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Usefulness of S100β protein in patients on antithrombotic drugs with mild traumatic brain injury: a prospective cohort study in an emergency department

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Abstract

Background S100β protein has interesting metrological characteristics in the general population with mild traumatic brain injury (TBI) but its value in the subpopulation of patients on antithrombotic drugs (ATD) remains poorly documented.

Objective The main objective was to evaluate the performance of S100β assay in ruling-out the presence of a cerebral injury after mTBI in subjects on ATD.

Design, settings and participants This prospective single-center study was conducted between March 2020 and September 2021 in the Emergency Department of a French hospital. Patients on ATD consulting for mTBI having occurred less than 6 h previously were included.

Outcomes measure and analysis The S100β assay was to have been performed within 6 h of the TBI, and a cut-off value of 0.105 µg/L was applied. The standard diagnosis was provided by cerebral computed tomography (CCT). The primary endpoint was the metrological qualities of S100β for detecting intracranial complication following TBI. Economic impact was evaluated as a secondary endpoint.

Results 245 patients were included, with a mean age of 81.5 (± 11.8) years. CCT showed cerebral injury for 15 (6.1%) patients. The S100β assay was negative for 58 (23.7%) patients. Sensitivity was 100% (95% CI: 78.2% – 100%), specificity 25.2% (95% CI: 19.7% – 31.3%), and NPV 100% (95% CI: 93.8% – 100%). The S100β assay could have avoided CCT for 23.7% of the subjects, which would save €82.03 per patient compared to the current strategy.

Conclusion The use of S100β within 6 h of a TBI among subjects on ATD is efficacious in safely discounting cerebral injury, with an appreciable economic saving.

Clinical trial registration NCT04305821 (2020-03-09)

Keywords Mild brain injury, S100β protein, Cerebral injury, Antithrombotic, Cerebral CT, Medico-economic

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Introduction

Traumatic brain injury (TBI) is a frequent cause of emergency department (ED) visits, with an estimated prevalence of 287.2/100,000 [1]. The incidence of intracranial complication following TBI is estimated at 7.1%, with neurosurgical intervention required in 0.9% of cases [2]. Cerebral computed tomography (CCT) is used for diagnosing post-traumatic injury, guided by the presence of risk factors [3, 4]. Treatment with antithrombotic drugs (ATD) is one of the risk factors for post-traumatic intracranial complication, with a recommendation for systematic CCT [3]. However, the incidence of cerebral injury in patients on ATD seems similar to that in the general population, ranging from 4.6% to 10.7% depending on the studies' populations [5–11]. Indeed, the association between the ageing population and an increase in the incidence of pathologies requiring the introduction of ATD [12], and the increased risk of falls among the elderly account for frequent resort to emergency units for patients with TBI [13].

The use of biomarkers has been studied in TBI, notably with the S100β protein. Indeed, recent studies show that S100β correlates with the severity of brain damage, the volume of the infarct or haematoma, and the functional prognosis. The direct impact of antithrombotic treatment on S100β therefore depends on the clinical context: beneficial in the prevention of ischaemia, harmful in the event of haemorrhagic complications [8, 11, 14, 15]. Its plasma elimination half-life is estimated at 97 min [14]. Screening for cerebral injury via S100β titration following mild traumatic brain injury (mTBI) has a sensitivity between 63% and 100%, a specificity between 5% and 58%, and a negative predictive value (NPV) between 81% and 100%, making it possible to reduce the need for CCT by up to 33% [8, 11, 15]. However, the value of S100β testing in the specific population of subjects on ATD remains poorly evaluated.

In this context, the main aim of the present study was to assess the metrological characteristics of S100β assay within 6 h of mTBI in a population of patients on ATD.

Methods

Study design

This was a prospective, single-center diagnostic study conducted from March 2020 to September 2021 in the ED of Rennes university hospital, a tertiary academic hospital with an annual attendance of 65,000 adults.

Population

The inclusion criteria were a patient on ATD, consulting in Rennes hospital ED for mild TBI within 6 h. Mild TBI was defined by a Glasgow coma score (GCS) ≥ 13 30 min after TBI. ATDs were classified in 5 categories: antiplatelet agents (APA: acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor), heparins and related agents (Unfractioned Heparin, Low-Molecular Weight Heparin, fondaparinux, danaparoid), vitamin K-antagonists (VKA: warfarin, fluindione, acenocoumarol), direct oral anticoagulants (DOAC: rivaroxaban, apixaban, dabigatran), anti-thrombotic combination (ATC: bi-APA or APA + anticoagulant).

