The diagnostic and prognostic value of S-100β protein in traumatic brain injuries

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Abstract

Background: The World Health Organization has stated that traumatic brain injuries (TBI) will be considered one of the most significant causes of death and disability in the near future. High costs to the healthcare system associated with TBI management have been well documented. Studies investigating the diagnostic and prognostic ability of the Glasgow Coma Scale (GCS), computed tomography (CT) scans, and magnetic resonance imaging (MRI) scans for TBI diagnosis are essential, however each has several pitfalls. The use of biomarkers has been proposed as an inexpensive alternative to assist with this clinical dilemma. Therefore, this literature review will examine the diagnostic and prognostic value of the most promising biomarker in TBI research, S-100β. **Methods:** A review was conducted spanning from 2000-2017 using the following databases: PubMed, Google Scholar and Scopus. Key search and MeSH terms included "Traumatic Brain Injury," "Biomarkers," "Diagnosis," and "Prognosis." Supplemental information was acquired by reviewing journals and systematic review bibliographies. **Results:** Six papers were analyzed and reviewed. S-100β protein was found to be a sensitive biomarker for mild to severe TBIs, while potentially reducing the costs of TBI management through reduced use of CT scans and hospitalizations. Elevated S-100β concentrations on admission were strongly correlated to elevated intracranial pressure and was a predictor of mortality. S-100β is not without its limitations, which includes debatable specificities and poor temporal resolution. **Conclusion:** It has been demonstrated that S-100β may be a promising biomarker for TBIs, with high sensitivity and negative predictive values, however controversy remains with respect to its relationship with mild TBIs (mTBI). Furthermore, S-100β has shown to reduce healthcare costs by preventing unnecessary CT scans

and hospitalizations in those with mTBIs. Elevated levels measured on admission have proven to be a prognostic indicator for increased intracranial pressure and mortality.

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Introduction

Background

Traumatic brain injuries (TBIs) present many unique obstacles to primary care practitioners in the healthcare system worldwide. As reported by the World Health Organization, TBIs will be the major cause of death and disability by the year 2020 (1). A TBI has been defined as an alteration in brain function or other evidence of brain abnormality, resulting from an external force applied to the head (2). Healthcare associated costs of TBIs have become a burden to the system's resources when considering time, finances and the human workforce. In the United States (US), the total lifetime costs of fatal, hospitalized, and non-hospitalized TBI cases that were medically treated in the year 2000 were estimated to be $60.4 billion, including productivity losses of $51.2 billion (3). In 2003, the US recorded approximately 1,565,000 TBIs, which included 224,000 ED visits, 290,000 hospitalizations, and 51,000 deaths (4). Additionally, a Canadian study found that severe TBIs accounted for 36,976 (46.9%) hospital admissions (5). Despite the apparent strain TBIs present on the healthcare system, classification of TBIs remains a contentious issue, resulting in diagnostic and prognostic challenges. Corrigan et al. (3) have expressed this sentiment by stating, "Measurement of TBI severity is essential to triage patient management and prognosticate injury trajectory but does not equate to outcome (p.74)."

Various tools exist to facilitate the diagnosis of a TBI, one of which is the Glasgow Coma Scale (GCS). Developed in 1974 in response to a need for an accepted universal method of communicating different states of altered levels of consciousness (6), the GCS has been essential in attempting to establish a clinical definition, prognosis, and guide to early management decisions (7). Traditionally, a GCS score of 14 or 15 is associated with mild TBI (mTBI);

moderate TBI is described as a GCS score of 9–13, and severe TBI is defined by a GCS score of 8 and below (8). Even with the GCS, however, a universally accepted definition of mTBI remains elusive.

