Archives of Academic Emergency Medicine. 2023; 11(1): e9

OPEN ACCESS

REVIEW ARTICLE

Serum Glial Fibrillary Acidic Protein in Detecting Intracranial Injuries Following Minor Head Trauma; a Systematic Review and Meta-Analysis

Sajjad Ahmadi[1], Shayan Roshdi Dizaji[2], Asrin Babahajian[3], Mohammadreza Alizadeh[2], Arash Sarveazad[4,5]*, Mahmoud Yousefifard[2,6]†

1. Emergency Medicine Research Team, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
2. Physiology Research Center, Iran University of Medical Sciences, Tehran, Iran.
3. Liver and Digestive Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran.
4. Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran.
5. Nursing Care Research Center, Iran University of Medical Sciences, Tehran, Iran.
6. Pediatric Chronic Kidney Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Received: October 2022; Accepted: December 2022; Published online: 1 January 2023

Abstract: **Introduction:** Developing novel diagnostic and screening tools for exploring intracranial injuries following minor head trauma is a necessity. This study aimed to evaluate the diagnostic value of serum glial fibrillary acidic protein (GFAP) in detecting intracranial injuries following minor head trauma. **Methods:** An extensive search was performed in Medline, Embase, Scopus, and Web of Science databases up to the end of April 2022. Human observational studies were chosen, regardless of sex and ethnicity of their participants. Pediatrics studies, report of diagnostic value of GFAP combined with other biomarkers (without reporting the GFAP alone), articles including patients with all trauma severity, defining minor head trauma without intracranial lesions as the outcome of the study, not reporting sensitivity/specificity or any other values essential for computation of true positive, true negative, false positive and false-negative, being performed in the prehospital setting, assessing the prognostic value of GFAP, duplicated reports, preclinical studies, retracted articles, and review papers were excluded. The result was provided as pooled sensitivity, specificity, diagnostic score and diagnostic odds ratio, and area under the summary receiver operating characteristic (SROC) curve with a 95% confidence interval (95% CI). **Results:** Eventually, 11 related articles were introduced into the meta-analysis. The pooled analysis implies that the area under the SROC curve for serum GFAP level in minor traumatic brain injuries (TBI) was 0.75 (95% CI: 0.71 to 0.78). Sensitivity and specificity of this biomarker in below 100 pg/ml cut-off were 0.83 (95% CI: 0.78 to 0.89) and 0.39 (95% CI: 0.24 to 0.53), respectively. The diagnostic score and diagnostic odds ratio of GFAP in detection of minor TBI were 1.13 (95% CI: 0.53 to 1.74) and 3.11 (95% CI: 1.69 to 5.72), respectively. The level of evidence for the presented results were moderate. **Conclusion:** The present study's findings demonstrate that serum GFAP can detect intracranial lesions in mild TBI patients. The optimum cut-off of GFAP in detection of TBI was below 100 pg/ml. As a result, implementing serum GFAP may be beneficial in mild TBI diagnosis for preventing unnecessary computed tomography (CT) scans and their related side effects.

Keywords: Brain Injuries, Traumatic; Diagnosis; Biomarkers

Cite this article as: Ahmadi S, Roshdi Dizaji S, Babahajian A, Alizadeh M, Sarveazad A, Yousefifard M. Serum Glial Fibrillary Acidic Protein in Detecting Intracranial Injuries Following Minor Head Trauma; a Systematic Review and Meta-Analysis. Arch Acad Emerg Med. 2023; 11(1): e9. https://doi.org/10.22037/aaem.v11i1.1682.

***Corresponding Author:** Arash Sarveazad; Colorectal Research Center, Rasoul-e-Akram Hospital, Nyaiesh Ave., Tehran, Iran; Tel/Fax: +982166554790; Email: Arashsarveazad@gmail.com, ORCID: https://orcid.org/0000-0001-9273-1940.

1. Introduction

Traumatic brain injury (TBI) is the leading cause of death and debilitation among the young population worldwide (1). Statistics demonstrate its worldwide prevalence at 8.4%, which has been considered a major health concern in developing countries. The incidence rate and disability-adjusted life years (DALY) of TBI increased significantly from 1990 to 2016. TBI is a significant burden on the healthcare system and constitutes a large portion of hospital visits and admissions (2). Based on clinical assessments, and typically, the Glasgow coma scale (GCS), TBI patients are commonly classified into three subgroups: mild (GCS:13-15), moderate (GCS:9-12), and severe (GCS:8-12), with mild TBI accounting for more than 85% of cases (3, 4).

The intracranial lesions caused by TBI are conventionally detected using imaging techniques, in particular, non-contrast-enhanced computed tomography (CT) scan and rarely, magnetic resonance imaging (MRI) (5, 6). However, the role of imaging techniques has been debated due to negative findings in a vast majority of mTBI patients and the considerable amount of hazardous ionizing radiation associated with it and cost implications imposed by it (7). According to available data, only 16% of mild TBI patients have demonstrable intracranial lesions on computed tomography (CT) imaging (8). To prevent unnecessary imaging, multiple clinical decision rules with varied diagnostic values have been developed to identify those who are at risk of having pathoanatomical intracolonial lesions (9). One limitation with current decision rules is the presence of clinical criteria, including headache, post-traumatic amnesia, nausea, vertigo, dizziness, and consciousness assessment that are self-reporting or non-specific and subject to clinical examiner bias.

The demand for minimally invasive objective parameters in detecting brain injury has led to increasing attention toward serum biomarkers serving as supplementary screening tools. In light of advancements in understanding the molecular biology and pathways involved in neuronal damage, S100-B and neuron specific-enolase (NSE), two brain-enriched cytoplasmic markers, were widely studied to aid in diagnosing central nervous system injuries (1, 10, 11). Although demonstrated to pose promising efficacy in providing insight into injury severity and progression, these biomarkers are subject to some drawbacks. Studies on multiple trauma have revealed that extracranial sources of NSE and S100-B release confound its interpretation and impede its practical clinical utility in acute settings (12, 13).

Among emerging serum biomarkers, studies outlined glial fibrillary acidic protein (GFAP) as a brain-specific astroglia cytoskeleton filament that is released into peripheral circulation upon neuronal injuries due to patency of the blood-brain barrier (BBB) (14).

Clinical investigations have demonstrated that the GFAP serum level has a high correlation with the lesion volume and severity in traumatic brain injuries. This made GFAP a potential candidate for diagnostic and prognostic purposes in TBI evaluation.

Although the evidence has supported that GFAP holds the potential to predict intracranial injuries in TBI patients, there is yet considerable heterogeneity among the available studies (9, 15, 16). Given the inconsistencies found between studies and the lack of a consensus, this systematic review with meta-analysis has been carried out to draw a conclusion on the diagnostic utility of GFAP in detecting intracranial lesions following mild TBI.

