Research Article

Plasma-based S100B testing for management of traumatic brain injury in emergency setting

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ABSTRACT

Background: Serum biomarker S100B has been explored for its potential benefit to improve clinical decision-making in the management of patients suffering from traumatic brain injury (TBI), especially as a pre-head computed-tomography screening test for patients with mild TBI. Although being already included into some guidelines, its implementation into standard care is still lacking. This might be explained by a turnaround time (TAT) too long for serum S100B to be used in clinical decision-making in emergency settings.
Methods: S100B concentrations were determined in 136 matching pairs of serum and lithium heparin blood samples. The concordance of the test results was assessed by linear regression, Passing Pablok regression and Bland-Altman analysis. Bias and within- and between-run imprecision were determined by a 5×4 model using pooled patient samples. CT scans were performed as clinically indicated.
Results: Overall, S100B levels between both blood constituents correlated very well. The suitability of S100B testing from plasma was verified according to ISO15189 requirements. Using a cut-off of 0.105 ng/ml, a sensitivity and negative predictive value of 100% were obtained for identifying patients with pathologic CT scans. Importantly, plasma-based testing reduced the TAT to 26 min allowing for quicker clinical decision-making. The clinical utility of integrating S100B in TBI management is highlighted by two case reports.
Conclusions: Plasma-based S100B testing compares favorably with serum-based testing, substantially reducing processing times as the prerequisite for integrating S100B level into management of TBI patients. The proposed new clinical decision algorithm for TBI management needs to be validated in further prospective large-scale studies.

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1. Introduction

Traumatic brain injury (TBI) is recognized by the Center of Disease Control and Prevention as serious health burden representing one of the most common causes of admittance to emergency department (ED) [1,2]. More than 90% of TBI patients are classified as mild TBI (mTBI) based on their initial Glasgow Coma Scale (GCS) of 13–15 [3,4]. Although most of mTBI patients will recover within a

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Abbreviations

CCT	Cranial computed tomography
C	Confidence interval
CR	Complete response
CT	Computed tomography
CV	Coefficient of variation
FDA	Food and Drug Administration
ED	Emergency Department
GCS	Glasgow Coma Scale
HGNC	Human Gene Nomenclature Committee
LoA	Limit of Agreement
LOC	Loss of consciousness
mTBI	Mild traumatic brain injury
NPV	Negative predictive value
PD	Progressive disease
PR	Partial response
SCN	Scandinavian Committee for Neurotrauma
SD	Standard Deviation
STD	Stable disease
TAT	Turnaround time
TBI	Traumatic brain injury

List of human genes
Gene symbol   Gene name according to HGNC
S100B	S100 calcium binding protein B

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short time, up to 15% have pathologic findings on cranial computed tomography (CCT) imaging and up to 1% will require neuro-surgical intervention [5–9]. Subsequently, a small but not negligible number of patients experience long-term disability or die due to intracranial complications. As the outcome depends on timely diagnosis and appropriate treatment of intracranial lesions [10,11], several guidelines have been developed to identify patients that can safely be discharged from those with a need for a CCT scan as the reference diagnostic tool [4,5,12–16].

These guidelines are based on clinical assessment (e.g. including GCS, headache, vomiting, deficits in short-term memory, seizures or loss of consciousness (LOC)) representing a challenge for physicians, as the clinical presentation does not necessarily correlate with the severity of the brain injury. Indeed, neurological deterioration is often attributed to alcohol intoxication with such patients accounting for up to 50% of TBI patients [10,17]. The resulting over-triage of CCT scans is widely accepted with up to 50% of patients receiving a head CT and 80–99.5% of these scans revealing normal findings([5,18,19]). In order to reduce costs and ED overcrowding, and to minimize radiation exposure, biomarkers are urgently needed allowing to safely identify patients for whom a CT scan can be avoided [3,4].

