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Review

Potential Biomarker to Diagnose Delayed Cerebral Ischemia among Subarachnoid Hemorrhage Patients: A Systematic Review and Diagnostic Meta-Analysis

Arya Marganda Simanjuntak[1*], Nabil Athoillah[2], Jeremia Aris Panjaitan[3], Meita Natasya[4], Felicita Gracia[5], Gatot Aji P.[6], Andrea Valentino[6], Daril Al Rasyid[7]

[1] Faculty of Medicine, Universitas Riau, Arifin Achmad General Hospital, Riau, Indonesia
[2] Faculty of Medicine, Universitas Jember, Jember, Indonesia
[3] Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[4] Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[5] Faculty of Medicine, Universitas Bangka Belitung, Bangka, Indonesia
[6] Department of Neurosurgery, Faculty of Medicine, Universitas Riau, Arifin Achmad General Hospital, Riau,Indonesia
[7] Department of Neurology, Faculty of Medicine, Universitas Riau, Arifin Achmad General Hospital, Riau, Indonesia

*Corresponding author: arya.marganda@gmail.com

Abstract

Determining the diagnosis of Delayed Cerebral Ischemia (DCI) in Subarachnoid Hemorrhage (SAH) patients is currently clinically and radiologically dependent, but it indicates brain ischemia has already occurred and has a poor prognosis. A good biomarker is needed to determine the diagnosis of DCI for faster and more accurate enforcement. A meta-analysis of proportional diagnostic accuracy with PRISMA guidance was conducted. Various databases (PubMed, ScienceDirect, etc) were utilized with the keywords “Delayed Cerebral Ischemia” AND “Biomarker”. We utilized PIROS framework such as Subarachnoid Hemorrhage (Patients), Laboratory Biomarker (Index), DCI Guideline Diagnosis (Reference), Confirmed Delayed Cerebral Ischaemia (Outcome), and Observational OR Validation design (Study). Statistical analysis was run with R Studio (R.4.4.3) [library (mada) and library (meta)] followed by risk of bias assessment using QUADAS 2 independently by each author. A total of 23 out of 203 articles were included. In general, the lab biomarkers had a sensitivity of 75% (95%CI: 69% - 80%) with a specificity of 72% (95%CI: 67% - 76%) and a Diagnostic Odds Ratio of 7.8 (95%CI: 5.7 - 10). Of all the biomarkers included, CSF LDH (Sensitivity 100%, Specificity 76.9%) and CSF Lactate (Sensitivity 83.3%, Specificity 88.9%) had good diagnostic value among others. SROC plot indicates moderate overall diagnostic accuracy, with an average sensitivity and specificity around 73-75%. However, substantial heterogeneity (shown by scattered points and a large predictive region) means individual biomarker performance varies considerably, and new study results may differ significantly from this average. QUADAS-2 analysis showed 95% of the included articles had a low risk of bias. CSF LDH and CSF Lactate show promise as diagnostic biomarkers for early detection of delayed cerebral ischemia (DCI) in subarachnoid hemorrhage (SAH), potentially preventing further brain damage. Laboratory biomarkers are valuable for early DCI detection.

Keywords: Biomarker, Delayed Cerebral Ischaemia, Diagnostic Accuracy, Subarachnoid Hemorrhage

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Corresponding author
Arya Marganda Simanjuntak
arya.marganda@gmail.com

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Data Availability Statement
All relevant data are within the paper and its Supporting Information files.

Introduction

Subarachnoid hemorrhage (SAH) is a life-threatening neurological condition with high mortality and morbidity, occurring ten times more frequently in Asia than in Europe.[1] A major complication is delayed cerebral ischemia (DCI), defined as a neurological impairment unexplained by other causes. The pathophysiology of DCI remains unclear but it is thought to be multifactorial, involving vasospasm, microcirculatory dysfunction, microthrombosis, cortical spreading ischemia, inflammation and impaired regulation. Diagnosis relies on neuroimaging and neurological examinations, which can delay interventions. This delay can worsen the overall prognosis of DCI.[2-4]

Biomarkers are measurable molecules in body fluids to indicate disease. Ideal biomarkers are non-invasive, easily detectable and highly sensitive and specific.[5] Considering this, a laboratory biomarker would be an ideal solution, which could provide a timely specific and sensitive method for diagnosing DCI in SAH patients. However, no reliable biomarkers are yet available to predict DCI. Although numerous studies have investigated potential biomarkers, limitations such as sample size, methodological heterogeneity, varying DCI definitions and cut-off values make its clinical application difficult.

