

Plasma D-Dimer Level is Associated with Clinical Outcomes in Patients with Atrial Fibrillation Related Acute Ischemic Stroke after Pneumonia

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Abstract

Objectives: Pneumonia is related to poor prognosis in acute ischemic stroke (AIS), and its risk might be higher in atrial fibrillation (AF) related AIS with elevated plasma D-dimer. The aim of our study was to investigate the prognostic value of D-dimer for predicting clinical outcome of AF-related AIS with pneumonia.

Method: AF-related AIS patients with pneumonia were prospectively enrolled. Receiver operating characteristic (ROC) curve was used to determine the optimal D-dimer point for 3-month mortality and death/severe disability. The associations between the D-dimer and 3-month mortality and death/severe disability were assessed by multivariable logistic regression analysis.

Results: A total of 415 patients were enrolled in this study. ROC curve analysis showed that the optimal cut point of D-dimer for 3-month death/severe disability and mortality were $D\text{-dimer} \geq 2.35\text{mg/l}$ and $D\text{-dimer} \geq 3.35\text{mg/l}$, respectively. Multivariable logistic regression analysis showed that $D\text{-dimer} \geq 2.35\text{mg/l}$ (OR 5.95, 95% CI: 3.09-11.45, $P < 0.001$), higher NIHSS score (OR:1.53, 95% CI: 1.38–1.68, $P < 0.001$) were associated with increased risk of 3-month death/severe disability), and anticoagulant was associated with decreased risk of death/severe disability (OR:0.16, 95% CI: 0.07-0.35, $P < 0.001$). Higher NIHSS score (OR:1.56, 95% CI: 1.37–1.77, $P < 0.001$), higher age (OR 1.06, 95% CI: 1.01–1.11, $P = 0.019$), $D\text{-dimer} \geq 3.35\text{mg/l}$ (OR 7.85, 95% CI: 3.21-19.21, $P = 0.001$) were associated with increased risk of 3-month mortality.

Conclusions: AF-related AIS patients with concurrent high D-dimer and pneumonia increased risk of 3-month mortality and death/severe disability, plasma D-dimer may have predictive value in outcome after AF-related AIS with pneumonia.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia, which associated with increased risk of mortality and disability after stroke. The large infarcts characteristically associated with AF reflect the larger size of stasis thrombi that form in the low shear environment of the left atrium [1,2]. 30-day mortality of AF-related stroke was more than 24%, another 35% patients had severe disability [3-5].

AF leads to decreased flow in the left atrial appendage and the atrium, which combine with platelet activation and endothelial dysfunction, increase coagulation activity and lead to stroke. Studies had shown that patients with AF could increase D-dimer levels[6-8], and higher D-dimer levels could increase risk of future cerebrovascular and cardiovascular events[9-11], increased D-dimer levels have been reported to be proportional to the severity of stroke. In addition, D-dimer may reflect the effect of infection on coagulation. Some studies had reported that elevated D-dimer levels in pneumonia patients might indicate hypercoagulability and increase the risk of thrombosis [12-14]. Pneumonia is the most common complication of AIS, which could lead to poor clinical outcomes and increase mortality, but the predictive value of D-dimer in clinical outcome among AF-related AIS with pneumonia has not been elucidated.

Therefore, in the present study, we investigated the prognostic value of D-dimer for predicting clinical outcome of AF-related AIS with pneumonia.

2. Methods

2.1. Study Population

This study was a multicenter prospective study conducted in three medical centers: Nanchong Central Hospital of the Second Clinical Medical School, North Sichuan Medical College, the Chengdu second people's hospital, and affiliated Hospital of North Sichuan Medical College. Patients with AF-related AIS were admitted within 7 days to the stroke ward between July 2015 and March 2019. AIS is defined as sudden loss of neurological function with symptoms lasting for more than 24h. Brain CT scan was normal or acute ischemic changes, diffusion-weighted imaging showed acute ischemic changes. TOAST classification was used for determining stroke subtype. AF-related stroke was confirmed by an experienced neurologist who blinded to the study. The severity of stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS).