Other commonly used TBI diagnostic tools include computed tomography (CT) scans and magnetic resonance imaging (MRI), and are considered the next steps in the evaluation of a head injury. These imaging techniques are known to be costly to the system, time consuming, and at times unnecessary. Indeed, a study in 2014 by Bermingham (9) revealed the cost of an MRI in Ontario to be $880.00, whereas the cost of a CT scan was approximately $517.00. The Canadian CT Head Rule study (CCHR) attempted to clarify this issue by developing clinical decision rules to determine clinical criteria for CT scanning. In the CCHR study (10), it was concluded that a head CT scan in mTBIs is indicated only in patients with one of five high-risk factors:

1. failure to reach a GCS score of 15 within two hours of injury; or
2. suspected open skull fracture; or
3. sign of basal skull fracture; or
4. vomiting more than once; or
5. age greater than 64 years.

A criticism to the CCHR is that the rule uses loss of consciousness (LOC) or amnesia as entry criteria, both of which are not required in the diagnosis of a concussion (11), a subset of mTBI. As a result, potential mTBIs may not receive appropriate care. Bruns and Jagoda (12) further expanded on the intrinsic problem of the CT scan stating, “Existing literature does not identify which mTBI patients with intracranial lesions clinically deteriorate, nor does it define the relationship between acute traumatic intracranial lesions and the development of post-concussive

symptoms (p.131).” Alternatively, another study points out that CT scans may be useful in identifying a structural injury to the brain region for severe and moderate TBIs, whereas they remain less useful for mTBIs due to the lack of structural damage to the brain (13). Le and Gean (13) continued by emphasizing the importance of MRI in acute TBI patients when the neurological findings appear to be functional as opposed to structural, and as a result are unexplained by CT imaging. The downside to MRIs include length of time needed to perform the evaluation, complications due to metal embedded in the body, and lack of patient tolerance for the closeness and noise of the device (14). The drawbacks to CT scans include a lack of sensitivity for diffuse axonal injury, early ischemia, and subtle posterior fossa pathology (7), in addition to exposure to ionizing radiation (15). Having an alternative method to diagnose TBIs and offer a prognosis would make the management of these injuries more efficient and less taxing on the medical system. For these reasons, the use of biomarkers for the diagnosis and management of TBIs would assist with this clinical dilemma.

Biomarkers for Brain Injury

Biomarkers play an important role in the diagnosis of several medical conditions, including myocardial infarctions, congestive heart failure, acute kidney injuries, and sepsis. Recent attempts have been made at identifying a biomarker of TBI, however many limitations have yet to be overcome in this area of research. Ideally, a biomarker for TBI should be sensitive and specific to a disease state, which could help in elucidating the underlying etiology and help guide therapy (14, 16). Other considerations for an ideal biomarker include a rapid appearance in interstitial fluids after injury and correlation with brain function, outcome and/or neuroimaging data (17, 18). Several biomarkers have been researched in the field of neuroscience and include,

lactate dehydrogenase, creatinine kinase, microtubule-associated protein tau, neurofilament, myelin basic protein, amyloid β, neuron-specific enolase, glial fibrillary acidic protein, ubiquitin carboxyl-terminal hydrolase isoenzyme L1, TNF-a, and S-100β protein (19, 20). Researchers have identified S-100β as one of the more specific biochemical markers of brain damage, and as a result it is currently one of the most studied TBI biomarkers (21, 22, 23, 24, 25).

Biochemistry and Properties of S-100β Protein

S-100β is a protein that is most abundant in the glial cells of both the central and peripheral nervous systems (21, 23, 26), but may also be found in cells such as adipocytes, chondrocytes, and melanoma cells (23, 27). S-100β is a membrane-bound homo- or hetero-dimer protein, bound mainly to calcium within the cell, and is involved in the cross-bridging of cytoskeleton components (23, 28). This protein can be measured in arterial and venous serum or plasma, and has been found to be metabolized in the kidney and excreted in the urine (23). It has also been reported that its half-life is approximately 30 minutes, with a rapid decrease of serum S-100β occurring within one hour of its release (28). Interestingly, Ingebrigtsen et al. (21) has shown increased serum S-100β concentrations within 12 hours following a minor head injury, likely due to disruption of the blood brain barrier. Despite the belief that this protein is specific to TBIs, its release has been noted in response to non-brain-related stressors, with elevated serum S-100β levels reported in patients with melanoma (28), uncomplicated orthopedic fractures (29), and following aerobic exercise (30). Raabe et al. (23) have also reported minor concentrations in fat tissue, chondrocytes, skeleton muscle and parenchyma organs. As a result, the use of S-100β as the ideal biomarker for TBIs remains controversial, and necessitates further research.