The best-studied biomarker is S100B, a well-established protein tumor marker commonly used for the follow-up of patients suffering from malignant melanoma [20]. In the case of TBI, S100B is elevated within 30 min after injury after release from the astroglia [11,21,22]. Its short half-life time of 60–120 min restricts the analysis to patients presenting within 6 h after injury [4,23]. Due to its high negative predictive value (NPV) of 99% for normal CCT findings [17], it has been included into few guidelines as pre-head CT screening test [12,13,17]. While it has been demonstrated that substantial reduction of CT scans is achieved by implementing these guidelines [15,24], S100B testing has not been widely adopted as a routine by ED-physicians yet. This may be explained by the long overall assay time of 1–2 h for the determination of S100B from serum (due to the necessary clotting time) [2] preventing the laboratory results to be taken into account before requesting a CCT scan that is usually required as soon as possible and, therefore, recommended by guidelines within 1 h [16].

The aim of our study was a) to determine the commutability of S100B results obtained from heparin plasma and serum, b) to evaluate the improvement in TAT of S100B results from heparin plasma over serum and c) to assess the diagnostic validity of S100B testing determined from both sources and the potential impact on clinical case management.

2. Material and methods

2.1. Patient enrollment

This retrospective study was conducted following approval by the local Institutional Review Board. For comparison, serum and lithium heparin blood samples from a total of 136 patients were analyzed for S100B concentrations. All blood samples were obtained as part of standard care with data analysis for method comparison and evaluation of clinical cases being performed retrospectively.

Specifically, 85 blood samples of stage I to IV melanoma patients were obtained during regular follow-up visits. Additionally, we enrolled 51 consecutive patients presenting with TBI at the ED of University Medical Center Mannheim. All patients included were aged 18 or older and presented at the ED within 6 h after injury. Patients had serum and lithium heparin blood samples withdrawn simultaneously and received a CCT according to in-house guidelines. TBI patients were managed according to Advanced Trauma Life Support guidelines, clinical examination and evaluation of GCS was performed by an attending ED physician. Out of the 51 TBI patients, 27 met the criteria for mTBI according to the American Congress of Rehabilitation Medicine: aged 18 or older, initial GCS of 13–15 with any period of LOC less than 20 min, or any post traumatic amnesia less than 24 h. Patients were excluded from the mTBI subgroup if a severe injury, including open fracture, thoracic or abdominal contusion or polytrauma was suspected.

2.2. Blood-collection and S100B analysis

In our hospital, blood samples tubes (Sarstedt, Germany) from TBI patients, polytraumatized patients or generally patients at risk of death are routinely marked by the ED-staff. Specifically, a neon-green-colored mini cap (Sarstedt, Germany) is stuck onto the top of the blood collection tube prior to sending the tubes to the laboratory. This assures the identification of emergency samples upon arrival by the laboratory staff. Such samples are immediately centrifuged at $2500 \times g$ for 3 min at 18 °C (reduced centrifugation time compared to 10 min for routine samples) in order to minimize processing delays, as reduced centrifugation times have been proven in various studies to not alter clinical chemistry analytes except LDH [25,26].

Serum samples were collected for the determination of S100B when clinically indicated together with lithium heparin blood for analysis of standard clinical chemistry analytes. Plasma-based S100B testing did not require additional blood draws. Upon receipt in the laboratory, lithium heparin blood samples were immediately centrifuged, while serum samples were allowed to sit for appropriate clotting of 20–60 min. S100B concentrations were determined using the Elecys® S100 (Roche Diagnostics, Germany) assay on a Cobas e411 instrument (Roche Diagnostics, Germany). The test is specified by the manufacturer for serum samples with a cut-off of 0.105 ng/ml and a linearity range of 0.005–39 ng/ml.

2.3. Preparation of controls for method verification

For determination of bias and within- and between-run imprecision, we generated in-house control materials, as no control samples were available for S100B testing in blood plasma. In detail, pooled serum and plasma samples were prepared at three different S100B concentration levels, i.e. low (0.024 ng/ml), medium (0.170 ng/ml) and high (1.133 ng/ml), aliquoted and kept for further use.

2.4. Imaging studies

CT examinations were performed with a 16-slice multi-detector CT scanner (Somatom Emotion, Siemens Healthineers, Germany) as part of our standard CT protocol for ED patients. CCT scans were analyzed by the respective on-call radiologist and reviewed by a consultant radiologist or neuroradiologist. CCT scans were considered positive in case of any signs of trauma-related cranial (skull fracture, mid face fracture) or intracranial (epidural hematoma or effusion, subdural hematoma, subarachnoidal hemorrhage, intraventricular hemorrhage, parenchymal hemorrhage, brain contusion, brain edema, diffuse axonal injury) pathology being recorded.