Despite numerous emerging biomarkers, no comprehensive analysis has evaluated their diagnostic accuracy for DCI. This meta-analysis aims to address these gaps by systematically assessing various biomarkers in accordance with PRISMA 2020 guidelines. A better understanding of these biomarkers could help with earlier diagnosis of DCI, improve treatment decisions and reduce its morbidity and mortality.

Methods

Data Exploration Strategy

All protocols employed in this study have been registered and accepted by PROSPERO, bearing the identification number **[CRD420251068271]**. This systematic review and meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[6]

Data Screening

In the course of exploring relevant literature, we consulted a number of databases, including PubMed, Science Direct, Epistemonikos and Cochrane Library. Keywords used: “Delayed Cerebral Ischemia” AND “Biomarker”. Screening for literature starts from 5 June 2024 until 31 July 2024. Filter selected on all databases only on “original research” if available on databases.

Eligibility Criteria

The eligbility criteria were based on the PIROS framework, as well as additional inclusion and exclusion criteria. The PIROS framework comprises the following elements: Subarachnoid Hemmorrage (Patients), Laboratory Biomarker (Index), DCI diagnosis guideline (References)[2], Diagnosed as DCI (Outcome), and Observational Study OR Validation Study (Study Design). Inclusion criteria as follows: (1) published within the last 10 years, (2) in Indonesian or English, and (3) providing the Diagnostic Value (sensitivity and Specificity) with %prevalence. Review articles, editorial, commentary and non-accessible articles were excluded.

Study Selection

Articles that fall within the eligibility criteria were determined by at least 2 authors in each database. It was considered appropriate if it met the inclusion and exclusion criteria, as well as PIROS framework. All authors acted independently. Any disagreements were resolved through discussion and deliberation among all authors to determine the feasibility of inclusion.

Data Extraction

All investigators independently extracted data following the PRISMA flowchart. Discrepancies in extracted data were resolved through discussion. A reference manager (Mendeley) was utilized to identify and collate duplicate articles from databases offering this functionality, using ‘.ris’ or other compatible formats. If a database lacked this feature, the process was completed manually. Missing data was sought by emailing the author; articles were excluded if no response was received.

Several data were extracted from the source material, including the author’s name, year of publication, country the study was conducted, number of samples, %prevalence (patients with disease), True Positive (TP), True Negative (TN), False Positive (FP), False Negative (FN), Sensitivity, Specificity, Index that were used, Sample that taken from, and Reference of Diagnosis.

If there was no data about TP, TN, FP, and FN provided in the manuscript, we calculate the number based on number of samples, %prevalence, Sensitivity

value, and Sensitivity value, with the formula as followed:

Number of Diseased Individuals = N Prevalence
Number of Non-Diseased Individuals = N (1 - Prevalence)
True Positive (TP) =
(Number of Diseased Individuals) x Sensitivity
False Negative (FN) =
(Number of Diseased Individuals) x (1-Sensitivity)
True Negative (TN) =
(Number of Non-Diseased Individuals) x Specificity
False Positive (FP) =
(Number of Non-Diseased Individuals) x (1- Specificity)

Abbreviation:
N = total number of samples in study
Prevalence: Proportion of individuals in the population who have disease. Often expressed as a precentage, which should be converted to decimals for calculations. (e.g. 20% = 0.20)
Sensitivity: Ability of the test to correctly identify those with the disease
Specificity: Ability of the test to correctly identify those without the disease

Statistical Analysis

Diagnostic meta-analysis was performed using R Studio (R.4.4.3), with packages mada and meta. Data such as TP, TN, FP, FN were used to analyze Sensitivity and Specificity. We proceed with subgroup analysis for each biomarker to determine each sensitivity and specificity based on forest plot. We visualized overall data in ROC space plot of Sensitivity and Specificity to simplify each sensitivity and specificity of each biomarker.

Risk of Bias

We conducted a risk of bias assessment using the QUADAS-2 questionnaire. Each article was reviewed by at least 2 investigators. Any disagreement was resolved by consensus. Results were displayed as traffic plot and summary plot.

