, respectively. The receiver operating characteristic (ROC) curve

was used to evaluate the prognosis effect of PNR. P < 0.05 was used to establish statistical significance in all comparisons between groups.

Results

1. Clinical characteristics of the study population

Of the 434 patients were analyzed in this study, 169 (40.4%) were female and 249 (59.6%) were male, with the age was 64.5 (53-72) years, NIHSS score on admission average 10 (IQR, 6-16). The most common risk factors are hypertension was found at 71.5%, followed by hyperlipidemia and diabetes, at 66 and 33.7%, respectively. The time from stroke onset to IVT infusion was 170 (124-218) min. Baseline clinical characteristics and outcomes are summarized in Table 1.

2. The Association of PNR Levels with END, HT, DND and poor 3-month outcome

We divided all eligible patients into groups according to the presence or absence of each clinical outcome indicators. The age was higher in END group with statistical significance (70 vs 64, p = 0.045). The group with END had higher proportions of other determined/undetermined and large-artery atherosclerosis than those group without END. Baseline blood sugar showed the group with END was higher than those group without END (164.5 vs 109 mg/dL, p< 0.001). Infarct volume in the group with END was higher than those group without END (34.42 vs 2.76 ml, p< 0.001), as shown in Table 2.

Patients who developed HT had higher proportions of other determined/undetermined, cardioembolic and large-artery atherosclerosis than those without HT, except the proportions of small-artery occlusion in patients who developed HT was less than those without HT (p < 0.001). The group with HT had NIHSS score on admission been higher than those group without HT (13 vs 10, p = 0.018). LDL in the group with HT was greater than those group without HT (119 vs 112, p = 0.001), as shown in Table 2.

The group with DND had higher age than those group without DND with statistical significance (67 vs 60 years, p < 0.001). Patients with hypertension developed a greater percentage of DND than those without hypertension (79.1% vs 62.6%, p < 0.001). We found the group with DND had the proportion of other determined/undetermined and large-artery atherosclerosis been greater than those without DND, while the proportion of cardioembolic and small-artery occlusion in the group with DND were significantly less than those group without DND with statistical significance (p=0.004). In DND group had higher NIHSS score on admission than those group without DND (17 vs 7 points, p < 0.001), as shown in Table 3.

We found age of the patients who had poor 3-month outcome was 69 years, which was higher than those group had good 3-month outcome been 60 years (p<0.001). A group with poor 3-month outcome had a greater proportion of other determined/undetermined and large-artery atherosclerosis than those group with good 3-month outcome, while a group with poor 3-month outcome had a lower proportion of cardioembolic and small-artery occlusion than those group with good 3-month outcome (p = 0.002). NIHSS score on admission in poor 3-month outcome group was higher than those group with good 3-month outcome (14 vs 8, p < 0.001). PLR and NLR in the group with poor 3-month outcome was significantly higher than the group with good 3-month outcome (126.57 vs

111.24, p = 0.021 and 2.8 vs 2.48, p = 0.026). The infarct volume in the group with the poor 3-month outcome had a median of 16.62 ml, which was significantly higher than the group with the good 3-month outcome with a median of 1.46 ml (p = 0.013), as shown in Table 3.

Based on the ROC and AUC analysis of platelet-to-neutrophil ratio (PNR) prognostic outcomes for 90-day outcomes in ischemic stroke after intravenous thrombolysis, it was found the optimal cutoff value of the PNR level to predict the 90-day prognosis of stroke patients was 43.4, with sensitivity 60.3% and specificity 52.5%. The PNR was statistically significant 56.2% accurate prognosis for the 90-day outcome in ischemic stroke after intravenous thrombolysis (AUC= 0.562, 95% CI 0.501-0.624, p = 0.048), as shown in Figure 1 and Table 4.

