Volume 22, No 3 | International Journal of Radiation Research, July 2024

Prognostic value of CT perfusion imaging, serum D-D and MMP-9 on hemorrhage transformation after thrombolysis in patients with acute cerebral infarction

L. Wang, G. Tian, H. Zhang, J. Chen, Z. Sun, F. Guo, J. Shen*

Department of Imaging Diagnosis, Inner Mongolia Medical University Affiliated Hospital, Hohhot, China

► ***Original article***

***Corresponding author:**
Jie Shen, MD.,
***E-mail:** shenjie_319@126.com*

Received: January 2024
Final revised: March 2024
Accepted: March 2024

Int. J. Radiat. Res., July 2024; 22(3): 711-717

DOI: 10.61186/ijrr.22.3.703

Keywords: *Perfusion imaging, thrombolytic therapy, hemorrhagic transformation, D-dimer, matrix metalloproteinase-9, computed tomography angiography.*

ABSTRACT

Background: This study explores the predictive value of Computerized Tomography (CT) perfusion imaging, serum D-dimer (D-D), and serum matrix metalloproteinase-9 (MMP-9) levels for hemorrhagic transformation (HT) in patients with acute cerebral infarction post-thrombolysis. ***Materials and Methods:*** Patients with acute cerebral infarction who underwent thrombolytic therapy from February 2021 to February 2022 were included. CT perfusion imaging was conducted within a week post-operation. The study compared CT perfusion parameters and serum markers, analyzing differences and conducting univariate and multivariate analyses to explore their predictive value for HT. ***Results:*** No significant differences were found in hypertension, hyperlipidemia, stroke history, mean arterial pressure, fasting blood glucose, and platelet count pre-thrombolysis ($P > 0.05$). However, infarct diameter ≥ 5 cm and atrial fibrillation were more common in the study group, with higher pre-thrombolysis National Institutes of Health Stroke Scale (NIHSS) score, D-D, and MMP-9 levels ($P < 0.05$). CT perfusion showed lower relative cerebral blood volume (rCBV, relative cerebral blood flow (rCBF, and higher relative mean transit time (rMTT), relative time to peak (rTTP) in the study group ($P < 0.05$). D-D and MMP-9 levels were negatively correlated with rCBV, rCBF, and positively with rTTP, CTP integration index ($P < 0.05$). ***Conclusion:*** CT perfusion imaging, serum D-D, and MMP-9 levels are effective predictors of hemorrhagic transformation in acute cerebral infarction patients post-thrombolysis. These findings are valuable for guiding clinical treatment and monitoring.

INTRODUCTION

Acute ischemic stroke (AIS) is a critical health condition caused by cerebral ischemia and hypoxia due to sudden occlusion of cerebral blood vessels, primarily from blood clots. As one of the leading causes of disability and death globally, Acute cerebral infarction（ACI necessitates prompt and effective treatment strategies. Intravenous Thrombolysis (IVT) plays a pivotal role in AIS management, aiming to dissolve cerebral blood clots, thereby reinstating blood flow and oxygen supply to the brain [1]. The efficacy of IVT is time-sensitive, with studies indicating significant patient prognosis improvements when administered within 4.5 hours of stroke onset [2].

However, the risk of hemorrhagic transformation (HT) post-thrombolysis poses a clinical challenge, necessitating careful patient monitoring and early intervention [3]. Identifying patients at high risk of HT is crucial for enhancing the safety and effectiveness of thrombolytic therapy [4]. In this regard, imaging techniques are invaluable for predicting HT in patients post-thrombolysis. CT perfusion imaging (CTP), for instance, offers insights into cerebral blood supply and hemodynamics in the ultra-early stage of ACI. Despite its utility, the sole reliance on CTP has limitations, including suitability issues for repeated use [5,6]. However, the prediction of HT using CTP has some shortcomings. First, the interpretation of CTP parameters may be influenced by differences in image processing software, which may limit their consistency and comparability across studies [7]. In addition, due to the limited sample size of the study, the interpretation of CTP parameters may not cover different parts of the total ischemic area, such as the perfusion and core infarction area. This can lead to limitations in the analysis, which in turn affect the overall assessment of HT risk [8]. HT is a complex process involving multiple pathophysiological factors, many of which cannot be detected from CTP imaging. In addition, in the post-processing of CTP images, information loss is inevitable [9].

In addition to imaging, serological markers like D-Dimer (D-D) and Matrix Metalloproteinase-9 (MMP -9) have emerged as potential predictive tools for cerebrovascular diseases. D-D reflects the fibrinolytic and coagulation system changes, while MMP-9 levels correlate with neurovascular unit injury and brain tissue edema [10,11]. However, the combined

[DOI: 10.61186/ijrr.22.3.711]

predictive value of CTP and serum D-D and MMP-9 levels for HT in ACI patients post-thrombolysis remains unclear [12].