Assessment of Evidence Certainty

We assessed the certainty of evidence for each outcome using the GRADE framework. RCT evidence was initially high certainty, observational studies low. Final certainty was determined after evaluating factors that could downgrade (risk of bias, inconsistency, indirectness, imprecision, publication bias) or upgrade (large effect, dose-response, confounding likely to diminish effect for observational studies) the initial level. Final certainty was classified as High, Moderate, Low, or Very Low, presented in a Summary of Findings table with effect estimates.

Results

Study Selection

In total, 401 identified from various databases and 60 of them were duplicate and excluded. We screened 341 articles with 305 excluded due to not fall into eligibility criteria. Four articles cannot be retrieved and two studies in animal models, six without diagnostic value data (only in OR), and an unclear reference standard. In the end, we include 23 articles that fall into the scope of our eligibility criteria. We visualize our identification until including articles in Fig.1.

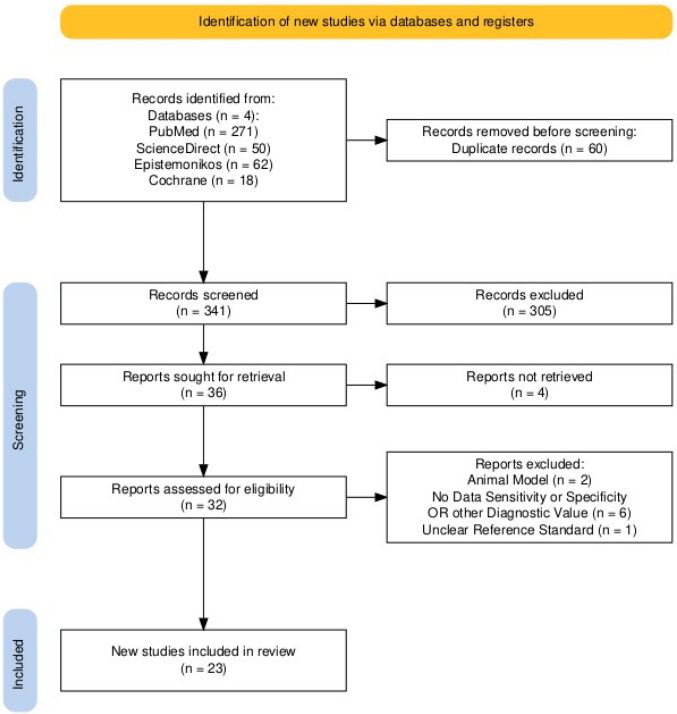


Figure 1. PRISMA Statement on Included Studies

Characteristics of Included Studies

We include articles from various countries such as France, China, and Many others with 4294 samples included for diagnostic meta-analysis. All characteristics of included studies compiled in Table 1. Various indexes such as MMP-9, CRP, Annexin V-RBC, CSF Lactate, CSF LDH, and many others. We found that indexes taken from various samples such as CSF, Plasma, even urine.

Table 1. Characteristics of Included Studies

Author, Year	Country	Total Sample	Index	Sampel Taken From
Triglia,2016[7] (a)	France	30	MMP-9 Antigen (ng/mL)	LCS
Triglia,2016[7] (b)				Plasma
Triglia,2016[7] (c)			MMP-9 Activity (AU/mL)	LCS
Triglia,2016[7] (d)				Plasma
Triglia,2016[7] (f)			ET-1 Antigen	LCS
Triglia,2016[7] (a)				Plasma
Li[8], 2024	German	450	CRP (mg/dL)	Blood (Vein)
Kanamaru[9], 2019	Japan	109	Matricellular Protein Periostin	Plasma
Kaliuzhka[10], 2023	Ukraine	21	Annexin V-RBC	LCS
Mufti[11], 2019	USA	1067	NLR	Serum
Narayan[12], 2024	India	98	MMP-9 (ng/mL)	Serum
Bian[13], 2020	China	92	Tissue Kallikrein (mg/l)	Serum Tissue
Ye-Yan Cai[14], 2022	China	257	HIF-1α (pg/ml)	Serum
Xiaoyu Wu[15], 2023	China	123	NOX-2 (pg/ml)	Serum
Wanwan Zhang[16], 2023	China	447	white blood cell to platelet ratio (WPR)	Serum
Feng Jiang[17], 2022	China	131	sSRA Levels (ng/mL)	Serum
Chen-Yu Ding[18], 2019	China	114	LP-pLA2	Serum
Ma[19], 2024	China	167	Secretoneurin	Serum
Zhang[20], 2022	China	241	Homocysteine	Serum
Hemmer[21], 2022	German	78	high mobility group box 1	serum
Anan[22], 2020 (a)	Japan	19	CSF Lactate	CSF Carotid cistern
Anan[22], 2020 (b)			CSF LDH	
Chen[23], 2021	China	333	SII	serum
Uryga[24], 2021	Poland	55	S100B	serum
Tao[25], 2017 (a)	China	247	NLR	Blood (Vein)
Tao[25], 2017 (b)			PLR	
Ding[26], 2019	China	126	NgB	Blood (vein)
Jayamanoharan[27], 2020	Australia	30	D-dimer	LCS
Wang[28], 2011	Taiwan	21	L-selectin	serum
Wiśniewski[29],2020	Poland	38	F2-IsoPs	urine

