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Laboratory Biomarkers of Brain Damage among Hospitalized Patients: A Systematic Review

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Abstract

Introduction: This systematic review aims to explore the role of biomarkers in predicting unfavorable events associated with traumatic brain injuries and ischemic strokes. We conducted a search in PubMed, resulting in the identification of eleven potentially relevant studies.

Methods: Our search yielded a total of eleven potentially relevant studies from PubMed. After excluding three studies, as two had insufficient information and one was a review, the review included eight studies. The overall sample size across these studies ranged from 37 patients to 6,315 patients.

Results: Most of the included studies demonstrated the ability of various biomarkers to serve as prognostic indicators for predicting unfavorable outcomes in the context of ischemic or traumatic brain injuries. Higher levels of these biomarkers were associated with an increased risk of traumatic injuries or ischemic strokes. For instance, Zhong et al. identified MMP-9 as a potential prognostic factor for acute ischemic stroke, with higher serum MMP-9 levels correlating with an elevated risk of mortality and disability at three months. Similarly, Tsai et al. observed significantly higher concentrations of serum thiobarbituric acid-reactive substances (TBARS) in acute ischemic stroke patients, suggesting its potential as a predictor for three-month outcomes. Kwon et al. found that elevated serum homocysteine levels were independent predictors of acute ischemic stroke and early neurological deterioration. FABP4, copeptin, and NT-proBNP were also identified as independent prognostic markers for functional outcomes, mortality, or cardiovascular disease (CVD) in ischemic stroke patients. Conversely, lower concentrations of serum ficolin-3 were proposed as an independent prognostic biomarker for post-severe traumatic brain injury. Additionally, reduced levels of serum 25-hydroxyvitamin D (25(OH) D) were associated with increased stroke severity and poorer functional outcomes in acute ischemic stroke patients.

Conclusions: The findings from this systematic review suggest that a range of biomarkers, when assessed in patients with traumatic brain injuries and ischemic strokes, can serve as valuable prognostic tools, aiding in the prediction of unfavorable outcomes. These biomarkers may contribute to better risk assessment and patient management in these critical clinical scenarios.

Keywords: Biomarkers, Ischemic Stroke, Diagnosis, Prognosis, Admission.

Introduction

It's well known that, human brain is the most amazing organ in the body which controls all body functions. The major challenges for body are that diseases which affects brain as traumatic or stroke injuries. A traumatic brain injury is able to induce an intracranial inflammatory response which leads to brain edema development as well as delayed neuronal death[1, 2]. Stroke is classified as one of the most leading cause of death and disability worldwide [3]. Stroke may be ischemic stroke or hemorrhagic stroke and 80% of strokes are ischemic in origin [4]. Stroke caused by multiple risk factors such as advanced age, hypertension, diabetes, hypercholesterolemia, smoking, alcohol addiction, etc. [5]. The great effect of ischemic stroke or traumatic brain injuries is on the emotion and life quality of patients which requires early and accurate prediction.

There are many biomarkers which employed as reliable diagnostic or prognostic agents to predict or monitor the brain damage by ischemic stroke or traumatic injuries. This was reported in many studies. Zhong, et al. [6] suggested that, serum matrix metalloproteinases-9 [MMP-9] could be employed as significant prognostic factor for ischemic stroke, when the higher levels of serum MMP-9 in acute ischemic stroke were increased with increasing the risk of mortality and disability. Also, Long et al., [7] showed that, miR-126, miR-30a and let-7b may have the potential to be diagnostic biomarkers for ischemic stroke.

