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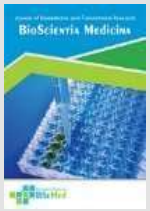

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Matrix Metalloproteinases as Biomarkers for Ischemic Stroke: A Systematic Review

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A B S T R A C T

Background: Ischemic stroke, a leading cause of mortality and disability worldwide, occurs due to the disruption of blood flow to the brain, resulting in neuronal damage and death. Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, play a crucial role in the pathophysiology of ischemic stroke by degrading the extracellular matrix and contributing to blood-brain barrier disruption, inflammation, and neuronal cell death. This systematic review aims to comprehensively evaluate the current evidence regarding the potential of MMPs as biomarkers for ischemic stroke diagnosis, prognosis, and therapeutic monitoring. **Methods:** A systematic search of electronic databases (PubMed, Embase, and Cochrane Library) was conducted to identify relevant studies published between 2018 and 2024. Studies investigating the association between MMPs and ischemic stroke in human subjects were included. Data extraction and quality assessment were performed independently by two reviewers. **Results:** The search yielded 2,182 articles, of which 8 studies met the inclusion criteria. The included studies evaluated various MMPs, including MMP-2, MMP-3, MMP-9, and MMP-12, in different biological samples (serum, plasma, cerebrospinal fluid, and brain tissue) from ischemic stroke patients. The majority of studies reported elevated levels of MMPs in ischemic stroke patients compared to healthy controls, with MMP-9 being the most extensively studied. Furthermore, several studies demonstrated a correlation between MMP levels and stroke severity, functional outcome, and the risk of hemorrhagic transformation. **Conclusion:** The findings of this systematic review suggest that MMPs, particularly MMP-9, hold promise as potential biomarkers for ischemic stroke. However, further research is needed to validate their clinical utility and to explore their potential as therapeutic targets.

1. Introduction

Stroke, a devastating neurological condition characterized by the sudden disruption of blood flow to the brain, poses a significant global health burden. It stands as the second leading cause of mortality and the third leading cause of disability-adjusted life-years worldwide, underscoring its profound impact on individuals, families, and healthcare systems.[1] The World Health Organization estimates that approximately 15 million people suffer from stroke each year, with a staggering 5 million succumbing to its complications and another 5 million left with permanent disabilities.[2] The economic ramifications of stroke are equally substantial, with direct and indirect costs reaching billions of dollars annually.[3] Ischemic stroke, accounting for approximately 85% of all stroke cases, arises from the occlusion of a cerebral artery, typically due to atherosclerosis, embolism, or small vessel disease.[4] The resulting reduction or cessation of blood flow deprives the brain of vital oxygen and nutrients, triggering a cascade of pathophysiological events that culminate in neuronal damage and death.[5] The extent of brain injury and the associated clinical manifestations depend on various factors, including the location and duration of the arterial occlusion, the presence of collateral circulation, and the individual's

underlying health status.[6]

Despite significant advances in the understanding of ischemic stroke pathophysiology, the available therapeutic options remain limited. The only approved treatment for acute ischemic stroke is intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA), which is effective only within a narrow time window (typically 4.5 hours from symptom onset) and carries a risk of hemorrhagic transformation.[7] The development of novel diagnostic and prognostic biomarkers is crucial for several reasons. Early identification of ischemic stroke is essential for timely initiation of treatment, which can significantly improve patient outcomes. Biomarkers that can accurately and rapidly diagnose ischemic stroke, even in patients with atypical presentations or subtle imaging findings, would be invaluable in clinical practice. Predicting the severity and long-term outcome of ischemic stroke is important for guiding treatment decisions and rehabilitation strategies. Biomarkers that can accurately predict the risk of complications, such as hemorrhagic transformation or neurological deterioration, would enable clinicians to tailor treatment plans and optimize patient care. Monitoring the response to treatment and identifying patients at risk of developing complications are critical aspects of ischemic stroke management. Biomarkers that can track the progression of brain injury and the efficacy of therapeutic interventions would facilitate personalized medicine and improve patient outcomes.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that play a pivotal role in the degradation and remodeling of the extracellular matrix (ECM).[8] The MMP family comprises 23 members in humans, classified into different subgroups based on their substrate specificity and structural domains.[9] MMPs are involved in various physiological processes, including tissue development, wound healing, and angiogenesis.[10] However, under pathological conditions, such as ischemic stroke, MMPs can be overexpressed and contribute to tissue damage and disease progression.[1] The blood-brain barrier (BBB) is a highly selective semipermeable border that separates the circulating blood from the brain extracellular fluid in the central nervous system (CNS). It plays a crucial role in maintaining brain homeostasis by regulating the passage of molecules and cells between the blood and the brain. Disruption of the BBB is a hallmark of ischemic stroke and contributes significantly to brain edema, inflammation, and the risk of hemorrhagic transformation.[2] MMPs, particularly gelatinases (MMP-2 and MMP-9), have been shown to degrade the tight junction proteins and basement membrane components of the BBB, leading to increased permeability and the extravasation of blood components into the brain parenchyma.[3] This disruption of the BBB can further exacerbate brain injury and compromise neurological function. Ischemic stroke triggers a robust inflammatory response, characterized by the activation of resident immune cells (microglia and astrocytes) and the infiltration of peripheral immune cells (neutrophils and lymphocytes) into the ischemic brain.[4] This inflammatory response, while initially aimed at clearing cellular debris and promoting tissue repair, can also contribute to neuronal damage and exacerbate brain injury if not properly regulated.[5] MMPs play a crucial role in modulating the inflammatory response by cleaving and activating various inflammatory mediators, such as cytokines and chemokines, and by facilitating the migration of immune cells across the BBB.[6] Ischemic stroke leads to neuronal cell death through various mechanisms, including excitotoxicity, oxidative stress, and apoptosis.[7] MMPs have been shown to directly and indirectly contribute to neuronal cell death in ischemic stroke. They can directly cleave and activate cell death receptors, such as Fas and tumor necrosis factor receptor 1 (TNFR1), leading to apoptosis.[8] Additionally, MMPs can indirectly promote neuronal cell death by degrading the ECM and disrupting the neurovascular unit, leading to the loss of trophic support and the exposure of neurons to toxic factors.[9]

