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## **Predictive performance of blood S100B in the management of patients over 65 years old with mild traumatic brain injury**

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1 **Title** Predictive performance of blood S100B in the management of patients over 65 years old  
2 with mild traumatic brain injury

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24

1 **ABSTRACT**

2 **Background:** We **previously assessed** the inclusion of S100B blood determination into clinical  
3 decision rules for mild traumatic brain injury (mTBI) management in the Emergency  
4 Department (ED) of Clermont-Ferrand Hospital. At the 0.10 µg/L threshold, S100B reduced  
5 the use of cranial computed tomography (CCT) scan in adults by at least 30% with a ~100%  
6 sensitivity. Older patients had higher serum S100B values, resulting in lower specificity  
7 (18.7%) and decreased CCT reduction. We conducted this study to confirm the age effect on  
8 S100B concentrations, and to propose new **decisional** thresholds for older patients.

9 **Methods:** A total of 1172 mTBI patients aged 65 and over were included. They were divided  
10 into three age-groups: **65-79**, **80-89**, and  $\geq 90$  years old. S100B's performance to identify  
11 intracranial lesions (sensitivity (SE) and specificity (SP)) was assessed using the routine 0.10  
12 µg/L threshold and also other more efficient thresholds established for each age group.

13 **Results:** S100B concentration medians were 0.18 µg/L, 0.26 µg/L, and 0.32 µg/L for the **65-**  
14 **79**, **80-89**, and  $\geq 90$  years old age-groups, respectively ( $p < 0.001$ ). The most efficient thresholds  
15 were 0.11 µg/L for the **65-79** age-group and 0.15 µg/L for the other groups. At these new  
16 thresholds, SP was respectively 28.4%, 34.3%, and 20.5% for each age-group vs. 24.9%,  
17 18.2%, and 10.5% at the 0.10 µg/L threshold.

18 **Conclusions:** Adjustment of the S100B threshold is necessary in older patients' management.  
19 An **increased** threshold of 0.15 µg/L is particularly interesting for patients  $\geq 80$  years old,  
20 allowing a significant increase of CCT scan reduction (29.3%).

21

22 **Keywords: biomarker, aging, dementia**

## 1 INTRODUCTION

2 Traumatic brain injury (TBI) constitutes a leading public health problem among older  
3 adults (> 60 years old) with an incidence of 275 per 100.000 in France (1). This is all the more  
4 important given the fact that the worldwide proportion of adults over 65 years old is expected  
5 to increase from 12.5% in 2010 to 20.0% by 2050, reaching this proportion by 2030 in  
6 industrialized countries (2).

7 Although the spectrum of TBI severity is variable, 80% of treated TBIs are mild (3). Mild  
8 traumatic brain injury (mTBI), is defined by a Glasgow Coma Scale (GCS) of 13–15 (4), and  
9 according to clinical and anamnestic criteria, mTBI can be categorized into three prognostic  
10 subgroups: mTBI with a low, medium or high risk of complications (5,6). The medium risk  
11 subgroup is particularly important as mTBI management guidelines recommend the use of  
12 cranial computed tomography (CCT) for this subgroup of patients although the vast majority  
13 (85%–99%) of the CCTs performed don't find significant intracranial lesions (7). In this  
14 context, blood biomarkers can be used as a diagnostic tool for their ability to exclude  
15 intracranial lesions thus reducing the use of CCT scans.

16 S100B protein, is a well-established TBI biomarker. It is a small dimeric protein (molecular  
17 weight of 21 kDa) that consists of  $\beta\beta$  or  $\alpha\beta$  chains. S100B is commonly expressed in astrocytes  
18 and Schwann cells but also in melanocytes, chondrocytes, adipocytes and skeletal muscle (8).  
19 S100B is involved in a variety of intracellular and extracellular regulatory activities in central  
20 nervous system cells where it is highly expressed (9,10). Increased blood S100B levels are  
21 associated with head trauma, in which damaged glial cells release S100B, it is then diffused  
22 into the bloodstream after passing through the blood-brain barrier (BBB). S100B is  
23 subsequently eliminated by the kidneys, with a short half-life of 30-100 minutes (11).

