S100-B Protein as a Screening Tool for the Early Assessment of Minor Head Injury

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Study objective: A computed tomography (CT) scan has high sensitivity in detecting intracranial injury in patients with minor head injury but is costly, exposes patients to high radiation doses, and reveals clinically relevant lesions in less than 10% of cases. We evaluate S100-B protein measurement as a screening tool in a large population of patients with minor head injury.

Methods: We conducted a prospective observational study in the emergency department of a teaching hospital (Bordeaux, France). Patients with minor head injury (2,128) were consecutively included from December 2007 to February 2009. CT scans and plasma S100-B levels were compared for 1,560 patients. The main outcome was to evaluate the diagnostic value of the S100-B test, focusing on the negative predictive value and the negative likelihood ratio.

Results: CT scan revealed intracranial lesions in 111 (7%) participants, and their median S100-B protein plasma level was 0.46 μg/L (interquartile range [IQR] 0.27 to 0.72) versus 0.22 μg/L (IQR 0.14 to 0.36) in the other 1,449 patients. With a cutoff of 0.12 μg/L, traumatic brain injuries on CT were identified with a sensitivity of 99.1% (95% confidence interval [CI] 95.0% to 100%), a specificity of 19.7% (95% CI 17.7% to 21.9%), a negative predictive value of 99.7% (95% CI 98.1% to 100%), a positive likelihood ratio of 1.24 (95% CI 1.20 to 1.28), and a negative likelihood ratio of 0.04 (95% CI 0.006 to 0.32).

Conclusion: Measurement of plasma S100-B on admission of patients with minor head injury is a promising screening tool that may be of help to support the clinician's decision not to perform CT imaging in certain cases of low-risk head injury. [Ann Emerg Med. 2012;59:209-218.]

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INTRODUCTION

The annual incidence of traumatic brain injuries ranges between 100 and 400 per 100,000 persons.[1-6] More than 90% of them are classified as minor head injuries corresponding to patients with an admission Glasgow Coma Scale (GCS) score ranging from 13 to 15.

The initial severity assessment includes GCS and clinical symptoms (loss of consciousness, amnesia, headache, vomiting), but the optimal clinical decision rule for an initial computed tomography (CT) scan is still a matter of debate[7-9] because of the low power of discrimination of clinical findings.

Head CT scan is currently considered the reference diagnostic method for identifying potentially life-threatening lesions.[10-13] It is, however, costly and not always available, exposes the patient to high radiation doses,[14] and reveals clinically relevant lesions in less than 10% of cases. Indicators that can safely identify patients for whom a CT scan can be avoided are thus needed. S100-B, a 21-kDa calcium-binding glial-specific protein mainly expressed by astrocytes, has been considered not only as an objective quantitative prognostic

Editor's Capsule Summary

What is already known on this topic

Emergency physicians liberally use head computed tomography (CT) for patients with minor head injury.

What question this study addressed

This observational study of 1,560 patients assessed whether plasma S100-B, a protein expressed by astrocytes, could detect neurologic injury identified by CT scan.

What this study adds to our knowledge

In a patient population with a low likelihood of disease (7%), S100-B has a poor positive likelihood ratio (1.24) but an excellent negative likelihood ratio (0.04).

How this is relevant to clinical practice

This study should not change practice but suggests that further research into how this test's predictive ability compares with physician judgment is warranted.

marker of severe head injury[15,16] but also as a potentially interesting tool for patients with minor head injury.[17-21] The measurement of S100-B has therefore recently been proposed and evaluated as an initial screening tool for brain damage.

The result of this test can be available within an hour of blood sampling.[17] Its cost is around $20.[22] Its negative predictive value is promising but has so far been estimated in a limited number of patients. Further research is therefore required to establish the clinical role of S100-B in patients with minor head injury and determine the appropriate decision rules before changing clinical management procedures.

Our aim was to assess the potential role of measuring blood S100-B protein levels as a screening tool for patients with minor head injury. The main outcome was the diagnostic performance of the S100-B test compared with CT scan findings.

MATERIALS AND METHODS

Study Design

Patients with minor head injury were consecutively included from December 2007 to February 2009 in a prospective study. Informed consent was obtained from all subjects. The protocol was approved by the regional ethics committee.

Setting

The study was conducted at an adult emergency department (ED) of a teaching hospital in Bordeaux, France, with 48,000 annual admissions, including 2,500 brain injury cases. Our study site is also the tertiary neurosurgical center in a region of more than 3 million inhabitants.