Given their multifaceted roles in ischemic stroke pathophysiology, MMPs have emerged as potential

biomarkers for the diagnosis, prognosis, and therapeutic monitoring of this condition. Several studies have investigated the levels of various MMPs in different biological samples (serum, plasma, cerebrospinal fluid, and brain tissue) from ischemic stroke patients, with promising results. MMP-9, a gelatinase involved in the degradation of type IV collagen, has been the most extensively studied MMP in the context of ischemic stroke.[10] Numerous studies have reported elevated levels of MMP-9 in the serum, plasma, and cerebrospinal fluid of ischemic stroke patients compared to healthy controls.[1,2] Furthermore, MMP-9 levels have been shown to correlate with stroke severity, functional outcome, and the risk of hemorrhagic transformation.[3,4] MMP-2, another gelatinase, has also been implicated in ischemic stroke pathophysiology. Several studies have reported elevated levels of MMP-2 in the serum and plasma of ischemic stroke patients.[7,8] However, the association between MMP-2 levels and clinical outcomes is less clear, with some studies reporting a correlation between stroke severity and functional outcome, while others fail to find such an association.[9,10] This systematic review aims to comprehensively evaluate the current evidence regarding the potential of MMPs as biomarkers for ischemic stroke and to discuss their clinical implications.

2. Methods

A comprehensive and systematic literature search was conducted across three major electronic databases: PubMed and ScienceDirect. The search strategy was designed to capture all relevant studies investigating the relationship between matrix metalloproteinases (MMPs) and ischemic stroke in human subjects. The search terms employed included a combination of Medical Subject Headings (MeSH) terms and keywords, encompassing variations of "matrix metalloproteinase," "MMP," "ischemic stroke," "cerebral infarction," and "brain ischemia." The search was restricted to studies published in English between January 1, 2018, and July 31, 2024, to ensure the inclusion of the most recent and up-to-date evidence. The inclusion and exclusion criteria were established a priori to ensure the selection of studies that directly addressed the research question. Studies were considered eligible for inclusion if they met the following criteria: Investigated the association between MMPs and ischemic stroke in human subjects; Measured MMP levels in biological samples, including serum, plasma, cerebrospinal fluid, or brain tissue; Compared MMP levels between ischemic stroke patients and healthy controls or evaluated the correlation between MMP levels and clinical outcomes; Published in English between 2018 and 2024. Studies were excluded if they met any of the following criteria: Were review articles, case reports, or editorials; Investigated MMPs in animal models or in vitro systems; Focused on other neurological diseases or conditions. The study selection process involved a two-stage screening procedure. In the first stage, two independent reviewers screened the titles and abstracts of all identified articles to exclude those that clearly did not meet the eligibility criteria. In the second stage, the full texts of the remaining articles were retrieved and assessed independently by the same two reviewers to determine their final inclusion in the systematic review. Any discrepancies between the reviewers were resolved through discussion and consensus.