Methodology

The literature search involved English-written articles ranging between the years 2000-2017. A review was undertaken from the PubMed, Google Scholar and Scopus databases. Key search terms and MeSH terms included “Traumatic Brain Injury,” “Biomarkers,” “Diagnosis,” and “Prognosis.” Supplemental information was acquired by manually searching through journals and bibliographies. Studies written in a language other than English, lacked original data, compared S-100β to other biomarkers, review articles, and articles that were outside the objectives of this review were excluded. The main objective of this project was to review literature on the S-100β protein, and to establish its efficacy as a serum-based biomarker for TBIs. Inclusion criteria consisted of original, peer-reviewed journal articles that used either a cohort or randomized controlled trial study design, and investigated the diagnostic and prognostic ability of S-100β. Each article was analyzed and then categorized into one of the following groups: 1- Diagnostic value or 2- Prognostic value.

Results

A total of 15 articles were identified and reviewed. Of the 15 papers, only six met the inclusion criteria. The time span of the literature review ranged from 2000-2017. Of the six articles reviewed, countries performing the research included: Scandinavia (Denmark, Norway, Sweden), United Kingdom, France, Slovakia, and Germany. All methodologies in this review were cohort studies using a prospective study design. Population sizes varied from 21 to 1,560.

Diagnostic Value

Four studies assessed the diagnostic value of S-100β for TBIs, including its sensitivity and specificity (31-33), and the associated cost benefits (34) (Table 1). In 2000, Romner et al. (31) conducted a prospective study looking at the correlation of S-100β to CT scan and MRI findings in patients having suffered from TBIs. A total of 278 patients were recruited from three separate university neurotrauma centers (Norway, Sweden and Denmark), and stratified based on the severity of TBI. Severity of the TBI was based on the GCS, where a GCS score of 3-8 was defined as severe, 9-13 was moderate and 14-15 was considered mild. Non-enhanced brain and cranium CT scans were performed on all patients, while MRIs of the brain were performed on 45 patients that did not show any neurological deficits or any intracranial abnormalities. Subgroups were made following non-enhanced CT scans for patients with mTBI as follows: normal radiographic findings, CT-verified skull fracture and normal intracranial findings, normal intracranial CT scans with cerebral contusion revealed by MRI, and CT verified intracranial pathology. S-100β protein analysis was taken in the emergency room, with a mean time of 3.8 hours (range 0.5-24 hours) post-injury. A detection limit of 0.2 μg/L was used, and participants were split into groups based on levels of S-100β (0.2 μg/L and greater, or less than 0.2 μg/L). One hundred and ten healthy individuals were enlisted as controls and had their S-100β serum levels measured, but non-enhanced CT scans were not performed. The results showed that all patients in the control group had non-detectable serum levels of S-100β, and 39% of brain injured patients had detectable levels of S-100β protein. More specifically, S-100β protein reached detectable levels in 75% of moderate TBI and 35% of mTBI patients, with means of 0.7 μg/L (range 0.2-2.2 μg/L) and 0.6 μg/L (range: 0.2-6.2 μg/L), respectively. S-100β serum levels correlated significantly ($p< 0.01$) to those with severe head injuries, with patients in this category

exhibiting elevated levels (3.6 µg/L; range: 1.2-12.5 µg/L). Furthermore, 92% of patients with intracranial lesions confirmed on CT scan had a detectable serum level of S-100β. It was established that the sensitivity of S-100β for detecting intracranial pathology was 92% and the specificity was 66%. Researchers also determined that mean S-100β serum levels were significantly higher in those with more profound radiographic findings. Finally, the authors concluded that S-100β protein is a serum marker for TBI, where undetectable levels of the protein predict normal intracranial findings on CT (31).