Selection of Participants

Patients included were aged 15 years or older, presenting to the ED within 6 hours of isolated head trauma, with a GCS of 13 to 15 as determined by the attending physician, and with one or more of the following risk factors: loss of consciousness, posttraumatic amnesia, repeated vomiting, severe headache, dizziness, vertigo, alcohol intoxication, anticoagulation, and age older than 65 years. The inclusion criteria were those used in our local emergency practice, which corresponded to the recommendation made by Servadei et al.[23] These criteria were broadly consistent with most international guidelines.[10,11,24,25] All consecutive patients meeting these criteria were considered for inclusion. This was made possible thanks to the presence of a clinical research associate 24 hours a day and 7 days a week.

Patients were excluded on admission if a severe injury was suspected (Abbreviated Injury Score obviously >2). Severe injury included open fracture, large open wounds, and intrathoracic or abdominal contusion. Our aim was to restrict the study to patients with isolated minor head injury because other traumatic injuries have been reported to increase serum S100-B levels, potentially leading to false positives.[26-28] In addition, seriously injured patients typically require rapid imaging of the head, chest, and abdomen and are not likely to be discharged without CT imaging.

Patients with a nontraumatic neurologic disease (eg, cerebral ischemia, chronic subdural hematoma) and patients with a known history of motor neuron disease were also excluded.[29] The half-life of the S100-B protein has been reported to range between 25 and 120 minutes.[30-32] Because of this short half-life, patients with an interval of more than 6 hours between head trauma and blood sampling were excluded from the analysis.

Methods of Measurement

An emergency physician performed the neurologic examination and assessed the level of consciousness. Patient-related data collected were demographic characteristic–associated medical conditions, usual medications, circumstances of the trauma, and associated injuries. Clinical findings and events occurring during the time spent at the ED, including change in GCS score and the lowest GCS score, were recorded. In the case of any hospitalization, we searched for the reason and the length of hospital stay. Minor head injury became clinically important traumatic brain injuries when they led to death, to a neurosurgical operation, to an intracranial pressure monitoring, to a sedation medication (general anesthesia), to a persistent confused state (patients who remained with a GCS score of 13 to 14 after their injury without returning to a normal conscious state), or to a loss of 2 points or more in the GCS score during the stay in the ED.

According to local routine procedures, in the absence of any initial neurologic deterioration the CT scan was performed within 6 hours after the head trauma with a Philips Brilliance