24 The usefulness of S100B in the management of mTBI has been established in many  
25 observational research and confirmed in two interventional studies (12,13). The addition of

1 blood S100B measurement to the Scandinavian guidelines decreased significantly the need for  
2 CCT scans. It allowed a one-third reduction of the CCT scans performed in adult mTBI patients  
3 (14). In a previous study, we validated the inclusion of S100B into our clinical decision rules  
4 for mTBI management in a cohort of 1449 patients presenting to the Emergency Department  
5 (ED) of Clermont-Ferrand's Hospital (15). In this study, at a threshold of 0.10  $\mu\text{g/L}$ , S100B  
6 reduced the use of CCT scans by 33.4% with a sensitivity of approximately 100%. However,  
7 older patients ( $> 65$  years old), representing more than a third of the cohort, had higher serum  
8 S100B values, resulting in a lower specificity of only 18.7% (15).

9 We conducted this study to evaluate in a larger cohort the effect of age on S100B  
10 concentrations. The main outcome of this study is to propose new **decisional** thresholds ( $\neq 0.10$   
11  $\mu\text{g/L}$ ) adapted to older populations in order to **improve** S100B's specificity.

## 1 **METHOD**

### 2 **Study design and patients**

3 This study was carried out from June 2014 to March 2020 at the ED of Clermont-Ferrand  
4 Hospital after approval by CPP Sud Est VI and in compliance with the Declaration of Helsinki  
5 ethical principles regarding medical research involving human study participants. Patients were  
6 informed of their right to express their disagreement regarding the use of their clinical  
7 information for research purposes. Each patient referred to the ED for an mTBI (with a GCS  $\geq$   
8 13) was classified into one of three prognostic subgroups according to the SFMU's  
9 recommendations (Société Française de Médecine d'Urgence) (5). The criteria regarding  
10 patients' categorization in the three subgroups and the clinical decision algorithm are presented  
11 in Figure 1.

12 The inclusion criteria were as follows: an age  $\geq$  65 years old, an mTBI with medium risk of  
13 complications (*i.e.* with a GCS equal to 15 and antiplatelet treatment or loss of consciousness  
14 or retrograde amnesia 30 minutes before injury) and a time interval between injury and blood  
15 sampling being less than 3 hours (16).

16 The exclusion criteria were as follows: an age  $<$  65 years old, an mTBI with a low risk of  
17 complications (*i.e.* asymptomatic patient without medium- or high-risk criteria and a GCS of  
18 15), an mTBI with a high risk of complications (Figure 1) and a time interval between injury  
19 and blood sampling being greater than 3 hours.

20 Concerning the clinical decision consecutive to S100B measurements: patients with S100B  
21 levels below the well-established decision threshold of 0.10  $\mu\text{g/L}$  were categorized as having a  
22 low risk of complications and discharged (15). A CCT was strongly recommended within 8  
23 hours for patients with S100B levels above the decision threshold (Figure 1).

24 For each patient who left the ED without a CCT, we checked if an hospitalization had occurred  
25 in the month following the mTBI.

26

## 1 **Serum S100B measurement**

2 Serum S100B concentrations were determined by an electrochemiluminescence immunoassay  
3 using a Roche Diagnostics Cobas e411<sup>®</sup> instrument (Meylan, France). S100B results were  
4 available within 1 hour after sampling. Based on other studies in adults, the cutoff was set at  
5 0.10 µg/L (17–19). Patients exhibiting serum concentrations below this threshold were  
6 considered S100B negative (S100B-), and those with concentrations above this cutoff were  
7 considered S100B positive (S100B+).