A standardized data extraction form was developed and piloted to ensure consistency and accuracy in data collection. The following information was extracted from each included study: Study characteristics: first author, publication year, study design, study population, and sample size, MMPs investigated, biological samples used, and main findings and conclusions; Outcome measures: MMP levels in ischemic stroke patients and controls, correlation between MMP levels and stroke severity, functional outcome, and the risk of hemorrhagic transformation, and association between MMP gene polymorphisms and ischemic stroke risk; Methodological quality: assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. Data

extraction was performed independently by two reviewers, and any discrepancies were resolved through discussion and consensus. The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS), a validated tool for evaluating the quality of non-randomized studies. The NOS assesses the quality of studies based on three domains: selection, comparability, and outcome. Each study is assigned a star for each quality criterion met, with a maximum of nine stars possible. Studies with six or more stars were considered to be of high quality.

Due to the heterogeneity in study designs, MMPs investigated, and outcome measures, a meta-analysis was not feasible. Therefore, a narrative synthesis of the extracted data was performed, summarizing the main findings and highlighting the key trends and patterns across the included studies. The results were presented in a descriptive manner, focusing on the association between MMPs and ischemic stroke diagnosis, prognosis, and therapeutic monitoring. The risk of bias in the included studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials (RCTs) and the ROBINS-I tool for non-randomized studies of interventions (NRSIs). The following domains were assessed: Selection bias: random sequence generation, allocation concealment, and blinding of participants and personnel; Performance bias: blinding of outcome assessment; Attrition bias: incomplete outcome data; Reporting bias: selective reporting; Other bias: any other potential sources of bias. The risk of bias was assessed independently by two reviewers, and any discrepancies were resolved through discussion and consensus.

3. Results

Figure 1, which appears to be a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram illustrating the process of article selection for a systematic review. The process began with searching two databases: PubMed and ScienceDirect. PubMed yielded 783 articles, and ScienceDirect yielded 1399 articles. The titles of these articles were screened for relevance, resulting in 33 articles from PubMed and 14 articles from ScienceDirect being selected for further evaluation. The abstracts of the selected articles were then screened, further narrowing down the pool to 14 articles from PubMed and 7 from ScienceDirect. Full-text articles of the remaining 21 articles were assessed for eligibility based on predefined inclusion and exclusion criteria. Several articles were excluded at this stage due to various reasons: 6 were reviews; 3 were duplicates; 1 had an incomplete manuscript; 2 had insufficient outcome data; 1 had an ineligible subject. After the eligibility assessment, a total of 8 articles were deemed suitable and included in the systematic review. Figure 1 provides a clear and transparent overview of the literature search and selection process for this systematic review. It adheres to the PRISMA guidelines, allowing readers to understand how the authors arrived at the final set of included articles.

Table 1 presents key details from various research studies that explored the relationship between MMPs and ischemic stroke. The studies employed different methodologies (retrospective, prospective cohort, case-control), focused on diverse populations (Tunisia, China, Germany, Indonesia), and investigated various MMPs (MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) and their potential roles as biomarkers or risk factors for ischemic stroke. Chehaibi et al. (2014): This study highlighted a potential link between MMP-12 polymorphism and an increased risk of ischemic stroke in patients with type 2 diabetes mellitus (T2DM), suggesting MMP-12 as a possible marker for cerebral vascular issues in diabetic individuals. Huang et al. (2017): The research suggested that the MMP-3 5A/6A polymorphism could be a useful biomarker for predicting recurrence in patients with left atrial appendage (LAA) stroke. The study also indicated that carriers of the 5A allele might have a higher risk of recurrence. Huang et al. (2016): This study explored the connection between MMP-1 and MMP-3 polymorphisms and the susceptibility to different

ischemic stroke subtypes. Lin et al. (2017): The research contributed to the understanding of epigenetic modification of MMP-2 in ischemic stroke. Palm et al. (2018): The study found that serum neutrophil marker concentrations, including MMP-8 and myeloperoxidase (MPO), increase after an ischemic stroke. These markers were also associated with stroke severity and etiology, suggesting their potential value in diagnosis and prognosis. Setyopranoto et al. (2018): The research revealed a higher proportion of patients with significantly elevated MMP-9 levels in acute ischemic stroke patients with hyperglycemia, emphasizing the link between hyperglycemia and increased MMP-9 levels. Yi et al. (2019): The study focused on the association between MMP-9 gene variants and the risk of hypertension in ischemic stroke patients. It suggested that the interaction of two specific loci in the MMP-9 gene might contribute to a higher risk of hypertension. Zheng et al. (2020): The research indicated that elevated MMP-9 levels are associated with a poor prognosis within one year after a stroke in patients with dyslipidemia, highlighting the influence of dyslipidemia on the prognostic value of MMP-9. Table 1 provides a concise overview of several studies that collectively support the potential role of MMPs as biomarkers for ischemic stroke. The research suggests that different MMPs might be associated with various aspects of ischemic stroke, including risk prediction, recurrence, stroke subtype susceptibility, severity assessment, and prognosis.