Quality Assessment

Most of the articles were low risk of bias, few of them with some concerns (4/23 articles), and one high risk of bias. Some that have some concerns in the conclusion have some concerns about risk of bias in domain Q1, namely patient selection that is not clear whether patient selection is consecutive or random. The study by Wang[28], 2011 has a high risk because in the Q1 domain there is a high exclusion rate for various reasons. The overall conclusion is summarized in Figure 2.

Diagnostic Accuracy of Biomarkers for DCI

Overall, the laboratory biomarkers had good sensitivity (75%, 95%CI: 69% - 80%), and specificity (72%, 95%CI: 67.3% - 76.5%) with reference standards using currently used DCI diagnostics. We assessed the Diagnostic Odds Ratio (DOR) to be 7.89 (95%CI: 5.7 - 10.6), indicating that laboratory biomarkers are almost 8 times more likely to be positive in patients who are actually sick than in patients who are not actually sick (high exact positivity). We provide forest plot of Sensitivity and Specificity of each included studies in Figure 3.

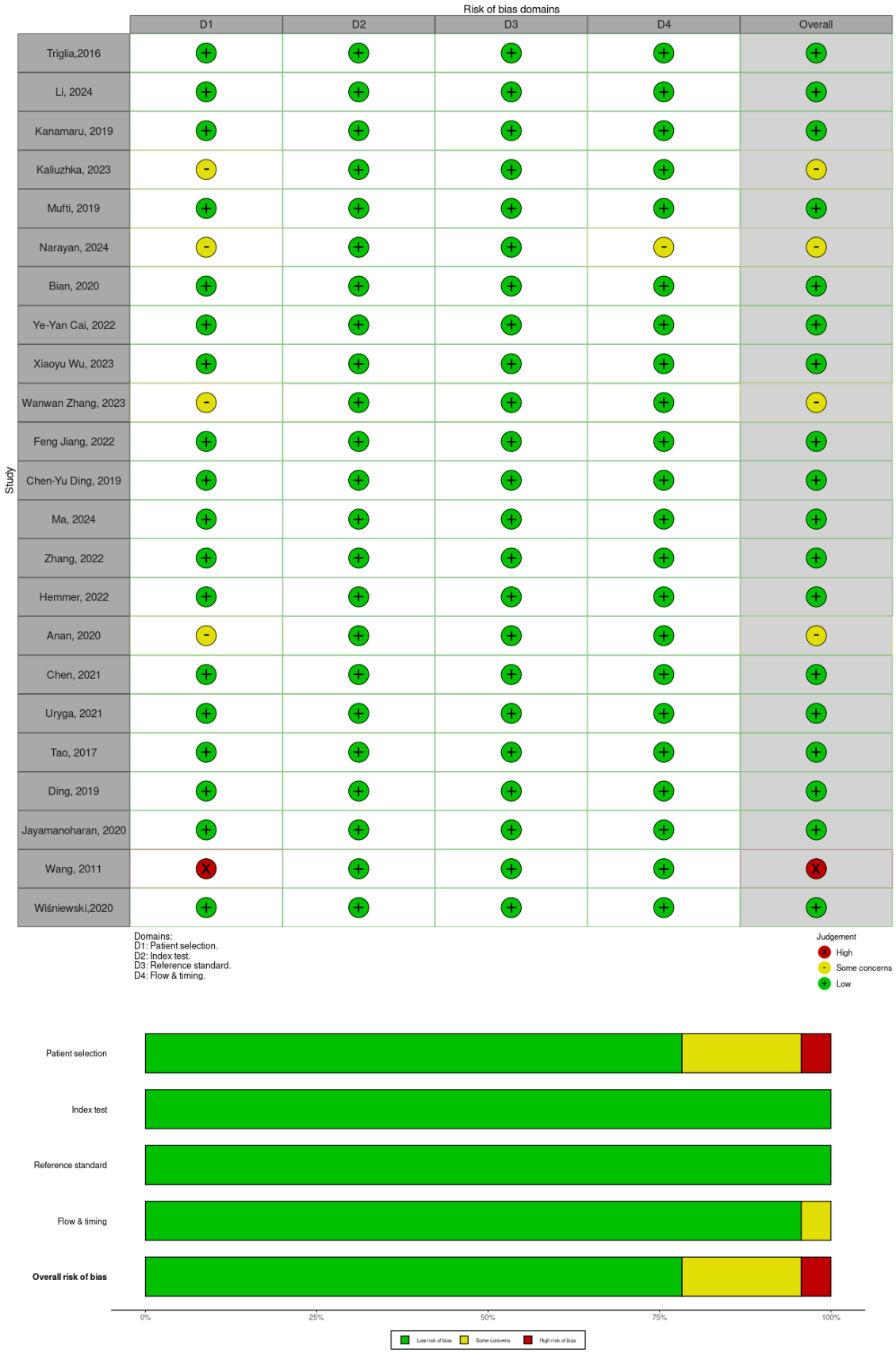


Figure 2. Summary and Traffic Plot of QUADAS-2 For Included Studies.