2. Methods

2.1. Study design

The present study is a systematic review to investigate the diagnostic value of GFAP in detecting traumatic intracranial lesions following TBI. An extensive search was performed in available electronic resources and databases to achieve this aim and discover all the relevant papers. The current study design adhered to MOOSE guidelines (17). The PICO description of the present study is shown below:

The Problem or Population (P) consists of human studies performed on patients with mild TBI. Mild TBI was defined as a GCS between 13 to 15. The index test (I) was the venous serum value of GFAP. The comparison (C) was done with reference standards such as CT scans, MRI, and standard guidelines for detecting sport-related concussions. The outcome (O) was intracranial lesions.

We have not previously registered our study protocol in any registries.

2.2. Search strategy

The keywords were selected by reviewing the MeSH and Emtree terms for Medline (via PubMed) and Embase databases, respectively. Other possibly related keywords were found by consulting the experts in the field and scrutinizing the jargon and related article titles and keywords. Subsequently, using the appropriate combination of the keywords, the exploration was executed in Medline, Embase, Scopus, and Web of Science databases from their inception to the end of April 2022. The detailed search queries on each database are presented in appendix 1. In addition, a manual search was done on the bibliography of related articles

† **Corresponding Author:** Mahmoud Yousefifard; Physiology Research Center, Iran University of Medical Sciences, Hemmat Highway, P.O Box: 14665-354, Tehran, Iran; Phone/Fax: +982186704771; Email: yousefifard.m@iums.ac.ir, ORCID: https://orcid.org/0000-0001-5181-4985.

and results obtained from Google and Google Scholar motor search engines.

2.3. Eligibility criteria

Diagnostic accuracy studies performed on the serum value of GFAP in mild TBI patients were considered relevant. Human studies on adult patients (age>15 years old) were chosen, regardless of participants' sex and ethnicity. Exclusion criteria included pediatrics studies, report of diagnostic value of GFAP combined with other biomarkers (without reporting the GFAP alone), no discrimination of TBI severity based on GCS, mild TBI without intracranial lesions as the outcome of the study, being performed in the prehospital setting, assessing the prognostic value of GFAP, and preclinical studies. We also excluded duplicated reports, reports with inadequate data on sensitivity/specificity or any corresponding values essential for computation of true positive (TP), true negative (TN), false positive (FP), and false-negative (FN), retracted articles, and reviews. We applied no restrictions on the language, geographical location, or publication year during our survey. We also excluded studies assessing the biomarker of interest qualitatively. If the serial serum level of GFAP was evaluated in a study, the first observation was included in the meta-analysis.

2.4. Screening and data extraction

Records collected during systematic and manual searches were exported to Endnote version 20.0 software (Clarivate Analytics, Philadelphia, PA, USA), and duplicates were removed. Two independent researchers screened the records by their titles and abstracts and determined those deemed as possibly related and retrieved the full text of relevant articles. Any discordances were resolved by discussion or consulting the third researcher. Eligible studies based on the abovementioned inclusion and exclusion criteria were included for data collection.

We extracted the data on study information (design, first author name, study time and location, publication year), patients' characteristics (sample size and demographics, level of consciousness based on GCS), outcome definition and standard reference, overall number and demographics of outcome and non-outcome groups, serum GFAP assay method, the time elapsed from the traumatic accident until blood acquisition, recommended GFAP cut-off points and associated sensitivity and specificity. Whenever two or more articles were extracted from the same registry, the article with larger sample size or longer follow-up duration was selected to be included. Additionally, if evaluated values were reported in distinct subgroups (e.g., age groups, sex groups, etc.), the data was documented and analyzed corresponding to that group. Reviewers manually entered all the extracted data into a predefined checklist in an Excel sheet (Microsoft, Redmond, Washington, USA).

2.5. Risk of bias assessment

The methodological quality of included articles was assessed using the Quality Assessment of Diagnostic Accuracy Studies Version 2 (QUADAS-2) tool (18). This implementation involves risk of bias and applicability, which were evaluated and reported in each article by two independent researchers. QUADAS-2 instruction classifies scores into three levels: low risk, high risk, and unclear. Any disagreements were addressed by discussion or consulting with the third researcher.

2.6. Level of evidence

Two independent reviewers determined the level of evidence for our primary interest outcome using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework (19). The GRADE framework consists of subjective evaluation of five domains of risk of bias, imprecision, inconsistency, indirectness, and publication bias.

2.7. Statistical analysis

Analyses were performed using STATA 17.0 statistical software. The studies were summarized and sorted based on their diagnostic value. Attaining the TP, TN, FP, and FN values was the priority in the data collection process. If the aforementioned data was not reported in the articles, the authors were contacted through email and asked to provide the required data. Finally, in the case of the authors' unresponsiveness, the data were extracted by employing analytics on reported sensitivity and specificity. Analyses were performed using the "Midas" package of STATA, which pools article diagnostic value data using a bivariate mixed-effects binary regression modeling framework. The result was provided as pooled sensitivity, specificity, diagnostic score and diagnostic odds ratio, and area under the summary receiver operating characteristic curve (SROC) with a 95% confidence interval (95% CI).

To measure the heterogeneity between studies, I2 statistics were performed. Whenever heterogeneity (I2>50%) was found, subgroup analysis was carried out to investigate the source of heterogeneity. Since three studies included a small portion of moderate TBI patients (1.0% to 3.6% of their total sample size), a sensitivity analysis was applied to studies that included only mild TBI patients. In addition, a sensitivity analysis was performed according to the definition of the non-TBI group and the setting of patients (mild-TBI vs. sport-related concussion). Meta-analysis was performed when the required data were reported in at least four distinct analyses. Publication bias was assessed using Deek's asymmetry funnel plot test.

3. Results

3.1. Screening and specificity of included papers

The search in databases led to 4475 articles. After removing the duplicate items, abstracts of 2352 papers were screened. In the next step, full texts of 84 articles were obtained for a more thorough evaluation. Eventually, 11 related articles (20-30) were introduced into the meta-analysis. Figure 1 represents the inclusion process and reasons for exclusions.

The eventual eligible papers included 8 cohort studies, 2 clinical trials, and 1 cross-sectional study. All studies were conducted on suspected or confirmed TBI patients who attended the hospital. The control group was composed of CT-negative patients in 10 papers, and both CT-negative and healthy individuals in 1 study. These studies included 4978 individuals (907 TBI patients and 4071 non-TBI subjects). The average age of included patients was 24 to 56.0 years old. Diagnosis of TBI was achieved employing CT scan or MRI in all studies.

