SCOPING REVIEW

Investigating the Prospect of C-Type Lectin-like Receptors-2 for Predicting Prognosis of Ischemic Stroke: Rapid Review of Molecular Mechanisms to Clinical Study

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ABSTRACT

Background: Every year, over 13.7 million individuals experience strokes, resulting in approximately 5.8 million deaths. C-type lectin-like receptor 2 (CLEC-2) plays a significant role in platelet activation, which is elevated in ischemic stroke and is associated with disease progression and prognosis. **Objective:** To review the literature on the potential of CLEC-2 as a biomarker for assessing the prognosis and progression of ischemic stroke. **Material and Method:** This rapid review followed the Cochrane interim guidelines and adhered to PRISMA standards. A comprehensive search was conducted in PubMed, Cochrane Library, and Google Scholar to identify original research articles published in English over the past 10 years. Studies at various stages—including in vitro, in vivo, and clinical trials—were included if they evaluated the association between CLEC-2 and acute ischemic stroke. Risk of bias was assessed using the QUIPS tool for clinical studies and SYRCLE's tool for animal studies. Study selection and data extraction were performed independently by three reviewers. **Result:** The search identified five relevant articles: two experimental studies and three clinical prognostic studies examining CLEC-2 in the context of ischemic stroke. CLEC-2, a receptor for podoplanin expressed in various tumors and lymphatic endothelial cells, induces a calcium surge independent of secondary platelet activation. In vivo studies have demonstrated increased levels of CLEC-2 and podoplanin, which are highly expressed on neurons and microglia in ischemic brain regions. The three clinical studies showed that plasma CLEC-2 levels have prognostic value in predicting recurrent vascular events and mortality in patients with acute ischemic stroke. **Conclusion:** Plasma CLEC-2 shows potential as a biomarker for evaluating the progression and prognosis of acute ischemic stroke.

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Highlights

1. The potential of CLEC-2 as a prognostic biomarker for ischemic stroke is supported by in vivo and clinical studies demonstrating its role in thrombo-inflammatory mechanisms and clinical outcome prediction.
2. Analysis of clinical studies indicates that elevated plasma CLEC-2 levels are associated with an increased risk of recurrent vascular events and mortality in acute ischemic stroke, suggesting its promise as a noninvasive tool for stroke prognosis assessment.

BACKGROUND

Stroke is a neurovascular condition that disrupts the brain's blood supply, leading to the death of brain cells. In 2012, the World Health Organization (WHO) reported that 6.7 million individuals died from stroke. Indonesia also experienced a comparable situation (World Health Organization, 2014). According to the 2013 Indonesia National Basic Health Research, stroke accounted for 12.1% of all noncommunicable diseases in the country (Indonesia Basic Health Research Team, 2013). Additionally, the 2014 Indonesian Sample Registration System (SRS) identified stroke as the leading cause of death, responsible for 21.1% of all fatalities across age groups (Ministry of Health of The Republic of Indonesia, 2017). Ischemic stroke is the most prevalent type, comprising approximately 87% of all stroke cases globally (Saini, et al., 2021). It occurs when a blood clot obstructs cerebral circulation, depriving the brain of oxygen and essential nutrients (Sierra, et al., 2011).

Currently, the evaluation of acute ischemic stroke progression and prognosis primarily depends on patient age and stroke severity. Stroke severity is typically assessed by neuroimaging techniques such as MRI and CT scans, which evaluate the size and location of the infarct, along with the degree of neurological impairment affecting cognitive function, language, behavior, vision, and motor skills (Kuriakose & Xiao, 2020). However, the pathophysiological mechanisms underlying ischemic stroke are still not fully understood (Zhang, et al., 2019). Recent evidence indicates that platelets play a critical role in the development of ischemic stroke, likely by initiating a complex thrombo-inflammatory response (De Meyer, et al., 2016).