Figure 4 provides a comparative visualization of the diagnostic utility of multiple biomarkers by plotting their performance as distinct points in Receiver Operating Characteristic (ROC) space. The vertical axis represents Sensitivity (True Positive Rate), which is the ability of a test to correctly identify subjects with the condition. The horizontal axis represents Specificity (True Negative Rate), indicating the test's ability to correctly identify subjects without the condition.

Each point on the plot corresponds to a specific biomarker at its predetermined cut-off value. The ideal biomarker would be located in the top-right corner, representing perfect (100%) sensitivity and specificity. The dashed diagonal line signifies the performance of a random, non-informative classifier. Biomarkers positioned further towards the top-right offer superior diagnostic accuracy, effectively balancing the trade-off between correctly identifying true positives and true negatives.

Based on the curve, in terms of sensitivity (Y axis), the highest value is owned by CSF LDH (Sensitivity 100%, Specificity 76.9%) and the highest specificity (X axis) is owned by CSF Lactate (Sensitivity 83.3%, Specificity 88.9%).

We also analyze SROC plot as presented in Figure 5. This SROC plot indicates moderate overall diagnostic accuracy, with an average sensitivity and specificity around 73-75%. However, substantial heterogeneity (shown by scattered points and a large predictive region) means individual biomarker performance varies considerably, and new study results may differ significantly from this average.