In all studies, the time interval between head trauma and GFAP measurement was less than 24 hours post-injury. Eight studies investigated mild TBI (21-25, 27, 28, 30), and 3 explored mild to moderate injuries (20, 26, 29). It is worth mentioning that moderate TBI cases comprised a small portion of all participants (1-3.6% of the whole population), so the study was mainly performed on mild TBI cases. It must be noted that in the included studies, data were reported in various subgroups and different GFAP cut-off points; therefore, data were formulated into 30 distinctive analyses in the current meta-analysis. Table 1 depicts a summary of included studies' characteristics.

3.2. Risk of bias

To investigate the risk of bias, the QUADAS-2 instrument was utilized. The risk of bias in all articles was categorized as low risk (Table 2). In conclusion, the overall risk of bias score was low.

3.3. Diagnostic value of GFAP in detecting intracranial lesions in mild TBI

The pooled analysis implies that the area under the SROC curve for GFAP serum level in mild TBI is 0.75 (95% CI: 0.71 to 0.78) (Figure 2). Sensitivity and specificity of this biomarker were calculated as 0.83 (95% CI: 0.78 to 0.87) and 0.38 (95% CI: 0.27 to 0.59), respectively (Figure 3). Diagnostic score and diagnostic odds ratio of GFAP in the detection of intracranial lesions in mild TBI were calculated to be 1.13 (95% CI: 0.53 to 1.74) and 3.11 (95% CI: 1.69 to 5.72), respectively (Figure 4).

3.4. Subgroup analysis

Subgroup analyses were performed in response to apparent heterogeneity among articles in analyses (I2 value between 91.55% and 100%). The findings of this analysis are presented in table 3. As was speculated, the type of the study had a profound impact on the findings. After performing separate analyses based on study type, the heterogeneity between studies decreased significantly and was figured to be 0.0%. Over and above that, the value for GFAP sensitivity in detection of intracranial lesions in mild TBI was evaluated as 0.62 (95% CI: 0.25, 1.00) for cross-sectional studies and 0.84 (95% CI: 0.79, 0.89) for cohorts, which can be concluded that cross-sectional studies had the least reported value among other studies.

Another subgroup analysis was performed based on reported GFAP cut-off points. The reported cut-off points varied from 3.0 to 848 pg/mL. As a result, they were grouped into three sets with values of less than 100 pg/mL, 100-300 pg/ml, and above 400 pg/mL. Analyses revealed that another source of heterogeneity among studies was variability in cut-off points recommended by studies. Grouping of analyses based on cut-off points led to a reduction in the heterogeneity to 0%. The sensitivity and specificity of GFAP in cut-offs below 100 pg/mL were estimated to 0.83 (95% CI: 0.78 to 0.89) and 0.39 (95% CI: 0.24 to 0.53), respectively. Additionally, the sensitivity and specificity of this biomarker in cut-offs between 100-300 pg/mL were 0.79 (95% CI: 0.67 to 0.90) and 0.32 (95% CI: 0.08 to 0.57), respectively. Finally, in cut-offs above 400 pg/mL the sensitivity and specificity were measured as 0.89 (95% CI:
0.81 to 0.96) and 0.43 (95% CI: 0.15 to 0.71), respectively. Seemingly, in cut-offs below 100 pg/mL and above 400 pg/mL, GFAP has the optimum performance in detecting intracranial lesions among mild TBI patients. There were 17 vs. 5 analyses in the group with cut-offs below 100 pg/mL and above 400 pg/mL, respectively. As a result, a cut-off below 100 pg/mL seems to be associated with more reliable diagnostic accuracy for GFAP in identifying intracranial lesions in mild TBI cases (Table 3).

3.5. Sensitivity analysis

In addition to subgroup analysis, sensitivity analysis was performed in the current study. Sensitivity analysis on studies in which the control group consisted of CT-negative patients revealed that the difference in the control group also does not influence sensitivity (sensitivity=0.84; p=0.16) and specificity (specificity=0.40; p=0.86) of GFAP in diagnosis of intracranial lesions of mild TBI patients. On the contrary, sensitivity analysis indicated that the studies that exclusively recruited mild TBI cases have reported significantly lower sensitivity than studies on mild to moderate TBI patient populations (0.80 vs. 0.95; p<0.001). However, it has no effect on specificity of GFAP (0.38 vs. 0.42; p=0.93) (Table 4).

3.6. Publication bias

Deek's asymmetry funnel plot test was performed to assess publication bias. The analysis implied no possible publication bias in the included studies (p=0.97) (Figure 5).

3.7. Certainty of evidence

There was high heterogeneity among included study, but our subgroup analysis could find the sources of heterogeneity. The overall grade was rated up one point due to large magnitude of effect size (based on diagnostic odds ratio). So, the level of evidence was graded moderate (Table 4).

4. Discussion

Our findings demonstrated that GFAP serum level is capable of detecting intracranial lesions in mild TBI patients (AUC:0.75 with 95% CI: 0.71 to 0.78). Our pooled analysis indicated that GFAP has a promising diagnostic value with 83% sensitivity and 39% specificity in cut-offs below 100 pg/ml. Utilizing serum GFAP measurement may aid healthcare providers in being more selective in imaging acquisition, while providing safe and efficient care in the emergency department and acute care settings. Measuring serum GFAP as a traumatic brain injury signature would lower the rate of unnecessary ionizing imaging and shorten the time spent for in-patient observation in the high-burden ED.

Based on our investigations, the proposed cut points for GFAP among studies varied in a range of 3-848 pg/ml. As a result, we categorized these cut points into 3 groups with values of less than 100 pg/ml, 100-300 pg/ml, and above 400 pg/ml based on the fact that the increase in cut point results in lower sensitivity and higher specificity (31). The analyses indicated that the serum level of GFAP has the optimum performance in cut-offs below 100 pg/ml and above 400 pg/ml. However, only 5 studies reported cut-offs above 400 pg/ml, compared to 17 studies on cut-offs below 100 pg/ml. Therefore, we can only rely on findings of cut-offs below 100 pg/ml, and there is a need to investigate the optimum cut-offs in future studies.

Application of imaging for diagnosis of sport-related concussion is limited when considering the fact that athletes sustain multiple head traumas during their sport career. So, diagnosis of this type of mild TBI is based on clinical judgment of team physicians and recommended guidelines. Meier et al. reported that GFAP is not significantly elevated from baseline preinjury level following sport-related concussion in football players, except for athletes with loss of consciousness and amnesia (32). Asken et al. concordantly showed moderate diagnostic accuracy of GFAP (AUC:0.67, 95%CI:0.57–0.78) for sport-related concussion and demonstrated superiority of S100b (AUC:0.72, 95%CU:0.63–0.81) in this regard (33). It can be concluded that this biomarker holds moderate potential in detecting clinically diagnosed sports-related concussions. Nevertheless, addition of objective brain biomarkers would be beneficial in diagnosis of concussion among athletes who have minimal or less severe self-reporting symptoms and thus, imposing a challenge for physicians. Objective assessment of biomarkers can reduce the reliance on symptoms for diagnosis of concussion as some athletes may deliberately not report them to avoid being prohibited from participation in the competitions (32). Also, the rise of biomarkers following concussion can represent the pathophysiological responses underlying the concussion and could provide prognostic information regarding the required time before clearance for full return to sport even when symptoms are alleviated. However, only 2 articles on the diagnostic accuracy of GFAP in sport-related concussion were found in our search, and further investigations are suggested in this regard.