Non-inclusion criteria were subjects under 18-year of age (minors), with GCS < 13, a time-lapse between TBI and sampling of more than 6 h, subjects presenting for polytrauma (defined as any Trauma intensive care unit admission needed), a history of skin or brain tumor, pregnant women, or subjects under legal protection.

The exclusion criteria were absence of CCT or not being on ATD.

Study protocol

Once all the subjects had confirmed their agreement to take part in the study, a blood sample was taken for S100β protein titration. A CCT was performed on the responsibility of the physician in charge without using the S100β, although its level was not blind.

Brain computed tomography was performed using either a Toshiba Medical Aquilon Prime 128 or an Aquilion Prime SP scanner. The CCT interpretation was made by either senior resident or attending radiologist, then systematically reassessed and validated by a senior radiologist. Cerebral injury was defined by the presence of intracranial haemorrhage (subarachnoid or subdural or epidural or intraventricular or parenchymal or petechiae), or cerebral contusion or edema. Regarding the kinetics of S100β allowing up to 6 h for biomarker sampling in clinical practice, the S100β protein assay was performed after centrifugation of the blood sample in a dry tube, and a Roche laboratory device (Cobas 8000 module e602) enabled determination via electrochemiluminescence with measurable concentrations ranged from 0.005 to 39 μg/L. The assay was considered normal at a value below 0.105 μg/L, according to the threshold provided by the manufacturer. These analyses were performed on all study subjects and stratified in 2 groups by time to S100β determination, H0-H3 for those who had blood sample before 3 h from mTBI, and H3-H6 for those with blood sample between 3 and 6 h after mTBI.

After collecting data for each included patient, the economic impact of implementing S100β in the management for these subjects was evaluated by comparison to the standard of care.

Each patient included received close monitoring until discharge from the emergency department, whether hospitalized or returns home.

Ethics committee approval The protocol for this study was approved by the Ethics Committee for the Protection of Individuals (Comité de Protection des Personnes; CPP Sud-Méditerranée; ID: RCB 2019-A03053-54). In accordance with French regulations, and Human Ethics and Consent to Participate declarations, verbal consent was sought by the investigators. Therefore, 'Consent to Publish declaration' is not applicable.

Clinical trial registration NCT04305821.

Data collection

A standardized questionnaire was used in the ED for inclusion by the emergency physician (Appendix 1). The variables collected concerned the subject (age and gender), the presence of risk factors (ATD type, loss of consciousness, at least 2 vomiting episodes, post-traumatic focal neurologic deficit, post-traumatic convulsions, retrograde amnesia lasting more than 30 min, severe post-traumatic headache, signs of skull base fracture, acute alcohol or drug intoxication), the head injury (time of onset, mechanism, Glasgow score on examination, type of injury on CCT), and overall management (length of stay in the ED, need for neurosurgical intervention, need and reason for hospitalization). Lengths of stay in the ED were collected retrospectively via the patient's computerized medical record.

Objectives and outcomes

The primary objective was the diagnostic performance of the S100β assay following mTBI to predict intracranial complication among patients treated with ATD. The primary endpoint was the metrological qualities of S100β (sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios).

The secondary objectives were to evaluate the diagnostic performance according to the time to sampling following mTBI, to investigate the presence of risk factors for cerebral injury, and to estimate the economic impact of the S100β assay ± CCT strategy. The secondary endpoints were the metrological qualities according to time to sampling between subgroups within the first 3 h range (H0-H3) compared to the 3 to 6 h range (H3-H6) after mTBI. Finally, the overall costs of mTBI's usual management and pathway of care for subjects on ATD were compared between the two diagnostic strategies (systematic CCT versus S100β assay ± CCT) using the French Healthcare Costs and Metrics Reference list of innovative procedures not included in the biology and anatomical pathology nomenclature (RHIN) [16].