The PNR prognostic outcome for DND in ischemic stroke after intravenous thrombolysis, the ROC curve was considered. The optimal cut off value of the PNR level in predicting prognosis for DND in stroke patients was 43.6 with a sensitivity of 67.3% and specificity 51.9%. The PNR was statistically significant 58.4% accurate prognosis for DND in ischemic stroke after intravenous thrombolysis (AUC = 0.584, 95% CI 0.504-0.664, p = 0.044), as shown in Figure 2 and Table 4.

The PNR in prognosis of hemorrhagic transformation in ischemic stroke after intravenous thrombolysis, it was found the optimal cutoff value of the PNR level to predict the prognosis for hemorrhagic transformation in stroke patients was 38.4, with sensitivity 67.0% and specificity 53.3. %. The PNR was statistically significant 60.7% accurate prognosis for hemorrhagic transformation in ischemic stroke after intravenous thrombolysis (AUC = 0.607, 95% CI 0.535-0.678, p = 0.004), as shown in Figure 3 and Table 4.

The PNR in the prognosis for END in ischemic stroke after intravenous thrombolysis, it was found the optimal cutoff value of PNR to predicting prognosis for END in stroke patients being 36.3, with sensitivity 68.4% and specificity 45.8%. The PNR was 57.6% accurate prognosis for END in ischemic stroke after intravenous thrombolysis. There was not statistically significant (AUC = 0.576, 95% CI 0.449-0.702, p = 0.214), as shown in Figure 4 and Table 4.

Table 1 Clinical characteristics of the study population

Characteristics	No.	%
Age (y), median (IQR)	64.5 (53-72)	
Sex		
Male	249	59.6
Female	169	40.4
Risk factor		
Hypertension	299	71.5
Dyslipidemia	276	66
Diabetes mellitus	141	33.7
Atrial fibrillation/ Atrial flutter	102	24.4
Old CVA	47	11.2
Current smoking	73	17.5
Current alcohol drinking	42	10
Etiology		
Other determined or undetermined	177	42.3
Cardioembolic	102	24.4
Small-artery occlusion	94	22.5
Large-artery atherosclerosis	42	10
Medication		
Antihypertensive therapy	202	45.6
antiplatelet therapy	81	18.3
Hypoglycemic therapy	121	27.3
Time for stroke onset to IVT infusion (min), median (IQR)	170.05 (124-218.25)	
Infarct volume (ml), median (IQR)	3.27 (0.58-24.24)	
Hemorrhagic transformation		
No	342	82
Yes	75	18
PH1	28	6.3
PH2	27	6.1
HI2	12	2.7
HI1	7	1.6
Baseline blood glucose (mg%), median (IQR)	110 (96-141)	
Laboratory tests, median (IQR)		
Hb	13.3 (12.2-14.4)	
WBC (10^9/L)	8.4 (6.81-10.51)	
Platelets (10^9/L)	227 (192-278)	
Neutrophil (10^9/L)	5.14 (3.8-7.06)	
Lymphocyte (109/L)	1.93 (1.36-2.7)	
PNR	43.73 (32.0-59.04)	
PLR	115.33 (87.17-170.64)	
NLR	2.56 (1.61-4.52)	
PWR	27.07 (21.4-33.99)	
LDL	114.5 (89-143)	
NISHH on admission, median (IQR)	10 (6-16)	
NIHSS score on discharge date (day 1-7), median (IQR)	5 (1-10)	
Outcome events		
Increase NIHSS from baseline or death within 7 days after IV rt-PA		
poor outcome (≥ 4 score)	24	5.7
good outcome (< 4 score)	394	94.3
mRS on admission, median (IQR)	5 (3.75-5)	
poor outcome (3-6)	348	83.3
good outcome (0-2)	70	16.7
mRS on discharge date (day1-7), median (IQR)	3 (1-4)	
poor outcome (3-6)	236	56.5
good outcome (0-2)	182	43.5
mRS at 3 months, median (IQR)	2 (0-4)	
poor outcome (3-6)	168	40.2
good outcome (0-2)	250	59.8

Table 2 Clinical characteristics of patients according to presence/absence of early neurological deterioration and Hemorrhagic transformation after IVT treatment