The reference standard imaging in many studies was the CT scan, and this would affect the judgment of the sensitivity and specificity of GFAP, as some forms of brain damage, such as micro-injuries and diffuse axonal injury (DAI), are not conspicuously visible in CT scans and require more advanced neuroimaging modalities such as MRI (34). Moreover, in the current meta-analysis, there were 3 studies on mild to moderate TBI patients. However, there were 1%, 1.6%, and 3.6% of patients in the moderate TBI group. Seemingly, a significant proportion of patients were in the mild TBI group; hence, including these studies in the pooled analysis is justifiable. We believe that akin to cardiac troponin for diagnosis of myocardial damage, a singular value of initial post-traumatic GFAP may not be able to provide concise and valid information on the extent of the patient's central nervous system (CNS) damage. Serial measurements of GFAP could be more informative since its concentration pattern, and bulk release can shed light on the dynamics of brain injury evolution and identification of delayed injuries. Additionally, the mere serum value of GFAP is not capable of characterizing different types of brain lesions (i.e., skull fractures, subdural hematoma, contusion, sub-arachnoid hemorrhage, etc.) and development of a model consisting of a panel of blood biomarkers originating from multiple types of cells engaged in TBI is under investigation. In 2018, the Food and Drug Administration (FDA) approved the clinical application of a semiquantitative kit developed by Banyan Biomarkers, Inc. for the measurement of GFAP and UCH-L1 to reduce the overuse of CT imaging in TBI (13). The concurrent measurement of UCH-L1 and GFAP enhanced their separate diagnostic values and 97.6% sensitivity and 37.4% specificity were reported when a combination assessment was performed (20). Other studies evaluated the incorporation of inflammatory, endothelial, and neural damage markers to reach a more favorable diagnostic accuracy. However, this multiplex assessment is associated with higher costs compared to the CT scan

and constrains health resources (24, 35). The value of integrating blood biomarkers into the existing clinical decision rules also deserves further research.

Kinetically, GFAP rises immediately after TBI with a peak level reached during the first 24 hours following injury and declines to near normal value in the next 14 to 30 days post-injury (22, 36). Although GFAP persists in circulation for a long time, the majority of studies included in this review had a time interval of less than 24 hours between traumatic accident and blood draw; hence, it is speculated that the delayed measurement of GFAP may yield different diagnostic value (4, 37). Moreover, the primary laboratory technique for GFAP assay was reported to be ELISA, which could take time for results to be prepared. Further studies are required to endorse the clinical utility of GFAP at bedside evaluation by introducing easy and rapid measurement techniques.

It should be noted that the presented cut-offs and associated sensitivity and specificity cannot be adopted for pediatric TBI or birth-inflicted brain injuries, since we primarily focused on adults. Additionally, caution should be implemented on the approach to GFAP values in patients with neuropsychological or renal function impairment, as these two disease categories may impact the serum GFAP concertation as a source of production and excretion, respectively. This brought up concerns about the reduced accuracy of GFAP in the diagnosis of intracranial injuries among the geriatric population, who suffer a higher rate of comorbidities and, are significantly more prone to harbor traumatic lesions yet symptomatically silent on presentation. To overcome this challenge, Gardner et al. recommended the integration of Tau level measurement to improve the diagnostic accuracy of GFAP in elder patients (38). Finally, we didn't aim to explore the cost-effectiveness of the proposed biomarker assessment, but it is worth stating that some studies reported controversial results on the costs of TBI biomarkers, and further studies in different contexts and healthcare systems are warranted to reach a common conclusion (38, 39).

5. Conclusions

The findings of the current review demonstrated that with a moderate level of evidence, GFAP serum level is capable of detecting intracranial lesions in mild TBI patients and might facilitate the clinical decision-making and delivery of targeted therapeutic care. Additionally, sensitivity and specificity of GFAP in cut-offs below 100 pg/ml were measured to be 0.83 and 0.42, respectively. Taken together, the measurement of GFAP after injury may be beneficial in mild TBI diagnosis and prevents unnecessary CT scans if used as a complementary indicator to individual patient clinical characteristics and examinations.

6. Declarations

6.1. Acknowledgments

Not applicable.

6.2. Ethics approval

Not applicable.

6.3. Patient consent

Not applicable

6.4. Informed consent

Not applicable.

6.5. Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information file.

6.6. Permission to reproduce material from other sources

Not applicable.

6.7. Clinical trial registration

Not applicable.

6.8. Conflicting interests

The authors declare that they have no competing interests.

6.9. Funding

Maragheh University of Medical Sciences supported this research.

6.10. Author contributions

Ideation and design: MY, and SA. Data collection: MY, SA, AB, AS, SRD. Analysis: MY, MA. Interpretation of results: All authors.

Drafting the work: MY, SA, MA. Revising draft critically for important intellectual content: All authors. The authors read and approved the final manuscript.

References

1. Gutierre MU, Telles JPM, Welling LC, Rabelo NN, Teixeira MJ, Figueiredo EG. Biomarkers for traumatic brain injury: a short review. Neurosurg Rev. 2021;44(4):2091-7.
2. James SL, Theadom A, Ellenbogen RG, Bannick MS, Montjoy-Venning W, Lucchesi LR, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(1):56-87.