Statistical analysis

The results are presented in accordance with the Standards for Reporting of Diagnostic Accuracy Studies (STARD) recommendations. Assuming an expected sensitivity of 99% of S100β at the threshold of 0.105 μg/L at 6 h and a precision of 0.223 of the two-sided 95% confidence intervals, with an expected prevalence of intracranial complication of 7%, 242 patients included provide 80% power to demonstrate the difference with a minimum acceptable sensitivity of 80%, at an alpha risk of 5% (nQuery 8.2 software). No patients were expected to be lost to follow-up before the primary endpoint is reached. As a result, the number of subjects required was estimated at 250 needed to complete the study. The characteristics of the study population were described using mean ± standard deviation for quantitative variables, and headcount (n) and percentage (%) for qualitative variables. Factors potentially associated with the presence of a cerebral injury on CCT were identified in bivariate analysis using Student's t test or Chi-square test (or Fisher's exact test), depending on the nature of the variables. The cerebral diagnosis gold standard was the results of CCT. Sensitivity, specificity, negative and positive predictive values, positive and negative likelihood ratios were calculated with a 95% confidence interval using Clopper-Pearson estimation method based on an exact binomial distribution. These analyses were performed on all study subjects and stratified by time to S100β determination (< or > 3 h). Finally, the costs potentially avoided by the systematic inclusion of S100β protein assay in the management of mTBI in subjects on ATD were estimated. The level of significance retained was $p < 0.05$. Analyses were performed using R software (version 4.1).

Analysis of estimated costs

The potential costs difference between the 2 diagnostic strategies, with and without S100β assay, was estimated according to the French Healthcare Costs and Metrics Reference list of innovative procedures not included in the biology and anatomical pathology nomenclature (RHIN) [16], the National Health Insurance Fund 2018 (CCAM) [17], and the Technical Agency for Information on Hospitalization Tariffication [18]. The costs were valued according to the fares in the French universal healthcare system in 2023, respectively €32.40 for the S100β assay [16], €102.61 for CCT [17], €380.21 for hospitalization in EDSSU [18]. In the reference strategy, we considered the cost of a CCT and hospitalization in the emergency department short-stay unit (EDSSU) for a neurological monitoring for all patients. In the diagnostic strategy integrating the S100β assay, we considered the cost of systematically measuring the S100β in all patients, the cost of a CCT and hospitalization in EDSSU only for patients with an S100β assay above the defined threshold.

Results

Of the 258 patients primarily eligible in the study, 7 were excluded because of deviations from the protocol with 2 subjects under legal protection, 1 subject screened outside the time range of 6 h after the mTBI, 3 subjects with skin cancer and 1 subject that was not on ATD when the file was reexamined. Among the 251 patients included, 6 subjects did not have a CCT prescribed by the physician in charge either because a negative S100β dosing (5 patients) or because of futility (1 patient in palliative condition) (Fig. 1). The clinical characteristics of the 245 subjects included are presented in Table 1. The mean age was 81.5 (± 11.8) years. The female/male ratio was 0.99. Falls accounted for 92% of the TBI. APAs were the type of ATD in 62% of cases. The GCS was impaired for 23 (9.4%) subjects.

Table 1. Demographic and clinical characteristics of the study population according to the CCT's result.

The mean S100β level was 0.322 (± 0.460) μg/L. S100β levels were normal for 58 (23.7%) patients. Cerebral injury was found for 15 (6.1%) patients. No patient required neurosurgical intervention. One subject died as a result of a parenchymal haemorrhage, which was deemed ineligible for neurosurgery. Of the subjects with a normal S100β assay, none had intracranial injury on CCT. The mean turnaround time for results once the tube has been received by the laboratory was 18 min. The overall turnaround mean time, including time required for blood collection, delivery to the laboratory, essay analysis and results availability to the physician in charge was 176.8 (± 64.1) minutes, with 139 (56.7%) patients in the H0-H3 subgroup. The mean S100β level was significantly higher in the H0-H3 subgroup, at 0.393 (± 0.501) μg/L, versus 0.229 (± 0.373) μg/L in the H3-H6 subgroup.

The diagnostic performances of S100β are described in Table 2. The number of true positives, false positives, true negatives, and false negatives populations are presented in Table 3. The area under the ROC curve was 0.629 [95% CI: 0.497–0.760].

The risk of cerebral injury was significantly higher among patients with a GCS < 15, or with a higher S100β level (Table 1).