C-type lectin-like receptor 2 (CLEC-2) is a type II transmembrane protein structurally related to other C-type lectin-like receptors (CLECs) found on natural killer (NK) cells, and is predominantly expressed by dendritic cells and platelets. In dendritic cells, CLEC-2 facilitates the migration of activated cells and reduces the contractility of fibroblastic reticular cells within lymph nodes. In the vasculature, CLEC-2 interacts with the tyrosine kinases Src and Syk, ultimately triggering platelet aggregation (Fu & Xia, 2016). CLECs, which are highly expressed on platelets, play a major role in platelet aggregation, lymphatic vessel formation, and in pathological processes such as tumor metastasis (Chatterjee, et al., 2020). Notably, (Roever, et al., 2019) suggested that changes in plasma CLEC-2 levels could serve as indicators for disease progression and prognosis in acute ischemic stroke (Roever, et al., 2019). While these insights are promising and open new avenues for exploration, no comprehensive analysis has yet been conducted on the specific role of CLEC-2 in ischemic stroke.

OBJECTIVE

This study aimed to explore the role of CLEC-2 in the process of thrombosis and the progression of ischemic stroke. The analysis encompassed multiple levels of investigation, including biomolecular mechanisms, in vivo experiments in animal models, and clinical studies involving patients with ischemic stroke, with a focus on the association between CLEC-2 and clinical outcomes.

MATERIAL AND METHOD

This review was conducted in accordance with the Cochrane interim guidelines for rapid reviews (Garritty, et al., 2021).

Eligibility Criteria

The primary objective of the literature search was to identify publications addressing the role of CLEC-2 in thrombosis associated with ischemic stroke. To ensure comprehensive coverage, inclusion criteria were defined to encompass original research articles investigating acute ischemic stroke in relation to CLEC-2. Studies at all research stages, including in vitro, in vivo, and clinical trials were eligible for inclusion. Studies that focused solely on CLEC-2 in blood coagulation or as a prognostic factor in diseases other than ischemic stroke were excluded. Additionally, review articles and other study types deemed unsuitable for systematic analysis were excluded. Only full-text articles published in English were included, with no restrictions on publication year, given that CLEC-2 has been a subject of interest primarily within the past decade.

Literature Search and Study Selection

A systematic literature search was performed using PubMed and the Cochrane Library databases to identify studies related to CLEC-2 and ischemic stroke (acute or transient). These databases were screened independently according to the defined eligibility criteria, and duplicate records were removed. To capture relevant gray literature not indexed in the primary databases, an additional search was conducted using Google Scholar.

Three independent reviewers assessed the eligibility of each study without knowledge of the others' evaluations. Any disagreements were resolved through discussion and consensus. The search strategy followed the PICO (Patients, Intervention, Comparison, Outcomes) framework. A rapid literature search, as described by Smela, et al., (2023), was conducted independently by two authors (RF and MID) between October and December 2023. Articles published in the last 10 years and written in English were included.

The study selection process followed PRISMA guidelines Page, et al., (2021) and is illustrated in Figure 1. For clinical prognostic studies, the risk of bias was assessed using the QUIPS tool (Hayden, et al., 2013), while animal studies were assessed using SYRCLE's risk of bias tool (Hooijmans, et al., 2014).

RESULT

A total of five articles were identified that discussed the role of CLEC-2 in the context of ischemic stroke. Two of these were experimental trials (Cherpokova, et al., 2015; Meng, et al., 2021), while the remaining three were clinical prognostic studies (Nishigaki, et al., 2021; Wu, et al., 2019; Zhang, et al., 2019). To the best of our knowledge, there is currently no established cutoff value for plasma CLEC-2 (p-CLEC-2) levels. Consequently, the study by Nishigaki, et al., (2021) was included in our analysis. The characteristics of all included clinical studies are summarized in Table 1.

Table 1. Characteristics of the included prognostic studies.