Variables	Total (n=418)	No END (n=394)	END (n=24)	P-value	No HT (n=342)	HT (n=75)	P-value
Age (y), median (IQR)	64.5(53-72)	64(52-71)	70(58.75-77.25)	0.045*	65(53-72)	64(52-74)	0.939*
Sex, n (%)							
Male	249(59.6)	237(60.2)	12(50)	0.325**	206(60.2)	42(56.0)	0.499**
Female	169(40.4)	157(39.8)	12(50)		136(39.8)	33(44.0)	
Risk factor, n (%)							
Hypertension	299(71.5)	279(71.2)	20(83.3)	0.198**	245(72.1)	53(70.7)	0.808**
Dyslipidemia	276(66.0)	261(66.9)	15(62.5)	0.655**	223(65.8)	52(70.3)	0.458**
Diabetes mellitus	141(33.7)	126(32.1)	15(62.5)	0.002**	114(33.4)	26(34.7)	0.838**
Atrial fibrillation/ Atrial flutter	102(24.4)	97(24.6)	5(20.8)	0.675**	81(23.7)	21(28.0)	0.431**
Old CVA	47(11.2)	44(11.3)	3(12.5)	0.852**	44(13.0)	3(4.0)	0.027**
Current smoking	73(17.5)	70(82.4)	3(100)	0.424**	62(83.8)	10(76.9)	0.546**
Current alcohol drinking	42(10.0)	42(91.3)	0(0)	0.003**	37(90.2)	5(83.3)	0.608**
Etiology, n (%)							
Other determined or undetermined	177(42.3)	161(41.2)	16(66.7)	0.005**	143(42.1)	34(45.3)	< 0.001**
Cardioembolic	102(24.4)	100(25.6)	2(8.3)		73(21.5)	29(38.7)	
Small-artery occlusion	94(22.5)	93(23.8)	1(4.2)		91(26.8)	3(4.0)	
Large-artery atherosclerosis	42(10)	37(9.5)	5(20.8)		33(9.7)	9(12.0)	
Medication, n(%)							
Antihypertensive therapy	202(45.6)	75(19.0)	6(25.0)	0.473**	165(48.2)	37(49.3)	0.864**
Antiplatelet therapy	81(18.3)	191(48.5)	11(45.8)	0.801**	63(18.4)	18(24.0)	0.269**
Hypoglycemic therapy	121(27.3)	111(28.2)	10(41.7)	0.16**	96(28.2)	25(33.3)	0.371**
Infarct volume (ml), median (IQR)	3.27 (0.58-24.24)	2.76(0.45-20.25)	34.42(5.57-303.93)	<0.001*	2.67(0.43-16.88)	13.99(1.11-73.07)	0.389*
Time for stroke onset to IVT infusion (min), median (IQR)	170.05 (124-218.25)	170(122-217)	180.5(147.5-232.25)	0.157*	172(124.85-218.25)	160(124-219)	0.516*
Baseline blood glucose (mg%), median (IQR)	110 (96-141)	109(96-137)	164.5(130.75-200.75)	< 0.001*	110(96-139)	115(98-158)	0.231*
NISHH on admission, median (IQR)	10 (6-16)	10(6-15)	11.5(6-18.5)	0.368*	10(6-15)	13(7-18)	0.018*
Laboratory tests, median (IQR)							
Hb	13.3(12.2-14.4)	13.3(12.2-14.4)	13.2(12.22-14.35)	0.796*	13.3(12.1-14.4)	13.3(12.3-14.4)	z0.735*
WBC (10^9/L)	8.4 (6.81-10.51)	8.4(6.81-10.4)	8.76(6.7-14.0)	0.306*	8.3(6.78-10.5)	8.7(7.2-10.81)	0.339*
