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# Specific Biomarkers of Prostate Cancer-Associated Ischemic Stroke: A Case-Control Study

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**Background:** Ischemic stroke in cancer patients is associated with poor prognosis. However, the specific biomarkers of cancer-associated ischemic stroke (CaIS) have not been well defined.





**Material/Methods:** A retrospective study was conducted on PCaIS patients. Clinical data and laboratory and imaging findings were collected. Multivariable logistic regression analysis was used to analyze the independent risk factors for PCaIS. A multiple model combining the independent risk factors of PCaIS was developed using the receiver operating characteristic (ROC) and area under the ROC curve (AUC).

**Results:** A total of 83 PCaIS patients and 83 prostate cancer (PCa) patients were included. PCaIS patients had higher levels of D-dimer, neutrophil-to-lymphocyte ratio (NLR), and total prostate-specific antigen (T-PSA). In the multivariate analysis, D-dimer [OR=1.001, 95% CI: 1.00,1.00,  $P=0.002$ ], NLR [OR=1.12, 95% CI: 1.04,1.22,  $P=0.005$ ], and T-PSA [OR=6.275, 95% CI: 2.57,15.31,  $P<0.001$ ] were independent risk factors of PCaIS. Additionally, the AUC of the multiple model of PCaIS was 0.815 (95% CI, 0.750-0.869), with sensitivity of 81.71% and specificity of 70.21%.

**Conclusions:** Elevated levels of D-dimer and T-PSA and increased NLR are independent risk factors of PCaIS. The multiple model of PCaIS can be a specific biomarker and is a reliable predictor of development of PCaIS.

**MeSH Keywords:** **Biological Markers • Prostatic Neoplasms • Stroke**

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## Background

Cancer patients are at high risk of stroke [1]. In an autopsy study of patients with malignancy, 7% had clinical symptoms and 15% had pathologic evidence of stroke [2]. Cancer may be associated with ischemic stroke via various mechanisms, including invasion of adjacent blood vessels, non-bacterial thrombotic endocarditis, tumor therapy, and coagulation disorders, especial cancer-associated hypercoagulability [3–9]. In addition, previous studies reported that cancer-associated ischemic stroke (CaIS) is characterized by lack of traditional stroke risk factors and multiple ischemic lesions on DWI [10–12], and serum D-dimer, NLR, high-sensitivity C-reactive protein (hs-CRP), cancer antigen125, and fibrinogen levels were reported to be significantly increased in CaIS patients [13–17]. These elevated biomarkers levels and multiple territorial ischemic lesions may be helpful to distinguish CaIS from other subtypes of stroke in term of etiology [18].

However, a recent study by Navi et al. reported varying degrees of risk by cancer type and correlated with cancer stage for stroke in patients with cancer [19], indicating that the mechanisms and biomarkers of ischemic stroke differ according to type of cancer. Therefore, studies on ischemic stroke patients with a particular cancer may help identify the specific biomarkers for CaIS.

Prostate cancer (PCa) is the second most common type of cancer among men [20]. Notably, it was reported that ischemic stroke in patients with PCa was 1.6 times higher than in the general population [21,22], indicating PCa may be an etiology of ischemic stroke, called prostate cancer-associated ischemic stroke (PCaIS). Once ischemic stroke occurs in PCa patients, neurological outcomes may significantly worsen. Thus, it is critical for clinicians to identify PCa patients who are at high risk of ischemic stroke. In the present study, we investigated whether a multiple model combining independent risk factors of PCaIS could be useful as a specific biomarker for PCaIS and be a predictor for the development of PCaIS.