In 2009, Morochovic et al. (32) studied the correlation between S-100β and cranial computed tomography (CCT) scans in patients post-mTBI. Their purpose was to assess the ability of S-100β to become an early screening tool for potential acute intracranial pathology. An additional goal was to determine if S-100β levels were altered by alcohol, injury severity score (ISS), and time from accident to blood sampling. The authors conducted a prospective study, tracking 102 consecutive patients presenting to a single trauma emergency department and a history consistent with mTBI. Patients were categorized and subdivided into groups based on four categories (32):

Category 0: GCS = 15, no LOC, no post-traumatic amnesia (PTA), no TBI, no risk factors

Category 1: GCS = 15, LOC < 30 min, PTA < 1 h, no risk factors

Category 2: GCS = 15 and risk factors present

Category 3: GCS = 13–14, LOC < 30 min, PTA < 1 h, with/without risk factors

Risk factors included unclear or ambiguous accident history, continued post-traumatic amnesia, retrograde amnesia longer than 30 minutes, trauma above the clavicles, severe headache, vomiting, focal neurological deficit, seizure, coagulation disorder, high energy accident,

intoxication with alcohol/drugs. Blood samples from the patients were taken within six hours of the incident and sent to the laboratory for evaluation within 30 minutes. S-100β venous concentrations of 0.1 ng/ml (μg/L) or greater were considered positive (S-100β+). A CCT scan was performed on all patients regardless of category allocation, and was performed within 30 minutes of blood being drawn. Any injury consistent with an acute intracranial injury detectable on CCT scan following interpretation by a radiologist was deemed a positive result (CCT+). Results demonstrated 72.5% of patients had a serum S-100β level above 0.1 ng/ml, while the sensitivity, specificity, positive predictive value, and negative predictive value of serum S-100β for CCT detectable abnormality were 83.3%, 29.8%, 20.3%, and 89.3%, respectively. A significant ($p < 0.0001$) association between S-100β concentration and the injury severity score (ISS) was found, however there was no correlation between S-100β and alcohol concentration, or time from injury to blood draw. Lastly, three false negative concentrations of S-100β protein were identified following confirmation of intracranial lesions on CCT. These brain lesions consisted of an epidural hematoma, acute subdural hematoma, and traumatic subarachnoid hemorrhage, all requiring surgical intervention. Interestingly, the mean time interval between injury and blood sampling for all subjects was 1.8 hours, and increased to 3.1 hours in the S-100β-/CCT+ subgroup. Despite finding no correlation between S-100β levels and time from injury to blood draw, the authors nonetheless offered the explanation that S-100β concentrations are negatively correlated to an increased time interval between injury and blood drawing, which resulted in S-100β levels being below the threshold in the S-100β- group (32). Ultimately, Morochovic et al. (32) concluded that S-100β serum concentrations may be an unreliable screening tool for determination of an intracranial injury due to low specificity and negative

predictive values observed in patients whose blood was drawn greater than three hours after an mTBI.

More recent research from Zongo et al. (33) used prospective study design and emergency department data from France, whereby 2,128 patients with minor head injury were studied consecutively. Computed tomography scans and plasma S-100β levels were compared and analyzed for 1,560 patients meeting the inclusion criteria. The inclusion criteria consisted of: patients 15 years and older presenting to the emergency department within six hours of head injury and a physician evaluated GCS = 13-15. In addition, they also required at least one of the following risk factors: loss of consciousness, post-traumatic amnesia, repeated vomiting, severe headache, dizziness, vertigo, alcohol intoxication, anticoagulation, or > 65 years of age. Authors chose to exclude those with non-traumatic neurologic disease, open fractures, large open wounds, and intra-thoracic or abdominal contusions, as it has been reported that severe injuries may increase serum S-100β levels which can lead to false-positives (29). Blood plasma levels were drawn routinely, with the first taken within six hours of head trauma. Results showed a positive CT scan for intracranial lesions in 111 patients with a median S-100β plasma concentration of 0.46 µg/L. The remaining 1,449 patients with negative CT scans had a recorded S-100β median of 0.22 µg/L. The authors reported that a cut-off level of 0.12 µg/L could identify a TBI with a sensitivity of 99.1% and a negative predictive value of 99.7%. It was therefore concluded that S-100β may decrease the requirement for CT scans by ruling out TBIs following a minor head injury (33).