Platelets (10^9/L)	227 (192-278)	227.05(192-278.5)	220.5(187.03-264)	0.569*	226.55(190.08-280)	229(193.1-278)	0.969*
Neutrophil (10^9/L)	5.14 (3.8-7.06)	5.14(3.82-6.92)	5.26(3.44-11.06)	0.375*	5.1(3.75-6.92)	5.4(1.01-7.97)	0.153*
Lymphocyte(10^9/L)	1.93 (1.36-2.7)	1.94(1.36-2.71)	1.71(1.36-2.24)	0.315*	1.94(1.36-2.7)	1.81(1.43-2.69)	0.825*
PNR	43.73 (32.0-59.04)	43.83-32.16-59.61)	38.39(26.95-55.96)	0.214*	44.14(33.45-60.25)	41.98(29.11-56.59)	0.179*
PLR	115.33 (87.17-170.64)	115.29(87.1-170.64)	117.75(95.16-201.13)	0.476*	115.29(87.22-174.67)	120.17(87.18-161.74)	0.907*
NLR	2.56 (1.61-4.52)	2.77(1.92-9.06)	2.77(1.92-9.06)	0.242*	2.54(1.58-4.13)	2.78(1.73-5.66)	0.362*
PWR	27.07 (21.4-33.99)	23.91(20.37-33.43)	23.91(20.37-33.43)	0.238*	27.27(21.4-34.37)	25.57(21.48-33.17)	0.345*
LDL	114.5 (89-143)	114(88.75-143.25)	120(99-136.25)	0.918*	112(87.75-142)	119(93-144)	0.001*
Baseline blood glucose (mg%), median (IQR)	110 (96-141)	109(96-137)	164.5(130.75-200.75)	< 0.001*	110(96-139)	115(98-158)	0.231*
NISHH on admission, median (IQR)	10 (6-16)	10(6-15)	11.5(6-18.5)	0.368*	10(6-15)	13(7-18)	0.018*
Laboratory tests, median (IQR)							
Hb	13.3(12.2-14.4)	13.3(12.2-14.4)	13.2(12.22-14.35)	0.796*	13.3(12.1-14.4)	13.3(12.3-14.4)	z0.735*
WBC (10^9/L)	8.4 (6.81-10.51)	8.4(6.81-10.4)	8.76(6.7-14.0)	0.306*	8.3(6.78-10.5)	8.7(7.2-10.81)	0.339*
Platelets (10^9/L)	227 (192-278)	227.05(192-278.5)	220.5(187.03-264)	0.569*	226.55(190.08-280)	229(193.1-278)	0.969*
Neutrophil (10^9/L)	5.14 (3.8-7.06)	5.14(3.82-6.92)	5.26(3.44-11.06)	0.375*	5.1(3.75-6.92)	5.4(1.01-7.97)	0.153*
Lymphocyte(10^9/L)	1.93 (1.36-2.7)	1.94(1.36-2.71)	1.71(1.36-2.24)	0.315*	1.94(1.36-2.7)	1.81(1.43-2.69)	0.825*
PNR	43.73 (32.0-59.04)	43.83-32.16-59.61)	38.39(26.95-55.96)	0.214*	44.14(33.45-60.25)	41.98(29.11-56.59)	0.179*
PLR	115.33 (87.17-170.64)	115.29(87.1-170.64)	117.75(95.16-201.13)	0.476*	115.29(87.22-174.67)	120.17(87.18-161.74)	0.907*
NLR	2.56 (1.61-4.52)	2.77(1.92-9.06)	2.77(1.92-9.06)	0.242*	2.54(1.58-4.13)	2.78(1.73-5.66)	0.362*
PWR	27.07 (21.4-33.99)	23.91(20.37-33.43)	23.91(20.37-33.43)	0.238*	27.27(21.4-34.37)	25.57(21.48-33.17)	0.345*
LDL	114.5 (89-143)	114(88.75-143.25)	120(99-136.25)	0.918*	112(87.75-142)	119(93-144)	0.001*

