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The Role Of Apolipoprotein Gene Allele E4 (APOE4) Rs429358 and RS7412, Glial Fibrillacry Acidic Protein, Phosphorylated Neurofilament Heavy Chain, And Neuron Specific Enolase Serum Levels with Traumatic Brain Injury Outcome: Literature Review

Dian Ayu Hamama Pitra, Yuliarni Syafrita*, Rika Susanti, Rauza Sukma Rita
Universitas Andalas, Indonesia
Email: yuliarni@med.unand.ac.id

KEYWORDS

Brain Injury, Glial Fibrillary Acidic Protein, Neuron Specific Enolase Serum, Phosphorylated Neurofilament Heavy Chain, Apolipoprotein E

ABSTRACT

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide, with clinical outcomes varying significantly among individuals depending on the severity and type of brain insult. Factors such as age, injury severity, mechanism of injury, abnormalities on computed tomography (CT) imaging, hypoxia, hypotension, and pupillary reflexes significantly influence TBI outcomes. This study investigates the critical roles of biomarkers such as Apolipoprotein E (APOE), Glial Fibrillary Acidic Protein (GFAP), Phosphorylated Neurofilament Heavy Chain (pNFH), and Neuron Specific Enolase (NSE) in the pathogenesis and recovery processes following TBI. A literature review of articles from databases including Google Scholar, ResearchGate, PubMed, and ScienceDirect indicates that these biomarkers are associated with distinct aspects of TBI, encompassing cognitive dysfunction, injury mechanisms, neurodegenerative changes, and reparative pathways. GFAP is recognized as a marker for astroglial injury, pNFH for axonal injury, and NSE for neuronal injury. The findings suggest that these biomarkers have significant potential in the monitoring of TBI and may contribute to the development of personalized therapeutic strategies based on individual genetic profiles. This study underscores the importance of elucidating the genetic and molecular underpinnings of TBI to optimize patient management and improve recovery outcomes. Future research in this domain may facilitate the creation of tailored therapeutic interventions, ultimately enhancing patient care and overall recovery.

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Corresponding Author: Yuliarni Syafrita*
Email: yuliarni@med.unand.ac.id

INTRODUCTION

Head injury is one of the leading causes of morbidity and mortality worldwide. According to data from the World Health Organization (WHO), head injuries account for a significant proportion of all traumatic injuries, with long-term impacts that can affect an individual's quality of life (WHO, 2021). Head injuries can result from various factors, including traffic accidents, falls, violence, and sports. The consequences range from mild injuries, such as concussions, to severe injuries, which can cause permanent brain damage or even death (Sutawan et al., 2021). Based on the morphology of the injury, head injuries are divided into two types: closed head injuries and open head injuries. Closed head injuries occur when the head experiences trauma without an open wound, while open head injuries involve damage to the scalp and underlying tissues. Closed head injuries are often more difficult to diagnose, as symptoms may not appear immediately and can develop over time (Gadberry, 2021).

Head injuries, which encompass a range of conditions from mild concussions to severe trauma, present a complex medical challenge with significant impacts on individuals and health systems. The

classification and assessment of head injuries, using methods such as the *Glasgow Coma Scale*, highlight the diversity in severity and outcomes. The pathogenesis of head injury involves both primary and secondary brain damage, requiring a comprehensive understanding of biological responses after trauma (Dash & Chavali, 2018). One of the main challenges in managing head injuries is the variability in individual responses to injury. Some patients may recover fully, while others experience long-term complications, such as cognitive impairment, behavioral changes, and emotional problems. Therefore, understanding the biological factors that contribute to head injury outcomes is crucial (Sutawan et al., 2021).