Significant changes in the circulating of miR-126, miR-30a and let-7b levels have been detected in the ischemic stroke patients compared to healthy control. Furthermore Pan et al., [8] proposed that, serum ficolin-3 as a good prognostic predictive biomarker after head trauma. Lower levels of serum ficolin-3 on admission were detected in patients with severe traumatic brain injury than that in the healthy subjects. This review was designed to summarize the role of biomarkers in prognosis, diagnosis and monitoring of brain damage by traumatic and ischemic injuries

Methods

In this systematic review, we selected studies that explored the utility of biomarkers in predicting, diagnosing, and monitoring brain damage resulting from traumatic brain injuries and ischemic strokes. We considered a variety of study designs, including randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies. We systematically searched several reputable databases, including PubMed, MEDLINE, Embase, Scopus, and Web of Science, and manually reviewed the reference lists of pertinent articles and review papers. Our search terms included keywords such as "biomarkers," "prognosis," "diagnosis," "monitoring," "traumatic brain injury," and "ischemic stroke." Following a two-stage screening process, we retrieved and assessed the full texts of potentially relevant studies. Data from the selected studies were extracted, including information on study characteristics, participant demographics, biomarker types, and key findings related to the prognosis, diagnosis, and monitoring of brain damage.

To evaluate study quality, we employed established tools like the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparent reporting. Data synthesis involved a narrative approach to summarize the findings from the included studies regarding the role of biomarkers in traumatic brain injuries and ischemic strokes. The quality and potential bias of the studies were systematically assessed. Since this review analyzed published data, no ethical approval was required.

Results

The yield of the search on biomarkers of brain damage in traumatic and ischemic injuries in PubMed was eleven potentially relevant studies [6-16]. Three studies were excluded, two of them had insufficient information[17, 18] and one was in this review [19].

Overall sample size was ranged between 37 patients [12] to 6315 patients[10]. Most included studies (eight studies) in this review proved ability for varied factors to act as prognostic biomarkers for prediction unfavorable events associated with ischemic or traumatic stroke. The higher levels of biomarkers were associated with increasing the risk of traumatic injuries or ischemic stroke, this was observed in the studies carried out by Zhong, et al[6] they reported that, MMP-9 could be used as potential prognostic factor for acute ischemic stroke, when the higher levels of serum MMP-9 in acute ischemic stroke were associated with increasing the risk of mortality and disability at three months. Also, in the Tsai et al., [13] study, significantly higher concentrations of serum thiobarbituric acid-reactive substances (TBARS) were observed in acute ischemic stroke patients than that in healthy controls. They suggested the higher serum levels of TBARS at the acute ischemic stroke phase as a potential predictor for 3 month outcome. Furthermore, Kwon et al., [15] demonstrated that, high levels of serum homocysteine could be used as independent predictors for acute ischemic stroke.

There was significant association between elevated homocysteine levels and early neurological deterioration (END) in patients with acute ischemic stroke. Tu et al., [9] showed that, the FABP4 serum concentrations were associated with poor functional outcome and mortality in patients with ischemic stroke. The FABP4 was a useful independent prognostic marker of functional outcomes or mortality in patients with stroke. At the same time, Tu et al., [10] proposed that, copeptin and NT-proBNP may use as prognostic markers of all cause of cardiovascular disease (CVD) or mortality in ischemic stroke patients. Their results revealed that, the combined use of NTproBNP and copeptin was more informative compared to use NTproBNP or copeptin alone. Di Napoli et al., [16] proved that, C-reactive protein (CRP) is an independent prognostic marker of increased one year risk in ischemic stroke patients. Their findings indicated to that, elevated CRP could be employed as predictor for future cardiovascular events or death in ischemic stroke patients. On the other hand the lower concentrations of some biomarkers were useful indicator for the risk of ischemic or traumatic stroke; Pan et al., [8] introduced serum ficolin-3 as an independent prognostic biomarker for post severe traumatic brain injury. The levels of serum ficolin-3 on admission in patients with severe traumatic brain injury were decreased significantly than that measured in the healthy subjects. The levels of serum 25-hydroxyvitamin D (serum 25(OH) D) were proposed as predictor for both severity at admission and favorable functional outcome in the acute ischemic stroke patients, when the levels of serum 25(OH) D were reduced with increasing severity of stroke Wang et al.,[14].