Study	Design	No Subject	Subjects Characteristics	Duration of Study	pCLEC-2 cutoff	Sensitivity & Specificity
Wu, et al., (2019) doi: 10.1111/ene.13984	Prospective Cohort Study	352	First-Ever Acute Ischemic Stroke confirmed by CT-Scan/MRI	12 months	184,38 pg/mL	54.3% & 64.3%
Zhang, et al., (2019) doi: 10.1161/STROKEAHA.118.022563	Prospective Cohort Study	352	First-Ever Acute Ischemic Stroke onset within 7 days confirmed by CT-Scan/MRI	8 months	207.08 pg/mL	48.5% & 71.7%
Nishigaki, et al., (2021) doi: 10.3390/jcm10153408	Cross-sectional Study	77	Acute cerebral infarction	8 months	Not mentioned explicitly (Median 256 pg/mL, lowest level 182 pg/mL, highest level 340 pg/mL)	Not mentioned.

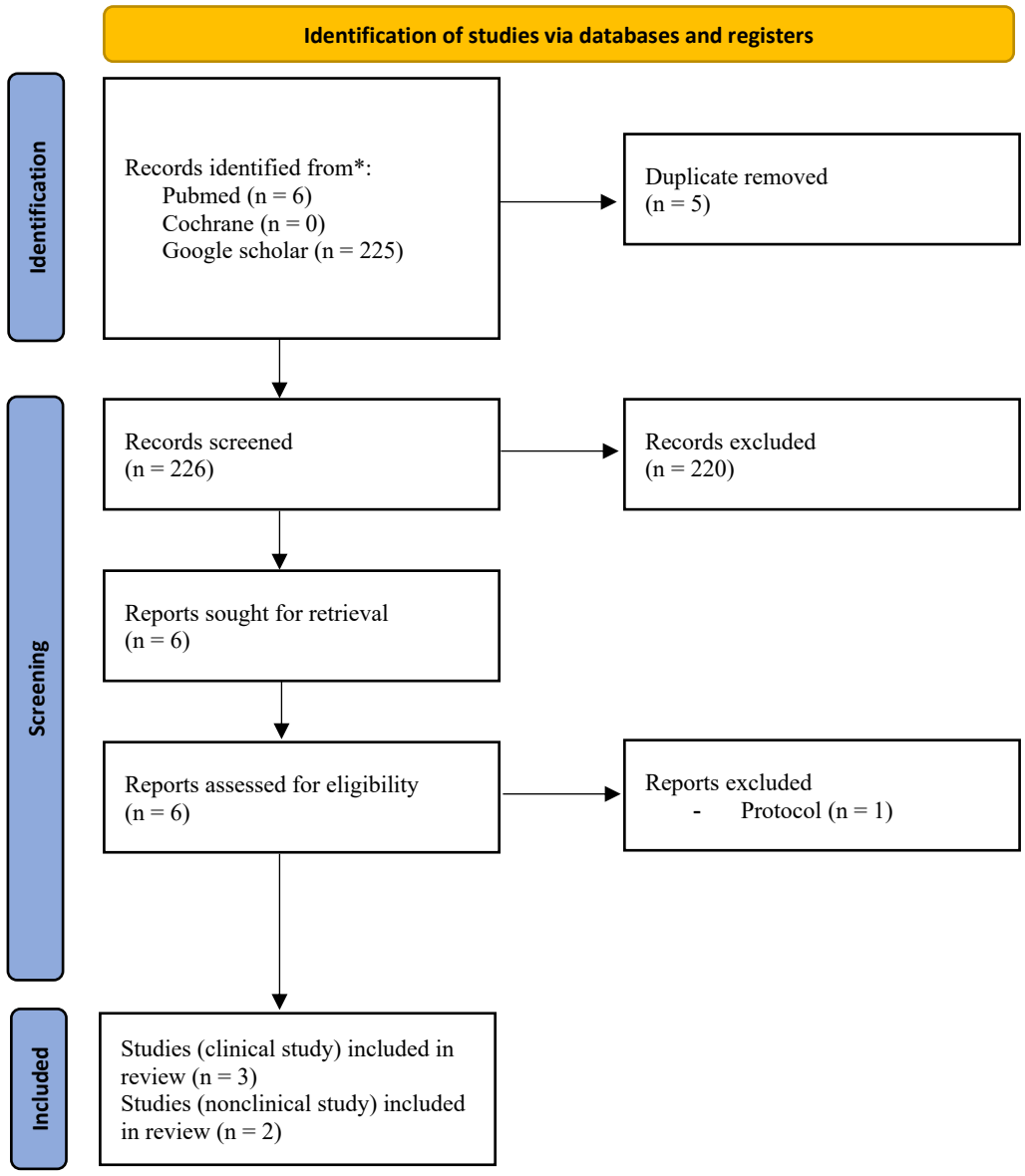

Figure 1. ScR PRISMA flowchart (Page, et al., 2021).

DISCUSSION

Ischemic strokes can be classified as either embolic or thrombotic. In embolic strokes, blood clots that originate in other organs, most commonly the heart, can travel to the brain. These clots obstruct cerebral blood vessels, cutting off blood flow and causing ischemic injury (Kuriakose & Xiao, 2020; Sierra, et al., 2011). Evidence indicates that platelets play a crucial role in the development of ischemic stroke by mediating a complex thrombo-inflammatory process. During this process, platelets interact with the contact activation system, which may ultimately result in neurological injury and disruption of the blood brain barrier. Although the precise mechanisms by which platelets contribute to infarct formation remain unclear, glycoprotein VI (GPVI) a platelet-activating receptor that signals through an immunoreceptor tyrosine-based activation motif (ITAM)-dependent pathway appears to be essential in infarct development (Chatterjee, et al., 2020).

Biomolecular mechanism

CLEC-2 (C-type lectin-like receptor 2), a receptor for podoplanin, is expressed by lymphatic endothelial cells and various tumor types. In humans, CLEC-2 is predominantly expressed in platelets and megakaryocytes, with minimal expression in Kupffer cells (Meng, et al., 2021). The thrombo-inflammatory mechanisms triggered by stroke are still not fully understood. However, the specific role of the podoplanin/CLEC-2 signaling pathway in neuroinflammation has been demonstrated in multiple sclerosis patients, who show podoplanin overexpression (Suzuki-Inoue, et al., 2018).