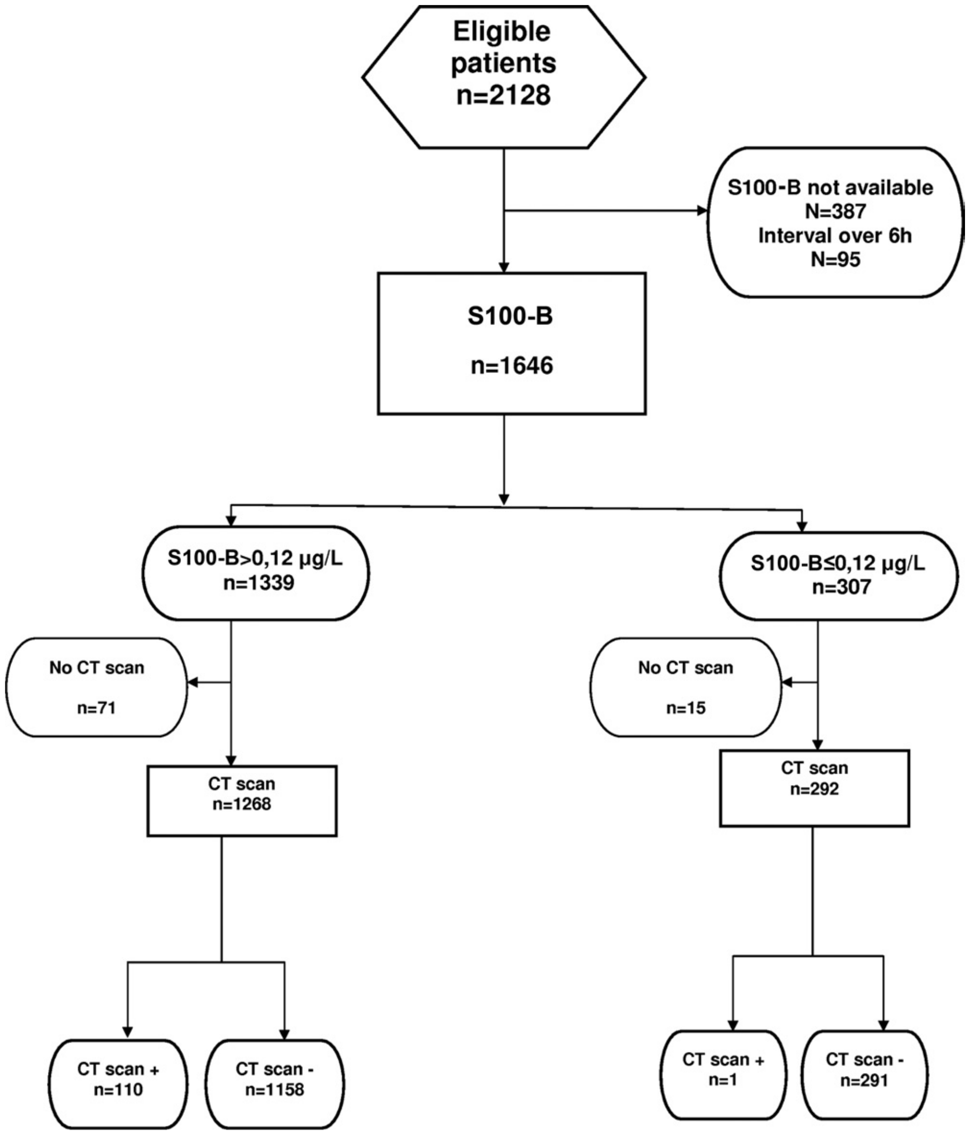

Figure 1. STARD flow diagram: diagnostic accuracy of blood S100-B protein determination in predicting CT scan findings after minor head injury.

CT 64-channel with 10-mm-thick slices through the skull base to the vertex. Trauma-relevant lesions (subdural, epidural, or intracerebral hemorrhages; bland contusion; edema; pneumocephalus; and skull fracture) were searched for and coded by a resident in radiology and confirmed by a board-certified radiologist, blinded to the S100-B level. Interrater reliability was measured by Cohen's κ coefficient. Patients were divided into 2 groups: CT scan–negative (minor head injury patients without any sign of trauma-relevant lesions) and CT scan–positive (minor head injury patients with at least 1 trauma-relevant lesion).

One milliliter of plasma was taken from each sample drawn routinely in the ED and frozen at −20°C (-4°F) until assayed with a fully automated system, using an electrochemiluminescence immunoassay kit (Elecsys; Roche Diagnostics, Mannheim, Germany). The results are reported in micrograms per liter and rounded off to 3 decimal places. The clinical management of the patients was not affected by the S100-B level measurement. To include this routine practice in our ED procedures, S100-B levels were determined in plasma and not in serum (as recommended by the manufacturer). We carried out a cross-validation study of 62 patients to compare measurement results between plasma and serum extracted from the same blood sample.

Data Collection and Processing

Data were collected by clinical research associates specially trained and dedicated to the study, who filled out the research data form from the medical records. They ensured that all patients with the inclusion criteria were recruited into the study.

Table 1. Demographic and clinical characteristics of patients with minor head injury by CT scan findings and participant status.

Demographic and Clinical Characteristics	No. (%) All, n=1,560	CT Scan Result Positive, n=111	CT Scan Result Negative, n=1,449	Excluded Patients, n=568
Age, y, median (IQR)	57 (32–82)	59 (31–82)	57 (32–82)	56 (31–81)
Sex				
Male	870 (55.8)	72 (64.9)	798 (55.1)	317 (55.8)
Trauma history				
Traffic accident	221 (14.2)	15 (13.5)	206 (14.2)	71 (12.5)
Fall	594 (38.1)	41 (36.9)	553 (38.2)	206 (36.3)
Fall from height	75 (4.8)	11 (9.9)	64 (4.4)	20 (3.5)
Assault	161 (10.3)	5 (4.5)	156 (10.8)	75 (13.2)
Other or unknown	509 (32.6)	39 (35.1)	470 (32.4)	196 (34.5)
Symptom				
Loss of consciousness	627 (40.2)	62 (55.9)	565 (39.0)	204 (35.9)
Amnesia	552 (35.4)	61 (55.0)	491 (33.9)	158 (27.8)
Convulsion	26 (1.7)	2 (1.8)	24 (1.7)	10 (1.8)
Confusion	230 (14.7)	23 (20.7)	207 (14.3)	74 (13.0)
Headache	273 (17.5)	24 (21.6)	249 (17.2)	99 (17.4)
Vomiting	83 (5.3)	10 (9.0)	73 (5.0)	24 (4.2)
Risk factors				
Anticoagulation	390 (25.0)	78 (29.7)	357 (24.6)	105 (18.5)
Alcohol poisoning	374 (24.0)	28 (25.2)	346 (23.9)	104 (18.4)
Age >65 y	690 (44.2)	48 (43.2)	642 (44.3)	238 (41.9)
GCS score				
13	39 (2.5)	7 (6.3)	32 (2.2)	25 (4.4)
14	335 (21.5)	30 (27.0)	305 (21.0)	94 (16.5)
15	1186 (76.0)	74 (66.7)	1112 (76.7)	449 (79.0)
S100-B protein (μg/l)				
≤0.12	292 (18.7)	1 (0.9)	291 (20.1)	39 (21.7)
0.12–0.16	193 (12.4)	5 (4.5)	188 (13.0)	29 (16.1)
0.16–0.20	192 (12.3)	4 (3.6)	188 (13.0)	28 (15.6)
>0.20	883 (56.6)	101 (91.0)	782 (54.0)	84 (46.7)