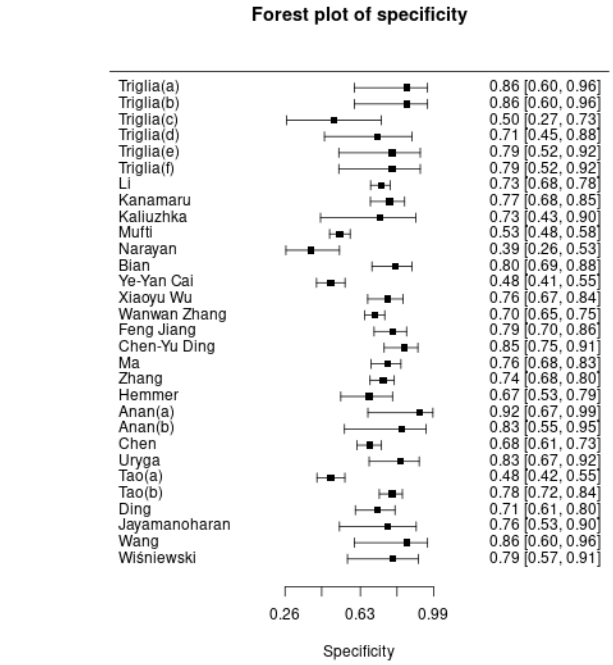


Figure 3. Forest Plot of Sensitivity and Specificity

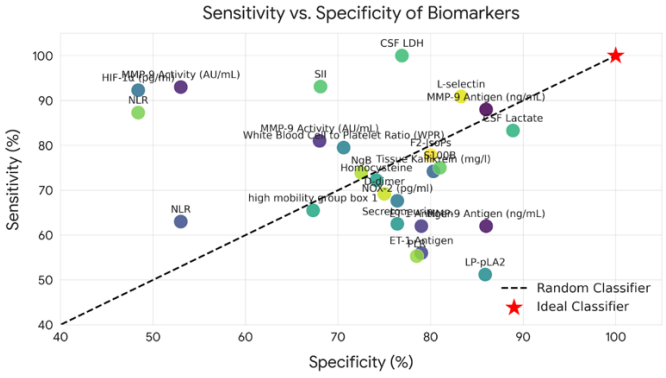
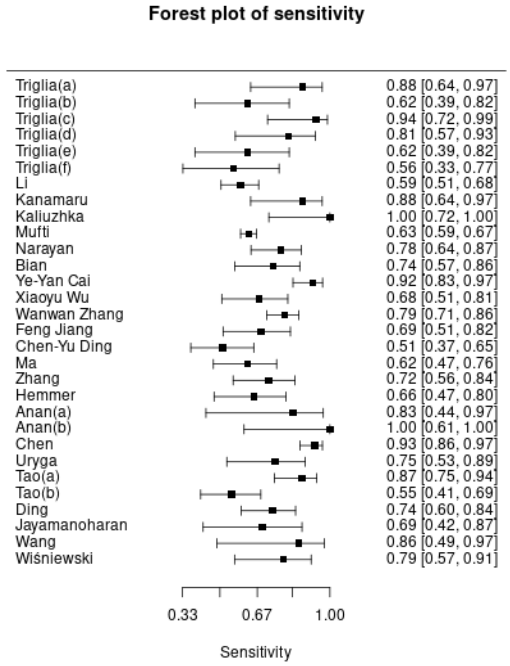


Figure 4. ROC Space Plot of Sensitivity and Specificity



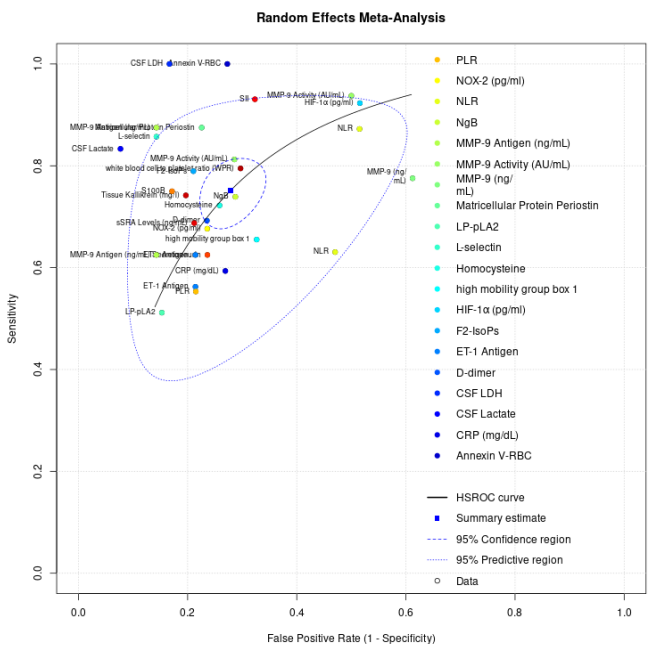


Figure 5. SROC Graph

Publication Bias

We assess publication bias using a funnel plot and Egger's regression test (Figure 6). The funnel plot displays each study's effect size (log diagnostic odds ratio) against its precision (standard error). In the absence of bias, the points should form a symmetrical inverted funnel. The provided plot clearly shows asymmetry, with a gap in the bottom-left corner where smaller studies with lower effect sizes would be expected. This visual finding is statistically confirmed by the highly significant Egger's test (p = 0.000329).

The combination of the asymmetrical plot and the significant p-value provide strong evidence for the presence of publication bias or "small-study effects." This suggests that smaller studies showing a weaker diagnostic effect are likely missing from the analysis, which may lead to an overestimation of the overall diagnostic accuracy in your meta-analysis.