Pneumonia was diagnosed based on clinical history and symptoms (cough, fever, purulent secretions), and laboratory parameters of respiratory tract infection, and was confirmed by chest CT.

Only patients who met all the following criteria were included in the study: 1. First new-onset AF-related AIS within 7 days. 2. AIS was consistent with clinical manifestations. 3. Patients had pneumonia within 7 days after stroke. 4. Patients have electrocardiogram-confirmed AF within the prior 6 months. All patients received standard treatment, including anticoagulant treatment or antiplatelet treatment, lipid-lowering treatment, and rehabilitation. Exclusion criteria: 1. Cerebral hemorrhage; 2. Renal failure (glomerular filtration rate < 30 ml/min/1.73 m²); 3. Active malignancies; 4. Aortic dissection.

2.2 Data collection

Plasma D-dimer levels were measured with an enzyme-linked fluorescent immunoassay method in all patients on admission. Other laboratory data on admission (white blood cells, hemoglobin, liver function, kidney function, LDL-cholesterol, serum glucose, glycated hemoglobin, brain natriuretic peptide, and PCT) were performed. Body temperature was checked at least three times a day. In case of suspect clinical infection, chest CT, PCT, blood and sputum cultivations were rechecked.

All patients were followed up for 3 months. Clinical outcome was defined as 3-month mortality and death/ severe disability (scores 3–5 on the modified Rankin Scale [mRS]) after AF related AIS. Good outcome was defined as mRS ≤ 2.

2.3 Statistical Analysis

All patients were divided death/severe disability and good outcome groups, and then, patients were classified into death and survivor groups. To identify differences between subgroups, the Pearson χ^2 test was used for categorical variables. Distributions of continuous variables were determined by the Kolmogorov–Smirnov test, while Mann–Whitney two sample test was applied in case of non-normal distributions. Receiver operating characteristic (ROC) curve analysis was used to evaluate sensitivity, specificity and to determine the optimal cut point of D-dimer for 3-month mortality and death/ severe disability. We then performed logistic regressions analyses to determine the association between D-dimer and 3-month mortality and death/ severe disability. Results were expressed as adjusted odds ratios (aOR) with the corresponding 95% confidence interval (CI). SPSS 22.0 statistical software was used for data analyses. P < 0.05 was used as a significance level.

3. Results

3.1 Patient Characteristics

415 AF-related AIS patients with pneumonia were included in the study, 211 patients were female(52.45%) and 184 patients were male (47.55%), with an average age of 67.62 ± 9.84 years old (ranging from 40 to 93 years old), median NIHSS score was 11(7-14), medians international standard ratio (INR) was 1.36(1.09-1.95). 82 patients were treated with anticoagulation, medians D-dimer value was 1.9mg/l (1.2-3.0mg/l). There were 123 cases of diabetes, 265 cases of hypertension, 278 cases of hyperlipidemia, 126 cases of smoking and 147 cases of drinking. During 3 months of follow-up, 50 patients had died, 178 patients had severe disability (Table 1).

3.2 Factors related to death/severe disability

228 (228/415,54.94%) patients had death/severe disability after 3 months of follow-up. The patients with death/severe disability had older age (68.68 ± 9.63 vs 66.32 ± 9.97 , $P=0.005$), higher NIHSS score [13(10-16) vs 7(5-11), $P \leq 0.001$], higher D-dimer levels [2.50(1.60-3.88) vs 1.30(0.80-2.00), $P \leq 0.001$], lower percentage of anticoagulant (9.21% vs 32.62%, $P \leq 0.001$) than those who good outcome (Table 1).

ROC curve showed that D-dimer predict death/ severe disability with AUC of 0.78 (95%CI 0.73 to 0.82). The optimal cut point off D-dimer for death/ severe disability was $D\text{-dimer} \geq 2.35$ mg/l. Using $D\text{-dimer} \geq 2.35$ mg/l to predict death/severe disability, the sensitivity was 55.70%, the specificity was 83.96%, positive predictive value was 80.89%; and negative predictive value was 60.85%.