* Mann whitney u test **Chi-square test

Table 3 Clinical characteristics of patients according to presence/absence of DND and 3 months outcome after IVT treatment

Variables	Total (n=418)	No DND (n=182)	DND (n=236)	P-value	Good 3-month (n=250)	Poor 3-month (n=168)	P-value
Age (y), median (IQR)	64.5 (53-72)	60(49-67.25)	67(58-76.75)	< 0.001*	60(50-68)	69(61-75)	< 0.001*
Sex, n (%)							
Male	249(59.6)	120(65.9)	129(54.7)	0.02**	162(64.8)	87(51.8)	0.008**
Female	169(40.4)	62(34.1)	107(45.3)		88(35.2)	81(48.2)	
Risk factor, n (%)							
Hypertension	299(71.5)	114(62.6)	185(79.1)	<0.001**	163(65.2)	136(81.9)	< 0.001**
Dyslipidemia	276(66.0)	113(62.8)	163(69.7)	0.141**	162(65.3)	114(68.7)	0.478**
Diabetes mellitus	141(33.7)	55(30.4)	86(36.4)	0.195**	73(29.3)	68(40.5)	0.018**
Atrial fibrillation/ Atrial flutter	102(24.4)	40(22.0)	62(26.3)	0.311**	53(21.2)	49(29.2)	0.063**
Old CVA	47(11.2)	16(8.8)	31(13.2)	0.16**	24(9.7)	23(13.7)	0.21**
Current smoking	73(17.5)	38(86.4)	35(79.5)	0.395**	52(85.2)	21(77.8)	0.39**
Current alcohol drinking	42(10.0)	20(95.2)	22(84.6)	0.24**	30(88.2)	12(92.3)	0.685**
Etiology, n (%)							
Other determined or undetermined	177(42.3)	69(38.3)	108(46.0)	0.004**	93(37.5)	84(50.3)	0.002**
Cardioembolic	102(24.4)	51(28.3)	51(21.7)		70(28.2)	32(19.2)	
Small-artery occlusion	94(22.5)	50(27.8)	44(18.7)		66(26.6)	28(16.8)	
Large-artery atherosclerosis	42(10)	10(5.6)	32(13.6)		19(7.7)	23(13.8)	
Medication, n (%)							
Antihypertensive therapy	202(45.6)	81(44.5)	121(51.3)	0.17**	111(44.4)	91(54.2)	0.05**
Antiplatelet therapy	81(18.3)	31(17.0)	50(21.2)	0.287**	44(17.6)	37(22.0)	0.262**
Hypoglycemic therapy	121(27.3)	53(29.1)	68(28.9)	0.967**	71(28.5)	50(29.8)	0.783**
Infarct volume (ml), median (IQR)	3.27 (0.58-24.24)	1.16(0.05-7.88)	7.61(1.53-63.41)	0.36*	1.46(0.13-7.93)	16.62(2.51-103.09)	0.013*
Time for stroke onset to IVT infusion (min), median (IQR)	170.05 (124-218.25)	182(0-125)	167.5(120-219.5)	0.528*	173.5(125-218)	166.5(120-220)	0.306*
Baseline blood glucose (mg%), median (IQR)	110 (96-141)	105(92.75-128.5)	117(98-152.75)	< 0.001*	107(94-131)	123(100.25-160.75)	< 0.001*
NISHH on admission, median (IQR)	10 (6-16)	7(5-12)	13(8-18)	< 0.001*	8(5-12)	14(9.25-18)	< 0.001*
Laboratory tests, median (IQR)							
Hb	13.3(12.2-14.4)	13.4(12.5-13.4)	13.2(11.9-14.3)	0.075*	13.5(12.5-14.6)	12.8(11.63-14.08)	< 0.001*
WBC (10^9/L)	8.4 (6.81-10.51)	8.7(7.2-10.3)	8.16(6.7-10.6)	0.391*	8.56(7.08-10.35)	8.11(6.63-10.75)	0.505*
Platelets (10^9/L)	227 (192-278)	232.55(199.08-280.5)	220.1(185.03-272.75)	0.162*	227.05(195.75-278)	224.6(184.25-279.5)	0.409*
Neutrophil (10^9/L)	5.14 (3.8-7.06)	5.2(3.89-6.83)	5.07(3.74-7.53)	0.965*	5.14(3.8-6.83)	5.13(3.81-7.63)	0.709*
Lymphocyte (10^9/L)	1.93 (1.36-2.7)	2.08(1.47-2.98)	1.81(1.28-2.48)	0.003*	2.04(1.41-2.93)	1.77(1.29-2.33)	0.005*
PNR	43.73 (32.0-59.04)	44.53(32.08-62.53)	43.29(31.77-56.98)	0.357*	44.4(32.46-62.63)	43.14(30.93-56.31)	0.286*
PLR	115.33 (87.17-170.64)	111.1(79.83-161.09)	121.91(92.51-180-08)	0.023*	111.24(81.33-165.56)	126.57(94.57-182.56)	0.021*
NLR	2.56 (1.61-4.52)	2.47(1.54-3.96)	2.66(1.73-5.07)	0.055*	2.48(1.49-4.09)	2.80(1.85-5.04)	0.026*
PWR	27.07 (21.4-33.99)	27.32(21.16-33.90)	26.78(21.44-34.11)	0.748*	27.12(21.14-34.13)	26.88(21.51-33.85)	0.887*
LDL	114.5 (89-143)	117(93.75-142)	112(85.25-144)	< 0.001*	119(93-144)	107(79.5-136)	< 0.001*