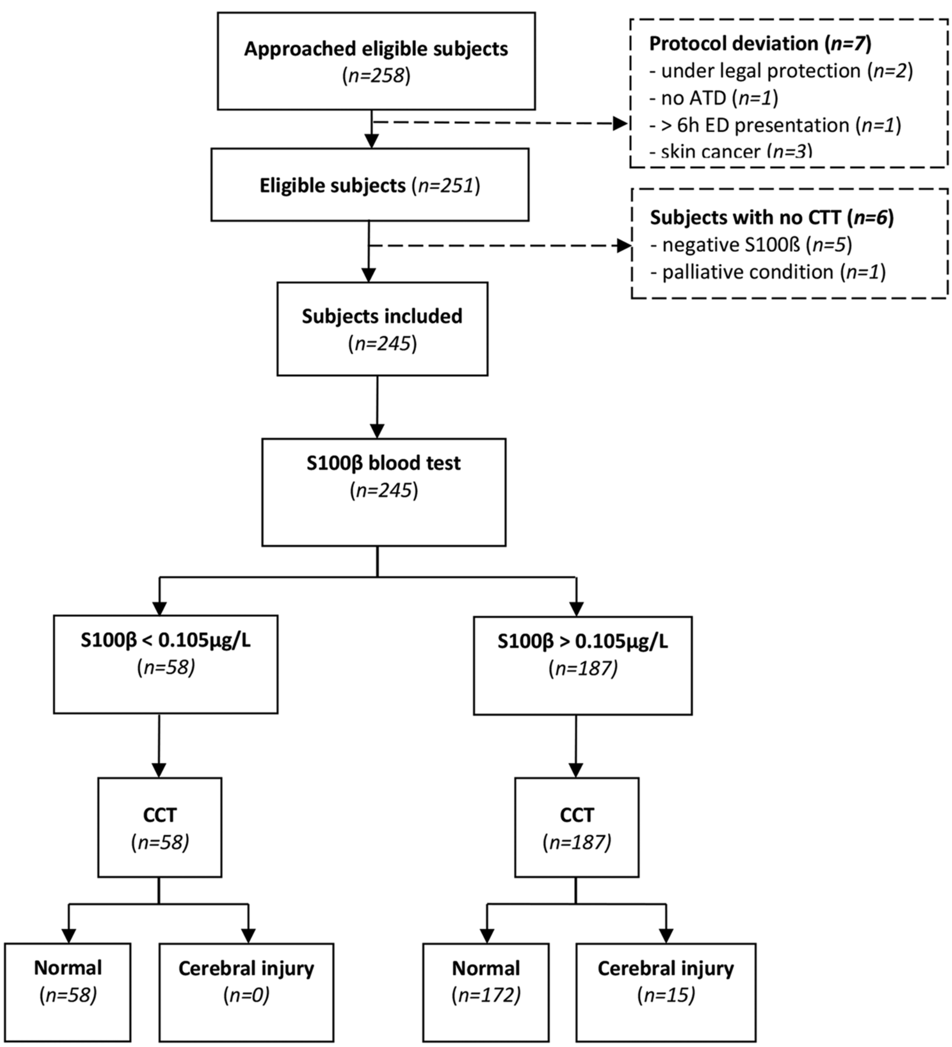

Fig. 1 Study flowchart. ATD: Anti Thrombotic Drug; ED: Emergency department; CCT: cerebral computed tomography

Table 1 Demographic and clinical characteristics of the study population according to the cct's result