2.5. Statistical analysis

All statistical analyses were carried out using Abacus 2.0 (LABanalytics GmbH, www.labanalytics.de, 2016, Germany) and R version 3.0.1 (The R Foundation for Statistical Computing).

Results of data analysis are presented as descriptive statistics by the mean with 95% confidence intervals (CI), standard deviation (SD), and coefficient of variation (CV) as appropriate. Linear and Passing Bablok regression as well as Bland-Altman analysis were determined for method comparison between S100B level obtained in plasma and serum. The allowable bias was calculated based on the calculation for uncertainty of measurement [27]. Data normality was calculated using the Cusum test. Between-group differences were assessed by Student's t –test. For determination of bias as well as within- and between-run imprecision, a 5 × 4 model was conducted.

Both S100B plasma and serum levels were tested for potential confounding variables. In detail, we tested age at diagnosis, gender, tumor stage, targeted therapy and immunotherapy for possible effects on the S100B levels. Tests were performed in R (www.r-project.org) as univariate linear regression using each variable individually and as multivariate linear regression using all variables.

For all statistical analyses, p-values less than 0.05 were considered statistically significant.

3. Results

For this study, 136 matching pairs of serum and lithium heparin plasma samples were analyzed in order to determine whether the S100B analysis from serum could be replaced by testing from blood plasma in order to allow for reduced turnaround times and thus improve the management of TBI patients in emergency settings.

3.1. S100B testing in serum and lithium heparin plasma

In total, 136 matching pairs of serum and plasma samples of patients suffering from TBI (n = 51) or malignant melanoma (n = 85) were included in the study (Table 1) with more detailed information being provided in Supplemental Tables 1 and 2 Interestingly, the mean S100B concentration in serum and plasma was lower in melanoma patients than in TBI patients, as shown in Table 1. This may be due to the fact that S100B level for melanoma patients was determined as part regular follow-up visits and hence the majority of patients were at stable disease (STD; n = 39; mean S100B level = 0.07 ng/ml), complete response (CR; n = 21; mean S100B level = 0.120) or partial response (PR; n = 8; mean S100B level = 0.129), and only the minority presented at progressive disease (PD; n = 11; mean S100B level = 0.298). We further investigated whether age, gender, tumor stage or type of therapy at time of blood sampling (immunotherapy or targeted therapy) were confounding variables for both, S100B level in plasma or serum. Here, only a weak significant impact was revealed for age (p00.04 for serum, p = 0.03 for plasma), whereas no significant association was identified for the other variables tested.

Linear regression analysis of S100B analyses in plasma and serum revealed an overall correlations of $r^2 = 0.9978$ (Fig. 1). When analyzed separately, the same applies for the subgroups of melanoma patients ($r^2 = 0.9456$) and TBI patients ($r^2 = 0.9977$). Both, Passing Bablok regression and Bland-Altman plot analyses conducted to investigate systematic bias, showed strong positive correlation for both test modalities (Kendall's tau = 0.0892). Additionally, a systematic or proportional error could be excluded (95%CI y-intercept = −0.000 – 0.005; 95%CI slope = 0.995–1.047). Notably, Bland-Altman analysis (difference against the average) showed that S100B results in plasma and serum are not equivalent for 9.4% of sample pairs with a 95%CI of the limit of agreement (LoA) (−33.38% – 45.59%) exceeding the allowable bias of±33.33%. However, all of these sample pairs belonged to the melanoma patient subgroup.

When performing the Passing Bablok regression analysis for the prime target group of TBI patients, a very high level of positive correlation could be demonstrated (Kendall's tau = 0.959). Furthermore, a systematic and proportional error could be excluded (95% CI y-intercept = −0.021 – 0.046; 95% CI slope = 1.000–1.060). Fig. 2 shows the results of Bland-Altman analysis. The mean difference was 0.06% (95% CI -2.94% – 3.07%) and results are demonstrating that measurement of S100B from serum and lithium heparin plasma is interchangeable (allowable bias = ±33.33%; 95% CI of LoA = −20.89% - 21.01%).