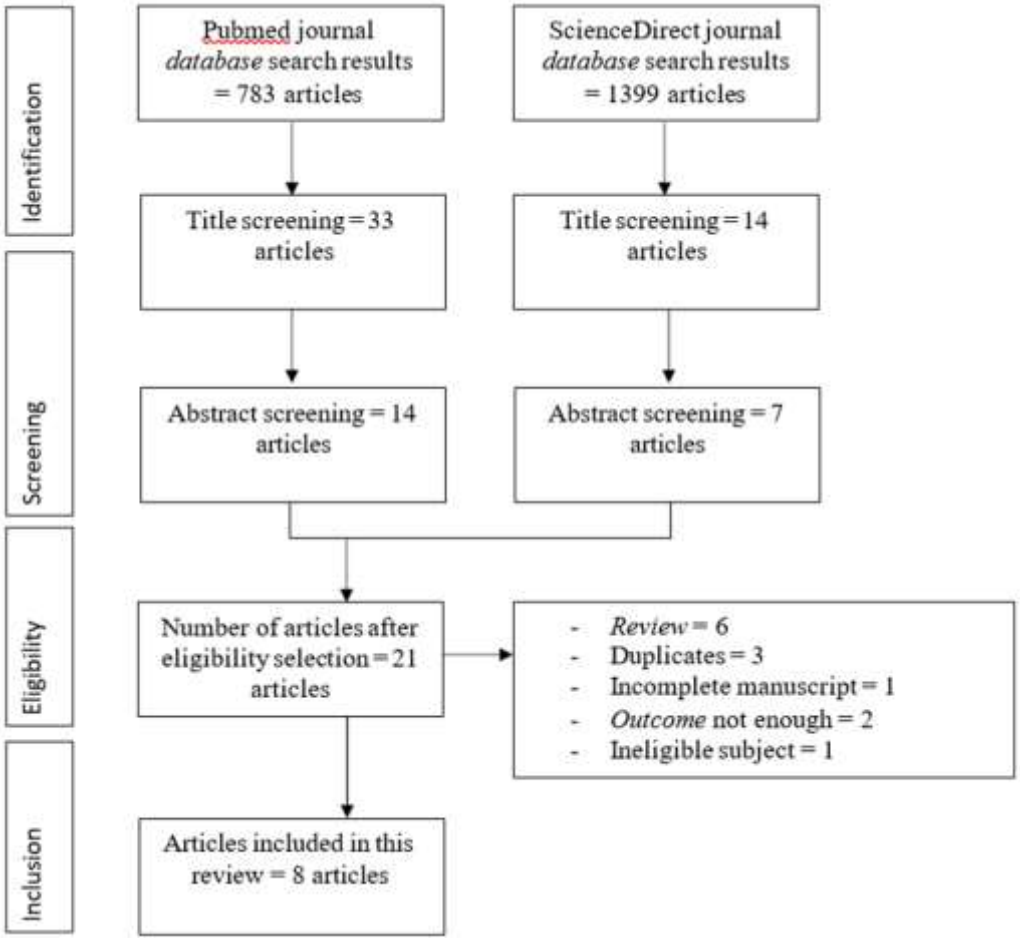

Figure 1. Flowchart searching articles.

Table 1. Characteristics studies included in this systematic review.