	Total *n* = 245	Normal CCT *n* = 230 (93.9%)	Injured CCT *n* = 15 (6.1%)	*p*
Mean age (years)	81.5 ± 11.8	81.4 ± 11.9	82.1 ± 10.2	*0.825*
Gender, **n (%) Men**	123 (50.2%)	114 (49.6%)	9 (60%)	*0.433*
Mechanism of the trauma, **n (%)**				
Fall	225 (91.8%)	212 (92.2%)	13 (86.7%)	
Road Accident	11 (4.5%)	10 (4.3%)	1 (6.7%)	
Assault	3 (1.2%)	3 (1.3%)	0 (0%)	
Sport	4 (1.6%)	3 (1.3%)	1 (6.7%)	
Other	2 (0.8%)	2 (0.9%)	0 (0%)	
Antithrombotic drugs, **n (%)**				*0.433*
Antiplatelet agent	151 (61.6%)	141 (61.3%)	10 (66.7%)	
Aspirin	132 (53.8%)	122 (53%)	10 (66.7%)	
Clopidogrel	19 (7.8%)	19 (8.3%)	0 (0%)	
Heparins	4 (1.6%)	4 (1.7%)	0 (0%)	
Vitamin-K antagonists	28 (11.4%)	27 (11.7%)	1 (6.7%)	
Warfarin	13 (5.3%)	12 (5.2%)	1 (6.7%)	
Fluindione	14 (5.7%)	14 (6.1%)	0 (0%)	
Acenocoumarol	1 (0.4%)	1 (0.4%)	0 (0%)	
Direct oral anticoagulants	57 (23.3%)	53 (23.0%)	4 (26.7%)	
Rivaroxaban	19 (7.8%)	16 (7.0%)	3 (20%)	
Apixaban	36 (14.7%)	35 (15.2%)	1 (6.7%)	
Dabigatran	2 (0.8%)	2 (0.8%)	0 (0%)	
Antithrombotic association	5 (2.0%)	5 (2.1%)	0 (0%)	
Aspirin + Clopidogrel	3 (1.2%)	3 (1.3%)	0 (0%)	
Aspirin + Apixaban	1 (0.4%)	1 (0.4%)	0 (0%)	
Aspirin + Fluindione	1 (0.4%)	1 (0.4%)	0 (0%)	
GCS, **n (%)**				***0.007***
15	222 (90.6%)	212 (92.2%)	10 (66.7%)	
14 or 13	23 (9.4%)	18 (7.8%)	5 (33.3%)	
Symptoms, **n (%)**				
Loss of consciousness	23 (9.4%)	21 (9.1%)	2 (13.3%)	*0.639*
Headache	0 (0%)	0 (0%)	0 (0%)	-
Vomits > 2 times	6 (2.4%)	6 (2.6%)	0 (0%)	*0.523*
Amnesia > 30 min	7 (2.9%)	7 (3.0%)	0 (0%)	*0.493*
Suspected skull fracture	5 (2.0%)	4 (1.7%)	1 (6.7%)	*0.272*
Focal neurologic deficit	2 (0.8%)	2 (0.8%)	0 (0%)	*1.000*
Convulsions	1 (0.4%)	1 (0.4%)	0 (0%)	*1.000*
Intoxication (alcohol or narcotics), **n (%)**	22 (9.0%)	21 (9.1%)	1 (6.7%)	*0.746*
Time between mTBI and S100β assay (minutes)	176.8 ± 64.1	168.6 ± 75.9	177.3 ± 63,2	*0.536*
< 180 min, n (%)	139 (56.7%)	129 (56.1%)	10 (66.7%)	
180–360 min, n (%)	106 (43.3%)	101 (43.9%)	5 (33.3%)	
S100β levels (µg/L), **mean ± SD**	0.322 ± 0.460	0.319 ± 0.466	0.379 ± 0.288	*0.620*
Normal, n (%)	58 (23.7%)	58 (25.2%)	0 (0%)	***0.025***

CCT: cerebral computed tomography; GCS: Glasgow coma scale; mTBI: mild traumatic brain injury; ED: Emergency department; SD: Standard deviation

The average length of stay in the ED was 8h39 (± 4h47). Hospitalization was deemed necessary for 95 (38.8%) patients. Of these 95 patients, 75 were hospitalized for reasons other than only neurological monitoring.

The theoretical costs of the current management strategy compare to those involving S100β show that by using S100β, 23.7% of CCT and EDSSU hospitalizations could be avoided, which it represents an average saving of €82.03 per patient. The results are presented in Table 4.

Discussion

Subjects on ATD with mTBI are classified as being at risk of cerebral injury, which should be investigated by CCT according to recommendations [3, 4]. The S100β appears

Table 2 Diagnostic performance of the S100β according to laboratory reference threshold

	Population *n* = 245	**H0-H3 Subgroup** *n* = 139	**H3-H6 Subgroup** *n* = 106
Sensitivity	100% [78.2% – 100%]	100% [66.4% – 100%]	100% [54.1% – 100%]
Specificity	25.2% [19.7% – 31.3%]	18.5% [12.2% – 26.2%]	34.0% [24.8% – 44.1%]
NPV	100% [93.8% – 100%]	100% [85.7% – 100%]	100% [89.7% – 100%]
PPV	8.0% [7.5% – 8.6%]	7.9% [7.3% – 8.5%]	8.3% [7.4% – 9.5%]
LR+	1.34 [1.24–1.44]	1.23 [1.13–1.33]	1.52 [1.32–1.74]
LR-	0	0	0
Avoidable CCT (%)	23.7%	17.3%	32.1%

NPV: negative predictive value; PPV: positive predictive value; LR+: positive likelihood; LR-: negative likelihood; CCT: cerebral computerized tomography; H0-H3 Subgroup: population with sampling in the first 3 h after TBI; H0-H6 Subgroup: population with sampling between 3 h to 6 hafter TBI

Laboratory threshold 0.105 µg/L; Avoidable CCT: rate of true negative results, calculated from the contingency table

Table 3 Number of true positives, false positives, true negatives, and false negatives in the cohort population of the study

	CCT (+)	**CCT (-)**	**Number of patients**
S100β (+)	TP = 15	FP = 172	187
S100β (-)	FN = 0	TN = 58	58
Number of patients	15	230	**245**