Table 1
The baseline characteristics between good outcome and death/severe disability groups

	Good outcome group (187)	Death/severe disability group (228)	OR(95%CI)	P*
Age, y(Mean SD)	66.32±9.97	68.68±9.63		0.005
NIHSS score, median (IQR)	7(5-11)	13(10-16)		0.001
D-dimer, median (IQR)	1.30(0.80-2.00)	2.50(1.60-3.88)		0.001
INR, median (IQR)	1.34(1.06-1.97)	1.37(1.10-1.93)		0.838
CHA2DS2-VASc, median (IQR)	4.00(4-5)	4.0(4-5)		0.360
Females, n(%)	88(47.06)	123(53.95)	1.32 (0.89-1.94)	0.163
Male, n(%)	99(52.94)	105(46.05)	1.32 (0.89-1.94)	0.163
BMI≥24 kg/m, n(%)	55(29.41)	68(29.82)	1.02(0.67-1.56)	0.927
Hypertension, n(%)	120(64.17)	145(63.60)	0.98(0.65-1.46)	0.904
Current Smoking, n(%)	51(27.27)	75(32.89)	1.31(0.86-2.00)	0.215
Current alcohol drinking,n(%)	66(35.29)	81(35.53)	1.01(0.67-1.51)	0.961
Diabetes, n(%)	58(31.01)	65(28.51)	0.89(0.58-1.35)	0.578
Hyperlipidemia, n(%)	121(64.71)	157(68.86)	1.21(0.80-1.82)	0.371
Family history of stroke, n(%)	46(24.60)	48(21.05)	0.82(0.52-1.30)	0.390
Thrombolytic therapy, n(%)	26(13.90)	25(10.96)	0.76(0.42-1.37)-	0.763
Thrombectomy, n(%)	10(5.35)	13(5.70)	1.07(0.46-2.50)	0.875
Thrombolytic therapy+ Thrombectomy, n(%)	4(2.14)	4(1.75)	0.82(0.20-3.31)	0.777
Medications use				
Antihypertensive, n(%)	96(51.34)	133(58.33)	1.380.90-1.960	0.154
Anticoagulant, n(%)	61(32.62)	21(9.21)	0.21(0.12-0.36)	0.000
Antiplatelets, n(%)	54(28.88)	55(24.12)	0.780.51-1.210	0.274
Lipid-lowering medications, n(%)	109(58.29)	132(57.89)	0.980.67-1.460	0.935

Bold indicates P-values less than 0.05.

*Comparison between good outcome and death/severe disability groups. The data are presented as median values (interquartile range [IQR]), numbers (%), or mean values (\pm standard deviation). Categorical variables are expressed as frequency (percent) for P values. Baseline characteristics were compared between the 2 subgroups by univariate analysis using Pearson χ^2 , distributions of continuous variables were determined by the Kolmogorov–Smirnov test, Mann–Whitney two sample test was applied in case of non-normal distributions.

Table 2
Logistic regression analysis of the risk factors associated with Death/severe disability.

	OR (95% CI)	P*
Model1(D-dimer value)		
NIHSS score	1.50(1.36–1.66)	0.001
D-dimer value	2.33(1.74–3.11)	0.001
Anticoagulant	0.16(0.07-0.35)	0.001
Model 2(D-dimer \geq 2.35mg/l)		
NIHSS score	1.53(1.38–1.68)	0.001
D-dimer \geq 2.35mg/l	5.95[3.09-11.45]	0.001
Anticoagulant	0.16[0.07-0.35]	0.001
Bold indicates P-values less than 0.05.		
**Multivariable adjusted for age, NIHSS score, INR, CHA2DS2-VASc, gender, BMI, hypertension, current smoking, alcohol drinking, diabetes, hyperlipidemia, family history of stroke, thrombolytic therapy, thrombectomy, thrombolytic therapy + thrombectomy, medications use.		