Missing data were verified later by 2 physicians (DZ and FM) against the patients' medical records. The data set was completed accordingly from the radiologic data and the written abstract was established when the patient left the hospital by the physician in charge of the patient. During this procedure, patients found to have associated injuries with an Abbreviated Injury Score greater than 2 were further excluded from the analysis. Each CT scan was interpreted by a resident in radiology and confirmed by a senior radiologist unaware of the patient outcome.

Outcome Measures

The primary outcome was to evaluate the diagnostic value of the S100-B test, focusing on the negative predictive value and the negative likelihood ratio.

The secondary outcomes were to evaluate the diagnostic value of the S100-B at different cutoff values near those proposed in literature (approximately 0.10 μg/L L) to maximize the proportion of CT scans potentially avoided while keeping a negative predictive value near 100%.

Primary Data Analysis

Comparisons of S100-B values between subgroups of patients were performed with the nonparametric Wilcoxon rank-sum test. Sensitivity, specificity, positive and negative predictive values, positive likelihood ratio, and negative likelihood ratio were estimated from contingency tables crossing S100-B results by CT scan findings. Ninety-five percent confidence intervals (CIs) were calculated with the exact binomial distribution function. A Bland-Altman analysis[33] and Pearson's correlation were used to compare measurements of S100-B protein in plasma and serum samples. Statistical analysis was performed with SAS (version 9.1.3; SAS Institute, Inc., Cary, NC) software.

RESULTS

Characteristics of Study Subjects

The STAndards for the Reporting of Diagnostic accuracy studies (STARD chart) flow is shown in Figure 1. A total of 2,128 patients fulfilled the inclusion criteria. Twenty-one patients were excluded because complete clinical assessment showed they had associated injuries with an Abbreviated Injury Score greater than 2.

The S100-B assay was not performed for 387 patients, corresponding to short periods of high activity in the ED during which the test could not be performed. A further 95 patients were excluded from the analysis because the interval between the traumatic event and blood collection was greater than 6

Table 2. Demographic and clinical characteristics of patients with minor head injury by S100-B diagnostic test results and presence of clinically important traumatic brain injury.*

	No. (%)			
Demographic and Clinical Characteristics	**All n=1,560 No (%)**	**False Positive (CT Scan Result Negative and S100-B >0.12), n=1,158 No (%)**	**True Negative (CT Scan Result Negative and S100-B ≤0.12), n=291 No (%)**	**Clinically Important Traumatic Brain Injury, n=12 No (%)**
Age, y, median (IQR)	57 (32–82)	59 (31–78)	60 (32–82)	53 (28–78)
Sex				
Male	870 (55.8)	626 (54.1)	172 (59.1)	8 (66.7)
Trauma history				
Traffic accident	221 (14.2)	167 (14.4)	39 (13.4)	2 (16.6)
Fall	594 (38.1)	450 (38.9)(6.9)	103 (35.4)	5 (41.6)
Fall from height	75 (4.8)	53 (4.6)	11 (3.8)	2 (16.6)
Assault	161 (10.3)	119 (10.3)	37 (12.7)	2 (16.6)
Other or unknown	509 (32.6)	369 (31.9)	101 (34.7)	1 (8.3)
Symptom				
Loss of consciousness	627 (40.2)	444 (38.3)	121 (41.6)	7 (58.3)
Amnesia	552 (35.4)	381 (32.9)	110 (37.8)	5 (41.7)
Convulsion	26 (1.7)	12 (1.0)	12 (4.1)	0
Confusion	230 (14.7)	164 (14.2)	43 (14.8)	4 (33.3)
Headache	273 (17.5)	191 (16.5)	58 (19.8)	3 (25.0)
Vomiting	83 (5.3)	55 (4.7)	18 (6.2)	2 (16.7)
Risk factors				
Anticoagulation	390 (25.0)	298 (25.7)	59 (20.3)	9 (75.0)
Alcohol poisoning	374 (24.0)	287 (24.8)	59 (20.3)	4 (33.3)
Age >65 y	690 (44.2)	98 (33.7)	98 (33.7)	4 (33.3)
GCS score				
13	39 (2.5)	25 (2.2)	7 (2.4)	4 (33.3)
14	335 (21.5)	254 (21.9)	51 (17.5)	2 (16.7)
15	1186 (76.0)	879 (75.9)	233 (80.1)	6 (50.0)
S100-B protein (μg/l)				
≤0.12	292 (18.7)	—	291 (100.0)	0
0.12-0.16	193 (12.4)	188 (16.2)	—	1 (8.3)
0.16-0.20	192 (12.3)	188 (16.2)	—	0
>0.20	883 (56.6)	782 (67.5)	—	11 (91.7)