In 2016, Calcagnile, Anell, and Undén (34) investigated the potential cost saving benefit of adding S-100β protein assessment to mTBI management guidelines, by prospectively following 726 mTBI patients at a level II trauma center in Sweden. Criteria indicative of mTBI

were: GCS 14-15 and/or a loss of consciousness for less than five minutes with no neurological deficits or any additional risk factors. A venous sample of S-100β was taken within three hours of injury, and a cut-off level of 0.1 μg/L was used as a reference value. If S-100β was < 0.1 μg/L, patients were discharged with oral/written information. However, a CT scan was recommended if patients had S-100β levels ≥ 0.1 μg/L, followed by a 12-hour observation depending on CT results. Computed tomography scans were performed and analyzed by a radiologist within 4 hours and 14 minutes from triage. All patients were sent a questionnaire by mail or telephone three months after the head injury, and if contact was unsuccessful, medical records and national mortality databases were used to obtain necessary information. The questionnaire attempted to identify a "significant intracranial lesion" by asking participants about occupation, sick-days, new contacts with medical professionals, and functionality and quality of life (QoL). Cost-analysis was based on standard costs according to the Halmstad Regional Hospital financial accounts and national reports. It was determined that the average cost of S-100β measurement was 21 Euros, the cost for a non-contrast CT was 130 Euros, the cost for one day on the surgical ward was 600 Euros/day, and observation of a minor head injury was 266 Euros/day. A total of 229 patients had S-100β levels below 0.1 μg/L, with 68% of these individuals being discharged without required observation or a CT scan. Alternatively, some patients with S-100β levels ≥ 0.1 μg/L were admitted to hospital for observation despite normal CT scans. In addition, 121 patients with normal 12 to 24-hour observation periods still underwent a CT scan contrary to guideline suggestions. With respect to follow-up questionnaire data, 190 out of 589 respondents were patients with normal S-100β levels, and none of these individuals sought further care for missed complications. Cost-analysis results determined that inclusion of S-100β serum measurement post-mTBI saved 39 Euros per patient. Unfortunately,

the study only showed 67% compliance to the aforementioned mTBI guidelines, with some individuals receiving CT scans despite having serum S-100β levels below the cutoff of 0.1 μg/L. Had the guidelines been followed strictly, the savings would have been 171 Euros per patient. As a result, the authors suggested that adding S-100β to existing guidelines as a negative predictor for normal CT scans may offer a cost savings of 39 Euros per patient (34).

Prognostic Value

Two studies (35, 36) in 2002 addressed the question of the prognostic ability of S-100β with regard to QoL and mortality in patients with TBIs (Table 2). In the first study, Woertgen, Rothoerl and Brawanski (35) questioned if serum concentrations of S-100β protein are specific and sensitive enough to correlate to QoL. Their prospective study included 51 patients with severe TBIs (GCS < 9) admitted between one to six hours following injury; 38 patients had an isolated intracranial lesion and 12 had a concomitant abdominal or thorax injury. Serum samples of S-100β protein were taken within 2.5 hours of admission, with concentrations ≥ 0.5 μg/L considered elevated. Glasgow Outcome Scale (GOS) and a modified questionnaire were administered at follow-up to assess overall QoL. For the GOS, values from one to three were considered unfavourable whereas values of four and five were deemed favourable. The additional modified questionnaire explored several aspects of life such as job, leisure, eating, sleeping, friends, money, family, partnership, health, and self-assessment. Follow-up rate for the study was 100%, and results showed that age and GCS score on admission had a significant correlation to the outcome according to the GOS. Additionally, elevated serum levels of S-100β on admission were also correlated to the GOS score calculated at follow-up. It is also interesting to note that QoL index and overall QoL were significantly higher in those who had serum levels

of S-100β less than or equal to 0.5 µg/L on admission. Based on these findings, the authors speculate that S-100β serum concentrations after a severe TBI are correlated to extensive structural brain damage, in turn impacting a variety of aspects making up one's QoL (35).