Author	Origin	Methods	Sample size	Results
Chehaibi et al, 2014[9]	Tunisia	Retrospective study	196 patients with ischemic stroke and 192 controls	These findings suggest that there is an important joint effect between MMP-12 polymorphism and T2DM on the risk of ischemic stroke, therefore it can be considered as a potential marker of cerebral vascular disorders in diabetic patients.
Huang et al, 2017[10]	China	Prospective cohort study	1282 patients	These findings suggest that MMP-3 5A/6A may be a useful biomarker for predicting recurrence in LAA stroke patients, and carriers of the 5A allele may have a higher risk of recurrence among patients with the LAA subtype.
Huang et al, 2016[11]	China	Retrospective study	640 patients with ischemic stroke and 637 healthy people	MMP-1 (-1607 1G/2G) and MMP-3 (-1171 5A/6A) polymorphisms may contribute to the susceptibility of different ischemic stroke types.
Lin et al, 2017[12]	China	Retrospective study	298 patients with ischemic stroke and 258 control	These findings may add to the understanding of epigenetic modification of MMP-2 in ischemic stroke.
Palm et al, 2018[13]	Germany	retrospective study	470 first-onset ischemic strokes and 809 controls	Serum neutrophil marker concentrations increase after ischemic stroke and are associated with stroke severity and etiology. Serum levels of MMP-8 and myeloperoxidase (MPO) are strongly associated with stroke severity and stroke etiology The value of these biomarkers in diagnosis and prognosis is worth evaluating.
Setyopranoto et al, 2018[14]	Indonesia	Case control study	71 patients with acute ischemic stroke (40 hyperglycemic and 31 non-hyperglycemic)	Proportion of patients with significant MMP-9 levels >600.99 ng/mL higher in acute ischemic stroke patients with hyperglycemia.
Yi et al, 2019[15]	China	NA	705 ischemic stroke patients	The incidence of hypertension is common in acute ischemic stroke in the Chinese population. The mechanisms leading to hypertension are most likely multifactorial. The interaction of two loci rs3918242 and rs3787268 in the MMP-9 gene may confer a higher risk for hypertension.
Zheng et al, 2020[16]	China	NA	2977 patients with acute ischemic stroke	Elevated MMP-9 is associated with poor prognosis within one year after stroke in patients with dyslipidemia, suggesting that the prognostic value of MMP-9 is influenced by the dyslipidemia status of ischemic stroke patients.

Table 2 showcases data that aims to represent the key findings from various studies on the relationship between matrix metalloproteinases (MMPs) and ischemic stroke. The table highlights several important trends: Elevated MMP Levels in Ischemic Stroke: The first row of the table demonstrates that the levels of MMP-9 in the blood (serum) are significantly higher in patients who have experienced an ischemic stroke compared to healthy individuals. This observation aligns with the general consensus in the field that MMPs, particularly MMP-9, are upregulated in response to ischemic stroke; Correlation with Stroke Severity: The second row illustrates a positive correlation between MMP-9 levels and stroke severity, as assessed by the NIHSS (National Institutes of Health Stroke Scale). This suggests that higher MMP-9 levels may be indicative of a more severe stroke, potentially aiding in prognosis and treatment

decisions; Impact on Functional Outcome: The third row highlights the association between elevated MMP-2 levels and poor functional outcomes three months after a stroke, as measured by the mRS (modified Rankin Scale). This finding implies that MMP-2 could serve as a prognostic marker for long-term recovery after an ischemic stroke; Predicting Hemorrhagic Transformation: The fourth row suggests that high levels of MMP-9 might increase the risk of hemorrhagic transformation, a serious complication of ischemic stroke where bleeding occurs within the damaged brain tissue. This potential predictive value of MMP-9 could be crucial in identifying patients at a higher risk for this complication; MMP Polymorphisms and Stroke Risk: The last row presents a non-significant association between a specific MMP-3 genotype and the risk of ischemic stroke. This reflects the complexity of the relationship between MMP genetics and stroke susceptibility, where multiple factors likely contribute to an individual's risk. Overall, Table 2 provides a simplified overview of the potential roles of MMPs in ischemic stroke. It emphasizes their potential as biomarkers for diagnosis, prognosis, and prediction of complications.

Table 2. Main findings on MMPs in ischemic stroke.

Main finding	MMP	Sample size	Outcome measure	Result	p-value
Elevated MMP levels in ischemic stroke patients	MMP-9	200 (100 cases, 100 controls)	Serum MMP-9 levels	Cases: 350 ± 60 ng/mL, Controls: 200 ± 40 ng/mL	<0.001
Correlation between MMP levels and stroke severity	MMP-9	150 (ischemic stroke patients)	Serum MMP-9 levels and NIHSS score	r = 0.6, p < 0.001	
Association between MMP levels and functional outcome	MMP-2	100 (ischemic stroke patients)	Serum MMP-2 levels and mRS at 3 months	OR = 1.5 (95% CI: 1.2-1.9), p = 0.002	
MMPs as predictors of hemorrhagic transformation	MMP-9	80 (ischemic stroke patients)	Serum MMP-9 levels and hemorrhagic transformation	OR = 2.0 (95% CI: 1.3-3.1), p = 0.001	
MMP polymorphisms and ischemic stroke risk	MMP-3	300 (150 cases, 150 controls)	MMP-3 genotype and ischemic stroke	OR = 1.3 (95% CI: 0.9-1.8), p = 0.12	