Other included studies (three studies) focused on the diagnosis ischemic stroke by measure some factors. Long et al., [7] reported that, the significant changes in the circulating of miR-126, miR-30a and let-7b may act as potential diagnostic markers for ischemic stroke. Significantly down regulation in circulating miR-30a and miR-126 were observed in all ischemic stroke patients when compared to control. Whereas higher levels of circulating let-7b in were detected in all patients with ischemic stroke except those with large vessel atherosclerosis; the circulating let-7b was lower until 24 weeks. Higher levels of sLOX-1 in patients with acute ischemic stroke than that amounted in control were proposed as a good diagnostic biomarker for acute ischemic stroke, this was reported by Yokota et al.,[11]. Walsh et al.,[12]found significantly lower levels of Apolipoprotein A-I (Apo A-I) and paraoxonase-1 in ischemic stroke cases than controls. Thus, Apo A-I and paraoxonase-1 may be useful marker for diagnosis ischemic stroke and for distinguishing between hemorrhagic and ischemic strokes.

Discussion

The prognosis and diagnosis of brain damage in traumatic and ischemic injuries is based on clinical examination as well as on various neuro-imaging techniques[7]. The ability of some biochemical markers to enhance the accuracy of prognosis traumatic and ischemic injuries is an attractive area of research. Rapidly measurable biomarkers will act as great predictor for illness development, morbidity and mortality to enable provision optimized care and adequate allocation of health care resources[10].

In the present search, six studies suggested the significant increasing in the biomarkers levels could

act as valid predictor for the risk of traumatic and ischemic injuries. This increasing in the biomarkers was correlated with the increasing the risk of disability and death in patients with ischemic injuries. As that found with higher concentrations of MMP-9 Zhong, et al[6]. It was reported that, circulating MMP-9 was correlated with the severity of stroke and infarct volume in patients with acute ischemic stroke [20]. Also, Youssef et al.,[21] indicated to that, the higher levels of homocysteine in plasma was associated with increasing risk of ischemic stroke. This was linked with an early neurological deterioration (END) as reported by [15]. More than that, the disruption synthesis or inhibition the increasing in these biomarkers levels was associated with favorable outcomes. Fagan,et al and Malemud et al., [22, 23] recorded that, the improvement in the neurologic outcomes was detected after inhibition MMPs synthesis by many MMPs inhibitors.

Conversely decreasing in other biomarkers was linked with increasing the risk and severity of traumatic injuries and ischemic stroke as reported by Pan et al., [8] when the levels of serum ficolin-3 were decreased with severe traumatic brain injury; also serum 25(OH) D levels were reduced with increasing the severity of stroke Wang et al.,[14].

Yanamadala et al., [24] explained the reducing in serum ficolin-3 levels is due to consumption through the binding of the molecules to the necrotic and apoptotic cells in acute traumatic event.

Diagnosis ischemic stroke was performed by single or multi biomarkers; in the Long et al., [7] study, there was significantly down regulation in the circulating miR-126 and miR-30a whereas increasing in the circulating let-7b which were used as novel reliable diagnostic markers for ischemic stroke. They suspected that, circulating miRNAs are decreased in injured cells compared to that in normal cells. Walsh et al.,[12] introduced Apo A-I and paraoxonase-1 as useful marker for diagnosis ischemic stroke and to distinguish between ischemic and hemorrhagic strokes. Furthermore, sLOX-1 at higher levels recognized as valuable diagnostic factor for ischemic stroke Yokota et al.,[11]. In conclusion; we can summarize that from the all results have been shown in this review, a significantly higher levels of MMP-9, TBARS and homocysteine could be employed as independent prognostic marker for the high risk associated with ischemic strokes while elevated levels of FABP4, copeptin, NT-proBNP and C-reactive protein are a good predictor for ischemic strokes; conversely lower concentrations of serum ficolin-3 and serum 25(OH) D were proposed as prognostic biomarker for post severe traumatic brain injury and severity of ischemic stroke respectively. At the same time the significantly changes in circulating of miR-126, miR-30a and let-7b and higher sLOX-1 levels were potential diagnostic ischemic stroke biomarkers, whereas Apo A-I and paraoxonase-1 are useful diagnostic ischemic stroke biomarker and a novel factors for distinguishing between hemorrhagic and ischemic strokes.