*One false negative was found: a 28-year-old man who had fallen. He had a GCS score of 15 on admission and a blood alcohol concentration of 3.0 g/L. The CT scan finding was a cerebral contusion that proved to be a petechia.

hours. Among the remaining patients, a total of 86 patients were not included because no CT scan was performed (the physician in charge at the ED did not prescribe the examination), leaving 1,560 patients in the analysis.

The study population is described in Tables 1 and 2. The median age of the participants was 57 years (interquartile range 32 to 82 years). More than one third (38%) of patients had fallen. In 53% of the sample, the head injury risk factor that prompted the CT scan indication was loss of consciousness, amnesia, or both. Only one quarter of patients had an initial GCS score below 15.

CT scan findings assessed by residents in radiology and by senior radiologists were concordant in 1,542 (99%) and discordant in 18 (1%) of the 1,560 patients, resulting in a very high κ coefficient value of 0.94 (95% CI 0.92 to 0.97).

Among patients with an Abbreviated Injury Score of 2 (n=289), the median S100-B level was higher: 0.31 μg/L (0.19 to 0.54) versus 0.21 μg/L (0.13 to 0.36).

Main Results

Median values and interquartile range of the S100-B concentrations in plasma, by CT scan findings, are given in Table 3. Patients with positive CT scan results had higher median S100-B levels than those with negative CT scan results: median value 0.46 μg/L (0.27 to 0.72) versus 0.22 μg/L (0.14 to 0.36), $P<.001$. The median delay for all patients with positive CT scan results was not different from those with negative CT scan results (138 [105 to 210] minutes versus 150 [100 to 211] minutes).

CT scan result was positive for 111 (7%) participants, 12 of whom afterwards had a clinically important traumatic brain injury (Table 4): 3 required a neurosurgical intervention and 3 died from their head trauma. The same patient can have more than 1 clinically important complication of traumatic brain injury.

Study outcomes (negative predictive value, number of patients with false-negative results, and number of patients

Table 3. S100-B protein concentration according to traumatic brain injury on CT and the occurrence of a clinically important traumatic brain injury.*

	n	S100-B Concentration, μg/L, Median (IQR Q1–Q3)
All	1,560	0.23 (0.14–0.38)
Positive CT scan result	111	0.46 (0.27–0.72)
Negative CT scan result	1,449	0.22 (0.14–0.36)
CT scan findings		
Epidural hematoma	9	0.71 (0.55–1.09)
Subdural hematoma	38	0.63 (0.28–0.88)
Cerebral edema	1	0.63
Subarachnoid hematoma	40	0.60 (0.34–0.77)
Pneumocephalus	7	0.53 (0.41–0.63)
Skull cap fracture	22	0.50 (0.30–0.71)
Skull base fracture	20	0.48 (0.27–0.62)
Cerebral contusion	53	0.46 (0.14–0.72)
Clinically important traumatic brain injury*		
Prolonged confusion	2	0.96 (0.77–1.15)
Death caused by MHI	3	0.93 (0.46–2.22)
Loss of 2 points in GCS score	5	0.68 (0.63–0.70)
Intravenous sedation	3	0.68 (0.46–1.24)
Monitoring of intracranial pressure	1	0.63
Neurosurgery	3	0.58 (0.33–0.67)