By exploring the combined use of CTP and serological markers (D-D, MMP-9) for HT prediction, this research contributes significantly to the field of radiological studies in stroke management. The integration of these diagnostic tools could provide a more comprehensive assessment, enhancing the safety and precision of thrombolytic therapy in AIS. This research introduces a novel approach by combining CT perfusion imaging with serological markers, D-Dimer and MMP-9, to predict hemorrhagic transformation in patients with acute cerebral infarction post-thrombolysis. While each of these diagnostic tools has been individually studied in the context of AIS, their combined use represents an innovative strategy that could significantly enhance early detection and intervention for HT. The findings of this study have the potential to pave the way for more targeted and personalized thrombolytic therapies, thereby improving patient outcomes and reducing the incidence of adverse effects associated with AIS treatment.

Acute Ischemic Stroke (AIS) is a disease of cerebral ischemia and hypoxia caused by sudden occlusion of blood vessels in the brain. The condition is usually caused by blood clots or other blocking substances that affect blood flow to the brain, thereby damaging brain cells. Acute cerebral infarction is one of the leading causes of disability and death worldwide. In the treatment of acute cerebral infarction, Intravenous Thrombolysis, IVT is an important treatment method. The main goal of this therapy is to dissolve clots that block blood vessels in the brain to restore blood flow and oxygen supply to the brain. The use of intravenous thrombolytic therapy is particularly critical in the acute phase. Studies have shown that intravenous thrombolysis, when administered within the first few hours (usually within 4.5 hours) after the onset of cerebral infarction, can significantly improve the prognosis of patients. This is because restoring blood flow in the early stages after cerebral infarction, when brain tissue is damaged but not yet completely dead, minimizes permanent brain damage [1]. However, due to the risk of hemorrhagic transformation, thrombolytic therapy needs to be performed under strict medical monitoring. Once hemorrhagic transformation occurs, the condition will deteriorate further and even threaten the life of the patient [2,3]. Therefore, it is of great significance to find the risk factors of hemorrhagic transformation, screen these high-risk patients before or during thrombolysis and actively intervene to reduce the risk of bleeding and improve the safety of thrombolysis [4]. imaging examinations are often used to predict the occurrence of hemorrhagic transformation in patients with acute cerebral infarction after thrombolysis. CT perfusion imaging (CTP) is an examination method that can evaluate the blood supply and hemodynamics of brain tissue in the ultra -early stage, but the effect of its use alone is not good, and it is not suitable for repeated use [5,6]. Serological markers have the advantages of simple operation and repeatable operation. D-Dimer (D-D) can reflect the changes of fibrinolysis and coagulation system of the body, and is gradually used in the diagnosis and prognosis of cerebrovascular diseases [7]. Changes in the level of Metalloproteinase-9 (MMP-9) are related to neurovascular unit injury and brain tissue edema [8]. However, the predictive value of CTP and serum D -D and MMP-9 for hemorrhagic transformation after thrombolysis in patients with acute cerebral infarction is still unclear [9]. Based on this, this study aims to provide a basis for the judgment of hemorrhagic transformation in patients with acute cerebral infarction after thrombolysis.

MATERIALS AND METHODS

Study design

Patients with acute cerebral infarction who received thrombolytic therapy in our hospital from February 2021 to February 2022 were selected as the research objects. CT perfusion imaging was performed within 1 week after operation. This study was approved by the Willowdale Hospital Ethics Committee, with the approval number WH-EC-2021-0321 dated March 21, 2021. Signed written informed consents were obtained from the patients and/or guardians.

Inclusion criteria: 1. The clinical diagnosis of patients met the relevant diagnostic criteria for acute cerebral infarction in the "Consensus on the diagnosis and Treatment of hemorrhagic transformation after acute Cerebral Infarction in China" [13]; 2.The time from onset to admission was less than 4 hours, and thrombolytic therapy was given within 4.5 hours after onset; 3. All patients underwent CT perfusion imaging. 4. are first onset, patients with a diagnosis of arterial cerebral infarction; 5.The patient was in good physical condition before onset and had the indication for surgery. Exclusion criteria: 1.Patients with previous history of cerebral infarction; 2. ultrasound tip of intracranial aneurysm; 3. The patient had liver and kidney dysfunction; 4. patients with severe malignant tumors; 5. There are contraindications to thrombolysis, such as hemorrhagic stroke, long-term use of anticoagulant drugs, abnormal blood glucose, gastrointestinal bleeding, and urethral bleeding. The diagnostic criteria for hemorrhagic transformation were as follows: no hemorrhagic lesions were found by CT examination at admission, and ultrasound examination was performed within one week after admission, which indicated the presence of

[DOI: 10.61186/ijrr.22.3.711]

hemorrhagic lesions.