8 According to the manufacturer's instructions, the test system requires 18 min and a probe  
9 volume of at least 120-µL serum. The lower limit of quantification (LLOQ) and lower limit of  
10 detection (LLOD) are 0.02 µg/L and 0.005 µg/L. Concentrations of up to 39 µg/L can be  
11 measured without dilution. The intra-assay and inter-assay coefficients of variation (CVs) are  
12 < 2.3% and < 5.6 %. The measurement uncertainty (calculated in the Biochemistry Department  
13 in Clermont-Ferrand, France) is 6% at a concentration of 0.183 µg/L. This uncertainty must be  
14 taken into account when interpreting values close to the decision threshold (0.10 µg/L).

## 15 **Definition of Dementia**

16 In our study, patients suffering from dementia had one of the following neurological disorders:  
17 Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia and  
18 dementia of unknown etiology.

## 19 **CCT examination**

20 Each CCT scan was performed using a GE Healthcare Revolution GSI<sup>®</sup> according to the  
21 following protocol: a helical mode with a slice thickness of 2.25 mm, interval of 1.25 mm, 120  
22 kV and a maximum of 280 mA from C1 to the top of the head with additional bone window  
23 reconstructions. To determine whether a patient had a trauma-relevant intracerebral lesion, the  
24 radiological parameters were recorded, and the patients were divided into two groups: one  
25 group with normal CCT scan for mTBI patients with no sign of trauma-relevant intracerebral

1 lesion and another group with abnormal CCT scan for mTBI patients with at least one  
2 pathophysiological trauma-relevant intracerebral lesion (such as petechiae, meningeal or  
3 intraparenchymal effusion, pneumocephaly reflecting an osteomeningeal breach, compression  
4 or ventricular hemorrhage).  
5



## 1 **Statistics**

2 All statistical analyses were performed using Stata software (Version 15, StataCorp, College  
3 Station, US) with a two-sided type I error at 5%. Continuous data were presented as the median  
4 and minimum (min), maximum (max) and interquartile range (IQR). To study the relationship  
5 between S100B concentration and age, patients (n = 1172) were first, categorized into the  
6 following age-groups: 65-69, 70-74, 75-79, 80-84, 85-89, 90-94,  $\geq 95$  years old. Then, they  
7 were divided into three age-groups according to statistical distribution and to two by two  
8 comparisons: 65-79, 80-89, and  $\geq 90$  years old. The comparisons between age-groups  
9 concerning continuous parameters such as S100B concentrations were performed using  
10 ANOVA or Kruskal-Wallis tests. The assumption of normality was assessed by the Shapiro-  
11 Wilk test and the homoscedasticity was evaluated using Bartlett's test. When appropriate  
12 (omnibus p-value less than 0.05), post-hoc tests for multiple comparisons were applied: Tukey-  
13 Kramer after ANOVA and Dunn after Kruskal-Wallis. Sensitivity (SE), specificity (SP),  
14 positive predictive value (PPV) and negative predictive value (NPV) were estimated using the  
15 adult routine threshold of 0.10  $\mu\text{g/L}$  for all patients and for each age-group. Then, based on the  
16 receiver operating characteristic (ROC) curve, the more efficient threshold (allowing the best  
17 SP keeping a 100% SE) was evaluated for each age-group. For the 65-79 age-group, it was 0.11  
18  $\mu\text{g/L}$  against 0.15  $\mu\text{g/L}$  for the two other age-groups. The comparisons for paired proportions  
19 were performed using McNemar test whereas comparisons between groups for categorical data  
20 were carried out using Chi-squared or Fisher's exact tests. Multivariable analysis (linear for  
21 S100B as continuous variable and logistic for S100B according to threshold of 0.10 $\mu\text{g/L}$  and  
22 optimal threshold) was conducted to take into account gender as confounder covariate. The  
23 residuals from these models was analyzed as aforementioned. When appropriate, a logarithmic  
24 transformation of dependent variable was applied. Sensitivity analyses were performed to

- 1 ensure the robustness of the results and conclusions, performing aforementioned analyses on
- 2 patients without intracranial lesions (n = 1109) and patients without dementia (n = 893).