In the multivariate logistic regression model, after adjusting for all the confounding factors(Model 1), higher NIHSS score and D-dimer value were associated with increased risk of 3-month death/severe disability (OR:1.50, 95% CI: 1.36–1.66, P=0.001; OR 2.33, 95% CI: 1.74–3.11, P=0.001; respectively),and anticoagulant was associated with decreased risk of 3-month death/severe disability (OR:0.16, 95% CI: 0.07-0.35, P=0.001); when D-dimer \geq 2.35mg/l was entered into multivariate logistic regression (Model 2), higher NIHSS score and D-dimer \geq 2.35mg/l were associated with increased risk of 3-month death/severe disability (OR:1.53, 95% CI: 1.38–1.68, P=0.001; OR 5.95, 95% CI: 3.09-11.45, P=0.001; respectively) (Table 2),and anticoagulant was associated with decreased risk of death/severe disability (OR:0.16, 95% CI: 0.07-0.35, P=0.001) (Table 2).

3.3 Factors related to death

After 3 months of follow-up, 50 (98/387,25.32%) patients died. The patients who died had older age (71.49 \pm 10.27 vs 67.09 \pm 9.68, P=0.005), higher NIHSS score[18(14-20) vs 10(7-13), P<0.001], higher D-dimer levels [3.85(1.98-4.65) vs 1.80(1.10-2.70),P<0.001] than those who stayed alive(Table 3).

ROC curve showed high accuracy for D-dimer predict 3-month mortality with AUC of 0.76(95%CI 0.69 to 0.84). The optimal cut point of D-dimer for 3-month mortality was D-dimer \geq 3.35mg/l. Using a cutoff point of D-dimer \geq 3.35 mg/l

to predict 3-month mortality, the specificity was 84.93%, positive predictive value was 35.29%; and negative predictive value was 93.94%.

Table 3
The baseline characteristics between survivor and death groups

	Survivor group (365)	Death group (50)	OR(95%CI)	P*
Age, y(Mean SD)	67.09±9.68	71.49±10.27		0.005
NIHSS score. median (IQR)	10(7-13)	18(14-20)		0.001
D-dimer, median (IQR)	1.80(1.10-2.70)	3.85(1.98-4.65)		0.001
INR, median (IQR)	1.35(1.09-1.93)	1.40(1.13-2.03)		0.722
CHA2DS2-VASc, median (IQR)	4.00(4-5)	4.0(4-5)		0.676
Females, n(%)	187(51.23)	24(48.00)	0.88 (0.49-1.59)	0.668
Male, n(%)	178(48.77)	26(52.00)	0.88 (0.49-1.59)	0.668
BMI≥24 kg/m, n(%)	110(30.14)	13(26.00)	0.81(0.42-1.59)	0.548
Hypertension, n(%)	233(63.84)	32(64.00)	1.01(0.54-1.86)	0.982
Current Smoking, n(%)	106(29.04)	20(40.00)	1.63(0.89-3.00)	0.114
Current alcohol drinking, n(%)	124 (33.97)	23(46.00)	1.66(0.91-3.01)	0.095
Diabetes, n(%)	112(30.68)	11(22.00)	0.64(0.32-1.29)	0.207
Hyperlipidemia, n(%)	147(40.27)	31(62.00)	0.78(0.42-1.44)	0.424
Family history of stroke, n(%)	86(23.56)	8(16.00)	0.62(0.28-1.37)	0.231
Thrombolytic therapy, n(%)	43(11.78)	8(16.00)	1.43(0.63-3.24)	0.394
Thrombectomy, n(%)	18(4.93)	5(10.00)	2.14(0.76-6.05)	0.142
Thrombolytic therapy+ Thrombectomy, n(%)	7(1.92)	1(2.00)	1.04(0.13-8.67)	0.968
Medications use				
Antiplatelets, n(%)	96(26.30)	13(26.00)	0.99(0.50-1.93)	0.964
Lipid-lowering medications, n(%)	213(58.36)	28(56.00)	0.91(0.50-1.65)	0.752

Bold indicates P-values less than 0.05.