In the second study, Petzold et al. (36) conducted a prospective, longitudinal, pilot study with an attempt to quantify S-100β as an early predictor of high intracranial pressure and mortality in brain injured patients. Twenty-one patients with TBI and 13 controls were examined in a surgical intensive care unit in the National Hospital for Neurology and Neurosurgery in the United Kingdom. Patients were stratified into two separate groups based on history and CT scan results; TBI and non-traumatic vascular brain injury. Individuals in the TBI group were further subdivided based on severity of TBI. As in the previous studies mentioned, a GCS of less than 9 was considered severe, 9-12 was moderate and 13-15 was mild. S-100β protein concentrations were collected on admission and continued daily over the following six days, with a cut-off value of 60 pg/mL used to define high versus low S-100β protein concentrations. All patients were sedated and mechanically ventilated, while body temperature, blood glucose, and electrolyte levels were kept within normal parameters, and patients' cerebral perfusion pressure targets were 70 mm Hg based on standardized protocols. While 8 of the 21 TBI patients died, results showed that S-100β levels were significantly greater in survivors from admission to day five compared to those in the control group, however these differences disappeared by day six. For the non-survivors, S-100β levels were significantly elevated throughout the entire six-day period compared to survivors, with mean concentrations of 110 pg/mL and mean 34 pg/mL, respectively. Furthermore, it was found that those with elevated S-100β concentration on admission and at one day post-injury had an 8.4-fold and an 11.6-fold increased risk of fatal

outcome, respectively. Petzold et al. (36) therefore concluded that S-100β is a sensitive biomarker for predicting mortality in patients with an acute TBI.

Discussion

S-100β protein is one of the most promising biomarkers for TBIs (24), with several prospective studies (31-36) having focused on S-100β's diagnostic and prognostic potential in individuals suffering from TBIs. The purpose of this literature review was to highlight, synthesize, and critique published research articles examining the diagnostic and prognostic value of the S-100β protein for TBIs. Of the 15 papers reviewed from 2000-2017, six met the inclusion criteria; all of which were prospective studies evaluating S-100β alone, and included a total of 2,738 study participants. Two of four studies evaluating S-100β's diagnostic value suggested adequate sensitivity (92% (31) and 99.1% (33)), and sufficient negative predictive value (99% (31) and 99.7% (33)) when using serum S-100β as a predictor for ruling-out intracranial pathology normally reserved for CT scanning. One study included in this review (32) did have contradictory findings, whereby the sensitivity and negative predictive value of S-100β were only 83.3% and 89.3%, respectively. However, it is important to note that there was a difference in time to blood draw (S-100β+/CCT+: 1.8 hours post-injury; S-100β-/CCT+: 3.1 hours) that may have been responsible for the low sensitivity and negative predictive values. Indeed, time between injury and blood draw appears to be important, as Raabe et al. (23) discovered an exponential decrease of serum S-100β concentration post-trauma as time from injury increased. This relationship would have a profound impact on post-injury S-100β concentrations depending on when blood samples were collected after trauma. Another possibility for the differences in reported sensitivities and specificities is the smaller sample size

in the Morochovic et al. study (n = 102 (32)) compared to the other studies (n = 278 (31); n = 1560 (33)), potentially leading to Morochovic's study (32) being underpowered. Further contributing to the discrepancy in results is the difference in eligibility criteria, where those with traumatic injuries in addition to their TBIs were included in the Morochovic et al. (32) study, whereas the other studies (31, 33) included only those with TBIs. Including individuals with additional traumatic injuries may result in even greater elevations in serum S-100β concentrations, as it has been suggested that elevated levels of S-100β may be a result of soft tissue injuries and bone fractures despite the absence of head injuries (29, 37). For example, Unden et al. (29) found mean S-100β levels of 0.13 +/- 0.11 μg/L within 23 hours of injury in patients with fractures only, while Anderson et al. (37) found elevated S-100β levels in patients with acute soft-tissue injuries and fractures. Berger et al. (38) reported conflicting results, however, claiming a lack of correlation between initial S-100β concentrations and non-head trauma injuries. Low specificities may also be explained by elevated S-100β levels due to exercise prior to blood sampling, or having comorbidities that were not disclosed to researchers in advance (28-30). Despite the counterarguments, it remains clear that the use of S-100β could be of potential benefit if used as a screening tool to reduce the use of CT scans (31, 32, 34), and reducing healthcare costs by up to 39 Euros (~$53 CAD) per patient (34).

