Systematic Review and Meta-Analysis

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Risk factors of haemorrhagic transformation for acute ischaemic stroke in Chinese patients receiving intravenous thrombolysis

A meta-analysis

Lihong Wen, MD, Song Zhang, MD, Kunzhen Wan, MM, Hong Zhang, MM*, Xiaoyun Zhang, BS*

Abstract

Aim: To determine the risk factors related to hemorrhagic transformation in Chinese patients with acute ischemic stroke treated with intravenous thrombolysis.

Methods: Studies published in different languages were retrieved by systematically searching PubMed, EMBASE, Vip, CNKI, and WanFang Data from the establishment of the library to December 31, 2018, as well as manually examining the references of the original articles. The outcome measures of efficacy covered risk factors. Safety evaluation was measured by relative ratio of complications.

Results: A total of 36 studies involving 5597 participants were covered in this meta-analysis. The results indicated that age [WMD = 2.44, 95% CI (1.39,3.48)], male [OR = 1.21, 95% CI (1.02, 1.44)], diabetes [OR = 2.05, 95%CI (1.72,2.44)], atrial fibrillation [OR = 2.85, 95%CI (2.40, 3.39)], previous stroke [OR = 1.8, 95%CI (1.33, 2.44)], onset to treatment time (OTT) [WMD = 3.74, 95%CI (2.91, 4.58)], National Institute of Health stroke scale scores (NIHSS) [WMD = 4.17, 95% CI (3.37, 4.97)], infarct size [WMD = 4.11, 95% CI (3.15, 5.37)], ischemic signs of computed tomography (CT) [OR = 3.49, 95%CI (2.47, 4.93)] were associated with increased risk of hemorrhagic transformation after intravenous thrombolysis.

Conclusion: The systematic review showed that male, age, diabetes, NIHSS, OTT, atrial fibrillation, post stroke, infarct size, and ischemic signs of CT were significantly correlated with hemorrhagic transformation (HT).

PROSPERO Registration number: CRD42019127499.

Abbreviations: CI = confidence interval, CT = computed tomography, ECASS = European Collaborative Acute Stroke Study, HT = hemorrhagic transformation, NIHSS = National Institute of Health stroke scale, NINDS = Neurological Disorders and Stroke, NOS = Newcastle Ottawa scale, OR = odds ratio, OTT = Onset to treatment time, WHO = World Health Organization, WMD = weighted mean differences.

Keywords: acute ischemic stroke, hemorrhagic transformation, intravenous thrombolysis, meta-analysis, risk factor

Editor: Stefano Omboni.

Key R&D Projects in Sichuan Province (Clinical Program Optimization and Evaluation of Major Chronic or Refractory Diseases in Prevention and Treatment of Traditional Chinese Medicine [TCM]): Evaluation and Optimization of TCM Comprehensive Treatment Program in Acute Cerebral Hemorrhage2019YFS0082.

The authors have no conflicts of interest to disclose.

Hospital of Chengdu University of Traditional Chinese Medicine,Chengdu, Sichuan Province, P.R. China.

** Correspondence: Hong Zhang, and Xiaoyun Zhang, Hospital of Chengdu University of Traditional Chinese Medicine, No. 39 Shi-er-qiao Road, Chengdu, 610072, Sichuan Province, P.R. China (e-mail: zhanghong1874@163.com, zhangxy1980@126.com).*

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How to cite this article: Wen L, Zhang S, Wan K, Zhang H, Zhang X. Risk factors of haemorrhagic transformation for acute ischaemic stroke in Chinese patients receiving Intravenous thrombolysis: A meta-analysis. Medicine 2020;99:7 (e18995).