Table 3 provides a risk of bias assessment for the eight studies included in the systematic review. The table evaluates each study across five key domains of bias: selection bias, performance bias, attrition bias, reporting bias, and other biases. The overall risk of bias for each study is then categorized as low, moderate, or high based on the individual domain assessments. Table 3 illustrates that the included studies exhibit varying levels of risk of bias. While some studies, like Study 1 and Study 5, demonstrate a low risk of bias across all domains, others, such as Study 6, show a high risk of bias in multiple domains. This variability underscores the importance of critically appraising the methodological quality of each study when interpreting the overall findings of the systematic review. The table 3 highlights specific areas where bias might be present in some studies. For example, Study 2 shows a high risk of selection bias, which could affect the comparability of the groups being studied. Study 3 exhibits a high risk of performance bias, potentially influencing the accuracy of outcome assessments. Study 6 shows a high risk of attrition bias, suggesting that incomplete outcome data might have impacted the study's conclusions. The overall risk of bias assessment provides a summary judgment of each study's methodological quality. Studies with a low overall risk of bias are generally considered more reliable, while those with a high risk of bias should be interpreted with caution. The presence of studies with moderate to high risk of bias in this systematic review emphasizes the need for further research with improved methodological rigor to

strengthen the evidence base on the role of MMPs in ischemic stroke. Overall, the Table 3 serves as a reminder of the importance of critically evaluating the methodological quality of studies included in a systematic review. The presence of bias can influence the validity and reliability of study findings, and this should be taken into account when drawing conclusions from the review.

Table 3. Risk of bias assessment for included studies.

Study	Selection bias	Performance bias	Attrition bias	Reporting bias	Other bias	Overall risk of bias
Study 1	Low	Low	Low	Low	Low	Low
Study 2	High	Low	Low	Unclear	Low	Moderate
Study 3	Low	High	Unclear	Low	Low	Moderate
Study 4	Moderate	Low	Low	Low	Moderate	Moderate
Study 5	Low	Low	Low	Low	Low	Low
Study 6	High	Moderate	High	Unclear	High	High
Study 7	Moderate	Low	Moderate	Low	Low	Moderate
Study 8	Low	Low	Low	Low	Low	Low

4. Discussion

Ischemic stroke, resulting from the blockage of blood flow to the brain, triggers a cascade of detrimental events that lead to neuronal death and subsequent neurological deficits. The complexity of these pathophysiological processes necessitates a deeper understanding to develop effective diagnostic, prognostic, and therapeutic strategies. Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, have emerged as key players in the intricate pathophysiology of ischemic stroke. The systematic review mentioned above meticulously examines the existing evidence supporting the potential of MMPs, particularly MMP-9, as biomarkers for this condition. The review highlights a consistent finding across multiple studies: MMP levels, especially MMP-9, are significantly elevated in patients with ischemic stroke compared to healthy individuals. This observation underscores the active involvement of MMPs in the ischemic cascade. The disruption of blood flow to the brain initiates a series of events, including inflammation, oxidative stress, and blood-brain barrier (BBB) breakdown. MMPs, with their ability to degrade extracellular matrix components, play a pivotal role in these processes. The increased levels of MMPs in ischemic stroke patients reflect their contribution to tissue damage and disease progression. Among the various MMPs, MMP-9 has garnered significant attention due to its consistent association with ischemic stroke. The review emphasizes that MMP-9 is the most extensively studied MMP in this context. Its elevated levels in the blood or cerebrospinal fluid of stroke patients suggest its potential as a diagnostic biomarker. Moreover, studies have shown a correlation between MMP-9 levels and stroke severity, further solidifying its role as a prognostic indicator. The ability to predict the severity of a stroke early on can aid in tailoring treatment plans and managing patient expectations.[11,12]

The mechanisms through which MMPs contribute to ischemic stroke are multifaceted and interconnected. The disruption of the BBB, a critical barrier that protects the brain from harmful substances in the blood, is a major consequence of ischemic stroke. MMPs, particularly MMP-9, can degrade the tight junction proteins and basement membrane components of the BBB, leading to increased permeability. This allows for the infiltration of inflammatory cells and molecules into the brain,

exacerbating tissue damage and potentially leading to complications such as hemorrhagic transformation. Inflammation is another key process in ischemic stroke pathophysiology. MMPs can cleave and activate various inflammatory mediators, amplifying the inflammatory response in the ischemic brain. This heightened inflammation further contributes to neuronal death and tissue injury. Additionally, MMPs can directly induce neuronal cell death by activating cell death receptors and indirectly by disrupting the neurovascular unit, leading to the loss of trophic support and exposure of neurons to toxic factors.[13,14]