CCT: cerebral computerized tomography; (+): positive; (-): negative; TP: True Positive; FP: False Positive; FN: False Negative; TN: True Negative

S100β Laboratory threshold 0.105µg/L

Table 4 Estimated costs (€) of diagnostic strategies for mTBI patients under ATD, with and without S100β assay

	CCT 102.61 €/ test (€)	**S100β 32.40 €/test (€)**	**EDSSU 380.21 €/ patient/ day (€)**	**Total cohort (€)**	**Cost/ patient (€)**
Current strategy	25 139.45	0	93 151.45	118 290.90	482.82
S100β ± CCT strategy					
Threshold > 0.105 µg/L Avoidable CCT *23.7%*	19 181.40	7 938.00	71 074.56	98 193.96	400.79
Difference				20 096.94	82.03

CCT: cerebral computerized tomography; EDSSU: Emergency department short stay unit

Laboratory threshold 0.105 µg/L; Avoidable CCT: rate of true negative results, calculated from the contingency table

as a valuable screening tool to target the need of CCT among these subjects.

In this study, the rate of cerebral injury following mTBI was 6.1%. This incidence was similar to those observed in the literature in this population (4.6% to 10.7%) [5–7, 9]. The mean age in this study was higher than other mTBI cohorts [15]. This might be explained by the design, considering the need to be on ATD for inclusion, and the increased need of ATD in older people [12]. However, the characteristics of our population did not differ from those found by David et al. Their cohort was similar to ours in terms of age, sex ratio and mechanism of fall, because of a close protocol to ours. In our cohort, 61% of patients were on APAs, and DOACs were 2 times more prevalent than VKAs. In the David et al. cohort, 75.6% of patients were on APAs, and VKAs were 4 times more prevalent than DOACs [9]. This difference from David et al. can be explained by the inclusion carried out in 2014–2015, when DOACs were less prescribed than today [19]. No significant difference according to ATD class on the occurrence of cerebral injury following mTBI was found. The diagnostic performances of the S100β report here was excellent. They are consistent with the literature in the general population and under ATD [8, 15, 20]. These performances need to be interpreted according to the maximum delay to sample. The time to sample S100β after mTBI varies in the literature, essentially between a maximum at 3 or at 6 h [15]. A maximum delay of 6 h (360 min.) was chosen for our protocol, as it was more applicable in current practice, and was based on Scandinavian Guidelines and the studies by Zongo et al. and David et al. [4, 9, 10]. The sensitivities and NPVs obtained were identical between the H0-H3 and H3-H6 subgroups. Despite the significant difference in mean S100β levels between the H0-H3 and H3-H6 subgroups, there were no false negatives in either subgroup. In the metanalysis by Rogan et al. metrological qualities were poorer among studies using a 6-hour delay, compared with those using a 3-hour delay [15]. The study by David et al. carried out in a population on ATD found no significant difference in NPV between these same 2 subgroups [9]. The other studies were carried out in the general population, limiting comparison with our cohort [15]. The updated French mTBI 2022 recommendations add the use of S100β in the first 3 h following a mTBI [21]. Our results are in favor of extending the sampling time up to 6 h after mTBI. Regarding the pathway of care, prospective implementation study tracking real CCT ordering patterns after introducing S100β could provide arguments to validate this diagnostic approach, thereby limiting the number of CCT scans. Indeed, it would clarify whether the predicted 24% reduction in imaging actually materializes in practice after a change in the pathway of care. In our study, the area under the ROC curve (AUC) was 0.629 (95% CI: 0.497–0.760), a modest value that reflects the low specificity observed (25.2%) even though this corresponds to the range found in the literature (5–58%) [8, 11, 15]. This contrasts with the excellent sensitivity (100%) and negative predictive value (100%). While the low AUC indicates limited overall discriminative capacity, the results underscore the practical role of S100β as a rule-out test, ensuring patient safety while potentially reducing unnecessary CCT scans.

As far as we are concerned, this study describes the first economic simulation on the contribution of S100β testing in the management strategy of mTBI in population of French patients under ATD attending the ED. Calcagnile et al. reported a saving of 71€ per patient when applying the recommendations in the Swedish adult general population [22]. This is a lower saving compared with the €82.03 per patient found in our study. This may be explained by higher S100β assay and hospitalization costs in France. In real-life practice, several reasons for hospitalization could co-exist among patients in our cohort. This estimating saving supports the updated French mTBI 2022 recommendations, which no longer advocate systematic hospitalization for surveillance in case of normal S100β assay [21].