Received: 11 September 2019 / Received in final form: 30 November 2019 / Accepted: 31 December 2019

http://dx.doi.org/10.1097/MD.0000000000018995

1. Introduction

Stroke is prevalent worldwide, which has been listed as the third most deadly disease.[1] According to the report of World Health Organization (WHO), there are 15 million people suffering from stroke every year.[2] Acute ischemic stroke is the most common type,[3] with the rate mortality >50%.[4] Thrombolysis is an effective treatment of acute ischemic stroke. The safety and efficacy of intravenous thrombolysis for acute ischemic stroke have been studied and recognized by multinational guidelines.[5] However, the data from the Chinese National Stroke Registry indicates that only 1.6% of patients receive rt-PA treatment in China.[6] One of the main reasons for therapy is that intravenous thrombolysis increases the risk of hemorrhagic transformation (HT). It can affect the efficacy and safety of thrombolysis, cause rapid deterioration and death of patients, and hinder the promotion of thrombolytic therapy. Some meta-analyses identified older age, higher neurological impairment, higher plasma glucose, antiplatelets, statins, computed tomography changes of acute ischemic stroke, leukoaraiosis, and the presence of atrial fibrillation, diabetes, previous ischemic heart or cerebral vascular diseases, and congestive cardiac failure as potential risk factor for HT,[7]which were based on Western populations. However, the influential factors may vary with race, geography, and others.

Hence, a systematic review of studies relevant to present practice based on a Chinese population study was conducted to clearly identify risk factors that may cause HT. If these risk factors can be decrease, it may reduce the occurrence of cerebral hemorrhage transformation in Chinese patients after thrombolysis.

2. Materials and methods

2.1. Search strategy

A systematic and comprehensive search of data was performed on PubMed, EMB-A-SE, Vip, CNKI, and Wanfang Database in terms of the literature published till December 31, 2018, without language restriction. Five search themes were combined using the Boolean operator "and" and "or." Search terms included "stroke or ischemic stroke or cerebrovascular disorders or brain infarction or cerebral infarction or intracranial embolism or thrombosis" and "intravenous thrombolysis or thrombolysis or tissue plasminogen activator or alteplase" and "brain hemorrhage or bleeding or HT" and "risk factor or correlative factor or relevant factor" and "Chinese or China." This study is a system review, without intervention and control measures, and has no effect on patients. Therefore, ethical requirements are unnecessary.

2.2. Eligibility criteria

Inclusion criteria:

1. Study type: case–control study or cohort study; retrospective or prospective design;
2. Subject: Intravenous thrombolysis;
3. Exposure factors: having similar definitions regarding each exposure factor, including demographic characteristics: age, gender, past health Condition: Hypertension, diabetes, heart disease (atrial fibrillation, coronary atherosclerotic heart disease, congestive heart failure or myocardial infarction), history of cerebrovascular disease (transient ischemic attack, hemorrhage or ischemic stroke);
4. Outcome indicators: factors related to cerebral hemorrhage conversion.

Exclusion criteria:

1. Cross-sectional study, no control, and only with clues of risk factors;
2. Outcome indicators include extracranial hemorrhage events;
3. Surgical intervention;
4. Secondary study: such as a review of the original study or a literature review;
5. Repeated reports; comments; abstracts, or no data that can be extracted from the study or with data error.

2.3. Studies

The research design was based on community, population or registered longitudinal cohort studies that reported relative impact estimates, such as Odds Ratio (ORs).

2.4. Study selection

Two authors independently evaluated potentially eligible studies that were identified by our search. Articles were screened for eligibility based on a review of title and abstract only, and disagreements were resolved by consensus. Regarding the remaining papers, their full text was accessed and read independently by the two reviewers mentioned above. The differences of opinion between reviewers were resolved by discussion with a third member of the research team, and the consensus was thereby reached.

2.5. Data collection

A standardized data collection sheet was used to extract all data. One author (Wen) extracted data from the included studies and another (Zhang) used statistical software to check the accuracy of inclusion. Any disagreement was resolved through discussions with the other authors. The data were extracted from each eligible study as follows: first author, year of publication, the number of cases, and risk factors. HT was defined according to the Neurological Disorders and Stroke (NINDS) criteria.[8]

2.6. Statistical analysis

For studies with sufficient quality data and similar simulation learning and result measurements, we used Newcastle Ottawa scale (NOS) for quality assessment of case–control or cohort studies in the current meta-analysis and combined the data in a meta-analysis to provide a summary effect estimate. All data were entered into RevMan 5.3, and the normalized deviation and 95% CI were calculated. Pooled ORs for categorical data, weighted mean differences (WMDs) for continuous data and 95% CI were estimated.[9]

For meta-analyses, I^2 statistics were used for heterogeneity testing. The degree of inconsistency between the measurements was roughly interpreted as the proportion of total variation between studies attributable to heterogeneity rather than chance. When $I^2 < 50\%$, a fixed effect model was applied. A random effect model was performed when the existing statistical heterogeneity was measured by $I^2 > 50\%$.