Uncontrolled inflammation following brain injury can lead to secondary damage and neuronal apoptosis (McKee & Lukens, 2016). Mechanistically, podoplanin promotes neuronal re-entry into the cell cycle by altering cyclin D1 and cyclin-dependent kinase 4 (CDK4) expression, ultimately triggering neuroinflammation and cell death. CLEC-2 expression on platelets is regulated by Src-like adaptor proteins (SLAP and SLAP2), which are downregulated following cerebral ischemia, contributing to worsened neurological outcomes after focal brain injury (Martyanov, et al., 2020; Meng, et al., 2021).

Martyanov, et al., (2020) also showed that CLEC-2 clustering upon ligand binding is essential for its platelet-activating function. CLEC-2 ligands can induce cytosolic calcium elevation independent of secondary platelet activation. Alongside tyrosine kinase activity, Syk kinase plays a key role in CLEC-2 signaling. Furthermore, CLEC-2 clustering and the formation of a linker for activation of T cells (LAT) signaling hub are pivotal limiting factors for downstream signaling (Fu & Xia, 2016; Martyanov, et al., 2020).

In Vivo Study

Animal models of ischemic stroke demonstrated increased levels of CLEC-2 and podoplanin in ischemia/reperfusion brain regions, with expression localized to neurons and microglia. (Meng, et al., 2021) reported that antipodoplanin treatment significantly reduced infarct volume and levels of CLEC-2/podoplanin, thereby improving neurological outcomes post-stroke. Their findings also showed that mice deficient in SLAP and SLAP2 negative regulators of platelet activation exhibited enhanced CLEC-2-mediated signaling, platelet hyperactivity, and exacerbated thrombo-inflammatory injury (Cherpokova, et al., 2015). Additionally, CLEC-2-deficient mice were found to have prolonged bleeding times under non-stroke conditions (Bender, et al., 2013).