MHI, Minor head injury.
*All clinically important traumatic brain injuries were in patients with positive CT scan results. Because some complications occurred simultaneously, the total numbers can exceed 12.

with clinically important traumatic brain injuries) were estimated for cutoff levels of 0.10, 0.12, and 0.14 μg/L (Table 5). At 0.10 and 0.12 μg/L, only 1 patient with plasma S100-B below the cutoff value had a positive CT scan result: a 28-year-old man with a cerebral contusion that proved to be a petechia and with a blood alcohol concentration of 3.0 g/L at admission. The patient required no further neurosurgery or intensive care. He stayed in the hospital for 30 hours for surveillance. The delay between trauma and blood drawing was 120 minutes.

Between 0.12 and 0.14 μg/L, 2 patients had a positive CT scan result: a cerebral petechia and a chronic subdural hemorrhage with recent bleeding. No neurosurgical care was required, and there was no further neurologic deterioration. The delay between trauma and blood drawing was 152 minutes and 255 minutes for these 2 patients.

Figure 2 depicts the negative predictive value graphed versus the proportion of positive CT scan results (prevalence). The negative predictive value remains above 99%, for an event prevalence up to 24%. This figure shows that the high level of the negative predictive value is not explained by the low prevalence of positive CT scan results.

Receiver operating characteristic curve analysis (Figure 3) showed the S100-B test to be a significant discriminator of CT scan abnormality (area under the curve value 0.76; 95% CI 0.72 to 0.80).

If we consider only patients with a GCS score of 15, the best cutoff of S100-B level was still found to be 0.12: the sensitivity was 98.6 (92.7 to 100), the negative predictive value was 99.6 (97.6 to 100), and the negative likelihood ratio was 0.06 (0.009 to 0.45).

Sensitivity Analyses

Measures of S100-B levels were compared between the 62 pairs of plasma and serum samples of the same patients. The correlation coefficient was 0.97. The Bland-Altman analysis (difference against the average) shows that the difference against the mean in this study did not vary in any systematic way over the range of S100-B measurement. The mean difference between plasma and serum was 0.04 (95% CI 0.02 to 0.06).

LIMITATIONS

The term *minor head injury* has been used in the literature with various meanings.[24,25] The question of how best to define a minor head injury still is of great importance and has been a source of confusion. Some authors have suggested that patients with a GCS score of 13 should be excluded from the minor head injury category. In our investigation, they were included because our priority was the clinical criteria that represent the typical appearance of patients with minor head injury in EDs, according to international guidelines.[10,12,13]

Our study was conducted in an ED in which data collection is often impeded by unexpected events, leading to a substantial number of patients with missing data and therefore to a potential selection bias. However, we found few differences between the patients included in the analysis and the 568 excluded from the analysis; those with no CT scan, no S100-B data, or neither; or those with a trauma blood sampling interval longer than 6 hours. The percentage of positive CT scan results was 7.1% versus 8.6% in patients excluded because S100-B measures were missing. Median S100-B levels were 0.23 μg/L (0.14 to 0.38) versus 0.19 μg/L (0.13 to 0.32) in patients excluded because CT scan was not performed.

To avoid the potential effect of other injuries on S100-B level, we restricted patient selection to those without significant injuries other than to the head. Some patients included in the study have an Abbreviated Injury Score of 2, which leaves room for injuries that can potentially affect S100-B levels. The specificity could have been affected by the inclusion of patients with a falsely increased S100-B level from nonbrain trauma.

All participants were recruited from a single center, which limits the external validity of the results. There is therefore a need for a further multicenter study because unrecognized variables in sample processing could contribute to different results in other settings. Such a study would also be useful to validate the cutoff value of 0.12 μg/L, which was retrospectively determined in our study.

The use of CT as a standard indicator of brain injury is supported by data gathered during several decades, showing that it is a very sensitive method of predicting the risk of worsening

Table 4. Basic demographic data of patients with a clinically important traumatic brain injury.