3. Result

The document retrieval and screening process are shown in the flowchart (Fig. 1). The electronic search of PubMed, EMBASE, Vip, CNKI, and Wanfang Database provided a total of 768 citations, and 13 citations were found manually. After removing duplicate manuscripts, 559 studies remained, among which 423 were excluded according to the review of title and abstract. Then 136 studies were left for full-text reviews regarding eligibility, 55 of which were excluded because of unqualified study design and result measurements. A total of 81 studies met all the criteria and were selected for initial inclusion; after review, 45 studies were excluded for duplicates, reviews, and literature reports. Eventually, 36 articles[10–45] were included in the final analysis (Table 1).

3.1. Study characteristics

For the risk factors mentioned in the 36 studies, the selected studies included 4575 cases, HT total of 1023 cases. A total of 22 risk factors related to cerebral hemorrhage after ischemic stroke were investigated. Among them, 16 factors such as age were mentioned in more than 10 studies, which hence were further analyzed and discussed; other risk factors were only mentioned in a few studies, and hence excluded in order to avoid the occurrence of bias. Table 1 depicts the basic characteristics and risk factors for HT of the included studies.

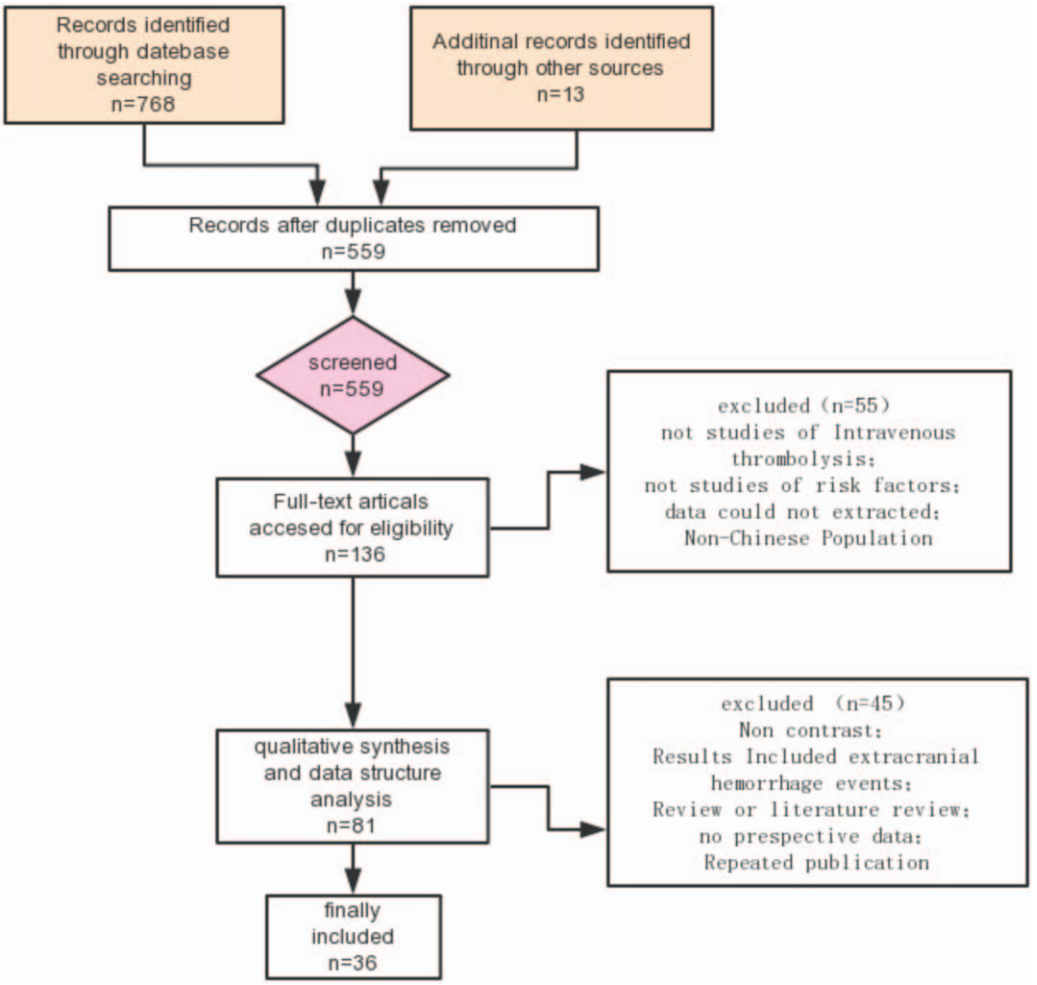

Figure 1. Flow diagram of retrieved, screened, and included studies.