Data on hypertension, hyperlipidemia, history of stroke, fasting blood glucose, mean arterial pressure, platelet count before thrombolysis, infarct diameter ≥ 5 cm, proportion of atrial fibrillation, and time from onset to treatment were collected. The national institutes of health stroke scale (NIHSS) score before thrombolysis has 11 items, and higher scores indicate more severe disease. CTP check instrument used for philips offerings 256 CT scanner (philips, USA), the scanning parameters as follows: 40 ml iopromide was injected into the cubital vein with a high pressure syringe at a speed of 4.0 mL/s at a voltage of 80 kV, tube current of 125 mA, slice thickness of 5 mm, and slice spacing of 5 mm. CTP scan was performed 5 s after injection, and the data were sent to EBW workstation. Using Perfusion 4.6software processing the data (GE,USA), to avoid the great vessels, cerebrospinal fluid, and to select the interested area of the brain. The cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP) of the healthy brain tissue were recorded. Relative cerebral blood flow (rCBF), relative mean transit time (rMTT), relative cerebral blood volume (rCBV) and relative time to peak (rTTP) were obtained by comparing the values of the affected side with those of the healthy side. CTP integration index = rCBV x rCBF/rTTP. Serum D-D and MMP - 9 test: collected on admission in patients with venous blood 3 ml, centrifugal separation (3500 r/min, 10 min), serum enzyme-linked immunosorbent method was applied to detect serum level of MMP - 9, D-D, bought kits from Jiangsu Kejing Biological Technology co., LTD. (Nanjing, China).

The clinical data of two groups of patients was collected to compare the differences between the groups. The CT perfusion imaging parameters of the two groups were compared and analyzed to obtain the rCBF, rMTT, rCBV, rTTP and CTP integration index of the affected and healthy sides of the patients.

Statistical analysis

Statistic Package for Social Science (SPSS) 23.0 software (IBM, Armonk, NY, USA) was used for data processing. The chi-square test was used to analysis categorical data such as patients' gender, smoking history, pathological changes and medical history; Continuous data such as serological indicators and CT perfusion imaging parameters of patients were expressed as (± SD), and independent sample t test was performed between groups. The Pearson correlation coefficient analysis patients' serum D - D, MMP - 9 level and the correlation of perfusion parameters; Using ROC curve to explore serum D - D, MMP - 9 level, blood perfusion parameters on the predictive value of transformation of bleeding in patients with. α=0.05 was considered as the test level.

RESULTS

Patient's demography and history

In the study conducted from February 2021 to February 2022, 112 patients with acute cerebral infarction were included, divided into a control group (n=79) with no hemorrhagic transformation and a research group (n = 33) with hemorrhagic transformation. The comparison between the transformation of bleeding and non-bleeding after thrombolysis and before and after thrombolysis is shown in figure 1. There were no significant differences between the two groups in terms of gender, age, BMI, smoking and drinking history, and lesion location (P > 0.05). These details are presented in table 1.

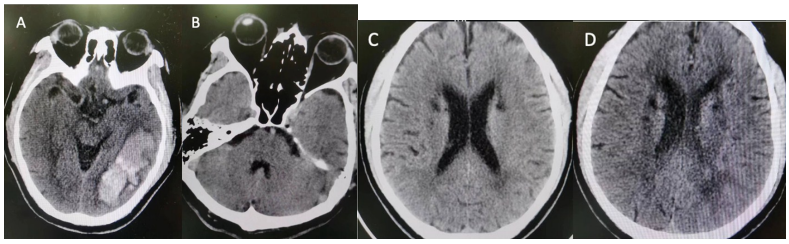

Figure 1. Comparison between bleeding and non-bleeding after thrombolysis and before and after thrombolysis. **A)**Bleeding transformed after thrombolysis; **B)** No-bleeding transformed after thrombolysis; **C)** Pre-thrombolysis; **D)** Post-thrombolysis.

Table 1. Comparison of general data between the two groupComparison of general data between the control and study groups [±s, n/(%)].