Patients Whose MHI Became Complicated	Age, Years	Sex	Trauma History	S100-B, μg/L	Traumatic Brain Injuries on CT	Type of Complication
1	79	Male	Fall from own height	2.22	Subarachnoid hematoma Subdural hematoma	Death caused by MHI
2	60	Male	Fall from height	0.68	Cerebral contusion	Loss of 2 points in GCS score Sedation
3	63	Male	Fall from own height	1.15	Subarachnoid hematoma Subdural hematoma Epidural hematoma	Prolonged confusion Sudden death 3 weeks after discharge (patient also with cardiac problems)
4	70	Female	Fall from own height	1.24	Cerebral contusion Subarachnoid hematoma Subdural hematoma Skull cap fracture	Loss of 2 points in GCS score Sedation
5	69	Female	Traffic accident (pedestrian)	0.63	Cerebral contusion Subarachnoid hematoma Subdural hematoma	Loss of 2 points in GCS score Sedation Neurosurgery
6	46	Female	Fall from own height	0.93	Cerebral contusion Subarachnoid hematoma	Death caused by MHI
7	80	Male	Fall from own height	0.70	Subdural hematoma	Loss of 2 points in GCS score Neurosurgery
8	22	Male	Sport accident (rollerblades)	0.72	Skull base fracture Cerebral contusion Epidural hematoma	Loss of 2 points in GCS score
9	40	Male	Traffic accident (pedestrian)	0.46	Subdural hematoma	Death caused by MHI
10	22	Male	Assault	0.53	Subarachnoid hematoma Skull cap fracture Pneumocephalus	Sedation Neurosurgery
11	33	Male	Fall from height (roof)	0.77	Cerebral contusion Subarachnoid hematoma Subdural hematoma	Prolonged confusion
12	19	Male	Assault	0.14	Skull base fracture Cerebral contusion	Loss of 2 points in GCS score

Table 5. Accuracy and performance parameters of S100-B measurement.

	Cutoff Value, μg/L		
	0.10	**0.12**	**0.14**
Sensitivity	99.1 (95.0–100)*	99.1 (95.0–100)	97.3 (92.3–99.4)
Specificity	12.2 (10.6–14.0)	19.7 (17.7–21.9)	26.8 (24.5–29.1)
Negative predictive value	99.4 (96.9–100)	99.7 (98.1–100)	99.2 (97.8–99.8)
Positive predictive value	8 (6.6–9.5)	8.6 (7.1–10.3)	9.2 (7.6–11.0)
LR+	1.13 (1.10–1.16)	1.24 (1.20–1.28)	1.33 (1.27–1.39)
LR–	0.07 (0.01–0.50)	0.04 (0.006–0.32)	0.06 (0.03–0.31)
No. of false-negative results	1	1	3
No. with clinically important traumatic brain injury among false negative results	0	0	0
CT scan potentially avoided, %†	12	19	25

LR+, Positive likelihood ratio; *LR–*, negative likelihood ratio.
*Numbers in parentheses are 95% CI.
†CT scan potentially avoided=number of patients with an S100-B measurement below the cutoff divided by the total number of samples.

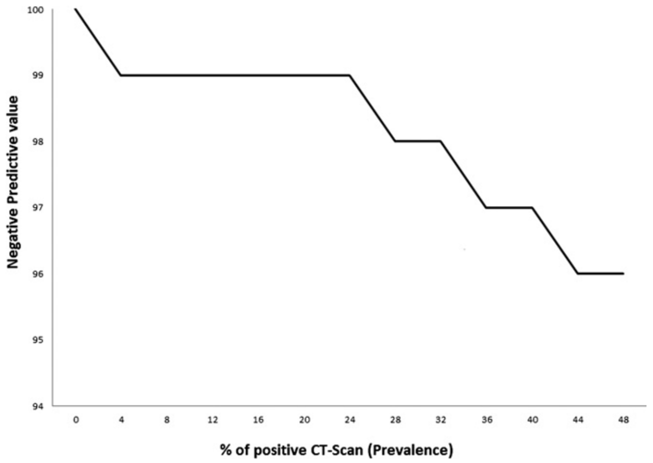

Figure 2. Negative predictive value versus proportion of positive CT scan results (prevalence).