3.2. Meta-analysis results

3.2.1. Age. Total of 29 studies reported age. The heterogeneity among the studies was high ($X^2=66.98$, $I^2=58\%$), a random effect model was applied. The result found that older age (WMD = 2.43, 95% CI [1.39, 3.46]) was significantly associated with HT.

3.2.2. Sex. Total of 32 studies reported sex (male). There was no heterogeneity among the studies ($X^2=30.45$, $I^2=0\%$), the fixed effect model was used. The results found that male (OR = 1.21, 95% CI [1.02, 1.44]) was associated with risk of HT.

3.2.3. Hypertension and diabetes. Total of 35 articles studied hypertension and diabetes. There was less heterogeneous among the trials ($X^2=48.44$, $I^2=30\%$) and ($X^2=57.72$, $I^2=43\%$), a fixed effect model were used. The results of meta-analysis demonstrated that hypertension (OR = 0.97, 95%CI [0.83, 1.14]) was not associated with HT, diabetes (OR = 2.05, 95% CI [1.72, 2.44]) was associated with HT.

3.2.4. Atrial fibrillation. Total of 32 studies considered atrial fibrillation. There was moderate heterogeneity ($X^2=59.04$, $I^2=47\%$), a fixed effect model was used for analysis. The results found that atrial fibrillation (OR = 2.85, 95% CI [2.40, 3.39]) was related to HT.

3.2.5. Stroke severity. Total of 25 studies reported the National Institute of Health stroke scale (NIHSS). The heterogeneity among the studies was high ($X^2=202.56$, $I^2=88\%$), a random effect model was used. The results show that NIHSS (WMD = 4.17, 95% CI [3.37, 4.97]) was related to HT.

3.2.6. Onset to treatment time. Total of 22 studies evaluated onset to treatment time (OTT). The heterogeneity among the studies was high ($X^2=178.02$, $I^2=88\%$), a random effect model was applied. The results showed that OTT (WMD = 3.74, 95% CI [2.91, 4.58]) was associated with HT obviously.

3.2.7. Infarct size. Total of 11 studies evaluated large-area infarction. The heterogeneity among the studies was high ($X^2=15.89$, $I^2=37\%$), a fixed effect model was used. The results found that the infarct size (WMD = 4.11, 95% CI [3.15, 5.37]) was associated with an increased risk of HT.

3.2.8. Ischemic signs of CT. Total of 10 studies reported ischemic signs of CT. There was no heterogeneity among the studies ($X^2=3.55$, $I^2=0\%$), a fixed effect model was used. The results found that early ischemic signs of CT (OR = 3.49, 95% CI [2.47, 4.93]) were significantly associated with HT.

3.2.9. Previous stroke. A total of 15 studies analyzed previous stroke. There was low heterogeneity among the studies ($X^2=$

Table 1

Basic characteristics of the included studies.