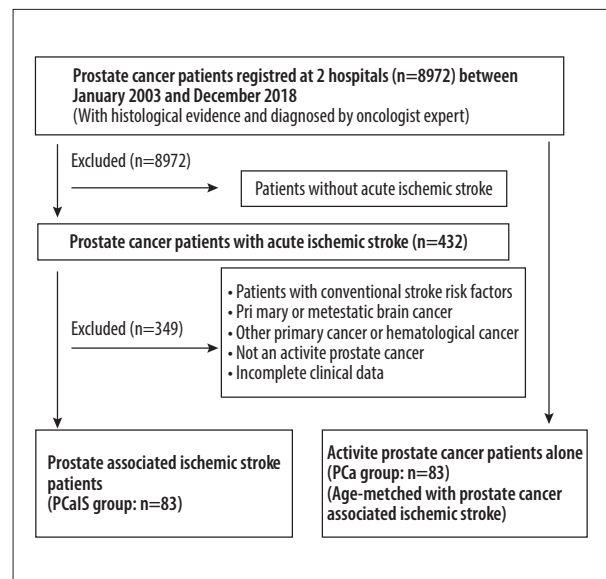
## Material and Methods

### Ethics statement

This case-control study was approved by the Guangxi Medical University Review Board. Patients provided written informed consent before their data were analyzed.

### Patients

We retrospectively identified newly diagnosed patients with PCaIS (acute ischemic stroke patients with active PCa and



**Figure 1.** Patient selection. PCa – prostate cancer; PCaIS – prostate cancer-associated ischemic stroke.

without traditional stroke risk factors [11,23,24]) and age-matched individuals with PCa for the control group admitted to our hospital and Guangxi Medical University Affiliated Tumor Hospital from January 2003 and December 2018. Acute ischemic stroke was defined according to the American Heart Association Diagnostic criteria for ischemic stroke [25]. The diagnosis of PCa for all patients was pathologically confirmed. Active PCa was confirmed as a new diagnosis, metastasis, progression, or recurrence of PCa within the 12 months prior to enrollment [26]. Patients were excluded if they had the following conditions: lack of clinical data, cerebrovascular disease, or a primary intracranial or hematologic malignancy (Figure 1).

### Data collection

The following data of included patients were obtained at baseline: age, stroke risk factors, NIHSS, features of imaging, pathology of cancer, metastasis, tumor treatments, and time interval from diagnosis of PCa to occurrence of ischemic stroke. Blood cell counts, NLR, coagulation studies, and levels of D-dimer and T-PSA were measured within 24 h after admission. The mRS score at 30 days after the discharge was collected. These data were also collected from the control group.

### Statistical analysis

All statistical analyses were performed using SPSS 23.0. Differences in quantity of normal distribution and homogeneity of variance were analyzed by *t* test. Differences in quantity of non-normal distribution were compared by the Mann-Whitney test. The independent variables associated with the PCaIS were analyzed by logistic regression analysis. Possible

**Table 1.** Clinical data of participants.

Characteristic	PCaIS (n=83)	PCa (n=83)	P value
Age, (y), Mean $\pm$ SD	74.64 $\pm$ 10.29	76.65 $\pm$ 13.02	0.257
Pathological types of PCa (n,%)			
Adenocarcinoma	83 (100.0%)	83 (100.0%)	
Cancer metastasis (n,%)			0.002 <sup>#</sup>
Yes	41 (49.4%)	22 (26.5%)	
No	42 (50.6%)	61 (73.5%)	
Type of therapy (n,%)			0.613
Surgery	59 (71.1%)	62 (74.7%)	
Others	24 (28.9%)	21 (25.3%)	
Blood tests			
WBC (10 <sup>9</sup> /L)	8.035 $\pm$ 2.35	16.47 $\pm$ 88.8	0.385
HGB (g/L)	117.11 $\pm$ 18.88	117.85 $\pm$ 21.24	0.809
PLT count (10 <sup>9</sup> /L)	223.74 $\pm$ 75.06	241.71 $\pm$ 78.37	0.491
NC (10 <sup>9</sup> /L)	5.69 $\pm$ 2.52	4.66 $\pm$ 2.25	0.005*
LC (10 <sup>9</sup> /L)	1.81 $\pm$ 5.69	1.96 $\pm$ 1.97	0.821
NLR	7.38 $\pm$ 8.04	3.55 $\pm$ 4.35	<0.001*
PT (s)	11.56 $\pm$ 3.93	10.81 $\pm$ 1.41	0.083
INR	1.32 $\pm$ 3.43	0.93 $\pm$ 0.078	0.262
APTT (s)	30.13 $\pm$ 5.63	29.66 $\pm$ 5.77	0.579
FIB (g/L)	4.52 $\pm$ 1.45	5.03 $\pm$ 4.07	0.28
D-dimer (ng/mL)	977.32 $\pm$ 1430.46	436.69 $\pm$ 604.29	0.001*
T-PSA (ng/mL)	41.31	5.18	<0.001*