Group	Age (years)	gender		BMI (kg/m^2)	Smoking history		Diseased region				Drinking history	
		Male	Female		Yes	No	The cerebral cortex and subcortical	brainstem	parencephalon	else	Yes	No
Control (n=79)	56.85± 6.45	42 (53.16)	37 (46.84)	22.54± 2.08	23 (29.11)	56 (70.89)	23 (29.11)	21 (26.58)	22 (27.85)	13 (16.46)	26 (32.91)	53 (67.09)
Research (n=33)	56.15± 6.98	16 (48.48)	17 (51.52)	22.64± 2.15	15 (45.45)	18 (54.55)	8(24.24)	9 (27.27)	5 (15.15)	11 (33.33)	14 (42.42)	19 (57.58)
χ^2/t	0.511	0.204		-0.230	2.773		4.854				0.917	
P	0.610	0.651		0.819	0.096		0.183				0.338	

[DOI: 10.61186/ijrr.22.3.711]

Clinical parameters

There were no significant differences between the two groups in hypertension, hyperlipidemia, history of hemorrhagic stroke, mean arterial pressure, fasting glucose, and platelets before thrombolysis (P > 0.05). However, the incidence of infarcts with a diameter of 5 cm or more and the occurrence of atrial fibrillation were higher in the research group. The time from onset to treatment, NIHSS score, and levels of D-D and MMP-9 before thrombolysis were also higher in the research group (P < 0.05) (table 2).

Table 2. Comparison of clinical data between the two groups (±s, n/%).

Variable	Control	Research	t/χ^2	P
Number of case	79	33		
Hypertension				
Y	35 (44.30)	19 (57.58)	1.642	0.200
N	44 (55.70)	14 (42.42)		
Hyperlipemia				
Y	26 (32.91)	15 (45.45)	1.578	0.209
N	53 (67.09)	18 (54.55)		
Stroke				
Y	16 (20.25)	10 (30.30)	1.319	0.251
N	63 (79.25)	23 (69.70)		
Infarcts diameter				
<5 cm	55 (69.62)	13 (39.39)	8.916	0.003
≥5 cm	24 (30.38)	20 (60.61)		
Atrial fibrillation				
Y	34 (43.04)	22 (66.67)	5.198	0.023
N	45 (56.96)	11 (33.33)		
Time from onset to treatment (h)	2.96±0.18	3.87±0.23	-22.415	0.000
NIHSS score before thrombolysis	14.56± 2.11	17.55± 1.98	-6.959	0.000
Mean arterial pressuremmHg)	118.26± 15.26	120.44± 13.68	-0.710	0.479
Fasting blood glucose (mmol/L)	6.88±0.92	7.15±0.89	-1.429	0.156
D-D (mg/L)	2.26±0.16	3.11±0.34	-18.022	0.000
MMP-9 (ug/L)	212.55± 32.56	323.45± 61.55	-12.427	0.000
Platelets before thrombolysis($\times10^9$/L)	215.26± 66.48	209.59± 71.29	0.403	0.688

Note: NIHSS: National Institutes of Health Stroke Scale; D-D: D-Dimer.

CT perfusion imaging parameters

The study group showed lower integration indexes of relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF), and higher relative mean transit time (rMTT) and relative time to peak (rTTP) compared to the control group (P < 0.05) (table 3).

Table 3. Comparison of CT perfusion parameters between the two groups (±s).

Group	rCBV	rCBF	rMTT	rTTP	CTP integration index
Control (n = 79)	0.74± 0.19	0.26± 0.07	2.13± 0.61	0.98± 0.13	0.21±0.05
Research (n=33)	0.51± 0.11	0.21± 0.05	2.33± 0.34	1.13± 0.09	0.10±0.06
χ^2/t	6.503	3.721	-1.769	-6.043	9.994
P	0.000	0.000	0.080	0.000	0.000

Note: CTP: Computed Tomography Perfusion; rCBF: Relative Cerebral Blood Flow; rMTT: Relative Mean Transit Time; rCBV: Relative Cerebral Blood Volume; rTTP: Relative Time to Peak.

Correlation analysis

Pearson correlation coefficient analysis revealed that serum levels of D-D and MMP-9 had no significant correlation with rMTT (P > 0.05), were negatively correlated with rCBV and rCBF, and positively correlated with rTTP and the CTP integration index (P < 0.05) (table 4).

Table 4. correlation analysis between serum D-D and MMP-9 levels and CT perfusion parameters.

Perasoncorrelation index		rCBV	rCBF	rMTT	rTTP	CTP integration index
D-D	*r*	-0.482	-0.308	0.148	0.465	-0.586
	P	0.000	0.001	0.118	0.000	0.000
MMP-9	*r*	-0.465	-0.381	0.107	0.433	-0.505
	P	0.000	0.000	0.261	0.000	0.000

Note; MMP-9: Matrix Metalloproteinase-9.