3.2. Evaluation of bias and within- and between-run imprecision

For method verification, determination of bias and within- and between-run imprecision are mandatory. Specifically, we measured S100B concentrations according to the 5 × 4 model in pools of serum or plasma at three different concentration levels (low = 0.024 ng/ml, medium = 0.170 ng/ml, high = 1.133 ng/ml). Results of measurement are plotted in density plots showing a Gaussian distribution (Supplemental Fig. 1). In the low and medium levels, the S100B results from plasma revealed slightly higher concentrations compared to those in serum (p < 0.001), whereas slightly lower concentrations are measured in the high level control (p < 0.001). However, statistical analysis revealed a very low within- and between-run imprecision with comparable CV for S100B testing in serum and plasma that does not exceed 5% at each control level, respectively (Table 2).

3.3. Evaluation of turnaround time

In emergency setting, the turnaround time (TAT) for reporting laboratory results to the treating physician should be as short as possible in order to allow laboratory findings to be integrated into clinical decision-making. To assess the average TAT for the analysis of S100B from serum, the time interval between receiving the samples through the pneumatic tube system and reporting the results

Table 1
Patient characteristics and S100B level of different patient cohorts.

Number of Patients		Total	Melanoma	TBI	mTBI	mTBI CCT-	mTBI CCT+
		n = 136 (%)	n = 85 (%)	n = 51 (%)	n = 27 (%)	n = 19 (%)	n = 9 (%)
sex	m	80 (58.8)	46 (54.1)	34 (66.7)	20 (74.1)	14 (73.7)	6 (75.0)
	f	56 (41.2)	39 (45.9)	17 (33.7)	7 (25.9)	5 (26.3)	2 (25.0)
Age	Median	58.2	62.6	50.9	42.9	38.5	53.1
	range	18–89	22–89	18–89	18–79	18–68	19–79
S100B Serum (ng/ml)	Mean	1.111	0.122	2.760	0.972	0.477	2.146
	95% CI	0.393–1.830	0.086–0.157	0.907–4.614	0.107–1.836	0.090–0.865	0.000–4.862
S100B Plasma (ng/ml)	Mean	1.139	0.128	2.823	0.943	0.469	2.069
	95% CI	0.418–1.859	0.094–0.162	0.968–4.679	0.123–1.763	0.069–0.868	0.000–4613

Abbreviations: CI = confidence interval; TBI = traumatic brain injury; mTBI = mild traumatic brain injury; CCT = cranial computed tomography.
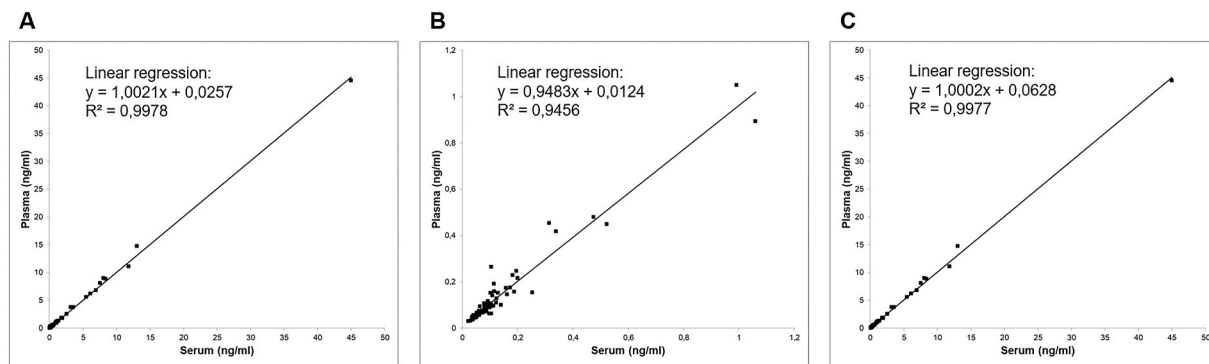
Fig. 1. Linear regression analysis of S100B concentration in serum and plasma.
The scatter shows the relation between the S100B levels of serum (x-axis) and plasma (y-axis) for (A) all 136 patients included in the study (r^2 = 0.99), (B) the 85 stage I to IV melanoma patients (r^2 = 0.95), and (C) the 51 patients with traumatic brain injury (r^2 = 0.99). Values above or below the drawn regression line represent increase or decrease, respectively, compared to serum.
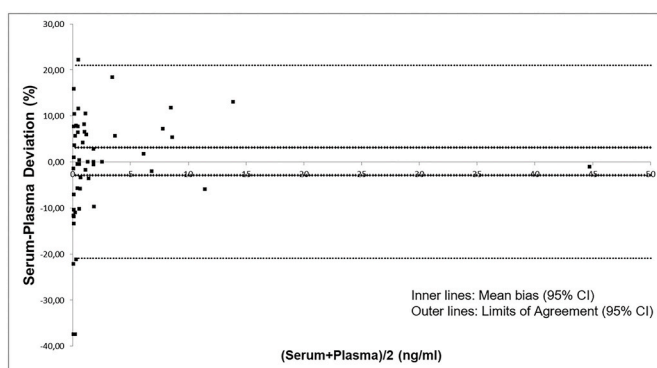
Fig. 2. Bland-Altman analysis for patients with TBI
Bland-Altman analysis was used to estimate the agreement between S100B analysis in serum and lithium heparin plasma. On the difference plot, the mean S100B concentration between the two blood constituents is plotted on the x-axis and the difference of S100B concentration between the two blood constituents on the y-axis. The inner lines show the 95% CI of the mean bias (95% CI -2.94% – 3.07%), the outer lines the 95% CI of the Limit of agreement (−20.89% - 21.01%). The later one means that 95% of measurement differences between serum and plasma samples are found within this range. As the calculated range of LoA is smaller than the allowable error limit of ± 33.3%, there is no significant difference between S100B results in serum and lithium heparin plasma.