* Mann whitney u test **Chi-square test

Table 4 Diagnostic values of the PNR for four outcome events.

	Outcome Events	Threshold	AUC	95% CI	Sensitivity, %	Specificity, %	P-value
Baseline PNR	END	36.3	0.576	0.449-0.702	68.40%	45.80%	0.214
	HT	38.4	0.607	0.535-0.678	67%	53.30%	0.004
	DND	43.6	0.584	0.504-0.664	67.30%	51.90%	0.044
	Poor 3-month outcome	43.4	0.562	0.501-0.624	60.30%	52.50%	0.048

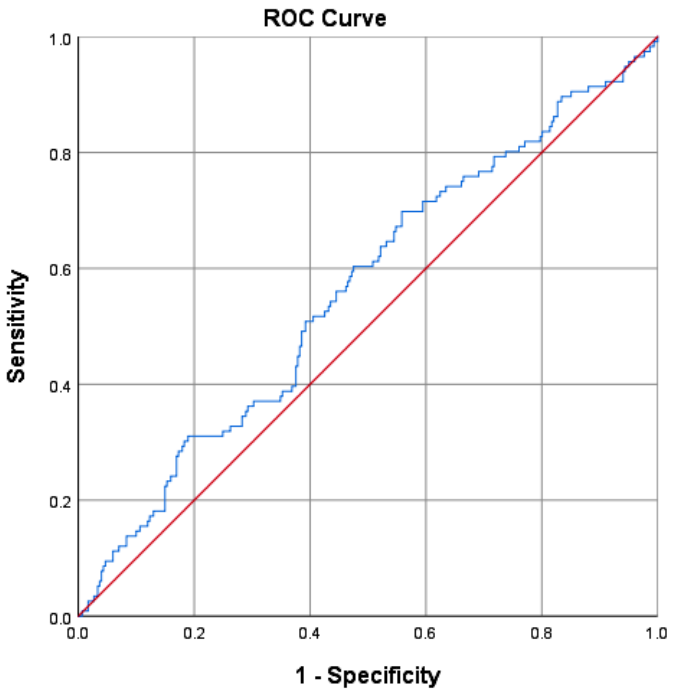

Figure 1 Receiver operating characteristic curve (ROC) of platelets to neutrophil ratio (PNR) for predict 90-days outcome in acute ischemic stroke after IVT