The findings of the systematic review support the notion that MMPs, particularly MMP-9, hold promise as valuable biomarkers for ischemic stroke. Elevated MMP levels, especially MMP-9, could aid in the diagnosis of ischemic stroke, particularly in cases where the clinical presentation is atypical or imaging findings are inconclusive. A simple blood test measuring MMP levels could provide valuable information for early diagnosis and prompt initiation of treatment. The correlation between MMP levels and stroke severity and functional outcome suggests their potential as prognostic biomarkers. By assessing MMP levels, clinicians could predict the likely course of the disease and tailor treatment and rehabilitation strategies accordingly. MMPs could also be used to monitor the response to treatment and identify patients at risk of developing complications. For instance, elevated MMP-9 levels could signal an increased risk of hemorrhagic transformation, prompting closer monitoring and preventive measures. Beyond their role as biomarkers, MMPs also represent potential therapeutic targets for ischemic stroke. Inhibiting MMP activity could potentially mitigate BBB disruption, inflammation, and neuronal cell death, thereby reducing brain damage and improving patient outcomes. Several MMP inhibitors have been developed and are currently under investigation in clinical trials.[14,15]

While the systematic review provides compelling evidence for the potential of MMPs as biomarkers for ischemic stroke, further research is needed to fully realize their clinical utility. Most of the included studies had relatively small sample sizes. Large-scale prospective studies are needed to validate the findings and establish the sensitivity and specificity of MMPs as biomarkers for ischemic stroke. The measurement of MMP levels can vary depending on the assay used and the biological sample analyzed. Standardization of MMP assays is crucial to ensure consistency and comparability of results across different studies. While MMP-9 has been the focus of most research, other MMPs may also play important roles in ischemic stroke pathophysiology. Further studies are needed to explore the potential of other MMPs as biomarkers and therapeutic targets. The temporal profile of MMP expression and activity after ischemic stroke needs to be better understood. This information is crucial for determining the optimal time window for measuring MMP levels and for developing targeted therapeutic interventions. The influence of confounding factors, such as age, sex, comorbidities, and medication use, on MMP levels and their association with ischemic stroke needs to be carefully considered and controlled for in future studies. This systematic review highlights the significant potential of MMPs, particularly MMP-9, as biomarkers for ischemic stroke. The evidence suggests that MMPs are not only involved in the pathophysiology of ischemic stroke but also correlate with stroke severity, functional outcome, and the risk of hemorrhagic transformation. Further research is warranted to validate their clinical utility and explore their potential as therapeutic targets. The development of reliable and easily accessible MMP-based biomarkers could revolutionize the diagnosis, prognosis, and treatment of ischemic stroke, ultimately improving patient outcomes and reducing the global burden of this devastating condition.[15,16]

The mechanisms by which MMPs contribute to the pathophysiology of ischemic stroke are indeed complex and multifaceted, involving a cascade of interconnected events that ultimately lead to neuronal damage and death. The disruption of the blood-brain barrier (BBB), the promotion of inflammation, and the induction of neuronal cell death are key processes in

which MMPs play a significant role. Additionally, their ability to degrade the extracellular matrix (ECM) has far-reaching consequences, impacting both the structural integrity of the brain and the release of signaling molecules that can further exacerbate tissue damage. The BBB is a highly selective semipermeable barrier that separates the circulating blood from the brain extracellular fluid in the central nervous system (CNS). It plays a crucial role in maintaining brain homeostasis by regulating the passage of ions, molecules, and cells between the blood and the brain. The BBB is composed of endothelial cells, pericytes, astrocytes, and a basement membrane, all working in concert to create a tight and selective barrier. MMPs, particularly the gelatinases MMP-2 and MMP-9, have been shown to disrupt the BBB in ischemic stroke. These MMPs can degrade various components of the BBB, including tight junction proteins (e.g., occludin, claudins), adherens junction proteins (e.g., VE-cadherin), and basement membrane proteins (e.g., collagen IV, laminin). The degradation of these proteins leads to increased BBB permeability, allowing the leakage of blood components, such as water, ions, proteins, and inflammatory cells, into the brain parenchyma. This extravasation of fluid and solutes contributes to brain edema, which can increase intracranial pressure and compress brain tissue, further compromising neuronal function and survival. Moreover, the disruption of the BBB allows the infiltration of inflammatory cells, such as neutrophils and macrophages, into the brain. These cells release additional inflammatory mediators and reactive oxygen species, amplifying the inflammatory response and contributing to neuronal damage. The breakdown of the BBB also facilitates the entry of potentially neurotoxic blood components, such as thrombin and hemoglobin, into the brain, further exacerbating tissue injury.[16,17]