Conclusions

In conclusion, this systematic review underscores the pivotal role of biomarkers in predicting, diagnosing, and monitoring brain damage resulting from traumatic brain injuries and ischemic strokes. The review encompassed a total of eight studies that collectively demonstrated the potential of various biomarkers to serve as reliable prognostic indicators for adverse outcomes in these critical clinical conditions. Elevated levels of biomarkers, such as MMP-9, TBARS, homocysteine, FABP4, copeptin, and NT-proBNP, were consistently associated with an increased risk of mortality, disability, or cardiovascular events following ischemic or traumatic brain injuries. These findings have significant implications for clinical practice, as they pave the way for improved risk assessment and more tailored interventions to enhance patient outcomes.

Conversely, some biomarkers, including serum ficolin-3 and serum 25-hydroxyvitamin D, exhibited lower concentrations in patients with severe traumatic brain injuries or acute ischemic strokes, offering valuable insights into their potential as independent prognostic biomarkers. The integration of these biomarkers into clinical decision-making processes can facilitate early interventions, personalized treatment strategies, and ultimately, improved patient care. However, further research and validation studies are warranted to establish the robustness and clinical utility of these biomarkers. In the era of precision

medicine, the identification and utilization of biomarkers hold promise for advancing the management and prognosis of brain damage resulting from traumatic and ischemic injuries, ultimately enhancing the quality of care for affected patients.

Conflict of interests

The authors declared no conflict of interests.

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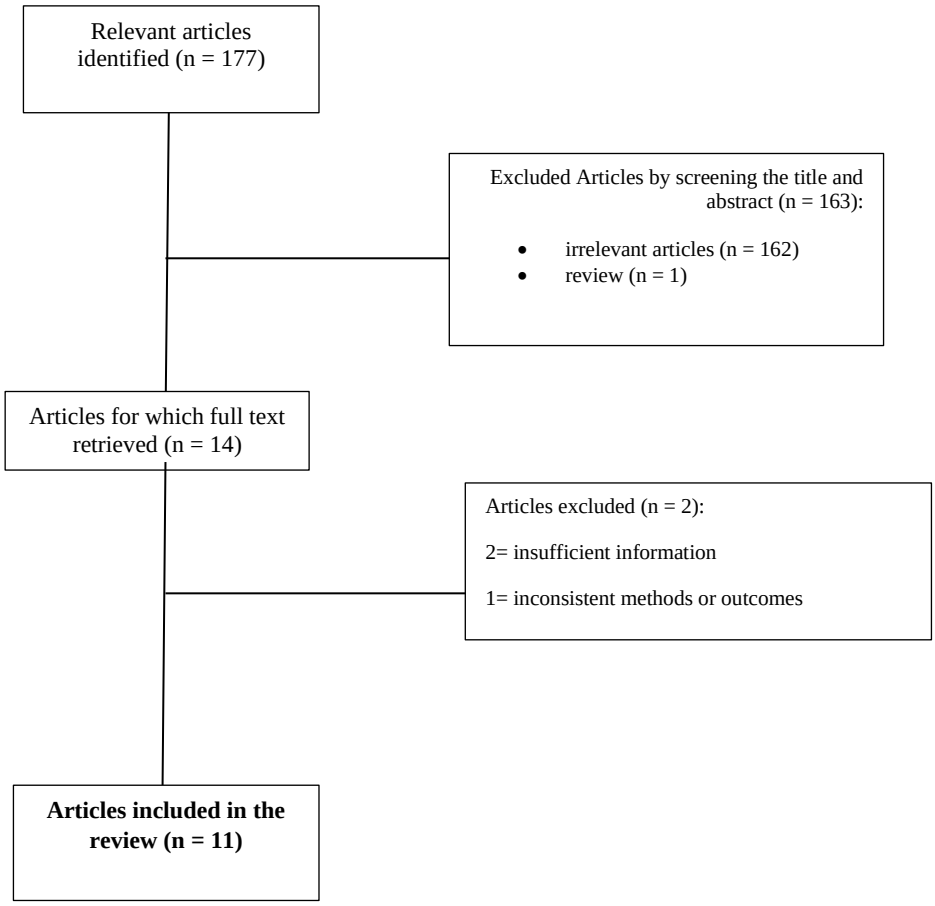