Table 2
Statistical evaluation of within- and between-run imprecision.

			Low Level	Medium Level	High Level
S100B target value (ng/ml)			0.024	0.170	1.132
S100B Serum	Within-run results	Mean CV (%)	3.40	3.29	1.99
		Bias range	−1.67 - 0.83	−1.29 - 1.76	−1.77 - 1.41
	Between-run results	Mean (ng/ml)	0.024	0.170	1.132
		SD	0.001	0.006	0.027
		CV (%)	3.43	3.370	2.324
		Inaccuracy (%)	0.21	0.09	0.13
S100B Plasma	Within-run results	Mean CV (%)	3.24	2.08	1.47
		Bias range	−0.74 - 0.74	−2.09 - 1.65	−1.42 - 1.23
	Between-run results	Mean (ng/ml)	0.027	0.182	1.059
		SD	0.001	0.005	0.020
		CV (%)	3.429	2.540	1.921
		Inaccuracy (%)	0.00	−0.30	−0.05

Abbreviations: SD = standard deviation; CV = coefficient of variation.

Table 3
Time sequence of S100B analysis.

		Time required (min)
Outside Laboratory	Blood withdrawal	5
	Transport	2
Inside laboratory	**Clotting time**	**20–60**
	Centrifugation	5
	Sample loading	1
	Analysis	18
	Reporting of results	2

was extracted from the laboratory information system. For ED samples, a minimal clotting time of 20 min and a reduced centrifugation time of 3 min were applied yielding an average TAT of 44 min (Table 3). In comparison, the TAT of S100B from plasma could be reduced by 40% resulting in an average TAT of 26 min.

3.4. Evaluation of S100B as pre-CCT screening test

To evaluate the suitability of S100B as a test to exclude TBI prior to CCT, only the subgroup of mild TBI patients was further investigated (n = 27). Descriptive data and results are shown in Table 1 (for more information, see Supplemental Table 3).

CCT-negative patients (n = 19) showed an average S100B concentration of 0.477 ng/ml and 0.469 ng/ml in serum and plasma, respectively. In contrast, patients with trauma-related pathology in CCT (n = 8) had a mean S100B concentration of 2.146 ng/ml in serum and 2.069 ng/ml in plasma (Table 1). The differences between CCT-negative and CCT-positive patients were marginally statistically significant (p = 0.08). Plasma levels were highly correlated with serum levels for both subgroups with $r^2 = 0.9996$ for the CCT-subgroup and $r^2 = 0.9883$ for the CCT + subgroup, respectively (Supplemental Fig. 2).