Predictive value for hemorrhagic transformation

The ROC curve results indicated that the Area Under the Curve (AUC) values of D-D, MMP-9, rCBV, rCBF, rMTT, rTTP, and the CTP integration index for predicting hemorrhagic transformation were 0.757, 0.707, 0.654, 0.750, 0.621, 0.804, and 0.752, respectively. These results are shown in table 5 and figure 2.

Table 5. ROC curve analysis for predicting hemorrhagic transformation.

Index	AUC	cut-off value	95%CI		sensitivity	specificity	*P*
			Floor	upper			
D-D	0.757	2.630	0.642	0.872	0.606	0.949	0.000
MMP-9	0.707	257.15	0.581	0.833	0.576	0.911	0.001
rCBV	0.654	0.605	0.534	0.774	0.606	0.747	0.011
rCBF	0.750	0.245	0.659	0.842	0.879	0.633	0.000
rMTT	0.621	1.925	0.521	0.722	0.809	0.543	0.043
rTTP	0.804	1.055	0.724	0.884	0.818	0.671	0.000
CTP integration index	0.752	0.135	0.644	0.860	0.606	0.873	0.000

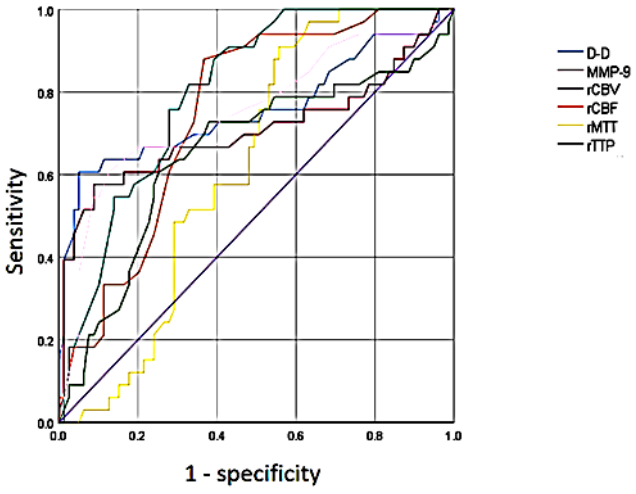

Figure 2. Predictive value of serum D-D and MMP-9 levels and CT perfusion parameters in patients with hemorrhagic transformation.

[DOI: 10.61186/ijrr.22.3.711]

DISCUSSION

Our study's findings indicate that CTP, serum D-Dimer, and MMP-9 levels can effectively predict hemorrhagic transformation in patients with acute cerebral infarction post-thrombolysis. This aligns with existing research, suggesting that these biomarkers are crucial in identifying patients at higher risk of bleeding complications. (refer to table 4 and figure 1). Specifically, the ROC curve analysis in our study (table 5) showed significant predictive values, which is consistent with the findings of Zhang *et al.* [1] and others in the field.

Furthermore, the negative correlation of serum D-D and MMP-9 levels with rCBV and rCBF, and their positive correlation with rTTP and the CTP integration index (table 4), highlighting the importance of these parameters in assessing hemorrhagic risks [6].

Hemorrhagic transformation is related to factors such as poor establishment of collateral circulation, reperfusion injury of brain tissue and changes in coagulation function during thrombolytic therapy [14]. How to predict hemorrhagic transformation after thrombolysis is a hot topic in clinical research. Studies have shown [15] that CTP can reflect the abnormal perfusion of brain tissue and the changes of blood-brain barrier in brain tissue, and CTP has certain predictive value for hemorrhagic transformation after thrombolysis.

This study showed that the integration index of rCBV, rCBF and CTP in the study group was lower than that in the control group, and rMTT and rTTP were higher than those in the control group ($P < 0.05$). CBV and CBF can be used to evaluate the cerebral perfusion and blood volume. The smaller the CBV and CBF are, the lower the blood flow and the longer the TTP will be. The blood flow of the contralateral brain tissue may be redistributed, rCBV and rCBF decrease, and rTTP is prolonged. The greater the difference in blood perfusion volume and blood perfusion between the two sides of brain tissue, the more serious the brain tissue injury is, and the risk of hemorrhagic transformation after thrombolysis increases accordingly. The rMTT value reflects the speed at which the contrast agent passes through the ischemic region of the brain and is prolonged when blood flow perfusion is abnormal. Studies have said [13], its value increases is a risk factor for bleeding transformation, rMTT missing image can clear and bleeding risk. This study are consistent with previous research results.According to recent studies, it has been observed that a rise in its measured value significantly correlates with an increased risk of bleeding transformation [16]. Furthermore, the lack of regional mean transit time (rMTT) imaging data can play a crucial role in clarifying this increased risk of bleeding. These findings are not isolated and align well with the results of previous research in the field, further reinforcing the understanding of these risk factors.