Clinical Study

Clinical evidence supports the prognostic value of plasma CLEC-2 (pCLEC-2) in predicting vascular event recurrence and mortality in patients with acute ischemic stroke. CLEC-2 has been detected in atherosclerotic lesions, particularly in advanced stages, emphasizing its contribution to disease progression (Hatakeyama, et al., 2012; Inoue, et al., 2015; Wu, et al., 2019). Wu, et al., (2019) demonstrated that elevated pCLEC-2 levels at hospital admission were associated with increased risks of death and recurrent vascular events.

Zhang, et al., (2019) further reported that higher pCLEC-2 levels were associated with aggravated stroke progression and poorer 90-day prognosis. Nishigaki, et al., (2021) observed that patients with acute cerebral infarction (ACI) especially those with atherosclerotic or lacunar subtypes had significantly elevated soluble CLEC-2 (sCLEC-2) levels. The sCLEC-2/D-dimer ratio showed diagnostic utility in distinguishing between atherosclerotic/lacunar ACI and cardioembolic ACI, as well as between venous thrombosis (e.g., cardioembolic ACI, venous thromboembolism) and atherosclerotic thrombosis (e.g., lacunar ACI, atherosclerotic ACI, acute myocardial infarction). Notably, this ratio may also serve as a useful biomarker in patients with COVID-19 (Wada, et al., 2022).

Future prospects of CLEC-2

CLEC-2 has been identified as a potential biomarker in several thrombotic disorders, including acute coronary syndrome (Inoue, et al., 2019), venous thromboembolism (Ando, et al., 2023), and disseminated intravascular coagulation (Ishikura, et al., 2022). This review has highlighted the potential of CLEC-2 in predicting the development and prognosis of ischemic stroke. Building on this evidence, Uchiyama, et al., (2023) have introduced the CLECSTRO study a multicenter, ongoing cohort study designed to evaluate the role of CLEC-2 in predicting clinical outcomes and disease severity in patients with ischemic stroke and transient ischemic attack (TIA) (Uchiyama, et al., 2023). The findings from

this prospective study are expected to provide further insights into the clinical utility of CLEC-2 and expand our understanding of its role in cerebrovascular disorders.