Using the cut-off for S100B recommended by the manufacturer for both serum and plasma (0.105 ng/ml), sensitivities of 100% and NPV of 100% were determined for both blood materials. Due to the limited number of patients, we did not pursue to calculate an optimal cut-off for S100B in plasma.

3.5. Illustrative cases

Case 1 – TBI with bilateral intima dissection of A. carotis communis missed by CT

A 25-year old patient was admitted to the ED following a low-speed motorcycle accident, during which he had hit the back end of a stopped car head-on while wearing a full face integrated helmet. At time of admittance to ED, he appeared unharmed except for superficial lacerations and a fractured elbow. Shortly after admission, the patient fainted briefly, but spontaneously recovered. During physical examination his GCS was assessed at 14. The CCT revealed no skull injury or intracranial pathology. While the patient was being scheduled for surgery of his fractured elbow, a very pronounced S100B elevation of 1.4 ng/ml was reported by the emergency laboratory suggesting a serious cerebral injury and leading to a. reevaluation of the initial CCT. It was found that dissections in the intima layers in both internal carotid arteries resulted in the formation of a pseudo-luminal stenosis.

Case 2 – patient with mTBI and small cortical bleeding missed by CT

A 28-year-old patient was admitted to ED following a car accident at approximately 35 mph. Upon admission to hospital, the patient presented with severe headache, but without signs of nausea, vomiting or dizziness. His physical examination and particularly the neurological status revealed no pathological findings, and his GCS was scored 15. Due to suspicion of a whiplash syndrome, a CCT was performed, but was evaluated as normal. The patient urged to be discharged against medical advice on his own account. The S100B level in serum sample drawn in ED was reported to be 0.71 ng/ml. A detailed reevaluation of the CCT revealed a single very discrete hyperdense lesion in the right fronto-basal lobe consistent with a small cortical bleeding, missed during first assessment.

4. Discussion

Calcium-binding protein S100B is predominantly present in astrocytes and Swans cells in the central nervous system, but also expressed by adipocytes, melanocytes and other cells [28]. Concentrations in peripheral blood of healthy individuals are low (<0.105 ng/ml) with elevated levels being associated with various pathologic conditions including TBI [23]. Nevertheless, in clinical practice S100B is mainly used as protein tumor marker for follow-up of melanoma patients [29]. Hence, in this elective setting, assay turn-around times are not decisive. Accordingly, all immunoassay test systems that are commercially available rely on serum as material for the analysis of S100B [11]. Notably, this also applies for measurement of S100B in cases of (suspected) TBI and mTBI potentially constituting critical emergency situations. In order to evaluate whether S100B testing from serum can generally be replaced by plasma-based testing particularly in TBI, a methodical comparison was conducted in 136 matching samples from melanoma and TBI patients. Although linear regression demonstrated a high level of agreement between testing modalities ($r^2 = 0.9978$) in the overall

group, a more detailed statistical analysis revealed that the results from both materials are not entirely commutable (95% LoA −33.8% – 45.59%). A detailed evaluation revealed that the main differences were found in the melanoma group. This is not surprising, as immunochemical determination of protein tumor markers regularly shows a pronounced method-dependency.

Since the prime objective of our study was the clinical decision-making for TBI patients in the ED, we placed main emphasis of our analysis to this subpopulation. Our study reveals a high level of concordance between testing modalities by linear regression, Passing Bablok regression and Bland-Altman analysis demonstrating that S100B can be determined from both blood matrices for TBI patients ($r^2 = 0.9977$, 95% LoA −20.89% - 21.01%). This is in line with former studies demonstrating a high linear correlation for S100B testing between serum and heparin plasma [30], and serum and citrate plasma [31], respectively. Although plasma was used for S100B measurement in few other studies [3,10], the authors did not report on verification of the tests. However, so far the comparability of test results was never demonstrated using the Elecys® S100 on a Cobas e411 test system with an analyzing time of 18 min being the fastest upon all systems currently available. To the best of our knowledge, this is the first study reporting on within- and between-run imprecision as prerequisite for verification of plasma-based S100B testing according to ISO15189. The determined CV of below 5% for both test modalities proves the clinical suitability for measurement of S100B level for TBI patients in plasma.

