The Accuracy of Serum Matrix Metalloproteinase-9 for Predicting Hemorrhagic Transformation After Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

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Background: Hemorrhagic transformation is a serious complication of acute ischemic stroke, which may cause detrimental outcomes and the delayed use of anticoagulation therapy. Early predicting and identifying the patients at high risk of hemorrhagic transformation before clinical deterioration occurrence become a research priority. *Objective:* To study the value of plasma matrix metalloproteinase-9 predicting hemorrhagic transformation after ischemic stroke. *Methods:* We searched PubMed, Ovid, Cochrane Library, and other 2 Chinese databases to identify literatures published up to September 2017 and performed meta-analysis by STATA (version 12.0, StataCorp LP, College Station, TX). *Results:* Twelve studies incorporating 1492 participants were included and 7 studies were included in the quantitative statistical analysis. The pooled sensitivity was 85% (95% confidence interval [CI]: 75%, 91%) and the pooled specificity was 79% (95% CI: 67%, 87%). The area under the receiver operating characteristic curve was .89 (95% CI .86, .91). Significant heterogeneity for all estimates value existed (all the P value < .05 and $I^2 > 50\%$). There is no threshold effect with P value greater than .05 of the correlation coefficient. Meta-regression and subgroup analysis showed cut-off value and hemorrhagic subtype contributed to heterogeneity. Deeks' funnel plot indicated no significant publication bias for 7 quantitative analysis studies. *Conclusions:* Matrix metalloproteinase-9 has high predictive value for hemorrhagic transformation after acute ischemic stroke. It may be useful to test matrix metalloproteinase-9 to exclude patients at low risk of hemorrhage for precise treatment in the future clinical work. **Key Words:** Acute ischemic stroke—hemorrhagic transformation—plasma matrix metalloproteinase-9—meta-analysis.

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Introduction

Stroke is one of most severe diseases with high mortality and disability rate with about 70% of the acute ischemic stroke.[1] As a frequent complication, hemorrhagic transformation (HT), a spectrum of ischemia-related brain hemorrhage detected by neuroimaging scan, is usually regarded as part of the natural history in the development of acute ischemic stroke, especially in embolic infraction and after thrombolytic therapy.[2] HT occurs in about 10% of patients with ischemic stroke, and the incidences of symptomatic and spontaneous HT are .6%-20% and 13%-43% in different studies, respectively.[3,4] HT is grouped into hemorrhagic infarct (HI) and parenchymal hematoma (PH) with 4 types: HI-1, HI-2, PH-1 and PH-2 according to the European Cooperative Acute Stroke Study criteria (I, II, or III),[5,6] which takes an important role in the detrimental outcome of ischemic stroke.[2] In addition, treatment such as recombinant tissue plasminogen activator (rt-PA) may increase the risk of hemorrhage, so some effective treatment would be delayed or avoided for fear of severe hemorrhagic complications. Therefore, early recognition of patients at high risk of HT will help clinicians to make the decision about thrombolytic agents usage or anticoagulation therapy initiation, or even the use of an antagonist to prevent HT.[2]

HT is often detected by computerized tomography (CT) or magnetic resonance imaging (MRI) when rapid neurological deterioration occurred.[2] However, considering that the occurrence time of HT is undetermined and neuroimaging examination tests are expensive and inconvenient for continuous dynamic monitoring, a cheap, convenient, and dynamic bedside test with biological fluids would be very helpful to identify patients at high risk for HT in an early time.[1]

Of all the biomarkers of acute ischemic stroke, matrix metalloproteinase-9 (MMP-9), a zinc-dependent enzyme compromising blood–brain-barrier integrity by degrading components of extracellular matrix,[1] draws most attention of researchers and has been studied relative extensively because more and more progress from animal experiments and clinical researches indicate that the high level of MMP-9 concentration is closely associated with infarct extension, neurologic deficits, and HT in acute ischemic patients.[7-12] However, current studies had inconsistent conclusions and the majority included small numbers of patients.[10,13-24] Although it is timely and needed, there is no existing systematic review to assess the accuracy of MMP-9 for the early prediction of HT after acute ischemic stroke. Therefore, we did a systematic review and meta-analysis to determine whether MMP-9 could predict and identify patients at high risk of HT at early stage after ischemic stroke.

Methods

Literature Search

We registered our study in the International Prospective Register of Ongoing Systematic Reviews website and the registration number is CRD42017076582. We searched databases including PubMed, Ovid (Medline and Embase), Cochrane Library, and other 2 Chinese databases (CNKI and Wangfang database) to identify literatures published up to September 2017 with Boolean combinations of generic terms and their synonyms: acute ischemic stroke AND matrix metalloproteinase 9 AND hemorrhagic transformation. The full search strategy was shown in the Supplementary Material (Appendix S1). No language was restricted. The references cited by topic-relevant studies were also screened to find out additional eligible studies.

Inclusion and Exclusion Criteria

We selected eligible literatures that met the following criteria: (1) full-text publications in English or Chinese; (2) study population were acute ischemic stroke patients; and (3) plasma MMP-9 was measured prior (pretreatment) to diagnose HT; (4) HT was confirmed by CT/MRI scan.

Some papers were excluded if: (1) studies were mainly related to the gene, genetic variety, the activity of MMP-9 or other irrelevant topic[11,25,26]; (2) sufficient information including treatment plan, study methods, and diagnostic data was not available[12]; and (3) they were conference abstracts, animal experiments, comments, reviews, and case reports.[8,9,27-30]

Data Extraction and Quality Assessment

Two authors (L.W. and LH.D.) independently reviewed the titles and abstracts and if necessary, full texts of retrieved papers were read. Any discrepancy would be discussed with the third reviewer (CC.W.). An excel sheet (Appendix S2) was designed to extract data and the corresponding authors were contacted if the eligible studies did not show all data available. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[31] to conduct research work and accessed the quality of selected literatures by checking items of Quality Assessment of Diagnostic Accuracy Studies-2 tool.[32]

Statistical Analysis

Only studies with available diagnostic data were enrolled into meta-analysis and the main characteristics of the remaining studies are descriptively analyzed. By meta-analytical integration of diagnostic accuracy studies module in STATA (version 12.0, StataCorp LP, College Station, TX), meta-analysis using the bivariate mixed effects model was conducted to calculate main outcome measures including: sensitivity and specificity,[33] positive/negative likelihood ratio (PLR/NLR) and the diagnostic odds ratio (DOR).[34] Pooled PLR greater than 10 indicates positive result is useful for the confirmation of HT and pooled NLR less than .1 for exclusion, whereas PLR greater than 5 and NLR less than .2 provide strong diagnostic evidence.[35]