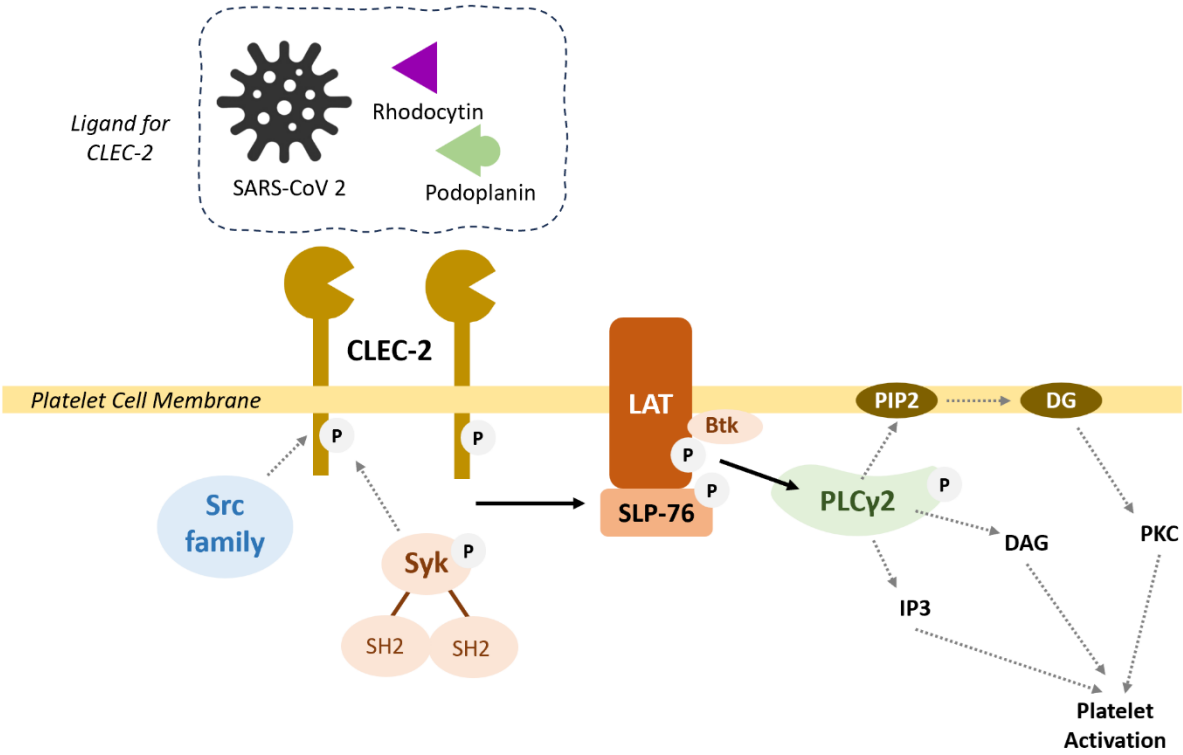

Figure 2. Mechanism of CLEC-2 in platelet aggregation and its role in ischemic stroke (Meng, et al., 2021; Sung, et al., 2023; Suzuki-Inoue, 2019; Yeung, et al., 2018).
Legends: Btk: Bruton's tyrosine kinase; CLEC-2: C-type lectin-like receptor 2; DG: diacyl-glycerol; IP3: inositol 1 4 5-trisphosphate; LAT: linker for the activation of T cells; PIP2: phosphatidylinositol 4,5-bisphosphate; PLCγ2: phospholipase Cγ2; Syk: spleen tyrosine kinase; SLP-76: SH2 domain-containing leukocyte phosphoprotein of 76 kDa. Rhodocytin and SARS-CoV-2 acts as an external ligand for CLEC-2.

Strength and limitations

This review was conducted in accordance with Cochrane's interim guidelines for rapid reviews, ensuring a systematic and comprehensive selection of current literature on CLEC-2 in ischemic stroke. A key strength of this review is the inclusion of both clinical and in vivo studies, allowing for a broader analysis from molecular mechanisms to potential clinical applications. However, the review is limited by the relatively small number of eligible studies, differences in study designs, and the lack of standardized cutoff values for CLEC-2 across studies. These factors may affect the comparability and generalizability of the findings. Future large-scale, multicenter clinical trials are warranted to validate the prognostic utility of CLEC-2 and determine its feasibility for routine use in clinical practice.

CONCLUSION

Plasma CLEC-2 level is a promising novel biomarker for the prognostic assessment of acute ischemic stroke, complementing traditional factors such as patient age and stroke severity. When combined with radiologic imaging, plasma CLEC-2 measurement may enhance the accuracy of predicting clinical outcomes. However, before CLEC-2 can be integrated into routine clinical practice, further prognostic studies with larger, well-defined patient cohorts are needed. Additionally, cost-effectiveness analyses should be conducted, particularly in settings like Indonesia where national health coverage is implemented, to ensure the feasibility of its widespread use.

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Conflict of Interest
All the authors have no conflicts of interest.

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None.

Author Contribution
RF and MID were equally involved from conception of study design, data analysis to writing and revision of the manuscript. MZB contributed to the process of data analysis and interpretation, as well as writing and revision of the manuscript until final. NGK played a role in providing input related to study design, supervision of data results and final approval of the manuscript.

Data Availability
None.

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