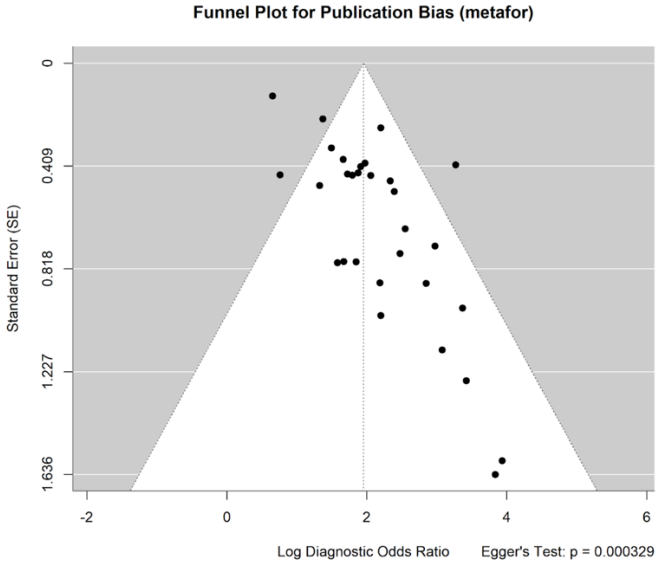


Figure 6. Publication Bias Analysis (Metafor)

Question: Should Laboratory Biomarker be used to diagnose Delayed Cerebral Ischemia in Subarachnoid Hemorraghe?

Sensitivity	0.75 (95% CI: 0.69 to 0.80)
Specificity	0.72 (95% CI: 0.67 to 0.76)

Prevalences	3%	10%	15%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%	pre-test probability of 10%	pre-test probability of 15%	
True positives (patients with Delayed Cerebral Ischemia)	23 studies 1726 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[a]	very serious[a]	publication bias strongly suspected strong association[b]	23 (21 to 24)	75 (69 to 80)	112 (104 to 120)	⨁◯◯◯ Very low[a,b]
False negatives (patients incorrectly classified as not having Delayed Cerebral Ischemia)								7 (6 to 9)	25 (20 to 31)	38 (30 to 46)	
True negatives (patients without Delayed Cerebral Ischemia)	23 studies 2980 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[a]	very serious[a]	publication bias strongly suspected strong association[b]	698 (650 to 737)	648 (603 to 684)	612 (570 to 646)	⨁◯◯◯ Very low[a,b]
False positives (patients incorrectly classified as having Delayed Cerebral Ischemia)								272 (233 to 320)	252 (216 to 297)	238 (204 to 280)	

Explanations

a. Most of the included studies using various biomarker, and most biomarker come from single study
b. Funnel Plot and Egger Test showed a presence of publication bias

Figure 7. GRADE Analysis using GRADE Pro

Certainty of Evidence

We assess certainty of Evidence with GRADE analysis using the GRADEPro website. For the test accuracy on all outcome, out certainty for test accuracy are very low. This was decided because the included studies used different biomarkers and also drew from different samples. This resulted in imprecise bias and inconsistency. And this study also found publication bias as mentioned earlier. The overall conclusion of GRADE has been visualized in Figure 7.

Discussion

Summary of Main Findings

There is potential that laboratory biomarkers as a diagnostic tool for DCI in SAH patients considering their good sensitivity and specificity (75% and 72%). Various biomarkers have been further explored with biomarkers that potentially have good sensitivity and specificity being CSF LDH (Sens 100%, Spec 76.9%), and CSF Lactate (Sens 83.3%, Spec 88.9%). Although the certainty evidence in this study is still low, this study can open hope for biomarkers that can be further explored to better diagnose DCI before it is too late.

Supporting that lab biomarkers can be the hope of a new diagnosis model is the DOR which shows that almost 8x positive results will be found in patients who are actually sick than those who are not actually sick (high exact positivity). Since this study included different biomarkers, it is reasonable to find publication bias. This supports the need for further research so that the results found will be more accurate.

Clinical Implications and Future Role of Biomarkers

The 2023 AHA/ASA guidelines remain the primary tool for identifying delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage. They define DCI as either a drop of ≥2 points on the Glasgow Coma Scale or the sudden appearance of a focal neurological deficit lasting at least one hour, provided no other cause is apparent. Radiological confirmation—typically via CT angiography or CT perfusion—supports the diagnosis.[30] Unfortunately, these clinical signs most often surface between days 4 and 14 post-bleed, by which time significant cerebral injury has usually already taken place. In practice, that delay translates into lost opportunities: the longer we wait, the higher the chances of irreversible infarction, greater morbidity, and increased mortality. In other words, we need tools that catch DCI earlier to give patients the best shot at recovery.