3. Lingsma HF, Yue JK, Maas AI, Steyerberg EW, Manley GT. Outcome prediction after mild and complicated mild traumatic brain injury: external validation of existing models and identification of new predictors using the TRACK-TBI pilot study. J Neurotrauma. 2015;32(2):83-94.
4. Bouvier D, Oris C, Brailova M, Durif J, Sapin V. Interest of blood biomarkers to predict lesions in medical imaging in the context of mild traumatic brain injury. Clin Biochem. 2020;85:5-11.
5. Calvi MR, Beretta L, Dell'Acqua A, Anzalone N, Licini G, Gemma M. Early prognosis after severe traumatic brain injury with minor or absent computed tomography scan lesions. J Trauma Acute Care Surg. 2011;70(2):447-51.
6. Laalo JP, Kurki TJ, Sonninen PH, Tenovuo OS. Reliability of diagnosis of traumatic brain injury by computed tomography in the acute phase. J Neurotrauma. 2009;26(12):2169-78.
7. Callahan MJ, MacDougall RD, Bixby SD, Voss SD, Robertson RL, Cravero JP. Ionizing radiation from computed tomography versus anesthesia for magnetic resonance imaging in infants and children: patient safety considerations. Pediatr Radiol. 2018;48(1):21-30.
8. Isokuortti H, Iverson GL, Silverberg ND, Kataja A, Brander A, Öhman J, et al. Characterizing the type and location of intracranial abnormalities in mild traumatic brain injury. J Neurosurg. 2018;129(6):1588-97.
9. Amoo M, Henry J, O'Halloran PJ, Brennan P, Husien MB, Campbell M, et al. S100B, GFAP, UCH-L1 and NSE as predictors of abnormalities on CT imaging following mild traumatic brain injury: a systematic review and meta-analysis of diagnostic test accuracy. Neurosurg Rev. 2022;45(2):1171-93.
10. Nakhjavan-Shahraki B, Yousefifard M, Oraii A, Sarveazad A, Hosseini M. Meta-analysis of neuron specific enolase in predicting pediatric brain injury outcomes. EXCLI J. 2017;16:995.
11. Edalatfar M, Piri SM, Mehrabinejad M-M, Mousavi M-S, Meknatkhah S, Fattahi M-R, et al. Biofluid biomarkers in traumatic brain injury: a systematic scoping review. Neurocrit Care. 2021;35(2):559-72.
12. Wang KK, Munoz Pareja JC, Mondello S, Diaz-Arrastia R, Wellington C, Kenney K, et al. Blood-based traumatic brain injury biomarkers - Clinical utilities and regulatory pathways in the United States, Europe and Canada. Expert Rev Mol Diagn. 2021;21(12):1303-21.
13. Mendoza D, López K, Echeverri R, Pastor L, Rueda S, Fernández Londoño L, et al. Utility of biomarkers in traumatic brain injury: a narrative review. Revista Colombiana de Anestesiologia. 2020;48:155-61.
14. Al-Adli N, Akbik OS, Rail B, Montgomery E, Caldwell C, Barrie U, et al. The Clinical Use of Serum Biomarkers in Traumatic Brain Injury: A Systematic Review Stratified by Injury Severity. World Neurosurg. 2021;155:e418-e38.
15. Seidenfaden S-C, Kjerulff JL, Juul N, Kirkegaard H, Møller MF, Münster A-MB, et al. Diagnostic accuracy of prehospital serum S100B and GFAP in patients with mild traumatic brain injury: a prospective observational multicenter cohort study–"the PreTBI I study". Scand J Trauma Resusc Emerg Med. 2021;29(1):75.
16. Middleton JL. UCH-L1 and GFAP Testing (i-STAT TBI Plasma) for the Detection of Intracranial Injury Following Mild Traumatic Brain Injury. Am Fam Physician. 2022;105(3):313-4.
17. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. JAMA Surg. 2021;156(8):787-8.
18. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
19. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.
20. Bazarian JJ, Biberthaler P, Welch RD, Lewis LM, Barzo P, Bogner-Flatz V, et al. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. Lancet Neurol. 2018;17(9):782-9.
21. Çevik S, Özgenç MM, Güneyk A, Evran Ş, Akkaya E, Çalış F, et al. NRGN, S100B and GFAP levels are significantly increased in patients with structural lesions resulting from mild traumatic brain injuries. Clin Neurol Neurosurg. 2019;183:105380.
22. Clarke GJB, Skandsen T, Zetterberg H, Einarsen CE, Feyling C, Follestad T, et al. One-Year Prospective Study of Plasma Biomarkers From CNS in Patients With Mild Traumatic Brain Injury. Front Neurol. 2021;12:643743.
23. Gardner RC, Rubenstein R, Wang KKW, Korley FK, Yue JK, Yuh EL, et al. Age-Related Differences in Diagnostic Accuracy of Plasma Glial Fibrillary Acidic Protein and Tau for Identifying Acute Intracranial Trauma on Computed Tomography: A TRACK-TBI Study. J Neurotrauma. 2018;35(20):2341-50.
24. Lagerstedt L, Egea-Guerrero JJ, Bustamante A, Rodríguez-Rodríguez A, El Rahal A, Quintana-Diaz M, et al. Combining H-FABP and GFAP increases the capacity to differentiate between CT-positive and CT-negative patients with mild traumatic brain injury. PLoS One. 2018;13(7):e0200394.
25. Okonkwo DO, Puffer RC, Puccio AM, Yuh EL, Yue JK, Diaz-Arrastia R, et al. Point-of-Care Platform Blood Biomarker Testing of Glial Fibrillary Acidic Protein versus S100 Calcium-Binding Protein B for Prediction of Trau-

matic Brain Injuries: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study. J Neurotrauma. 2020;37(23):2460-7.
26. Papa L, Lewis LM, Falk JL, Zhang Z, Silvestri S, Giordano P, et al. Elevated levels of serum glial fibrillary acidic protein breakdown products in mild and moderate traumatic brain injury are associated with intracranial lesions and neurosurgical intervention. Ann Emerg Med. 2012;59(6):471-83.
27. Papa L, Ladde JG, O'Brien JF, Thundiyil JG, Tesar J, Leech S, et al. Evaluation of Glial and Neuronal Blood Biomarkers Compared With Clinical Decision Rules in Assessing the Need for Computed Tomography in Patients With Mild Traumatic Brain Injury. JAMA Netw Open. 2022;5(3):e221302.
28. Posti JP, Takala RSK, Lagerstedt L, Dickens AM, Hossain I, Mohammadian M, et al. Correlation of Blood Biomarkers and Biomarker Panels with Traumatic Findings on Computed Tomography after Traumatic Brain Injury. J Neurotrauma. 2019;36(14):2178-89.
29. Welch RD, Ayaz SI, Lewis LM, Unden J, Chen JY, Mika VH, et al. Ability of Serum Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase-L1, and S100B To Differentiate Normal and Abnormal Head Computed Tomography Findings in Patients with Suspected Mild or Moderate Traumatic Brain Injury. J Neurotrauma. 2016;33(2):203-14.
30. Yue JK, Yuh EL, Korley FK, Winkler EA, Sun X, Puffer RC, et al. Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study. Lancet Neurol. 2019;18(10):953-61.
31. Safari S, Radfar F, Baratloo A. Thoracic injury rule out criteria and NEXUS chest in predicting the risk of traumatic intra-thoracic injuries: A diagnostic accuracy study. Injury. 2018;49(5):959-62.
32. Meier TB, Huber DL, Bohorquez-Montoya L, Nitta ME, Savitz J, Teague TK, et al. A Prospective Study of Acute Blood-Based Biomarkers for Sport-Related Concussion. Ann Neurol. 2020;87(6):907-20.
33. Asken BM, Bauer RM, DeKosky ST, Svingos AM, Hromas G, Boone JK, et al. Concussion BASICS III: Serum biomarker changes following sport-related concussion. Neurology. 2018;91(23):e2133-e43.
34. Yuh EL, Cooper SR, Mukherjee P, Yue JK, Lingsma HF, Gordon WA, et al. Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study. J Neurotrauma. 2014;31(17):1457-77.
35. Sharma R, Rosenberg A, Bennett ER, Laskowitz DT, Acheson SK. A blood-based biomarker panel to risk-stratify mild traumatic brain injury. PLoS One. 2017;12(3):e0173798.
36. Bogoslovsky T, Wilson D, Chen Y, Hanlon D, Gill J, Jeromin A, et al. Increases of Plasma Levels of Glial Fibrillary Acidic Protein, Tau, and Amyloid β up to 90 Days after Traumatic Brain Injury. J Neurotrauma. 2017;34(1):66-73.
37. Thelin EP, Zeiler FA, Ercole A, Mondello S, Büki A, Bellander BM, et al. Serial Sampling of Serum Protein Biomarkers for Monitoring Human Traumatic Brain Injury Dynamics: A Systematic Review. Front Neurol. 2017;8:300.
38. Calcagnile O, Anell A, Undén J. The addition of S100B to guidelines for management of mild head injury is potentially cost saving. BMC Neurol. 2016;16(1):200.
39. Ruan S, Noyes K, Bazarian JJ. The economic impact of S-100B as a pre-head CT screening test on emergency department management of adult patients with mild traumatic brain injury. J Neurotrauma. 2009;26(10):1655-64.