The data are presented as mean  $\pm$ SD; \* rank sum test, # chi-square test, and the rest are *t* tests. y – year; PCaIS – prostate cancer-associated ischemic stroke; PCa – prostate cancer; WBC – white blood cell; NC – neutrophil count; NLR – neutrophil-to-lymphocyte ratio; LC – leukomonocyte; HGB – hemoglobin; PLT – platelet; PT – prothrombin time; APTT – activated partial thromboplastin time; INR – international normalized ratio; FIB – fibrinogen; T-PSA – total prostate-specific antigen.

risk factors were tested by univariable regression analysis. Then, multivariable logistic regression analysis was used to test risk factors with a *P* value <0.01 and estimate their ability to predict ischemic stroke. One-way ANOVA was used to evaluate the differences in ability to identify risk factors. The cut-offs with sensitivities and specificities were identified by ROC analysis. MedCalc software was used to compare the differences among 2 ROC curves of the risk factors. The significance level was 0.05. All tests were 2-tailed.

### Multiple model of PCaIS

To explore specific biomarkers of PCaIS, a multiple model was developed. First, we used a multivariate model of logistic regression to identify the independent risk factors of PCaIS. Second, we developed a multiple model by combining the possible risk

factors, called the multiple model of PCaIS. Finally, we estimated the ability of the multiple model of PCaIS to predict PCaIS.

### Results

A total of 83 PCaIS patients (mean age, 74.64 $\pm$ 10.29 years) and 83 age-matched PCa controls (mean age, 76.65 $\pm$ 13.02 years) were included. The pathological type of PCa was adenocarcinoma in all patients. No significant difference was observed in primary form of treatment between the 2 groups. The rate of systemic metastasis was higher in the PCaIS group than in the PCa group (49.4% vs. 26.5%, *p*=0.002) (Table 1).

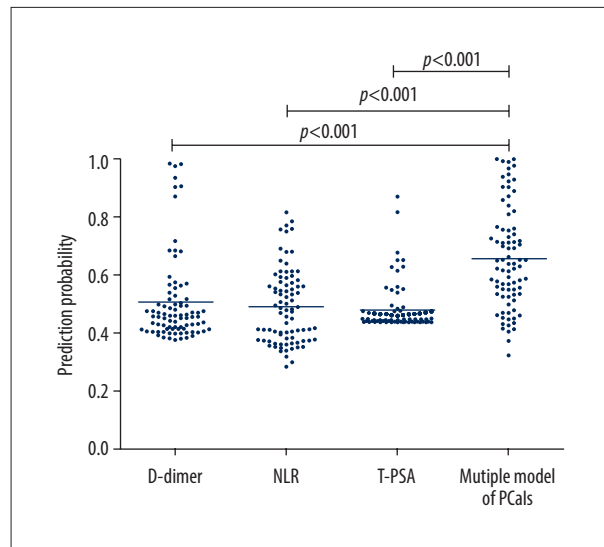
Among 83 PCaIS patients, 47 (56.6%) experienced ischemic stroke within the first 6 months after being diagnosed with

**Table 2.** Clinical data of ischemia stroke onset, n (%).

Characteristic	Number of patients (n=83)
NIHSS scores at the day of ischemic stroke onset	
0–5	18 (21.7%)
6–15	48 (57.8%)
16–20	12 (14.5%)
>20	5 (6.0%)
30d mRS	
0–3	52 (62.7%)
4–5	26 (31.3%)
6	5 (6.0%)
Ischemic territory pattern (DWI)	
Single arterial territory	27 (32.5%)
Multiple arterial territories	56 (67.5%)
Time interval between diagnosis of PCaIS and ischemic stroke onset	
Ischemic stroke as the first manifestation of PCaIS	12 (14.5%)
Ischemic stroke after diagnosis	
0–6 mo	42 (50.6%)
7–12 mo	23 (27.7%)
>12 mo	6 (7.2%)

NIHSS – National Institutes of Health Stroke Scale; mRS – modified rankin scale; PCaIS – prostate cancer-associated ischemic stroke; PCa – prostate cancer; DWI – diffusion-weighted image; mo – month.