One genetic factor that has been extensively studied is the apolipoprotein E (APOE) gene, particularly the E4 allele (APOE4). This genetic variation, characterized by the rs429358 and rs7412 polymorphisms, has been identified as a risk factor for various neurological conditions, including Alzheimer's disease and traumatic brain injury (TBI). Studies show that individuals with the APOE4 allele may have different inflammatory responses and increased susceptibility to brain injury, which can affect prognosis and recovery (Huang et al., 2017; Safieh et al., 2019). In addition to genetic factors, serum biomarkers such as glial fibrillary acidic protein (GFAP), phosphorylated neurofilament heavy chain (pNfH), and neuron specific enolase (NSE), which can be identified through blood or other body fluids, offer great potential in detecting, assessing, and monitoring brain injury. GFAP, a major structural protein in glial cells, has been shown to increase significantly after brain injury, reflecting neural tissue damage (Papa et al., 2016). Similarly, pNfH and NSE also function as biomarkers indicating neuronal damage and can provide prognostic information about clinical outcomes (Zetterberg et al., 2016).

Previous research has emphasized the importance of genetic and biomarker factors in predicting and understanding the outcomes of head injuries. For instance, Huang et al. (2017) identified the apolipoprotein E (APOE4) allele as a significant genetic factor influencing the inflammatory response and susceptibility to brain injury, thereby affecting recovery. Additionally, studies by Papa et al. (2016) and Zetterberg et al. (2016) demonstrated that biomarkers such as GFAP, pNfH, and NSE provide valuable information regarding the severity of brain damage, aiding in the prognosis of head injury patients. However, these studies focused primarily on one or two biomarkers or genetic factors, without an integrated view of the combined impact of genetics and biomarkers on brain injury outcomes.

The aim of this literature review is to examine the role of the APOE4 gene (rs429358 and rs7412), GFAP, pNfH, and NSE serum levels in the context of head injury outcomes. This article delves deeper into the classification, pathophysiological mechanisms, genetic roles, and significance of biomarkers in addressing the complexity of head injuries, with the goal of improving diagnostic, management, and rehabilitation approaches. By analyzing studies published between 2015 and 2025, it is hoped that a better understanding of the complex relationship between genetic factors and biomarkers in determining head injury outcomes can be achieved, leading to the development of more effective diagnostic and therapeutic strategies for patients with head injuries.

METHOD

This study utilized a literature review design to determine the role of the *apolipoprotein E4* (*APOE4*) gene alleles rs429358 and rs7412, glial fibrillary acidic protein (GFAP) levels, phosphorylated neurofilament heavy chain (pNfH), and neuron specific enolase (NSE) serum concentrations in relation to head injury outcomes. The literature analyzed comprised scientific journals published in the last ten years, with article searches conducted using relevant keywords on databases

such as Google Scholar, ResearchGate, PubMed, and ScienceDirect. Articles that met the inclusion criteria were selected for analysis, and the results were presented in a table to facilitate comparison.

Data collection focused on articles that were relevant to the study's objectives and fulfilled the inclusion criteria, specifically those examining the relationship between the identified genetic and biomarker factors and traumatic brain injury (TBI) outcomes. The data analysis technique involved a qualitative synthesis of the selected literature, where key findings were compared and analyzed to assess the correlation between genetic factors, biomarkers, and TBI outcomes. The results were then summarized and presented in a tabular format for clarity.

The population in this research consisted of various studies on TBI, including clinical trials, observational studies, and biomarker analysis studies. The sampling method was purposive, selecting only those studies that specifically focused on the relationship between the identified biomarkers and genetic factors with TBI outcomes. This approach allowed for a comprehensive evaluation of the existing evidence regarding the prognostic value of *APOE4*, GFAP, pNfH, and NSE in the context of traumatic brain injury.