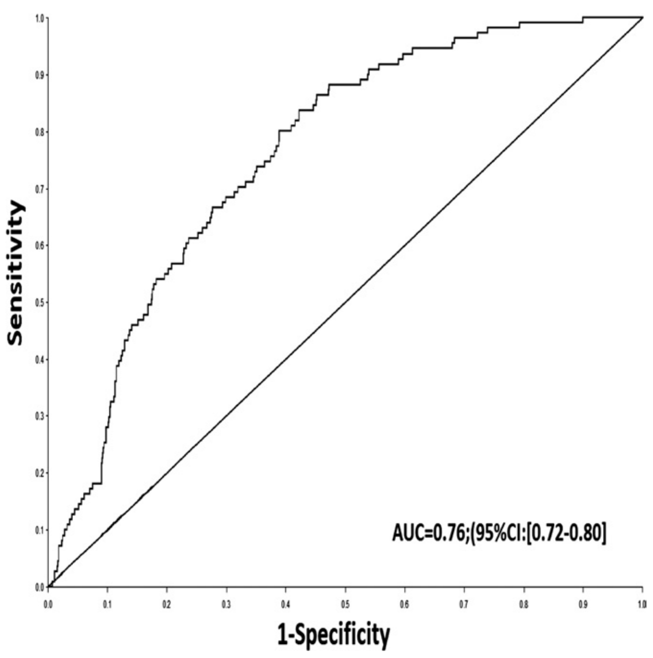

Figure 3. Receiver operating characteristic curve of S100-B measurement for discrimination between positive and negative CT scan results.

in the case of initial minor head injury. The main clinical outcome of interest, however, is not the radiology image itself but the neurologic deterioration. Only 12 patients (0.7%) experienced a clinically important traumatic brain injury, and 3 of them eventually died. Using clinical outcome as the criterion standard would be a better choice, but such a study would require more participants than we can include in a reasonable time.

Our study center is a tertiary neurosurgical regional center, which might have led to a higher incidence of patients with positive CT scan results because of the potential that the radiologists might have advanced expertise at detecting subtle radiographic abnormalities on CT.

In our study, frozen samples were analyzed. We do not have our own data demonstrating that quantitative measurements are the same for fresh and frozen samples. However, a previous study has shown that the stability of serum S100B stored at −80°C was good.[34]

Finally, no data were available on the ethnicity of the participants, although it has been suggested that skin melanocytes could produce S100-B protein.[35] This point should also be addressed in a further validation study.

DISCUSSION

We report here the largest study ever conducted, to our knowledge, on a consecutive sample of 1,560 patients with minor head injury, comparing initial blood levels of S100-B protein with head trauma–relevant CT scan findings. Our results show that blood S100-B measurement within 6 hours of minor head injury compared with CT scan has a high negative predictive value.

Our results are consistent with those of the only other large-scale study, reported by Biberthaler et al,[17] who found in a sample of 1,309 patients with minor head injury a negative predictive value of 99.7% (95% CI 99% to 100%), with 28% of CT scans potentially avoided. Median blood S100-B level of patients with a negative CT scan result in the study by Biberthaler et al[17] was 0.16 (95% CI 0.09 to 0.33). In our study, the median S100-B value for these patients was significantly higher: 0.22 (95% CI 0.14 to 0.36). An explanation may be that Biberthaler et al[17] measured S100-B level in serum and not plasma samples, which is consistent with the results of our comparison of 62 pairs of plasma and serum samples of the same patients. This is also consistent with another comparison study performed between serum and plasma samples of 18 patients that found a 0.99 correlation and a 20% mean increase in S100-B levels measured in plasma compared with those measured in serum.[36] A greater percentage of CT scans potentially avoided was found in the German study (30%). An explanation can be that the difference is caused by some clinical inclusion/exclusion criteria or the different maximum periods from injury to blood sampling (3 versus 6 hours).

Our results are highly consistent with those of the few other studies of the role of S100-B in the early management of patients with minor head injury.[37-40]

In this study, 44% of patients were older than 65 years because such a limit was considered a risk factor for complications after an initial mild head injury. The population of included patients was considered as a whole, and more study is needed to determine whether S100-B expression differs according to age groups. Some studies have already expressed an interest in S100-B analysis in children, in whom exposure to radiation must be avoided as much as possible. Moreover, in France, where refunding of medical costs is assured in case of hospitalization, patients are admitted very easily, even in the case of a head trauma that could be considered mild in other circumstances.

In our hospital, head injuries account for 5% of all patients presenting to the ED, and CT scan is among the most expensive tests ordered. This study suggests that S100-B could be helpful to safely rule out clinically important traumatic brain injury after minor head injury and thereby reduce the need for CT scans performed in the ED. This will decrease exposure to radiation and the time spent in the ED by patients enduring the 6-hour delay before their CT scan. The S100-B test is inexpensive and does not require expensive equipment. The comprehensive clinical judgment of the treating physician, including careful patient history taking and clinical examination, should, however, remain pivotal in the management of minor head injury. Further analysis of our database will be conducted to assess the relevance of different clinical decisions rules based on clinical factors or S100-B measurement for patients with minor head injury.

Moreover, there is a need for a prospective, multicenter evaluation of the cost-effectiveness of the S100-B test used in patients with minor head injury on admission to the ED.

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