Recognizing this gap, researchers have turned to blood and CSF biomarkers as potential "early warning" signals. By looking back at the timing of sample collection versus when DCI actually appeared, several markers have emerged as promising candidates. For instance, a drop in ADAMTS13 activity and a rise in von Willebrand factor can be detected about 4–5 days before symptoms arise.[31] An elevated neutrophil–lymphocyte ratio at admission may foreshadow DCI by roughly 3–6 days[11], and increases in 8-iso-Prostaglandin $F_2\alpha$ in CSF on post-bleed day 1 seem to predict DCI around day 5 (lead time ~4 days).[32] It is important to note, however, that none of these studies report their lead-time values explicitly; rather, they are retrospective estimates based solely on the difference between the timing of sample collection and the documented onset of clinical DCI. Prospective validation will be essential to establish precise, actionable thresholds for truly preclinical detection

Delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage (SAH) is a complex secondary complication that significantly worsens neurological outcomes. The pathophysiological cascade begins with aneurysmal rupture, which leads to a sudden increase in intracranial pressure (ICP) and transient global cerebral hypoperfusion.[33] This initial ischemic insult is followed by inflammatory activation, oxidative stress, microthrombi formation, and microvascular dysfunction, contributing to sustained cerebral hypoperfusion and energy failure. In response to reduced oxygen delivery, neurons and glial cells shift from aerobic to anaerobic metabolism, leading to the accumulation of lactate in the extracellular space and, subsequently, the cerebrospinal fluid (CSF).[22]

CSF lactate, therefore, serves as a direct surrogate for cerebral metabolic distress in the early phase post-SAH. Continued ischemia results in cytotoxic edema and neuronal membrane disruption. This leads to the release of intracellular enzymes, including lactate dehydrogenase (LDH), into the extracellular and CSF compartments.[22,28,34] Thus, elevated CSF LDH reflects structural cellular injury rather than merely metabolic dysfunction.

Clinical studies have demonstrated that both CSF lactate and LDH are significantly elevated in patients who develop DCI, often preceding radiographic evidence of infarction.[35] However, elevations can also occur in other conditions such as central nervous system infection (meningitis and encephalitis), systemic hypoxia (anemia), liver disease, bone fractures, muscle trauma, and cancers.[36] Despite these limitations, the pathophysiological coherence and practical accessibility of these biomarkers support

their integration into early DCI surveillance protocols and justify further validation in prospective cohorts.

Strength, Limitation and Future Research Direction

The strength and novelty of this study lies as the first meta-analysis to show that laboratory biomarkers could potentially be our hope in diagnosing early DCI in SAH patients. The sensitivity and specificity of the laboratory biomarkers were assessed as good and need to be further explored. The limitation of this study lies in the many types of laboratory biomarkers that have been studied, but each of them has only very few or even only one biomarker that has been newly studied for the diagnosis of DCI. So, for certainty evidence in this study is still very low.

For future research, considering that this study proves the potential of CSF LDH and CSF lactate to have better sensitivity and specificity, further exploration of the study can be done by considering various other diagnoses that may be false positives in both biomarkers because these biomarkers can also be found such as in meningitis

Conclusion

This meta-analysis is the first to demonstrate the potential of laboratory biomarkers for early diagnosis of Delayed Cerebral Ischemia (DCI) in Subarachnoid Hemorrhage (SAH) patients. Overall, these biomarkers exhibit good diagnostic accuracy with 75% sensitivity and 72% specificity. Notably, CSF LDH (100% sensitivity, 76.9% specificity) and CSF Lactate (83.3% sensitivity, 88.9% specificity) show particular promise, offering a significant advantage in identifying DCI before irreversible brain damage occurs.

Despite these encouraging findings and the high diagnostic odds ratio, the certainty of evidence remains low due to the heterogeneity of biomarkers and sample types across included studies, along with detected publication bias. Future research should focus on validating CSF LDH and CSF Lactate in prospective studies, while also investigating potential false positives from other conditions like meningitis to refine their clinical utility. This will enhance the accuracy and reliability of these novel diagnostic tools for DCI.

Ethics approval

Not required.

Acknowledgments

None to declare

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study received no external funding.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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