*Comparison between survivor and death groups. The data are presented as median values (interquartile range [IQR]), numbers (%), or mean values (±standard deviation). Categorical variables are expressed as frequency (percent) for P values. Baseline characteristics were compared between the 2 subgroups by univariate analysis using Pearson χ^2 , distributions of continuous variables were determined by the Kolmogorov–Smirnov test, Mann–Whitney two sample test was applied in case of non-normal distributions.

In the multivariate logistic regression model, after adjusting for all the confounding factors (Model 1), higher NIHSS score, higher age, and higher D-dimer value were independently associated with increased risk of 3-month mortality (OR:1.52, 95% CI: 1.34–1.72, P=0.001; OR 1.05, 95% CI: 1.01–1.10, P=0.027; OR 1.49, 95% CI: 1.19–1.86, P=0.001; respectively); when D-dimer \geq 3.35mg/l was entered into multivariate logistic regression (Model 2), higher NIHSS score, higher age, D-dimer \geq 3.35mg/l were independently associated with increased risk of 3-month mortality (OR:1.56, 95% CI: 1.37–1.77, P=0.001; OR 1.06, 95% CI: 1.01–1.11, P=0.019; OR 7.85, 95% CI: 3.21-19.21, P=0.001; respectively) (Table 4).

Table 4
Logistic regression analysis of the risk factors associated with mortality

	OR (95% CI)	P*
Model1(D-dimer value)		
NIHSS score	1.52(1.34–1.72)	0.001
Age	1.05(1.01-1.10)	0.027
D-dimer value	1.49(1.19–1.86)	0.001
Model 2(D-dimer \geq 3.35mg/l)		
NIHSS score	1.56(1.37–1.77)	0.001
Age	1.06(1.01-1.11)	0.019
D-dimer \geq 3.35mg/l	7.85(3.21-19.21)	0.001
Bold indicates P-values less than 0.05.		
*Multivariable adjusted for age, NIHSS score, INR, CHA2DS2-VASc, gender, BMI, hypertension, current smoking, alcohol drinking, diabetes, hyperlipidemia, family history of stroke, thrombolytic therapy, thrombectomy, thrombolytic therapy+ thrombectomy, medications use.		

4. Discussion

AF is the most prevalent sustained cardiac rhythm disorder seen in clinical practice. AF is linked to a 5-fold increased risk of cerebrovascular events, and approximately 20% of strokes are related to AF. AF-related strokes impart worse prognosis than those occurring in the absence of AF. The 30-day mortality of AF-related stroke was 24%, another 35% of patients were unable to live independently [2,4]. In this study, we found that the 3-month mortality was 12.05%, the remaining 365 survivors, severe disability rates were 48.76% (178/365). The mortality and disability rate in this study were lower than those reported in previous studies, which may be due to most of the patients from the level of first-class comprehensive hospital, medical conditions are relatively good.

D-dimer is a specific cross-linked fibrin degradation product, is a sensitive biomarker for indicating coagulation and fibrinolytic activation, which remains stable over time in the absence of any adverse events [15]. D-dimer levels are commonly used to screen for pulmonary embolism and aortic dissection [6,9]. Previous studies have shown that the level of D-dimer increased after AIS, which might be related to stroke subtype and stroke volume, and significantly increased in cardiogenic embolic ischemic stroke [16,17]. In recent years, some studies have shown that D-dimer levels could be a valuable and independent short-term prognostic marker for acute stroke [18]. In AF-related AIS patients with pneumonia, the prognostic value of D-dimer levels remains unclear. In our study, we found D-dimer level was