D-D is commonly used indicator of thrombotic diseases. MMP-9 is an important member of the matrix metalloproteinase family, and its increased value will lead to the destruction of the vascular basement membrane, leading to vascular rupture [15]. The results showed that team D -D, MMP-9 patients were higher than the control group. Tips on serum D-D, MMP-9 level and thrombolysis in patients with acute cerebral infarction associated bleeding after transformation. It is suggested that it is necessary to strengthen the monitoring of D-D and MMP-9 levels and evaluate brain injury, which is of great significance for improving the prognosis of patients. Prior research has additionally revealed that D-dimer levels possess considerable diagnostic significance in identifying hemorrhage transformation following thrombolytic therapy in cases of acute cerebral infarction [17]. This biomarker is particularly noted for its high specificity. This means that elevated D-dimer levels can be a reliable indicator of potential hemorrhagic complications post-thrombolysis. This insight is crucial, as it assists clinicians in making more informed decisions about patient care, balancing the benefits of thrombolytic therapy with its risks. It also underscores the importance of monitoring D-dimer levels as part of the comprehensive assessment and management of patients with acute cerebral infarction.

The decrease of fibrinogen caused by thrombolysis may lead to coagulation dysfunction, prolong prothrombin time and partial thrombin time, and eventually lead to the occurrence of hemorrhagic transformation after thrombolysis. D-D expression shows that the body of the double activation of blood coagulation and fibrinolytic activity, existing on D-D and the transformation of thrombolysis hemorrhage occurs after stroke study is less, combining with the research view, higher serum D - D levels may be induced by activating inflammation hematoma enlargement, increased risk of hemorrhage transformation. Abnormal level of MMP-9 can accentuate increase neuronal apoptosis and the degree of brain injury, damage the integrity of the blood-brain barrier, promote the risk of bleeding after thrombolysis transformation. The results also indicate that the patient's serum D - D, MMP - 9 level and rCBV, rCBF negatively correlated, and rTTP, CTP integration index were positively correlated. The results of ROC curve showed that D-D, MMP-9, rCBV, rCBF, rMTT, rTTP, and CTP integration index had better efficacy in predicting hemorrhagic transformation of patients. Abnormal CTP index suggests that the patient's brain tissue perfusion is insufficient, the patient's collateral circulation is poorly established, which aggravates the destruction of the arterial basement membrane, indirectly leads to the activation of plasmin and hyperfibrinolysis,

[DOI: 10.61186/ijrr.22.3.711]

leading to the abnormal increase of serum D-D and MMP-9. The above phenomena jointly promote the occurrence of hemorrhagic transformation.

This study points out that: two groups of patients in hypertension, hyperlipidemia, hemorrhagic stroke, mean arterial pressure, fasting glucose, platelets before thrombolysis is no difference between groups ($P > 0.05$), the results are consistent with previous research is not entirely. Studies have found that [18], fasting blood glucose can lead to the body's endocrine disorder, and increase the risk of thrombolysis bleeding transformation. Patients with elevated arterial pressure before thrombolysis have a higher rate of ischemic perfusion injury and a corresponding increased risk of hemorrhagic transformation. The reason for the inconsistency between this study and previous studies may be related to the small sample size. This study shows that: the team infarcts in patients with a diameter of 5 cm or more, the occurrence of af were higher than control group, time of onset to treatment, thrombolysis NIHSS score were higher than the control group. The relationship between NIHSS score before thrombolysis and hemorrhagic transformation after thrombolysis has been clinically confirmed [19]. The higher the score is, the more serious the cerebral ischemia and vascular damage are. The above conditions provide the conditions for the occurrence of hemorrhagic transformation. Large area cerebral infarction is easy to cause compression of blood vessels around the lesion, resulting in mass effect or brain edema, and increasing the risk of intracerebral hemorrhagic transformation [20]. Cerebral infarction patients with atrial fibrillation have complex thrombus components, which may not be easily dissolved by thrombolytic therapy, resulting in a longer time for vascular recanalization and an increased risk of cerebral hemorrhage transformation [21]. Cerebral infarction onset to treatment time is too long to make blood perfusion to the damaged blood vessels, this phenomenon is a risk factor for cerebral hemorrhage transformation. Studies have shown [18] that for every 1 h increase in the time from onset to thrombolysis, the weight of the nomogram model score of hemorrhagic transformation increases by 18.2 points. In combination with the results of this study, thrombolysis treatment delays, the longer the brain artery occlusion, the longer the brain necrosis degree is more serious, vascular permeability also increases, the increased risk of hemorrhage transformation. Research findings indicate that for every one-hour delay in administering thrombolytic therapy from the onset of symptoms, the nomogram model score predicting hemorrhagic transformation escalates by 18.2 points [22]. This finding is critical in understanding the dynamics of stroke management. The longer the delay in thrombolysis, the more prolonged is the occlusion of the brain artery, leading to more severe brain tissue necrosis. This progression not only exacerbates the degree of damage but also increases vascular permeability, which in turn significantly elevates the risk of hemorrhagic transformation. Thus, these insights highlight the importance of prompt thrombolytic treatment in acute stroke cases to minimize the risk of hemorrhage and to preserve brain function as much as possible. Timely intervention becomes a key factor not just in preventing further neurological damage, but also in reducing the likelihood of complications arising from the treatment itself.