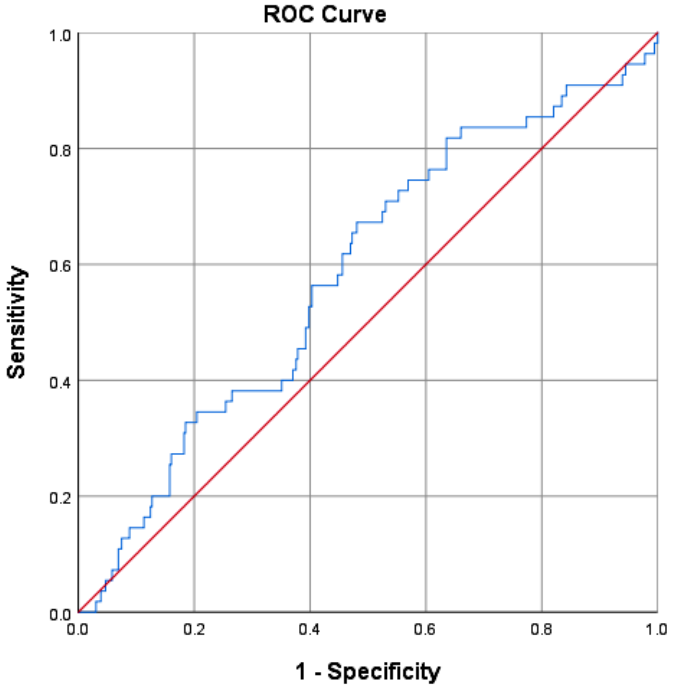

Figure 2 Receiver operating characteristic curve (ROC) of platelets to neutrophil ratio (PNR) for predict delay neurological deterioration (DND) in acute ischemic stroke after IVT

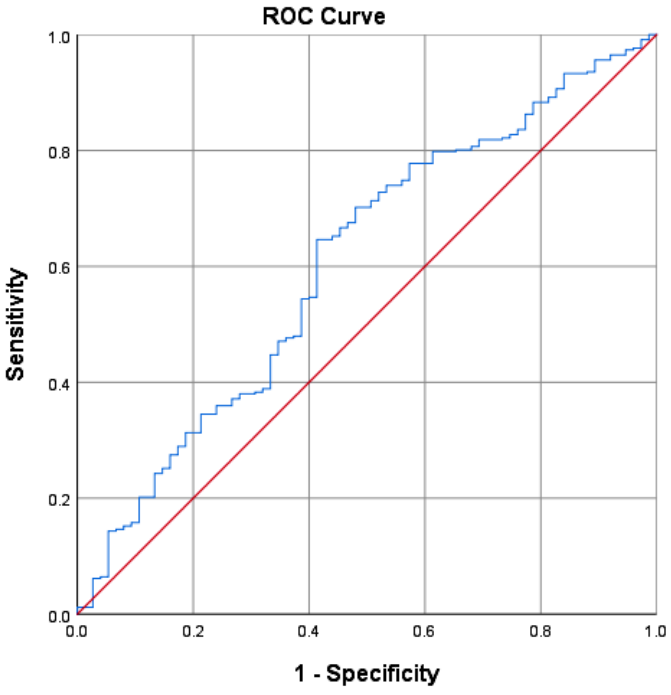

Figure 3 Receiver operating characteristic curve (ROC) of platelets to neutrophil ratio (PNR) for predict hemorrhagic transformation (HT) in acute ischemic stroke after IVT