For integration of laboratory test results into clinical decision-making in emergency settings as in case of TBI, fast assays and short turn-around times are critical. From the perspective of an integrated diagnostic workflow in an emergency setting, diagnostic imaging is the gold standard and firmly embedded into clinical routine. To contribute valuable information to an optimized diagnostic workflow, our laboratory has implemented several rules: blood samples from patients at risk of death are labeled in the ED using colored mini-caps, thereby allowing their immediate identification by the laboratory staff upon arrival. Furthermore, optimized processing with reduced centrifugation and clotting times allowed for a TAT of 44 min for S100B results from serum samples representing a substantial reduction from the 1–2 h reported in literature(2). However, reducing the clotting time of serum samples bears the risk of analytical errors or clogging of the analyzer due to ongoing clotting during the test procedure. Using plasma would prove superior to serum in said emergency situation allowing for a total assay time of 26 min as noted in our study. This is of special importance as according to our hospital standard operation procedure as well as to other guidelines [16], a CCT has to be carried out within 1 h after admittance to ED for patients with GCS<13, GCS<15 within 2 h after injury, repeated vomiting, age over 65 years, and for patients with anticoagulation or platelet inhibition. Accordingly, S100B test results available within approximately 30 min will allow physicians to rule out the necessity of performing CCT scans for mTBI patients as well as to integrate laboratory and imaging findings as independent diagnostic modalities for further assessments in case of 'shock room' patients.

For mTBI, S100B is proposed as pre-CCT screening test. A recent meta-analysis reported a pooled NPV of 99% (95% CI 98%–100%) to predict a normal CT and revealed only 1/2264 patients with non-elevated S100B level and need for neurosurgical intervention [17]. The NPV of 100% reported here is in accord with the literature. Importantly, by using plasma S100B with a cut-off of 0.105 ng/ml none patient with pathologic CCT findings would have been missed, while CCT scans could have been reduced by 16%. In addition to reducing unnecessary radiation exposure, substantial savings in health care costs of up to 30% have been reported associated with
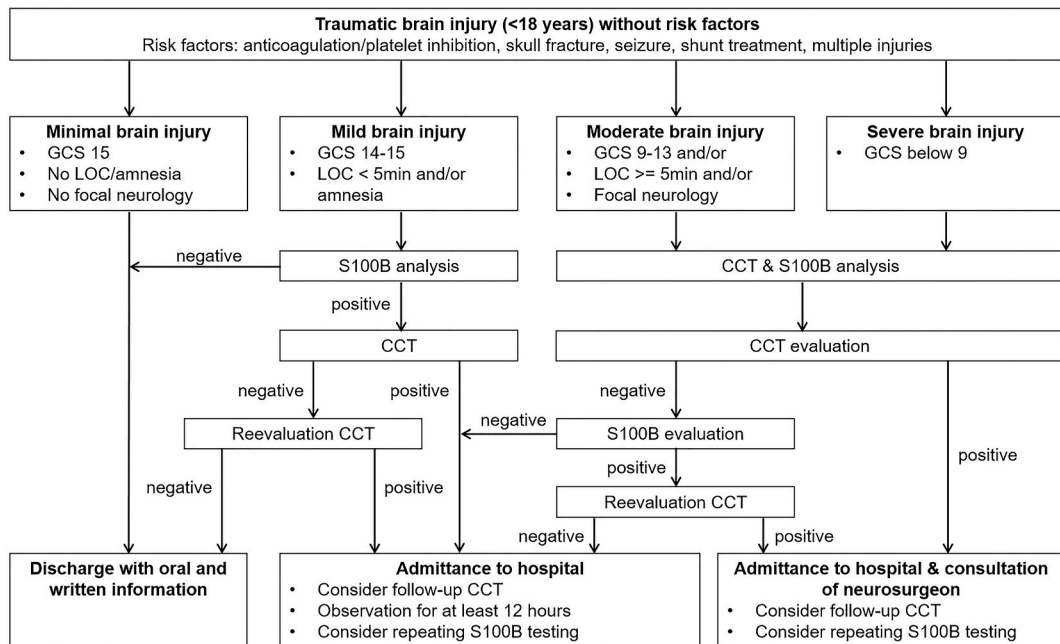