RESULT AND DISCUSSION

Table 1. Summary of the APOE Study

Studies	Population	Findings
(Giarratana et al., 2020c)	1,132 patients with traumatic brain injury (TBI)	The ApoEε4 allele provides a small risk of poor *outcomes* after TBI. Analysis based on TBI severity could not be performed due to limited data.
(Washington & Burns, 2016)	Mouse model with closed head injury	ApoE4 mice were twice as likely to die or have a higher neurological severity score compared to ApoE3 mice after a head injury.
(Reuter-Rice et al., 2018a)	118 children with moderate to severe TBI	APOE polymorphisms are associated with cerebral vasospasm and *poor outcomes* in children with TBI. There is a significant inverse comparison between pNF-H and GCS

Source: author

APOE is produced in the brain that has neurotrophic (membrane repair and neuroplasticity) and neuroprotective (antioxidant and anti-inflammatory) effects (Reuter-Rice et al., 2018b). The presence of the ApoE4 allele is often associated with poorer outcomes after head injury. Although the exact mechanism is still being researched, some studies suggest that ApoE4 may affect the brain's recovery process and increase susceptibility to neurological damage.

Table 2. Summary of the GFAP Study

Study	Population	GFAP sample collection time	Up to peak GFAP	Duration of increased GFAP levels
(Papa et al., 2016)	584 patients with mild to moderate TBI	Within 1 hour after injury	20 hours post-injury	Detected up to 7 days
(Lei et al., 2015)	67 patients with severe TBI	Upon entry and every day for the first 5 days	Not reported	6 days
(Huebschmann et al., 2020)	50 patients with mild to moderate TBI	Within 4 hours after injury	Not reported	Serum and plasma GFAP levels were higher in patients with

Study	Population	GFAP sample collection time	Up to peak GFAP	Duration of increased GFAP levels
				unfavorable outcomes, indicating the potential of GFAP as a biomarker for predicting post-TBI outcomes.
(McMahon et al., 2015)	108 patients with mild to severe TBI	Within 24 hours after injury	Not reported	GFAP levels are elevated in patients with TBI, with higher levels associated with poorer outcomes.
(Mathew et al., 2024)	40 patients with mild TBI, 40 with severe TBI, and 40 healthy controls	Not reported	Not reported	GFAP levels were higher in patients with severe TBI compared to healthy controls, suggesting the potential for GFAP as a biomarker for TBI diagnosis and prognosis.

Source: author

Several studies have examined GFAP as a marker to determine the diagnosis and prognosis of head injuries. The use of GFAP as a diagnostic test is based on its ability to distinguish patients with brain injury from those without brain injury. Thus, its diagnostic function is highly dependent on the time of detection of GFAP in various forms of brain injury. Some studies examining GFAP in head injuries based on their release time are relatively few. (Hossain et al., 2024).

In table 2, several studies examining GFAP can be concluded that GFAP levels increase immediately after traumatic brain injury, peak within a few hours to days, and remain detected for several post-injury days. Higher levels of GFAP are often associated with greater injury severity and poorer clinical outcomes, demonstrating its potential as a biomarker for TBI diagnosis and prognosis (Hier et al., 2021).

Neuron-specific enolase is associated with glucose metabolism in acute head injuries, where NSE plays a role in the ninth chain of the glycolysis process. Animal studies have found that glucose use increases sharply 30 minutes after secondary head injury, and after that glucose uptake decreases for 5-10 days. The increased activity of various membrane pumps to restore ion balance leads to increased glucose consumption. This likely explains that the increase in NSE occurs indirectly at the time of primary head injury, since at the beginning of the head injury, the process of glycolysis is still ongoing (L. Zhang et al., 2023).

The serum concentration of NSE increases in the first 12 hours after a head injury and decreases within a few hours or days. Patients with increased secondary NSE showed worse outcomes. In patients with moderate and severe head injuries, serum NSE levels can increase significantly and are at risk of adverse neurological effects up to mortality (Ghaith et al., 2022)

Studies assessing NSE levels in cerebrospinal fluid in patients with moderate head injuries are still few. In addition, because NSE biomarkers are at high risk of hemolysis, they are significantly limited to being used as potential serum biomarkers. NSE is also detected in erythrocytes and endocrine cells, so it has the potential to interfere with NSE levels due to actual head injuries (H. J. Kim et al., 2018).