Table 1: Summary characteristics of included studies

Author, year, country	Study type	GCS1	Sample size	Mean Age (year)	Male (n)	Assay	TBI criteria	Timing (hrs)	TBI patients (n)	Non-TBI patients (n)	Cut-offs (pg/ml)
Bazarian, 2018, Multiple countries	Trial	9 to 15	1780	49.9	1107	ELISA	CT	<12	107	1673	22
Cevik, 2019, Turkey	Cross-sectional	14 to 15	48	24	38	ELISA	CT	<4	24	24	230
Clarke, 2021, Norway	Cohort	13 to 15	343	32.5	206	ELISA	CT and MRI	<24	76	267	57.5
Gardner, 2018, USA	Cohort	13 to 15	169	41.88	127	ELISA	CT	<24	56	113	430
Lagerstedt, 2018, Spain and Switzerland	Cohort	15	241	48.7 to 52.4	96 and 67	ELISA	CT	<6	38	203	97.3
Okonkwo, 2020, USA	Trial	13 to 15	1137	40.12	435	ELISA	CT	<24	358	779	13.1, 37.8, 113.3, 190.1
Papa, 2012, USA	Cohort	9 to 15	117	38		ELISA	CT	<4	32	85	35
Papa, 2022, USA	Cohort	13 to 15	349	40	240	ELISA	CT	<4	23	326	67
Posti, 2019, Finland	Cohort	13 to 15	93	56	37	ELISA	CT	<24	37	56	66.62, 132, and 540
Welch, 2016, Multiple countries	Cohort	9 to 15	251	45.6	151	ELISA	CT	6	36	215	15
Yue, 2019, USA	Cohort	13 to 15	450	36.3	285	ELISA	MRI	<24	120	330	4.4, 12.95, 25.15, 71.95, 282.7, and 848.75,

1- Data was presented as range.
CT: Computed tomography scan; ELISA: enzyme-linked immunosorbent assay; GCS: Glasgow coma scale; N: Number; TBI: Traumatic brain injury; MRI: magnetic resonance imaging.

Table 2: Risk of bias assessment of included studies based on QUADAS-2 tool

Study	Risk of bias				Applicability			
	Patients' selection	Index test	Reference standard	Flow and timing	Patients' selection	Index test	Reference standard	Overall
Bazarian, 2018	☺	☺	☺	☺	☺	☺	☺	☺
Cevik, 2019	☺	☺	☺	☺	☺	☺	☺	☺
Clarke, 2021	☺	☺	☺	☺	☺	☺	☺	☺
Gardner, 2018	☺	☺	☺	☺	☺	☺	☺	☺
Lagerstedt, 2018	☺	☺	☺	☺	☺	☺	☺	☺
Okonkwo, 2020	☺	☺	☺	☺	☺	☺	☺	☺
Papa, 2012	☺	☺	☺	☺	☺	☺	☺	☺
Papa, 2022	☺	☺	☺	☺	☺	☺	☺	☺
Posti, 2019	☺	☺	☺	☺	☺	☺	☺	☺
Welch, 2016	☺	☺	☺	☺	☺	☺	☺	☺
Yue, 2019	☺	☺	☺	☺	☺	☺	☺	☺

☺: Low risk

Table 3: Subgroup and sensitivity analyses for identification of source of heterogeneity among included studies

Parameter	No. of analyses	Sensitivity	P	Specificity	p2	I2(%)
Study type						
Cohort	21	0.84 [0.79, 0.89]	0.03	0.42 [0.29, 0.55]	0.16	0.0
Cross-sectional	1	0.62 [0.25, 1.00]	0.14	0.39 [0.27, 0.50]	0.64	0.0
Trial	5	0.83 [0.73, 0.92]	0.01	0.27 [0.06, 0.47]	0.65	0.0
GFAP cut-offs (pg/ml)						
<100	17	0.83 [0.78, 0.89]	<0.001	0.39 [0.24, 0.53]	0.60	0.0
100 to 300	5	0.79 [0.67, 0.90]	<0.001	0.32 [0.08, 0.57]	0.94	0.0
>400	5	0.89 [0.81, 0.96]	0.12	0.43 [0.15, 0.71]	0.60	0.0
Control group						
CT negative patients	25	0.84 [0.79, 0.89]	0.16	0.40 [0.28, 0.52]	0.86	0.0
Healthy control	2	0.79 [0.61, 0.97]	0.15	0.22 [0.00, 0.52]	42	0.0
Severity of TBI						
Mild	24	0.80 [0.76, 0.84]	<0.001	0.38 [0.25, 0.50]	0.93	82.0
Moderate to mild	3	0.95 [0.92, 0.99]	0.95	0.42 [0.08, 0.77]	0.74	82.0

GFAP: glial fibrillary acidic protein; CT: computed tomography scan; TBI: Traumatic brain injuries.