Fig. 3. Algorithm for management of TBI patients
The depicted algorithm is modified from the Scandinavia Neurotrauma Committee guideline.
Abbreviations: GCS = Glasgow Coma Scale, LOC = Loss of Consciousness, CCT = cranial computed tomography.

reductions of up to 50% of CCTs [32–34]. We suggest that an optimal cut-off of plasma S100B in patients with suspected mTBI/TBI may decrease CCT examinations beyond the 16% found, but larger studies are needed.

So far, S100B has only been included as pre-CCT test for mTBI patients into clinical guidelines. Nevertheless, it is well known that the S100B level is associated with the severity of the brain injury and the outcome of patients [11,17]. In clinical emergency situations, misinterpretation rates of CT scans of 2–24% have been reported with over 85% being detectable by reevaluation [35,36]. Consequently, the two exemplary case reports provided in this report emphasize that S100B concentrations – preferably from plasma samples for shortest TAT - should be determined for all TBI patients leading to CCT reevaluation in all cases with elevated S100B. Based on our experience, we propose an algorithm for management of TBI patients (Fig. 3) based on the amended SCN guidelines [24]. We emphasize that the depicted integrated approach of laboratory and imaging findings could help to identify false-negative CCT scans and add potentially critical information to guide further clinical decision. In case of persistent discrepant results, patients should be kept under neurological surveillance enabling an immediate control CCT, if indicated. Considering its short half-life time, using S100B for follow-up of admitted patients with discrepant results may add additional benefit, but again larger studies would need to substantiate this hypothesis. Being based on a small case number, the proposed algorithm has to be validated in further large-scale studies. This would include the determination of optimal cut-off concentrations for plasma-based S100B testing as screening tool to avoid unnecessary CCTs as well as for reevaluation of head CTs that are likely to differ from one another. Further studies should also address whether the same applies for patient under anticoagulation, platelet inhibition or intoxicated patients as these risk factors hamper the clinical assessment whereas S100B level does not seem to be affected by either of them [10,37].

In summary, our study demonstrates the commutability of serum- and heparin-plasma-based S100B testing for TBI patients requiring rapid exclusion of organic brain damage. The analytical reliability of S100B testing from plasma was further proved by verification studies. We consider it important to integrate in-vitro and in-vivo diagnostic medicine in a systematic fashion. In this respect, substantially reduced TAT times of S100B tailored to meet clinical requirements allow to better integrate important laboratory results into the clinical decision-making process e.g. in the ED. The algorithm proposed here should be considered as a first approximation for this integrated strategy in the management of TBI patients. Specifically, it proposes an interdisciplinary workflow for the first time by not only including S100B result as a pre-CCT test in mTBI patients, but also integrates the results for reevaluation of imaging findings.

Contribution

FT, SJ, DE, MN, ENP designed the study. FT, SJ, VH, DE, ENP were responsible for data collection and management. DE, ENP enrolled patients. VH, FT, VA were responsible for biostatistics analyses. VH, CS, MS, FT, MFF, MK were responsible for interpretation of data. VH, MS, VA prepared the tables and figures. VH did drafting of manuscript. All authors contributed to revision of the manuscript, and approved it for submission.

CRediT author statement

Verena Haselmann: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Visualization. Christian Schamberger: Formal analysis, Visualization, Writing – review & editing. Feodora Trifonova: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Visualization, Writing – review & editing. Volker Ast: Formal analysis, Visualization, Writing – review & editing. Matthias F Froelich: Formal analysis, Writing – review & editing. Maximilian Strauß; : Validation, Formal analysis, Writing – review & editing. Maximilian Kittel: Writing – review & editing. Sabine Jaruschewski: Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. David Eschmann: Conceptualization, Writing – review & editing. Michael Neumaier: Conceptualization, Project administration, Writing – review & editing. Eva Neumaier-Probst: Conceptualization, Methodology, Validation, Project administration, Writing – original draft.

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Declaration of competing interest

The authors have declared no conflicts of interest.

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Appendix A. Supplementary data

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