Table 3. Clinical Findings of pNF-H in Head Injuries

Study	Injury	Findings
(Young et al., 2016)	Pediatric TBI	Serum pNF-H levels were significantly increased during DAI on initial CT The pNF-H rate increases on days 2-4 at GOS=1 The comparison of serum pNF-H levels on days 2-6 and day 1 differed significantly between GOS=1 and GOS>1
(Siedler et al., 2014)	DAI and focal TBI	Median serum pNF-H was higher in DAI than in focal TBI for 1-10 days after admission
(Ljungqvist et al., 2017)	Mild TBI	Serum pNF-H levels were higher and significantly higher than controls on days 1-3 Higher and significant in mild CT+TBI There is a significant inverse comparison between pNF-H and GCS

Source: author

The study shows that pNF-H has the potential to be a biomarker that can be used to assess the severity of head injuries and predict patient prognosis. Increased levels of pNF-H correlate with the type of injury and clinical outcomes, so it can be a useful tool in the clinical management of patients with head injuries. More research is needed to confirm these findings and explore the clinical applications of pNF-H.

The mechanism of APOE affects outcomes after head injury related to several neurobiological functions of APOE that are thought to affect neurological homeostasis. These functions are also directly or indirectly related to the pathophysiology of Alzheimer's disease. These include amyloid deposition, the formation of neurofibrillary tangles (NFTs), cholinergic transmission disorders, oxidative stress, and CNS regeneration and injury repair (Sun et al., 2023).

One mechanism of action is that APOE e4 may be associated with increased amyloid deposition after head injury. APOE plays a role in promoting and/or modulating the formation of Ab fibrils and the absence of APOE dramatically reduces Ab deposition and limits the neuritic degeneration associated with Ab deposition. In the brains of late-onset Alzheimer's patients' postmortem, a strong association between the presence of the e4 allele and increased Ab deposits compared to homozygous patients for APOE e3 has been noted. APOE is associated with neuropathology based on the interaction of Ab preptids on the amyloid cascade or can be independent of the AB peptide itself (Sun et al., 2023).

The APOE genotype may play a role in the stability and metabolism of neuronal cytoskeletal and influence the formation of NFTs. Transgenic mice that overexpressed human APOE e4 showed increased hyperphosphorylation of microtubules-related tau proteins in the brain that correlated with APOE e4 expression. In vitro studies show that there is an isoform-specific interaction of APOE with tau microtubules-related proteins that can regulate intraneuronal tau metabolism and the formation of paired helical filaments and NFTs. APOE e3 binds more to tau forming biomolecular complexes than APOE e4, therefore suggesting that APOE e4 is more likely to be associated with NFT formation. APOE may also have an influence on cholinergic integrity and function (Sun et al., 2023; L. Zhang et al., 2023)

Anti-oxy and APOE activity may play a role in mediating nerve maintenance and repair after a HEAD INJURY. The APOE e4 gene increases the susceptibility of CA1 neurons to trauma and oxidative stress through an excitotoxic mechanism. Postmortem examination of patients' brains that

assessed the different antioxidant activity of the APOE isoform showed that e4 had the lowest antioxidant activity and e2 had the highest antioxidant activity (Sun et al., 2023).

Another possible mechanism to show how the APOE genotype may affect outcomes after a HEAD INJURY is through neuroprotectiveness. In transgenic mice expressing human APOE, APOEe3 may be more neuroprotective than e4 after HEAD INJURY. In response to HEAD INJURY, apoE is regulated and partially protects primary neuronal-glial cultures against glutamate excitotoxicity (Sun et al., 2023).