Based on the clinical characteristics, imaging examination and related serological indicators of patients, this study predicts the risk factors of hemorrhagic transformation after thrombolysis, which has certain guiding significance for alert high-risk patients and prevent the occurrence of complications. CTP time density curve is obtained by injection of contrast agent, to gain parameters of tissue perfusion, and to win more time for the next treatment. Imaging findings are often related to factors such as infarct location, severity of cerebral infarction, and examination time [23], and combined with serum D-D and MMP-9 examination can further improve the clinical predictive value. But, belong to the retrospective study, this study included in the sample less blood loss, might be in a lot of bleeding is not suitable for, further studies are needed to verify in the future.

Above all, CTP, serum D - D and the level of MMP - 9 can effectively predict the patients with acute cerebral infarction after thrombolysis treatment will appear haemorrhage transformation, for the clinical doctors in treatment and monitoring is of important guidance value.

CONCLUSION

In conclusion, these findings highlight the importance of a multimodal diagnostic approach in clinical decision-making, potentially improving patient outcomes by facilitating early identification and intervention for those at risk of bleeding complications. While further research is needed to reinforce these results, particularly in larger and more diverse patient cohorts, our study contributes valuable insights to the field of stroke management and emphasizes the critical role of combined imaging and serological assessments in acute stroke care.

Conflict of Interests: The authors declared no conflict of interest.
Funding: This study did not receive any funding in any form.
Ethical Compliance: This study was conducted in line with the ethical standards of the Zhoushan Hospital of Zhejiang Province Ethics Committee.

[DOI: 10.61186/ijrr.22.3.711]

Ethical approval was granted with due consideration for the welfare of the participants. Signed written informed consents were obtained from all patients and/or their guardians.