Reference	Study location	Publication year	Sample size	Included prognosis factors	NOS scores
Su et al	Zhejiang	2011	128	①②③④⑤⑥⑦⑧⑨⑪⑫⑬⑭⑮⑯	7
He et al	Guangdong	2012	62	①②③④⑤⑩⑬⑭⑯	6
Huang et al	Fujian	2013	171	①②③④⑤⑥⑦⑧⑨⑪⑫⑬⑭⑮⑯	6
Wang et al	Guangdong	2013	98	①②③④⑦⑨⑫⑬⑭⑮	6
Su et al	Zhejiang	2013	44	①②③④⑤⑦⑧⑪⑬⑭⑮	6
Ai et al	Jiangsu	2015	45	①③④⑨⑫⑬⑭	8
Yang et al	Henan	2015	196	②③④⑦⑨⑩⑬⑭	6
Xian et al	Guangdong	2015	156	①②③④⑧⑨⑩⑫⑬⑭⑮	7
Wang et al	Henan	2015	189	①②③④⑤⑥⑦⑧⑨⑪⑫⑯	6
Li et al	Hubei	2015	60	①③④⑤⑥⑨⑩⑪⑫⑬⑭⑮	6
Xu et al	Jiangsu	2015	55	①②③④⑤⑦⑧⑨⑫⑬⑭⑮	7
Yang et al	Jiangsu	2015	100	①②③④⑥⑦⑧⑨⑪⑫⑬⑭⑮⑯	7
Wei et al	Hubei	2015	143	①②③④⑤⑦⑧⑨⑫⑬⑭⑮⑯	6
Liu et al	Hubei	2016	60	①③④⑥⑨⑫	6
Wu et al	Shanxi	2016	80	①②③④⑥⑦⑧⑨⑫⑬⑭⑮⑯	6
Long et al	Guizhou	2016	100	①②③④⑥⑦⑧⑨⑪⑬⑭⑮	6
Chen et al	Sichuan	2016	150	①②③④⑦⑨⑩⑬⑭	6
Yan et al	Hubei	2016	186	①②③④⑥⑦⑧⑨⑩⑬⑭	6
Wang et al	Jiangsu	2016	295	①②⑦⑫⑮	6
Zhu et al	Neimenggu	2016	112	①②③④⑥⑦⑧⑨⑩⑫⑬⑭	7
Yu et al	Shanxi	2017	112	①②③④⑥⑦⑧⑨⑪⑫⑬⑭⑮⑯	6
Chen et al	Guangdong	2017	80	②③④⑥⑧⑨⑪	6
Wang et al	Henan	2017	90	③④⑥⑨⑫	6
Wang et al	Liaoling	2017	91	①②③④⑤⑦⑧⑨⑫⑬⑭⑮⑯	7
Xu et al	Guangxi	2017	40	①②③④⑤⑦⑧⑨⑫	6
Zhang et al	Guangdong	2017	75	①②③④⑥⑦⑧⑨⑬⑭	6
Wei et al	Guangxi	2017	62	①③④⑥⑨⑫	6
Shang et al	Beijing	2017	124	①②③④⑤⑥⑦⑧⑨⑪⑫⑬⑭⑮	6
Zhang et al	Hebei	2017	50	①②③④⑤⑥⑦⑨⑩⑮	6
Lin et al	Fujian	2017	187	①③④⑤⑥⑩⑪	6
Li et al	Henan	2017	97	①②③④⑤⑦⑧⑨⑬⑭⑮	6
Li et al	Hunan	2017	69	①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭⑮⑯	6
Wang et al	Liaoling	2017	246	①②③④⑦⑧⑨⑫	7
Zhou et al	Liaoling	2017	84	①②③④⑦⑨⑬⑭⑮	6
Wei et al	Fujian	2017	67	①②③④⑨⑫	6
Li et al	Beijing	2018	287	③④⑦⑧⑨⑩	7

① gender, ② age, ③ history of hypertension, ④ history of diabetes, ⑤ past stroke, ⑥ hyperlipidemia, ⑦ National Institutes of Health Stroke Scale, ⑧ onset-to-needle, ⑨ atrial fibrillation, ⑩ large area cerebral infarction, ⑪ Pre-antiplatelet aggregation therapy, ⑫ smoking, ⑬ basal systolic blood pressure, ⑭ basal diastolic blood pressure, ⑮ basal blood glucose, ⑯ CT Ischemic lesions. NOS: Newcastle-Ottawa scale.

22.5; $I^2=38\%$), a fixed effect model was used. The results indicated that previous stroke (OR = 1.8, 95%CI [1.33, 2.44]) was associated with HT.

3.2.10. Blood pressure and serum glucose level on admission. Systolic blood pressure, diastolic blood pressure, and blood glucose levels were studied in a partial inclusion study. The heterogeneities ($X^2=237.19$, $I^2=90\%$), ($X^2=63.64$, $I^2=64\%$) and ($X^2=260.63$, $I^2=93\%$) were high among the studies, the random effect model were adopted. Meta-analysis showed that systolic blood pressure (WMD = 6.03, 95%CI [0.26, 1.8]), diastolic blood pressure (WMD = 2.46, 95%CI [0.52, 4.4]), and basal blood glucose (WMD = 1.66, 95%CI [0.98, 2.35]) were not associated with HT.