The results of our study should be considered in the light of certain limitations. This is a single-center study, with a small cohort size, mainly with elder people, raising questions about external validity. A selection bias is to be feared, as the completeness of inclusions could not be verified and depends on the availability of investigators. Furthermore, type of ATD were not balance in our cohort as 60% of subjects were on AAP.

The economic analysis remains theoretical, based on the assumption of strict application of the recommendations and the absence of any other reason for hospitalization.

Conclusion

S100β assay within 6 h following mTBI among subjects on ATD safely discount the risk of cerebral injury, and it entails a relevant economic contribution in the management of patients in the ED by reducing the use of CCT and hospitalization. Multi-center, interventional studies are required to confirm the maximum sampling time after mTBI, and to objectivize the medical and economic contributions in current practice. Still, as S100β is a highly sensitive screening tool with good NPV but with low specificity, its relevance and limits should discuss the potential of a biomarker-based classification system, including for mTBI.

Abbreviations

APA	Anti-platelet agents
ATC	Antithrombotic combination
ATD	Antithrombotic drugs
CCT	Cerebral computed tomography
DOAC	Direct oral anticoagulants
ED	Emergency department
EDSSU	Emergency department short-stay unit
GCS	Glasgow coma score
H0-H3	Sampling in the first 3 h after TBI
H3-H6	Sampling between 3 h and 6 h after TBI
LMWH	Low-molecular weight heparin
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operating characteristic
SD	Standard deviation
STARD	Standards for reporting of diagnostic accuracy studies
TBI	Traumatic brain injury
UFH	Unfractioned heparin
VKA	Vitamin K-antagonists

Supplementary Information

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Supplementary Material 1

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Author contributions

XQ and NP conceived the study and supervised its design. XQ managed the data collection. EB and MD did the statistical analyses. XQ, EB, PGR, and NP participated in the interpretation of data and drafting the article. All authors participated in the critical revision for important intellectual content. XQ and NP made the revision after the first reviewing. All authors declare that they have read and approved the final version of the manuscript and have provided their permission to publish the manuscript. On behalf of all authors, the corresponding author states that there is no conflict of interest. We declare no financial support is for this work.

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None.

Data availability

Data that support the findings of this study have been deposited in the cloud storage of the Rennes University Hospital CIC Department and are available on request.

Declarations

Ethics committee approval

The protocol for this study was approved by the Comité de Protection des Personnes (CPP) de Sud-Méditerranée (ID: RCB 2019-A03053-54). In accordance with French regulations, and Human Ethics and Consent to Participate declarations, verbal consent was sought by the investigators.

Human ethics and consent to participate

Consent to Participate declarations are not available as a verbal consent was sought by the investigators for each patient according to the research protocol acceptance by the Ethics committee. The Consent to Participate declaration information letter was given to the patient in accordance with the Human Ethics and Consent to Participate following French Regulations. The information of the research protocol document about verbal consent was added in the complementary material section of the submission and given to each patient.