## 1 **RESULTS**

### 2 **Patient management and serum S100B concentration levels**

3 Between June 2014 and March 2020, serum S100B assays were performed for 1314 patients.  
4 A total of 1172 mTBI patients were enrolled in this study, 142 patients, meeting the exclusion  
5 criteria, were excluded (Figure 2). Of the 1172 patients, 504 were already included in our  
6 previous study (15). The median interval between brain injury and blood sampling was 1.6  
7 hours (min: 0.2 hours, max: 3.0 hours, IQR: 1.3-2.1 hours). The median serum S100B level was  
8 0.23 µg/L (min: 0.03 µg/L; max: 8.97 µg/L; IQR: 0.12-0.46 µg/L). Of the 1172 patients  
9 included in the study, 954 (81.4%) were S100B+ and 218 (18.6%) were S100B- (Figure 2).  
10 Nevertheless, a CCT scan was performed for 67 S100B- patients, no abnormal scan was  
11 observed for these patients. Of the 954 S100B+ patients, 60 were discharged without CCT scan,  
12 831 had a normal CCT scan and 63 had an abnormal CCT scan (Figure 2). For 127 patients  
13 (10.8%), the decision algorithm (Figure 2) was not followed by the physicians (CCT scan  
14 prescription despite S100B- or no prescription of CCT scan despite S100B+) (Figure 2).  
15 Patients who left the ED without CCT scan did not develop any clinical signs suggestive of an  
16 intracerebral lesion in the month following mTBI. Moreover, we didn't find any hospitalization  
17 nor any death for these patients. Therefore, patients without CCT scans were considered as  
18 having no intracerebral lesions.

### 19 **S100B levels according to age (Table 1)**

20 For patients aged 65 to 80, the median S100B concentration was 0.184 µg/L (min: 0.029 µg/L;  
21 max: 7.74 µg/L; IQR: 0.103-0.360 µg/L). For patients aged 80 to 90, the median S100B  
22 concentration was 0.255 µg/L (min: 0.032 µg/L; max: 8.97 µg/L; IQR: 0.129-0.474 µg/L). For  
23 patients aged 90 years and over, the median S100B concentration was 0.318 µg/L (min: 0.039  
24 µg/L; max: 4.68 µg/L; IQR: 0.178-0.609 µg/L). S100B concentrations were significantly  
25 different between these three age-groups ( $p < 0.001$ ).

1 **Population characteristics according to age** (Table 2)

2 For patients aged 65 to 80, median age was 73.5 years old (min: 65.0; max: 79.9; IQR: 69.4-  
3 76.9) and the sex ratio (M/F) was 1.1. For patients aged 80 to 90, median age was 85.1 years  
4 old (min: 80.0; max: 89.9; IQR: 82.9-87.4) and the sex ratio (M/F) was 0.7. For patients aged  
5 90 years and over, median age was 92.9 years old (min: 90.0; max: 105.1; IQR: 91.2-94.9) and  
6 the sex ratio (M/F) was 0.5. The median time interval between mTBI and blood sample was not  
7 significantly different between the three age-groups ( $p = 0.413$ ). The proportions of S100B  
8 concentrations above the usual threshold of  $0.10 \mu\text{g/L}$  were 76.1%, 82.9%, and 90.2% for the  
9 three age-groups (65-79, 80-89, and  $\geq 90$  years old), respectively ( $p < 0.001$ ). The proportion  
10 of positive CCT scans was not significantly different between the three age-groups ( $p = 0.11$ ).  
11 Antiplatelet treatment was the most common risk factor:  $n = 272$ ,  $n = 386$ , and  $n = 165$  for the  
12 three age-groups, respectively.