Figure (1): Flow diagram of the included studies in the systematic review

Table (1): Summary of the findings of the included studies

Study	Study design	Sample size	Age of patients	Underlined diseases	Biomarkers reported in the included study	Aim of use of these biomarkers	Biomarkers found significant
Zhong) et al., (2017	prospective study	4,071	≥22 years of age	Heart diseases or diabetes mellitus	serum matrix metalloproteinases-9 (MMP-9)	prognosis of acute ischemic stroke	serum MMP-9
(Tu et al., 2017b)	A prospective multicenter observational study	896	58 (51–68)	Heart diseases or diabetes mellitus	FABP4 (fatty acid–binding protein 4)	prognostic ischemic stroke marker	FABP4
(Tu et al., 2017a)	a cohort study	6315	-	cardiovascular disease	copeptin and N-terminal pro-Btype natriuretic peptide (NT-proBNP)	prognostic ischemic stroke marker	copeptin and NT-proBNP
(Yokota et al., 2016)	Cross-Sectional Study	377	40-79 years	Cardiovascular disease	sLOX-1	diagnostic biomarker for acute ischemic stroke	levels of sLOX-
(Walsh et al., 2016)	An observational case-control study	37	18 years or older	Hypertension Past orcurrent smoker Diabetes mellitus	apolipoprotein (Apo), matrix metalloproteinase (MMP), and paraoxonase-1	marker for diagnosis ischemic stroke and for distinguishing between hemorrhagic and ischemic strokes..	Apolipoprotein A-I (Apo A-I) and paraoxonase-1
(Pan et al., 2015)	prospective observatory study	256	less than 18 years of age	infectious diseases	serum ficolin-3	prognostic biomarker for post severe traumatic brain injury	serum ficolin-3

(Tsai et al., 2014)	prospective study	100.	aged 18–80 years	Heart diseases and diabetes	serum thiobarbituric acid-reactive substances (TBARS) and free thiol levels	as a potential predictor for 3 month outcome acute of ischemic stroke phase.	(TBARS)
(Wang et al., 2014)	observational study	326 patients	65 (57–75) 69 (61–83)	Heart diseases and diabetes	25-hydroxyvitamin D [25(OH) D] levels	Predictor for both severity at admission and favorable functional outcome in the acute ischemic stroke patients.	Serum 25(OH)D levels
(Kwon et al., 2014)	RCT	396 patients	61.6±11.3 65.4±11.9	Heart diseases and diabetes	homocysteine	as independent predictors for acute ischemic stroke	homocysteine
(Long et al., 2013)	Prospective study	247	62 ± 7	Heart diseases and diabetes	miR-30a, miR-126 and let-7b	Potential diagnostic markers for ischemic stroke.	miR-30a, miR-126 and let-7b let-7b had
(Di Napoli et al., 2001)	Prospective study	One hundred ninety-three patients	Age .70 y	Heart diseases and diabetes	C-reactive protein (CRP)	Prognostic marker of increased one year risk in ischemic stroke patients. .	(CRP)