PCa, 28 (33.7%) had an ischemic stroke within 7–12 months, and 8 (9.7%) had an ischemic stroke more than 1 year after diagnosis. In addition, 12 (14.5%) patients were diagnosis



**Figure 2.** The distribution of prediction probability of D-dimer, NLR, and T-PSA and multiple model of PCaIS for each PCaIS patient. NLR – neutrophil-to-lymphocyte ratio; T-PSA – total prostate-specific antigen.

with PCa during hospitalization related to ischemic stroke. Multiple infarctions in multiple arterial territories were found in 56 (67.5%) PCaIS patients. The initial NIHSS score at onset ranged from 0 to 21 (Table 2).

Compared with the controls, patients with PCaIS had higher prothrombin time (PT), D-dimer, NLR, neutrophil count (NC), and T-PSA ( $P < 0.05$ ) (Table 1). In the multivariate analysis, elevated plasma D-dimer [OR=1.001, 95% CI: 1.000,1.001,  $P=0.002$ ], NLR [OR=1.12, 95% CI: 1.036,1.219,  $P=0.005$ ], and T-PSA [OR=6.275, 95% CI: 2.572,15.310,  $P < 0.001$ ] remained independent risk factors of PCaIS (Table 3).

In addition, we developed a multiple model of PCaIS by combining independent risk factors of PCaIS (plasma D-dimer, NLR, and T-PSA) during the process of ROC analysis. The distribution of prediction probability of D-dimer, NLR, T-PSA, and

**Table 3.** Predictors of ischemic stroke in patients with prostate cancer by multivariable logistic regression analyses.