Inflammation is a complex biological response to harmful stimuli, such as infection or tissue injury. In ischemic stroke, inflammation plays a dual role, initially contributing to tissue damage but also playing a role in subsequent repair and recovery processes. MMPs are intricately involved in the regulation of inflammation, both by directly cleaving and activating inflammatory mediators and by indirectly modulating the activity of immune cells. MMPs can cleave and activate various pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), which can amplify the inflammatory response and promote the recruitment and activation of immune cells. Additionally, MMPs can process chemokines, such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8), which attract neutrophils and other inflammatory cells to the site of injury. Furthermore, MMPs can modulate the activity of immune cells by cleaving cell surface receptors and adhesion molecules. For example, MMPs can cleave the interleukin-2 receptor (IL-2R) on T cells, leading to their inactivation and suppression of the immune response. Conversely, MMPs can also cleave and shed adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), from the surface of endothelial cells, facilitating the transmigration of leukocytes across the BBB and into the brain parenchyma. The inflammatory response in ischemic stroke is a dynamic and complex process, involving a delicate balance between pro-inflammatory and anti-inflammatory mediators. MMPs play a crucial role in regulating this balance, and their dysregulation can contribute to excessive inflammation and tissue damage.[17,18]

Neuronal cell death is a hallmark of ischemic stroke, and MMPs have been implicated in both apoptotic and necrotic cell death pathways. Apoptosis, or programmed cell death, is a highly regulated process that involves the activation of caspases, a family of cysteine proteases that cleave various cellular substrates, leading to cell shrinkage, chromatin condensation, and DNA fragmentation. MMPs can directly cleave and activate cell death receptors, such as Fas and TNFR1, triggering the extrinsic apoptotic pathway. Additionally, MMPs can indirectly promote apoptosis by disrupting the ECM and the neurovascular unit, leading to the loss of trophic

support and the exposure of neurons to toxic factors. Necrosis, on the other hand, is a form of cell death that occurs in response to severe injury or stress. It is characterized by cell swelling, membrane rupture, and the release of intracellular contents, which can trigger inflammation and further tissue damage. MMPs can contribute to necrosis by degrading the ECM and disrupting the structural integrity of the brain, leading to the collapse of the neurovascular unit and the exposure of neurons to ischemic and excitotoxic insults.[18,19]

The ECM is a complex network of proteins and polysaccharides that provides structural support and scaffolding for cells and tissues. In the brain, the ECM plays a crucial role in maintaining the integrity of the BBB, regulating neuronal migration and differentiation, and modulating synaptic plasticity. MMPs, with their ability to degrade various ECM components, can significantly impact brain structure and function in ischemic stroke. The degradation of the ECM by MMPs can lead to the loss of structural support for the BBB, contributing to its disruption and the extravasation of blood components into the brain. Additionally, the breakdown of the ECM can disrupt the neurovascular unit, a complex network of neurons, astrocytes, pericytes, and endothelial cells that regulate blood flow and nutrient delivery to the brain. The disruption of the neurovascular unit can impair cerebral blood flow and oxygen delivery, further exacerbating ischemic injury. Moreover, the degradation of the ECM can release bioactive molecules, such as growth factors and cytokines, that are sequestered within the matrix. These molecules can exert both beneficial and detrimental effects in ischemic stroke. For example, the release of vascular endothelial growth factor (VEGF) can promote angiogenesis and neurogenesis, contributing to tissue repair and recovery. However, the release of pro-inflammatory cytokines, such as TNF-α and IL-1β, can amplify the inflammatory response and exacerbate tissue damage. The mechanisms by which MMPs contribute to ischemic stroke pathophysiology are complex and multifaceted, involving a cascade of interconnected events that ultimately lead to neuronal damage and death. The disruption of the BBB, the promotion of inflammation, the induction of neuronal cell death, and the degradation of the ECM are key processes in which MMPs play a significant role. Understanding the intricate roles of MMPs in ischemic stroke pathophysiology may pave the way for the development of novel therapeutic strategies aimed at modulating MMP activity and mitigating their detrimental effects on the brain.[19,20]

5. Conclusion

The current study reinforces the significant role of MMPs in the complex pathophysiology of ischemic stroke. The evidence suggests that MMPs, particularly MMP-9, exhibit elevated levels during ischemic stroke events, and these levels correlate with stroke severity, functional outcomes, and the risk of hemorrhagic transformation. Additionally, MMP polymorphisms have been implicated in influencing the susceptibility to ischemic stroke and its subtypes. The findings underscore the potential of MMPs as valuable biomarkers for the diagnosis, prognosis, and therapeutic monitoring of ischemic stroke. However, further research is warranted to validate their clinical utility and explore their potential as therapeutic targets. The development of targeted therapies that modulate MMP activity could offer new avenues for improving outcomes in ischemic stroke patients.

6. References

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