ApoE and ApoE-derived peptides activate a number of intracellular kinases, including ERK1/2 and Dab1, ApoE receptor adapter proteins In particular, activation of the ERK signaling pathway by ApoE may play an important role in neuroplasticity and neurodegeneration, as it is associated with the activation of the transcription factor CREB and promotes the growth of neurites. Signaling via ERK is also required for spontaneous neurite initiation and extension (Sun et al., 2023)

Although the effect on plasticity may be particularly important in the context of neurodegenerative disease and subacute recovery from brain injury, the developing literature also has implications for ApoE in modifying N-methyl-daspartate-mediated (NMDA) electrotoxic nerve injury in acute settings. Several mechanisms have been proposed to explain the effects of ApoE on NMDA function. Recent research shows that ApoE can modulate NMDA function and intracellular interactions by interacting with ApoE 2 receptors present in neurons (Sun et al., 2023).

Recent data also suggest that the activation of the LRP1 receptor can modify NMDA function via the scaffolding protein PSD-95, which is a target for neural protection. The role of ApoE-LRP interactions in reducing NMDA-mediated excitotoxicity is consistent with the observation that ApoE and ApoE peptides inhibit NMDA function through direct LRP interactions (Sun et al., 2023)

Some previous studies have shown a positive correlation between GFAP levels and the severity of head injuries. By observing GFAP levels, it can assess the condition of minor head injuries and evaluate the need for the use of neuroimaging such as CT and MRI, thus the unnecessary use of CT and MRI can be reduced. GFAP can identify the need for intensive monitoring and predict poor outcomes and risks for developing cognitive and psychiatric abilities (Ghaith et al., 2022).

Neuron-specific enolases are used as markers of acute brain damage. NSE is a promising biomarker in acute neuronal damage. NSE levels in the CSS ventricles correlated with mortality after head injury and/or with other head injury severity scores, such as the Glasgow Coma Scale and the Glasgow Outcome Scale. Neuron-specific enolase is a marker of neuronal death and increases after head injury of all severity (Ghaith et al., 2022; Syafrita & Nora Fitri, 2021).

The main limitation of using NSE levels in CSS as a biomarker of neuronal injury is the high propensity for hemolysis, where NSE levels increase in erythrocyte lysis derived from blood-contaminated samples (Ganeshalingham & Beca, 2021).

Serum pNF-H levels measured on the second to fourth days post-TBI were significantly higher in patients with worse outcomes at 6 months. Similarly, serum pNF-H was significantly higher in adults with mild TBI with positive CT scans compared to negative CT scans (Manivannan et al., 2018).

In a study of 20 patients with TBI, pNF-H did not increase in patients without brain parenchyma damage, but pNF-H levels increased based on the severity of brain damage. Elevated serum pNF-H levels in patients with brain tissue damage after TBI that peaked at 2 weeks to 1 month after injury were significantly correlated with outcomes after TBI. In addition, measurement of peak levels of pNF-H can be useful as a biomarker to determine the prognosis after TBI (Otani et al., 2020).

CONCLUSION

Genetic factors play a crucial role in determining both the immediate and long-term functional outcomes of patients with traumatic brain injury (TBI). Variations in genes such as *apolipoprotein E* (APOE), *brain derived neurotrophic factor* (BDNF), cytokines, neurotransmitters, and mitochondrial gene families influence cognitive function, inflammatory responses, neurodegenerative changes, and repair processes following TBI. Among these, the APOE gene has received significant attention due to its strong association with TBI prognosis. Additionally, biomarkers including glial fibrillary acidic protein (GFAP), phosphorylated neurofilament heavy chain (pNFH), and neuron specific enolase (NSE) serve as specific indicators of glial, axonal, and neuronal damage, respectively, providing valuable information for assessing injury severity and predicting outcomes. For future research, it is recommended to conduct large-scale, longitudinal studies that integrate genetic profiling and biomarker analysis to better understand their combined predictive value, ultimately guiding more personalized and effective interventions for TBI patients.

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