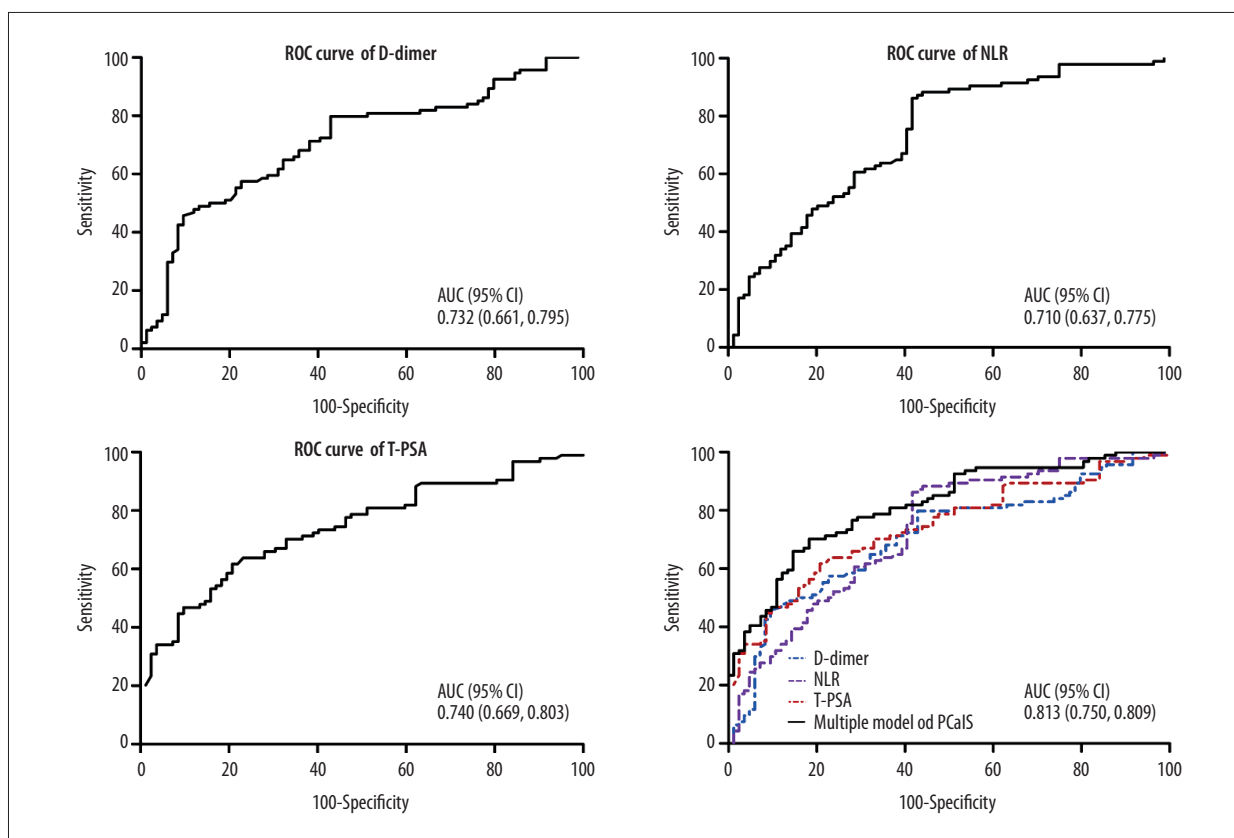
Factors	$\beta$	SE	Wals	P value	OR	95% CI
PT	0.204	0.134	2.326	0.127	1.226	(2.572, 15.310)
NLR	0.117	0.042	7.899	0.005	1.124	(0.944, 1.593)
D-dimer	0.001	0.000	9.701	0.002	1.001	(1.000, 1.001)
T-PSA	1.837	0.455	16.284	<0.001	6.275	(1.036, 1.219)
Constant	-6.60	1.707	14.958	<0.001	0.001	

SE – standard error; T-PSA – total prostate-specific antigen; CI – confidence interval; PT – prothrombin time; OR – odds ratio; NLR – neutrophil-to-lymphocyte ratio.

**Table 4.** Receiver operating characteristic curve analysis of predictive score values.

Factors	AUC	SE	95% CI	Sensitivity	Specificity
D-dimer	0.710	0.0390	(0.637, 0.775)	57.14%	79.79%
NLR	0.732	0.0378	(0.661, 0.795)	58.33%	86.17%
T-PSA	0.740	0.0371	(0.669, 0.803)	79.27%	61.70%
Multiple model of PCaIS	0.815	0.0297	(0.750, 0.869)	81.71%	70.21%

NLR – neutrophil-to-lymphocyte ratio; T-PSA – total prostate-specific antigen; CI – confidence interval.



**Figure 3.** Receiver operating characteristic (ROC) curve for D-dimer, NLR, and T-PSA and multiple model of PCaIS to predict PCaIS. NLR – neutrophil-to-lymphocyte ratio; T-PSA – total prostate-specific antigen; CI – confidence interval; ROC – receiver operating characteristic; AUC – area under the curve.

the multiple model of PCaIS are shown in Figure 2. One-way ANOVA showed that the predictive ability of the multiple model of PCaIS ( $0.61 \pm 0.22$ ) was significantly higher than that of each individual risk factor ( $P < 0.05$ ).

The ROC curve showed the AUC values of plasma D-dimer, NLR, T-PSA, and multiple model of PCaIS were 0.710 (95% CI, 0.637–0.775), 0.732 (95% CI, 0.661–0.795), 0.740 (95% CI, 0.669–0.803), and 0.815 (95% CI, 0.750–0.869), respectively. DeLong test analysis revealed that the AUC of the multiple model of PCaIS was the largest ( $P < 0.05$ ), with sensitivity of 81.71% and specificity of 70.21% (Table 4, Figure 3).