Authors' contributions: LW and JS designed the study and performed the experiments, GT and HZ collected the data, JC, ZS and FG analyzed the data, LW and JS prepared the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Zhang XX, Yao FR, Zhu JH, *et al*. (2022) Nomogram to predict haemorrhagic transformation after stroke thrombolysis: a combined brain imaging and clinical study. *Clinical Radiology*, ***77(1):*** *e92-e98.*
2. Yu X, Pan J, Zhao X, Hou Q, Liu B (2022) Predicting hemorrhagic transformation after thrombectomy in acute ischemic stroke: a multimodal score of the regional pial collateral. *Neuroradiology*, ***64 (3):*** *493-502.*
3. Ni H, Lu, Hang Y, *et al.* (2023) Association between Infarct Location and Hemorrhagic Transformation of Acute Ischemic Stroke following Successful Recanalization after Mechanical Thrombectomy. *American Journal of Neuroradiology*, ***44(1):*** *54-59*.
4. Elsaid N, Bigliardi G, Dell'Acqua ML, *et al*. (2023) Proposal of multimodal computed tomography-based scoring system in prediction of hemorrhagic transformation in acute ischemic stroke. *Acta Neurologica Belgica*, ***123(4):*** *1405-1411*.
5. Xu J, Dai F, Wang B, *et al*. (2023) Predictive Value of CT Perfusion in Hemorrhagic Transformation after Acute Ischemic Stroke: A Systematic Review and Meta-Analysis. *Brain Sciences*, ***13(1):*** *156.*
6. Han S, Huang R, Yao F, *et al*. (2022) Pre-treatment spectral CT combined with CT perfusion can predict hemorrhagic transformation after thrombolysis in patients with acute ischemic stroke. *European Journal of Radiology*, ***156:*** *110543*.
7. Jain AR, Jain M, Kanthala AR, *et al.* (2013) Association of CT perfusion parameters with hemorrhagic transformation in acute ischemic stroke. *American Journal of Neuroradiology,* ***34(10):*** *1895-1900.*
8. Biesbroek JM, Niesten JM, Dankbaar JW, *et al.* (2013) Diagnostic accuracy of CT perfusion imaging for detecting acute ischemic stroke: a systematic review and meta-analysis. *Cerebrovascular Diseases,* ***35(6):*** *493-501.*
9. Li X, Liu H, Zeng W, *et al*. (2020) The Value of Whole-Brain Perfusion Parameters Combined with Multiphase Computed Tomography Angiography in Predicting Hemorrhagic Transformation in Ischemic Stroke. *Journal of Stroke & Cerebrovascular Diseases,* ***29 (4):*** *104690.*
10. Zoller B, Sundquist J, Sundquist K, Ohlsson H (2024) The risk for venous thromboembolism and cardiometabolic disorders in offspring from thrombosis-prone pedigrees. *Journal of Thrombosis and Haemostasis:* ***22(3):*** *775-784.*
11. Ling C, Cao S, Kong X (2022) Changes of FSTL1 and MMP-9 levels in patients with acute cerebral infarction and its relationship with hemorrhagic transformation. *Journal of Clinical Neuroscience*, ***99:*** *164-168*.
12. Li C, Hao X, Lin L, *et al.* (2021) Prognostic Value of a New Integrated Parameter-Both Collateral Circulation and Permeability Surface-in Hemorrhagic Transformation of Middle Cerebral Artery Occlusion Acute Ischemic Stroke: Retrospective Cohort Study. *Frontiers in Aging Neuroscience*, ***13:*** *703734*.
13. Fan H, Wei L, Zhao X, *et al*. (2023) White matter hyperintensity burden and functional outcomes in acute ischemic stroke patients after mechanical thrombectomy: A systematic review and meta-analysis. *Neuroimage-Clinical*, ***41:*** *103549*.
14. Shafique MA, Ali S, Mustafa MS, *et al.* (2023) Meta-analysis of direct endovascular thrombectomy vs bridging therapy in the management of acute ischemic stroke with large vessel occlusion. *Clinical Neurology and Neurosurgery*, ***236:*** *108070.*
15. Fu Y, Zheng S, Kong H, *et al*. (2022) Clinical Value of Combined Detection of UA and MMP-9 in Evaluating Bleeding Transformation and Prognosis After Thrombolysis in Acute Cerebral Infarction. *Applied Biochemistry and Biotechnology*, ***194(11):*** *5236-5254*.
16. Laskowitz DT, Troy J, Poehlein E, *et al.* (2024) A Randomized, Placebo-Controlled, Phase II Trial of Intravenous Allogeneic Non-HLA Matched, Unrelated Donor, Cord Blood Infusion for Ischemic Stroke. *Stem Cells Translational Medicine:* ***13(2):****125-136.*
17. Fu Y, Zheng S, Kong H, *et al.* (2022) Clinical Value of Combined Detection of UA and MMP-9 in Evaluating Bleeding Transformation and Prognosis After Thrombolysis in Acute Cerebral Infarction. *Applied Biochemistry and Biotechnology,* ***194(11):*** *5236-5254.*
18. Xu Y, Hu Y, Wu G, *et al*. (2023) Specific inhibition on PAI-1 reduces the dose of Alteplase for ischemic stroke treatment. *International Journal of Biological Macromolecules: 128618*.
19. Kim JE, Lee RP, Yazigi E, *et al.* (2023) Soluble PD-L1 reprograms blood monocytes to prevent cerebral edema and facilitate recovery after ischemic stroke. *Brain Behavior and Immunity*, ***116:*** *160-174*.
20. Wilson JL, Waak M, Barry M, Jordan LC, Sun LR (2023) Tenecteplase in Pediatric Stroke: Ready or Not. *Pediatric Neurology*, ***151:*** *17-20*.
21. Bellam KG, Sabe SA, Chalasani N, *et al*. (2023) Association Between Marijuana Use and Clinical Outcomes After Coronary Artery Bypass Grafting. *Journal of Surgical Research*, ***295:*** *442-448*.
22. Nam KW, Kim CK, Yu S, *et al*. (2023) Corrigendum to "D-dimer to fibrinogen ratio predicts early neurological deterioration in ischemic stroke with atrial fibrillation" [Thromb. Res. 229 (2023) 219-224]. *Thrombosis Research*, ***233:*** *173*.
23. Yin P, Wu Y, Long X, *et al*. (2023) HACE1 expression in heart failure patients might promote mitochondrial oxidative stress and ferroptosis by targeting NRF2. *Aging (Albany Ny)*, ***15(23):*** *13888-13900.*

[DOI: 10.61186/ijrr.22.3.711]