Strong evidence has supported the prognostic value of serum S-100β, which was a focus in two of the reviewed articles (35, 36). With respect to QoL, Woertgen et al. (35) found that those with initial S-100β values above 2 μg/L demonstrated lower QoL based on questionnaires, while QoL index and overall QoL were higher in those with S-100β concentrations less or equal to 0.5 μg/L on admission, provided the participant survived to the end of the study. High serum S-100β concentrations (110 +/- 70 μg/L) in the first 36 hours post-TBI were also able to predict

mortality three to four days before ICP readings could (36). Both studies (35, 36) unequivocally found that higher values of S-100β on admission reflected a higher mortality rate. These facts can be supported by the Raabe, Grolms and Seifert study (39) whereby patients with S-100β levels above 2.5 µg/L showed a strong association with mortality. Moreover, S-100β levels above the cut-off of 0.5 µg/L 24-hours post-head injury had a sensitivity of >80% to predict death (40). Additional findings from a meta-analysis by Mercier et al. (41) found that S-100β levels between 1.3 µg/L to 10.5 µg/L had a 100% specificity for mortality, and levels between 2.1 µg/L to 14.0 µg/L were associated with a GCS = 3.

Despite the literature supporting the use of S-100β as a diagnostic biomarker of TBI, S-100β continues to lack the specificity required to reliably rule-out TBIs, particularly mTBIs, without the use of CT scans and other diagnostic testing. The concern with S-100β is its elevated levels in individuals with poly-trauma or in those who have been exercising prior to incurring an mTBI in sports. At this time, emergency clinicians would need to use their clinical judgment on the reliability of S-100β levels for case specific presentations, as they do with other biomarkers like troponin T in patients with chest pain (16). It would perhaps be of benefit to also use another biomarker for TBI that is more specific to glial tissue injury, in conjunction with S-100β to strengthen its diagnostic value. As for its ability to offer a prognosis, elevated S-100β concentrations (>2 µg/L) within 24-hours of the TBI seems to reliably correlate to poor QoL, while concentrations greater than this would consistently predict mortality. For S-100β to be considered a useful biomarker in an emergency setting, researchers need to accurately quantify what concentration would be considered a "normal" cut-off level of S-100β, and the specific concentrations that would indicate an mTBI, moderate TBI, or severe TBI.

Limitations

This study identifies research focusing on the diagnostic and prognostic value of S-100β since 2000. While investigations have found S-100β to demonstrate adequate sensitivity and negative predictive values for TBI, opponents have indicated that it fails to demonstrate sufficient sensitivity and specificity for mTBIs. The issue with elevated S-100β levels in blood samples for diagnosing mTBIs is that exercise may be also contributing to elevated levels seen post-mTBI, thereby decreasing the specificity of S-100β in these instances. Indeed, S-100β levels have been shown to rise with non-maximal exercise and certain disease states, which ultimately hinders the ability to determine if the levels are unique to glial cell injury or that of extra-glial cell sources. In these cases, a baseline S-100β level for individuals would need to be established, further complicating the ease of its use as a biomarker. Another limitation of the studies included in this review is the inconsistent inclusion/exclusion criteria. In some instances, TBI patients with associated extracranial traumatic injuries were included (32), while others were not (33) or failed to mention its implication (31). This supports the need for further research involving the control for associated injuries, amount of exercise prior to injury, or disease states as a potential confounder altering S-100β levels.