3.2.11. Previous antiplatelet treatment. The results indicated that previous antiplatelet treatment (OR = 1.05, 95%CI [0.76, 1.47]) was not significantly associated with HT.

3.2.12. Hyperlipidemia. The results indicated that hyperlipidemia (OR = 1.29, 95%CI [0.84, 1.99]) was not associated with HT.

3.2.13. Smoking. The results found that smoking (OR = 1.01, 95%CI [0.82, 1.25]) was not significantly associated with HT.

3.3. Sensitivity analysis and meta-regression

We conducted a sensitivity analysis by excluding every single study to explore the stability of the combined results. The range

Table 2

Heterogeneity and sensitivity analysis of prognosis factors among included studies.

Prognosis factor	Number of studies	HT	Non-HT	I^2	Statistic method	OR and 95%CI	Sensitivity analysis	
							Lower limit	Upper limit
Age	29	783	2627	58%	I-V, random, WMD	2.43 (1.39, 3.46)	2.16 (1.18,3.13)	2.64(1.64,3.64)
Male	32	761	2777	0%	M-H, fixed, COR	1.21 (1.02, 1.44)	1.12(0.94,1.34)	1.24 (1.04,1.48)
Hypertension	34	907	3009	30%	M-H, fixed, COR	0.97 (0.83;1.14)	0.94(0.79,1.10)	1.01 (0.85,1.18)
Diabetes	35	907	2940	43%	M-H, fixed, COR	2.05 (1.72;2.44)	1.83(1.53,2.20)	2.13(1.78, 2.54)
Atrial fibrillation	32	831	2792	47%	M-H, fixed, COR	2.85 (2.40, 3.39)	2.69(2.25,3.22)	3.04 (2.54,3.63)
NIHSS	25	703	2521	88%	I-V, random, WMD	4.17 (3.37,4.97)	3.98(3.25,4.72)	4.31(3.49,5.12)
OTT	22	530	2155	88%	I-V, random, WMD	3.74 (2.91, 4.58)	3.50(2.75,4.25)	3.91 (3.08,4.75)
Systolic pressure	24	585	1973	90%	I-V, random, WMD	6.03 (0.26;11.8)	4.61(-0.51,9.73)	6.89 (1.15,12.63)
Diastolic pressure	24	585	1973	64%	I-V, random, WMD	2.46 (0.52;4.4)	2.18(0.23,4.13)	2.67 (0.68,4.67)
Serum glucose	18	414	1583	93%	I-V, random, WMD	1.66 (0.98;2.35)	1.17(0.76,1.58)	1.88 (1.22,2.55)
Previous stroke	15	324	1206	38%	M-H, fixed, COR	1.8 (1.33;2.44)	1.46(1.03,2.06)	1.98(1.43, 2.74)
Hyperlipidemia	17	451	1435	60%	M-H, random, COR	1.29 (0.84;1.99)	1.14(0.81,1.61)	1.40 (0.91,2.13)
Infarct size	11	352	1183	37%	M-H, fixed, COR	4.11 (3.15, 5.37)	3.56(2.68,4.78)	4.50 (3.34,6.08)
Ischemic signs of CT	10	253	892	0%	M-H, fixed, COR	3.49 (2.47, 4.93)	3.36(2.34,4.82)	3.71 (2.60,5.30)
Previous antiplatelet treatment	11	297	1087	49%	M-H, fixed, COR	1.05 (0.76;1.47)	0.94(0.66,1.33)	1.20 (0.85,1.70)
Smoking	21	547	1873	0%	M-H, fixed, COR	1.01 (0.82;1.25)	0.98(0.79,1.23)	1.04(0.84,1.30)

of the combined ORs or WWMDs for potential risk factors is shown in Table 2.