Table 4: Certainty of evidence based on GRADE framework

Outcome	Sample size	Diagnostic odds ratio	Risk of bias	Imprecision	Inconsistency (I2)	Indirectness	Publication bias	Judgment and level of evidence*
Intracranial lesion	4978	3.11 (95% CI: 1.69 to 5.72)	Not serious	Not present	Not present	Not present	Not present	Moderate: ⊕⊕⊕⊕ Rated up one point: • Large magnitude of effect**

*, based on our judgment

**, based on diagnostic odds ratio

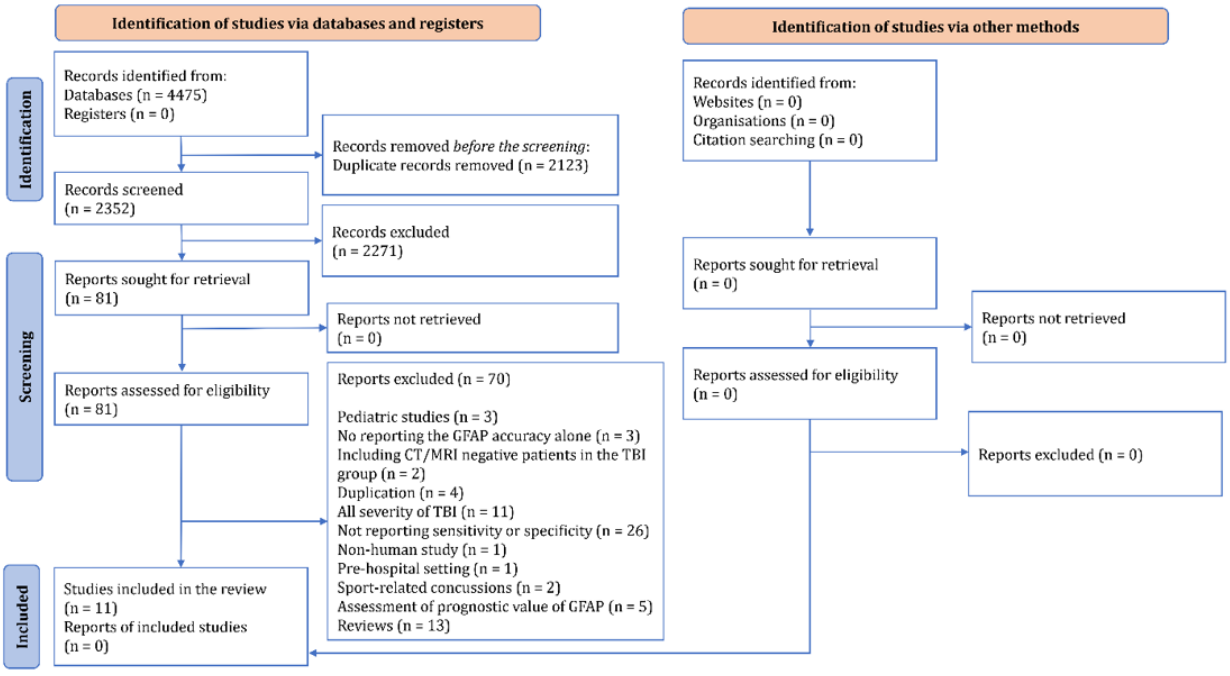

Figure 1: Flow diagram of screening in current meta-analysis. GFAP: Glial fibrillary acidic protein; CT: Computed tomography scan; MRI: Magnetic resonance imaging; TBI: Traumatic brain injury.

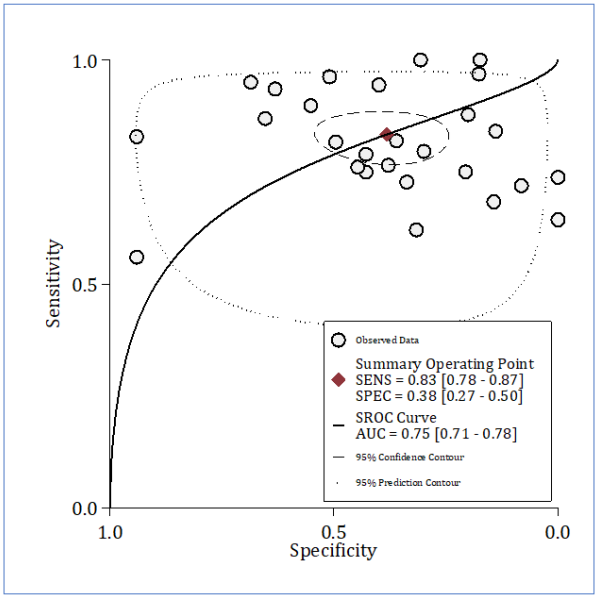

Figure 2: Summary receiver operating characteristics (SROC) of glial fibrillary acidic protein)GFAP(in diagnosis of mild traumatic brain injuries. AUC: Area under the curve; SENS: Sensitivity; SPEC: Specificity.