Consent to publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Majdan M, Plancikova D, Brazinova A, Rusnak M, Nieboer D, Feigin V, et al. Epidemiology of traumatic brain injuries in europe: a cross-sectional analysis. Lancet Public Health. 2016;1:e76–83.
2. Easter JS, Haukoos JS, Meehan WP, Novack V, Edlow JA. Will neuroimaging reveal a severe intracranial injury in this adult with minor head trauma? The rational clinical examination systematic review. JAMA. 2015;314:2672.
3. Jehlé E, Honnart D, Grasleguen C, Bouget J, Dejoux C, Lestavel P, et al. Traumatisme crânien léger (score de Glasgow de 13 à 15): triage, évaluation, examens complémentaires et prise En charge précoce Chez Le nouveau-né, l'enfant et l'adulte: Société française de médecine d'urgence. Ann Fr Médecine Urgence. 2012;2:199–214.
4. Undén J, Ingebrigtsen T, Romner B, Scandinavian Neurotrauma Committee (SNC). Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med. 2013;11:50.
5. Galliazzo S, Bianchi MD, Virano A, Trucchi A, Donadini MP, Dentali F, et al. Intracranial bleeding risk after minor traumatic brain injury in patients on antithrombotic drugs. Thromb Res. 2019;174:113–20.
6. Nishijima DK, Gaona SD, Waechter T, Maloney R, Blitz A, Elms AR, et al. The incidence of traumatic intracranial hemorrhage in Head-Injured older adults transported by EMS with and without anticoagulant or antiplatelet use. J Neurotrauma. 2018;35:750–9.
7. Colas L, Budzik J-F, Toledano M, Norberciak L, Verclytte S, Etude. TC3A: Évaluation de l'intérêt des scanners cérébraux pour traumatisme crânien léger Chez les patients Sous anti-agrégants plaquettaires, anticoagulants et anticoagulants Oraux directs : Étude prospective Chez 847 patients. J Neuroradiol. 2019;46:79.
8. Oris C, Bouillon-Minois J-B, Pinguet J, Kahouadji S, Durif J, Meslé V, et al. Predictive performance of blood S100B in the management of patients over 65 years old with mild traumatic brain injury. J Gerontol Ser A. 2021;76:1471–9.
9. David A, Mari C, Vignaud F, Masson D, Planche L, Bord E, et al. Evaluation of S100B blood level as a biomarker to avoid computed tomography in patients with mild head trauma under antithrombotic medication. Diagn Interv Imaging. 2017;98:551–6.
10. Zongo D, Ribéreau-Gayon R, Masson F, Laborey M, Contrand B, Salmi LR, et al. S100-B protein as a screening tool for the early assessment of minor head injury. Ann Emerg Med. 2012;59:209–18.
11. Thaler HW, Schmidsfeld J, Pusch M, Pienaar S, Wunderer J, Pittermann P, et al. Evaluation of S100B in the diagnosis of suspected intracranial hemorrhage after minor head injury in patients who are receiving platelet aggregation inhibitors and in patients 65 years of age and older. J Neurosurg. 2015;123(5):1202–8.
12. Andreotti F, Rocca B, Husted S, Ajjan RA, ten Berg J, Cattaneo M, et al. Antithrombotic therapy in the elderly: expert position paper of the European society of cardiology working group on thrombosis. Eur Heart J. 2015;36(46):3238–49.
13. Nilsson M, Eriksson J, Larsson B, Odèn A, Johansson H, Lorentzon M. Fall risk assessment predicts Fall-Related injury, hip Fracture, and head injury in older adults. J Am Geriatr Soc. 2016;66:2242–50.
14. Townend W, Dibble C, Abid K, Vail A, Sherwood R, Lecky F. Rapid elimination of protein S-100B from serum after minor head trauma. J Neurotrauma. 2006;23:149–55.
15. Rogan A, O'Sullivan MB, Holley A, McQuade D, Larsen P. Can serum biomarkers be used to rule out significant intracranial pathology in emergency department patients with mild traumatic brain injury? A systemic review & Meta-Analysis. Injury. 2022;53:259–71.
16. Ministère des Solidarités et de la Santé. Référentiel des actes innovants hors nomenclature de biologie et d'anatomopathologie (RIHN) - Liste complémentaire d'actes 2023. https://sante.gouv.fr/IMG/xlsx/ahn_liste-complementaire_v2023.xlsx. Accessed 4 Jun 2023.
17. Rozière T, Rodts U, Igondjo L, Choukroun S, Berton E, Boule D. L'activité des médecins libéraux à travers la CCAM. Caisse Nationale d'Assurance Maladie 2018. https://www.ameli.fr/fileadmin/user_upload/documents/Points_de_repere_n_50_-_L_activite_des_medecins_liberaux_a_travers_la_CCAM.pdf. Accessed 4 Jun 2023.
18. Agence technique de l'information sur l'hospitalisation. Tarifs MCO et HAD – 2023. https://www.atih.sante.fr/sites/default/files/public/content/1568/tarif_arrete_2023.xlsx. Accessed 5 Jul 2023.
19. Grymonprez M, Simoens C, Steurbaut S, De Backer TL, Lahousse L. Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: a systematic review and meta-analysis. EP Eur. 2022;24:887–98.
20. Rogan A, Sik A, Dickinson E, Patel V, Peckler B, McQuade D, et al. Diagnostic performance of S100B as a rule-out test for intracranial pathology in head-injured patients presenting to the emergency department who Meet NICE head injury guideline criteria for CT-head scan. Emerg Med J. 2022;40(3):159–66.
21. Gil-Jardiné C, Payen J-F, Bernard R, Bobbia X, Bouzat P, Catoire P, et al. Management of patients suffering from mild traumatic brain injury 2023. Anaesth Crit Care Pain Med. 2023;42(4):101260.
22. Calcagnile O, Anell A, Undén J. The addition of S100B to guidelines for management of mild head injury is potentially cost saving. BMC Neurol. 2016;16(1):200.

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