4. Discussion

HT is considered to be the most serious complication of intravenous thrombolysis in ischemic stroke. The incidence rate of symptomatic intracranial hemorrhage is 2.2% to 8% across the world and 4.87% to 7.3% in China,[46] increasing disability and mortality. Therefore, it is important to find out the risk factors of HT. Some studies on HT risk factors have drawn different conclusions. For example, Su[10] and others proposed that the history of atrial fibrillation and hyperlipidemia were important factors of HT, but Chen[26] and others failed to find such a correlation. These disputes and other similar divergences indicate the need for a meta-analysis of this important topic. The meta-analysis was performed among 4575 patients undergoing thrombolytic therapy. It showed that age, male, diabetes, NIHSS, OTT, atrial fibrillation, stroke, infarct size, and ischemic signs of CT were significantly correlated with HT; in contrast, targeting Western populations, meta-analyses showed that older age, higher neurological impairment, higher plasma glucose, antiplatelets, statins, computed tomography changes of acute ischemic stroke, leukoaraiosis, and the presence of atrial fibrillation, diabetes, previous ischemic heart or cerebral vascular diseases, and congestive cardiac failure were significantly correlated with HT.[7]

The high incidence of HT after thrombolysis in patients with high NIHSS before thrombolysis was confirmed by many large studies at home and abroad.[47,48] NINDS studies have shown that the baseline stroke severity as indicated by NIHSS was an independent risk factor for HT, and an NIHSS score >25 was considered a contraindication to thrombolysis.[49]

The European Collaborative Acute Stroke Study (ECASS) I phase study also suggested that NIHSS score before thrombolysis was significantly correlated with HT, and that the disadvantage of rt-PA treatment for an ischemic area >1/3 of the middle cerebral artery distribution was more obvious than the advantage.[48,50] Therefore, according to the results of these studies, ischemic stroke with high NIHSS score (NIHSS score > 18) should be carefully weighed for intravenous thrombolysis.

The studies by Xuemei Mu et al[51] calculated the incidence of HT in patients with massive cerebral infarction to be 29.4%, much higher than that in patients with lacunar infarction (0.94%). The reason may be that that the larger the area of cerebral infarction, the secondary cerebral edema to oppress the surrounding blood vessels, and the corresponding autophagy and elevated plasma TAT levels may lead to the heavier secondary injury in patients with cerebral hemorrhage.[52] It hence is more likely to increase the permeability of the vascular wall and cause post-reperfusion hemorrhage when the vessels are recanalized.

This study found that the incidence of HT after thrombolysis was higher in patients with early ischemic changes on CT before thrombolysis. Tanne et al[50] found that the incidence of HT in patients with early ischemic changes on CT before thrombolysis was 5.63 times higher than that in patients without ischemic changes. Many studies at home and abroad confirmed that ischemic changes on CT before thrombolysis were an independent risk factor for HT after thrombolysis.[47,53,54] Therefore, this study suggested that thrombolysis should be carefully selected for patients with early ischemic changes on CT before thrombolysis, so as to reduce the occurrence of HT and improve the thrombolytic effect.

Leukoplakia was also considered as a risk factor for risk of hemorrhagic stroke in Reference 55.[55] However, there is less research literature, so no analysis.

If some of these risk factors can be avoided or prevented, it will help to better select thrombolytic indications and improve the safety of thrombolytic therapy for Chinese patients, thus reducing bleeding and enhancing efficacy.

5. Limitations

There are some differences in the experimental design among the included studies. In some studies, specific values for infarct size were not mentioned, and some of the inter-study analysis indicators were not uniform, which may affect the quality of meta-analysis. In order to demonstrate its significant advantages, subgroup analysis is needed to identify these findings.

6. Conclusion

The systematic review showed that male, age, diabetes, NIHSS, OTT, atrial fibrillation, post stroke, infarct size, and ischemic signs of CT were significantly associated with a higher risk of HT.

Given the risk of bias, these results should not justify withholding intravenous thrombolysis.

Acknowledgments

We thank the authors and participants of the included studies for their important contributions.

Author contributions

Conceptualization: Xiaoyun Zhang.
Data curation: Song Zhang.
Formal analysis: Song Zhang, Kunzhen Wan.
Funding acquisition: Xiaoyun Zhang, Hong Zhang.
Software: Kunzhen Wan.
Validation: Xiaoyun Zhang, Hong Zhang.
Visualization: Xiaoyun Zhang, Kunzhen Wan.
Writing – original draft: Kunzhen Wan.

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