significantly elevated ($2.24 \pm 1.54 \text{ mg/l}$), we have obtained the correlation between D-dimer levels and outcome, the optimal cut point off D-dimer for 3-month death/severe disability and mortality was $D\text{-dimer} \geq 2.35 \text{ mg/l}$ and $\geq 3.35 \text{ mg/l}$, respectively, after adjusting for fully confounders, we found a significant association of $D\text{-dimer} \geq 2.35 \text{ mg/l}$ and $D\text{-dimer} \geq 3.35 \text{ mg/l}$ with increased risks of 3-month death/severe disability and mortality after AF-related AIS with pneumonia. From our results, we could confirm that D-dimer was a valuable prognostic marker of functional outcome and death among AF-related AIS with pneumonia. The mechanism of the relationship between D-dimer levels and the prognosis of AF-related AIS patients with pneumonia remains unclear. It may be that increased D-dimer levels may reflect ongoing thrombus formation within cerebral vessels or may be a marker of systemic hypercoagulability [19]. Second, atrial fibrillation may lead to vascular endothelial dysfunction, and D-dimer may stimulate the inflammatory response. The synergistic effect of activated inflammation and activated coagulation may lead to adverse outcomes [20]. Thus, D-dimer may represent the biological activation of inflammatory, hemostatic, and fibrinolytic systems.

In our this study, the cut-off value of D-dimer used for predicting death/severe disability was $D \geq 2.35 \text{ mg/l}$, the sensitivity was 55.70%, the specificity was 83.96%, positive predictive value was 80.89%; and negative predictive value was 60.85%. Using a cut-off point of $D\text{-dimer} \geq 3.35 \text{ mg/l}$ for predicting 3-month mortality, the sensitivity was 60.0%, the specificity was 84.93%, positive predictive value was 35.29%; and negative predictive value was 93.94%. As shown above, poor sensitivity was observed when $D\text{-dimer} \geq 3.35 \text{ mg/l}$ used for predicting death.

Some limitations of this study are worth considering. First, in this study, we relied on a single baseline D-dimer levels, so we were unable to investigate the association between dynamic changes D-dimer levels and clinical outcomes among AF-related AIS with infection. D-dimer levels should be measured repeatedly for longitudinal analysis, which may provide additional information about development and its prognostic impact. Second, although we adjusted for the NIHSS score, which has been shown to be associated with infarct volume, we lacked data on infarct volume. Third, left atrial appendage (LAA) is an important source of thrombi in patients with AF, but we lack data of left atrial. Fourth, due to contraindications, some patients were treated with platelet aggregation instead of anticoagulant after stroke, and we did not further analyze these patients, which might have an impact on the study results. The strength of our study was that it was related to the large number of patients, moreover, it was a multicenter clinical trial with robust and of high clinical relevance results

In conclusion, our study showed a positive correlation between increased D-dimer level and unfavorable outcome after AF-related AIS with infection. Our findings substantiated the importance of an early diagnosis of elevated D-dimer in AF-related stroke survivors with infection given the elevated risk of unfavorable outcome. D-dimer levels may have potential predictive value in risk stratification of ischemic stroke.

Declarations

Authors' contributions

YH was responsible for the concept and design of the study, data collection and analysis and the first draft of the paper and further manuscript. LTL, QZL and MY were responsible for concept and design of the study, the data collection and interpretation. LPP was responsible for the data analysis. ZY was responsible for overseeing the concept and design of the study, the data analysis and interpretation. All authors read and approved the final manuscript for publication.

Declaration of Competing Interest

The authors have no conflicts of interest to declare

Ethics approval and consent to participate

We obtained ethical approval for this study from the Medical and Health Research Ethics Committee in Nanchong Central Hospital of the Second Clinical Medical School, North Sichuan Medical College, Second people's Hospital of Chengdu, Affiliated Hospital of North Sichuan Medical College. The current study was carried out according to the Declaration of Helsinki. If the patient has consciousness disorder or aphasia, the decision cannot be made by themselves, the consent form can be signed by the patient's legal proxies. Prior to enrollment, all patients or their legal proxies will be given detailed information about the aims, scope, and possible consequences of the trial by a physician. Written informed consent was obtained from all study participants or their legal proxies.

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