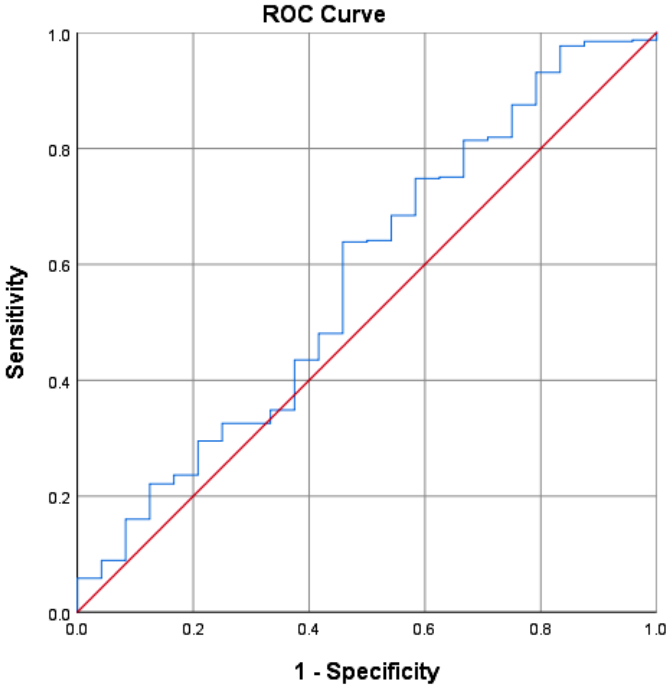

Figure 4 Receiver operating characteristic curve (ROC) of platelets to neutrophil ratio (PNR) for predict early neurological deterioration (END) in acute ischemic stroke after IVT

Discussion

In this study, we found that PNR was associated with poor 3-months clinical outcome, HT and DND. Lower PNR level was associated with worse outcomes. Our results indicated that PNR level might become a new predictor of prognosis and complications in patients with acute ischemic stroke after IVT.

As a new parameter put forward recently, the research of PNR in the stroke field is still rare. The study of Jin et al.[9] indicated that PNR might be an autocephaly protective predictor for 90-days outcome in acute ischemic stroke (AIS). They also suggested that lower PNR level was associated with short-term adverse outcomes. Similarly, the study of Wang et al.[13] found that post-IVT PNR was independently associated with END, HT, DND and poor 3-month outcome. Lower PNR can predict a worse outcome. In addition, several studies found PNR was correlated with thrombosis.[14] For example, Long et al.[15] proposed that PNR might be an indicator of blood hypercoagulable state, and an in creased PNR level may induce a gastric cancer-related ischemic stroke. However, the relationship between PNR and the prognosis of IVT patients has not been explored. Besides, the platelet-neutrophil crosstalk is increase recognized as a driver of inflammation and thrombosis[16], and in the process of the AIS, the form of the intravascular thrombosis and the inflammation response could cause the decrease of platelets and increase of neutrophils, which ultimately accounted for decrease of PNR levels. Therefore, we reasonably found that the low levels of PNR were independently associated with poor outcome for AIS. Thus, the indicator of PNR may be a novel predictor for the prognosis of AIS patients receiving thrombolysis.

For another, combined with the thrombolysis, the symptoms could get worsen more easier due to the symptomatic intracranial hemorrhage. A mount of studies revealed that decreased platelets and increased neutrophils could account for symptomatic intracranial hemorrhage.[17-19] Moreover, according to Gensicke et al.[20], decreasing platelet counts are associated with the occurrence of HT in IVT-treated stroke patients. They assessed the potential mechanism for explaining the relationship between poor outcome and neutrophil in the disruption of the blood-brain barrier by releasing MMP-9 and increased reactive oxygen and nitrogen species.[19] All above studies suggested that PNR could be a potential predictor for prognosis of patients.

Compared with other studies, there was several advantages to our study. First, based on a large sample size, our result became more reliable and convincing. Second, to the best knowledge, it was one of few that focused on the association between PNR and prognosis in IVT-treated AIS patients. However, our results should be considered in the context of several limitations. First, the study had all of common drawbacks retrospective studies, and a further confounder may exist. Second, all data were collected only in one hospital, and it might lead to selection bias. Third, PNR level were recorded only once on admission and were not monitored dynamically. Finally, many diseases and infection may affect inflammation that occurred during treatment were not taken into consideration.

Conclusion

In summary, we found PNR was independently associated with poor 3-month outcome (mRS ≥ 3), hemorrhagic transformation and delay neurological

deterioration. Lower PNR could predict a worse outcome. This finding could help neurologists predict stroke outcome in clinical setting. Further prospective studies with larger sample sizes and dynamic PNR are warranted.

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