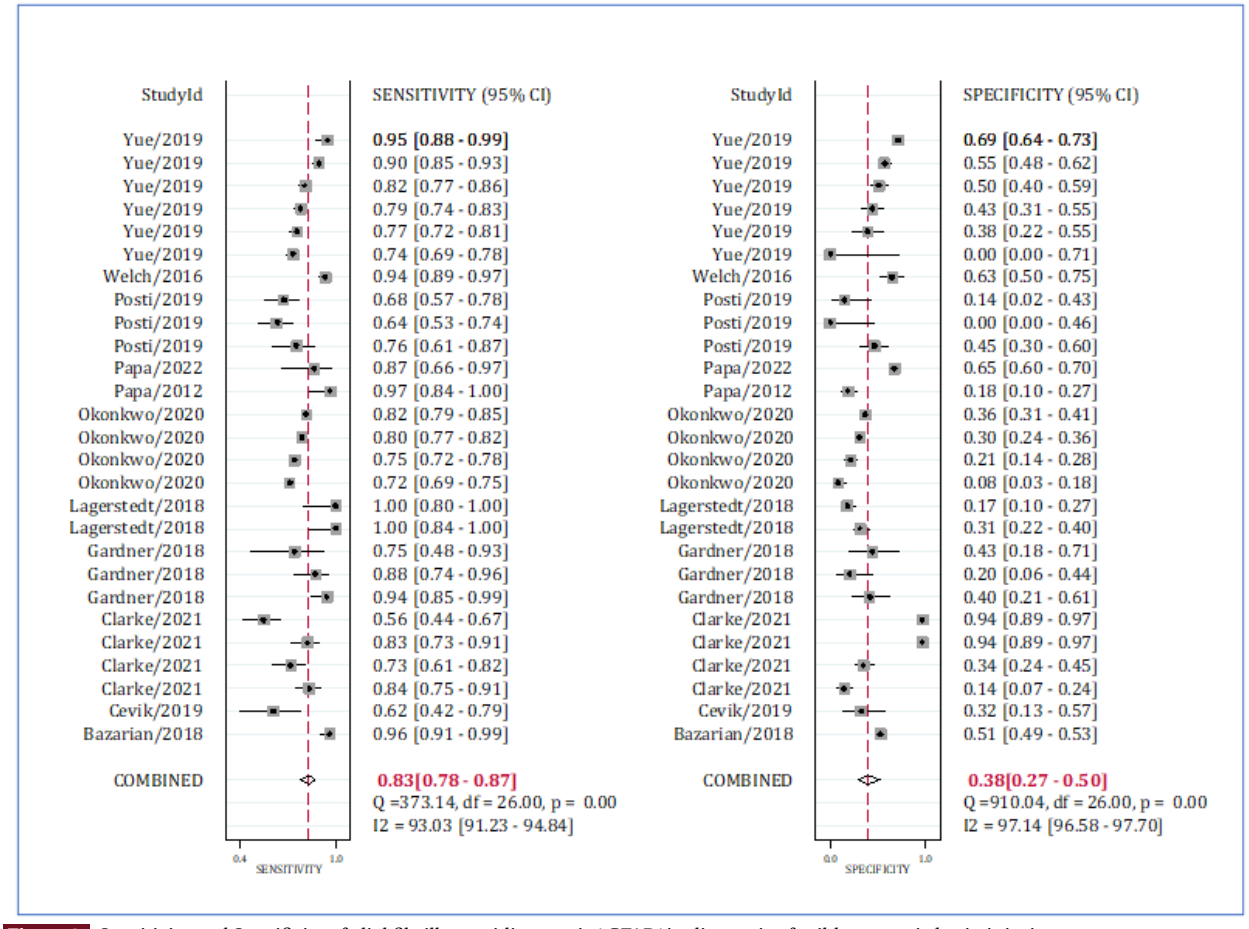

Figure 3: Sensitivity and Specificity of glial fibrillary acidic protein)GFAP(in diagnosis of mild traumatic brain injuries.

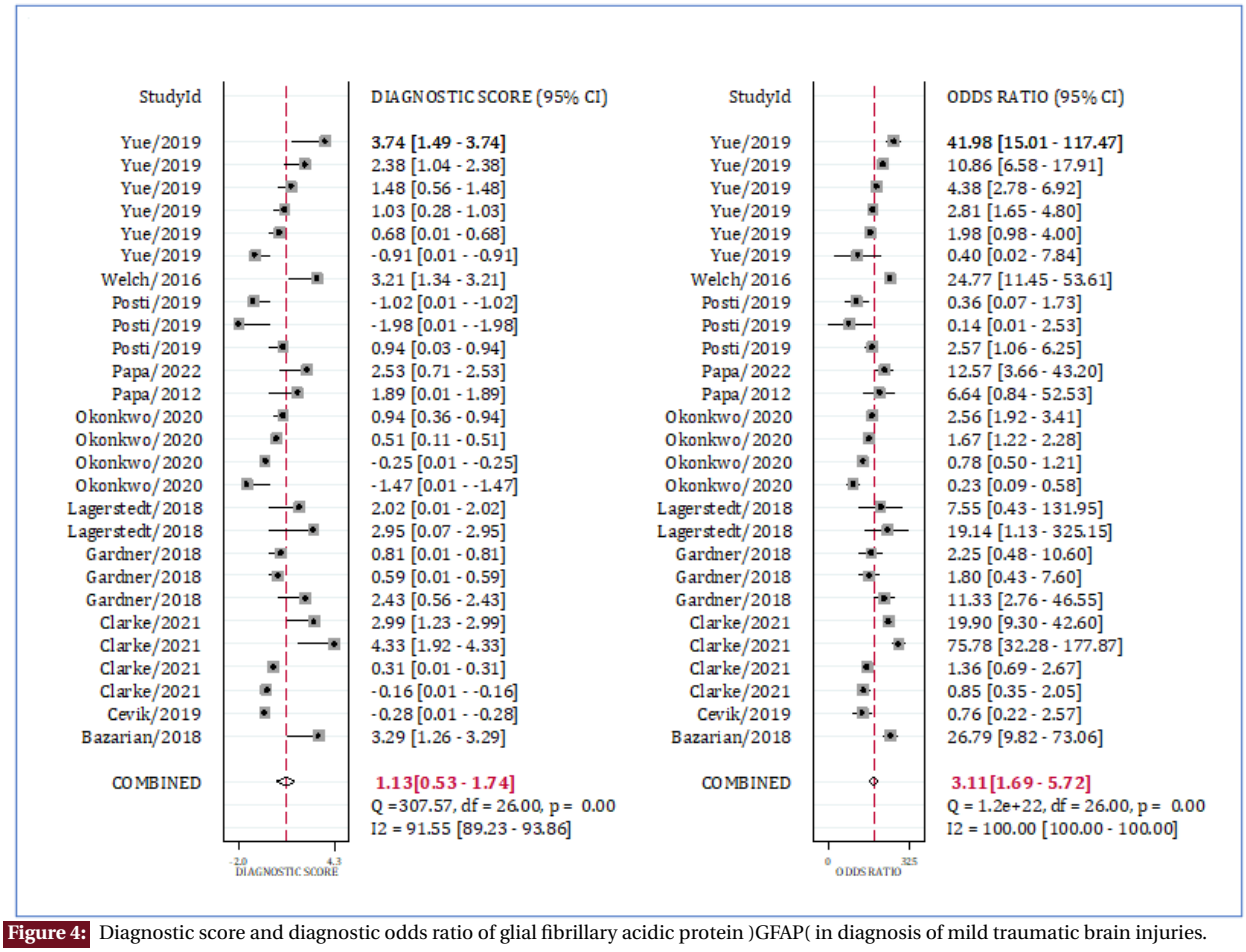

Figure 4: Diagnostic score and diagnostic odds ratio of glial fibrillary acidic protein)GFAP(in diagnosis of mild traumatic brain injuries.

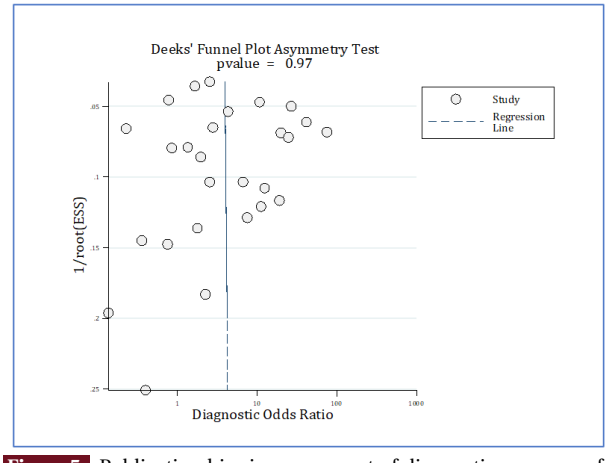

Figure 5: Publication bias in assessment of diagnostic accuracy of glial fibrillary acidic protein)GFAP(in detection of mild traumatic brain injuries.