### Discussion

Previous studies have reported that multiple vascular territorial ischemic lesions are associated with CaIS [10]. Moreover, increased serum D-dimer levels and multiple infarctions involving multiple arterial vascular have been suggested to be independent predictors of cancer-related stroke [12]. In the present study, most PCaIS patients showed multiple territorial ischemic lesions on DWI. However, it was difficult to distinguish the PCaIS from other subtypes of ischemic stroke based on brain DWI patterns alone because multiple territorial ischemic lesions were also commonly observed in patients

with cardioembolic stroke. Importantly, we found that plasma D-dimer, T-PSA, and NLR were significantly higher in PCaIS patients, and multivariate analysis revealed these 3 biomarkers were independent risk factors for PCaIS. These results suggest that elevated serum D-dimer T-PSA and increased NLR combined with multiple territorial ischemic lesions may help distinguish PCaIS from other subtypes of ischemic stroke.

Due to advances in cancer therapy and the extended survival of PCa patients, the incidence of PCaIS is also increasing. Thus, it is urgent to elucidate the pathogenesis of PCaIS to help clinicians to prevent stroke in high-risk PCa patients. Recent studies have shown that elevated plasma D-dimer levels are associated with development of cancer-related stroke [11,13]. Moreover, the frequency of microembolic signals in the internal carotid arteries on transcranial Doppler images were found to be linearly associated with the level of serum D-dimer in cancer patients with cryptogenic stroke, indicating that microthrombosis caused by hypercoagulability may be the main cause of ischemic stroke [27]. In our study, elevated serum D-dimer level was an independent risk factor of PCaIS, suggesting that cancer-induced hypercoagulability is the main pathogenesis of PCaIS.

Cancers are associated with hypercoagulable and prothrombotic states due to the ability of tumor cells to activate the coagulation system [9,28]. An animal experiment confirmed that the mucins secreted by cancer cells bind to blood platelets and P-selectin, triggering the reciprocal activation of platelets and neutrophils, which finally leads to hypercoagulability and promotes thrombus formation [29]. Furthermore, in solid tumor models, neutrophil extracellular traps (NETs) secreted from neutrophils were reported to be involved in hypercoagulability by stimulating platelet activation [30]. Therefore, the interaction of mucins, platelets, and neutrophils that lead to hypercoagulability and thrombosis may be the most important cause of CaIS. In the present study, T-PSA and NLR were significantly elevated in PCaIS patients, and in multivariate analysis these 2 biomarkers were independent risk factors of PCaIS. Because increased NLR indicates the proliferation and activation of neutrophils, and because T-PSA may be a kind

of mucin generated from prostate cancer cells, we speculated that activated neutrophil cells and T-PSA lead to hypercoagulability in the ways detailed above. However, these results need to be confirmed by further studies.

To sum up, elevated plasma D-dimer and T-PSA and increased NLR may each play a role in the development of PCaIS. The development of PCaIS in the present study may be the result of the combined effect of these 3 factors. However, since elevated plasma D-dimer and T-PSA and increased NLR are also common in other diseases or pathological conditions [31–33], it is difficult to use them individually to predict the development of PCaIS. Therefore, to predict the occurrence of ischemic stroke in PCa patients more quickly and accurately in clinical practice, we developed a multiple model of PCaIS by combining these 3 risk factors. We found that the multiple model of PCaIS had the largest AUCROC compared to each of the 3 individual risk factors, with high sensitivity and specificity, indicating that the multiple model of PCaIS could be a specific biomarker of PCaIS and may serve as a predictor of the development of PCaIS.

Due to its retrospective design, our study has some limitations, including the relatively small sample size and incomplete variables related to PCaIS. Therefore, further exploration of this aspect using larger prospective population studies and animal experiments are needed, which would help to elucidate the biomarkers of PCaIS patients.

## Conclusions

Elevated levels of D-dimer and T-PSA and increased NLR are independent risk factors of PCaIS. The multiple model of PCaIS can be a specific biomarker and is a reliable predictor of development of PCaIS.

## Conflict of interests

None.

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