Another issue exists when considering individuals that may have suffered a TBI but fail to seek immediate medical attention. When considering S-100β's short half-life (28), the potential of a false-negative is increased in those who did not present to an emergency department for evaluation directly following the TBI. An alternative approach would need to be in place to prevent missed TBIs in instances where the initial S-100β concentration would not be useful to rule out intracranial pathology.

It has been discussed in the literature that a set cut-off level for S-100β needs to be established. To date, this issue has not been rectified which impedes its use by primary care practitioners working in an acute setting. Some strides have been made for establishing cut-off values for negative prognosis and mortality following TBI, however specific cut-off values that maximize sensitivity and specificity for mTBIs remain elusive, warranting further research in this area.

Conclusion

Since 2000, data has shown that S-100β is a promising biomarker for TBIs with high sensitivity and negative predictive value, and good prognostic value with reference to QoL and mortality. It has also demonstrated an ability to reduce healthcare costs by preventing unnecessary CT scans in those with mTBIs. Despite these facts, a body of research has found S-100β to be an unreliable biomarker due to its lower specificity, indicating a need for additional research to further elucidate S-100β's ability to serve as a reliable biomarker for diagnosing TBIs in an acute setting. Research combining the use of S-100β and other biomarkers specific to glial tissues may be warranted in the future.

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Appendix

Table 1: Summary of Reviewed Articles: Diagnostic Value

First Author (Year)	Journal	Objective	Target Population (Study Population)	Methods	Conclusion
Romner (2000)	Journal of Neurotrauma	Investigate the correlation between S-100β levels and neuroradiological findings in patients with head injuries.	Patients with mild to severe head injuries without neurological disease (278)	Prospective study	- S-100β is a sensitive biomarker for mild-severe brain injuries.
Morochovic (2009)	European Journal of Neurology	To correlate early S-100β concentrations and initial cranial CT findings in the patients with mild TBI.	Patients presenting to the emergency department with history of mild TBI (102)	Prospective study	-Serum S-100β protein may be an unreliable screening tool for the intracranial injury risk group due to low sensitivity and negative predictive values seen in samples taken greater than 3 hours after a mild TBI.
Zongo (2012)	Annals of Emergency Medicine	Assess the potential role of measuring blood S-100β levels as a screening tool for patients with minor head injury.	Patients presenting to emergency within 6 hours of isolated head trauma, with a GCS of 13 to 15 (1560)	Prospective study	-Plasma S-100β levels on admission in patients with minor head injury is a promising screening tool to support the clinician's decision not to perform CT imaging in certain cases of low-risk head injury.
Calcagnile (2016)	BMC Neurology	Establish adding S-100β to management routines resulted in a decrease in health care costs and waiting time for patients.	Patients with acute trauma to the head with GCS 14-15 and/or loss of consciousness for less than 5 min with no neurological deficits nor additional risk factors. (726)	Prospective study	-Adding S-100β to existing guidelines for mild TBI seems to reduce CT usage and costs, especially if guideline compliance could be increased.

CT = Computed Tomography
TBI= Traumatic Brain Injury
GCS= Glasgow Coma Scale

Table 2: Summary of Reviewed Articles: Prognostic Value

First Author (Year)	Journal	Objective	Target Population (Study Population)	Methods	Conclusion
Woertgen (2002)	Brain Injury	Investigate the correlation of early S-100β serum level to QoL.	Patients with severe head injury GCS < 9 who had been admitted between 1 +/- 6 hours after injury. (51)	Prospective study	-An unfavourable outcome had significantly higher serum concentrations of S-100β compared to the patients with favourable outcome. -Patients with an S-100β serum level of 2 ug/L showed a significantly lower QoL, reflecting a mortality of 41%.
Petzold (2002)	Critical Care Medicine	Investigate whether serum S-100β is suitable as a sensitive biomarker for early prediction of ICP and mortality rates after brain injury.	Patients with an acute brain injury (21)	Prospective study	-Serum S-100β is a sensitive biomarker for early prediction of the development of high ICP and mortality following acute brain injury.

QoL = Quality of Life
GCS = Glasgow Coma Scale
ICP = Intracranial Pressure