13 **S100B decisional threshold for older patients' management** (Table 3)

14 Of the 1172 patients included, 218 (18.6%) had a negative S100B ( $\leq 0.10 \mu\text{g/L}$ ). At the  $0.10$   
15  $\mu\text{g/L}$  threshold, S100B identified intracranial lesions observed in CCT scans with a sensitivity  
16 of 100% (95% CI: 94.3-100%), a specificity of 19.7% (95%CI: 17.4-22.1%) and a negative  
17 predictive value of 100% (95% CI: 98.3-100%). For each age-group (65-79, 80-89, and  $\geq 90$   
18 years old), specificity was 24.9% (95%CI: 21.0-29.1%), 18.2% (95%CI: 14.8-22.1%), and  
19 10.5% (95%CI: 6.6-15.8%), respectively. A statistically significant difference was observed  
20 when comparing the specificities obtained for each age-group ( $p < 0.001$  between patients aged  
21 65 to 80 and patients aged 90 years and over,  $p = 0.02$  between patients aged 80 to 90 and  
22 patients aged 90 years and over, and  $p = 0.01$  between patients aged 65 to 80 and patients aged  
23 80 to 90).

24 Optimal S100B thresholds (allowing the best specificity while keeping a 100% sensitivity) for  
25 each age group were determined and were as follows:  $0.11 \mu\text{g/L}$  for patients aged 65 to 80 and

1 0.15 µg/L for the others. For patients aged 65 to 80, the sensitivity was 100% (95%CI: 81.5-  
2 100%), the specificity was 28.4% (95%CI: 24.3-32.8%), and the negative predictive value was  
3 100% (95% CI: 97.2-100%). For patients aged 80 to 90, the sensitivity was 100% (95%CI:  
4 88.4-100%), the specificity was 34.3% (95%CI: 29.9-38.8%), and the negative predictive value  
5 was 100% (95% CI: 97.7-100%). For patients aged 90 years and over, the sensitivity was 100%  
6 (95%CI: 78.2-100%), the specificity was 20.5% (95%CI: 15.0-27.0%), and the negative  
7 predictive value was 100% (95% CI: 91.0-100%). For each age-group, the specificity allowed  
8 by the optimal thresholds was significantly higher than the one observed with a 0.10 µg/L  
9 threshold (28.4% vs 24.9%, 34.3% vs 18.2%, and 20.5% vs 10.5%;  $p < 0.001$ ).

10 As the 0.15 µg/L threshold was common to both age-groups (80-89 and  $\geq 90$  years old),  
11 performance was also assessed at this threshold for patients over the age of 80. In these  
12 conditions, the sensitivity was 100% (95% CI: 92.1-100%), the specificity was 29.3% (95%CI:  
13 25.9-33.0%), and the negative predictive value was 100% (95% CI: 98.1-100%). Furthermore,  
14 with the 0.15 µg/L threshold, the specificity for the 80-89 age group (34.3%) was significantly  
15 higher than the specificity for the  $\geq 90$  years old age group (20.5%), ( $p = 0.001$ ).

#### 16 **Influence of Dementia** (eTable 1)

17 In our cohort, a total of 279 patients were suffering from dementia. The proportion of patients  
18 with dementia increased significantly with age: 11.3% for the age group 65-79, 28.7% for the  
19 age group 80-89, and 41.0% for the age group  $\geq 90$  ( $p < 0.001$ ). Median S100B concentrations  
20 were significantly different when comparing patients with dementia (0.301 µg/L; min: 0.035;  
21 max: 8.97; IQR: 0.159-0.568) and others (0.207 µg/L; min: 0.029; max: 5.40; IQR: 0.113-  
22 0.415) ( $p < 0.001$ ).

23 The performance of the optimal thresholds was re-evaluated in patients without dementia ( $n =$   
24 893). For patients aged 65 to 80, the specificity was 28.7% (95%CI: 24.3-33.3%) vs. 28.4%  
25 (95%CI: 24.3-32.8%), ( $p = 0.92$ ). For patients aged 80 to 90, the specificity was 37.5% (95%CI:

1 32.2-42.9%) vs. 34.3% (95%CI: 29.9-38.8%), (p = 0.36). For patients aged 90 years and over,  
2 the specificity was 25.4% (95%CI: 17.7-34.4%) vs. 20.5% (95%CI: 15.0-27.0%), (p = 0.32).  
3 The performance of the optimal thresholds was re-evaluated in patients with dementia (n =  
4 279). For patients aged 65 to 80, the specificity was 25.9% (95%CI: 15.0-39.7%) vs. 28.4%  
5 (95%CI: 24.3-32.8%), (p = 0.70). For patients aged 80 to 90, the specificity was 26.2% (95%CI:  
6 18.8-34.6%) vs. 34.3% (95%CI: 29.9-38.8%), (p = 0.08). For patients aged 90 years and over,  
7 the specificity was 13.2% (95%CI: 6.5-22.9%) vs. 20.5% (95%CI: 15.0-27.0%), (p = 0.16).

## 1 DISCUSSION

2           The age effect on S100B blood concentrations was poorly investigated in previous  
3 studies. Children have higher levels of S100B concentrations than adults (20,21). However,  
4 S100B levels in older mTBI patients are less known. In 2013, Calgagnile *et al.* showed that  
5 S100B in older patients may be less effective regarding CCT scans reduction due to a very poor  
6 specificity (22). In a recent study including 504 mTBI patients over 65 years old, we established  
7 that these patients had higher serum S100B values than overall adult populations resulting in a  
8 low specificity of 18.7% (15). In order to study the age effect on S100B levels, we conducted  
9 this study on a larger cohort of 1172 older patients. The decision algorithm (Figure 1) was not  
10 applied by physicians for 127 (10.8%) patients. This observation is similar to the 14% described  
11 by Calgagnile *et al.* (12). Our results confirm the low overall specificity (19.7%). We also  
12 showed that S100B concentrations increase significantly with age. As expected, when using the  
13 routine 0.10 µg/L threshold, specificity is lower in older patients: 24.9%, 18.2%, and 10.5% for  
14 the age-groups 65-79, 80-89, and ≥ 90 years old, respectively. In order to regain specificity for  
15 older patients (≥ 65 years old), we propose new decisional thresholds based on ROC curves  
16 analysis.

17 For patients aged 65 to 80, a 0.11 µg/L threshold provides a 28.4% specificity instead of 24.9%  
18 with the 0.10 µg/L routine threshold. For patients aged 80 to 90, specificity increases  
19 considerably with the new threshold of 0.15 µg/L (18.2% to 34.3%), while sensitivity remains  
20 at 100%. For patients aged 90 years and over, a 0.15 µg/L threshold enables a two-fold  
21 specificity increase (10.5% to 20.5%) and a 100% sensitivity. Therefore, we propose the use of  
22 a 0.15 µg/L threshold for routine management of patients aged 80 years and over. This threshold  
23 (0.15 µg/L) is particularly interesting, allowing a 29.3% CCT scan reduction which is similar  
24 to the proportion in global adult population (~ 30%) (17–19). On the other hand, the threshold  
25 of 0.11 µg/L is less relevant for routine application due to the measurement uncertainty at this  
26 concentration level (~ 6%), which can lead to confusion with the 0.10 µg/L threshold. The

1 determination of age related S100B clinical decision thresholds is consistent with recently  
2 published articles supporting the need for age-centered patients management (23). This is all  
3 the more important given the fact that older age is often included as a risk factor for  
4 complications consecutive to mTBI. In mTBI clinical decision rules, patients' age is the only  
5 demographic criterion used for risk stratification. Indeed, in most guidelines, patients aged over  
6 65 years old are considered being at higher risk for having brain injury on CCT scan (5,6,14).  
7 The SFMU's recommendations consider amnesia or loss of consciousness as an intermediate  
8 risk factor if the symptom is associated with any of the following factors: dangerous mechanism  
9 of injury or patient's aged  $\geq 65$  years old (5). Moreover, antiplatelet medication intake is also  
10 considered as an intermediate risk factor. Antiplatelet therapy is more common in older patients  
11 (24).

12 Sheng *et al.* showed that cortical expression of S100B increases with age (25). S100B levels  
13 measured in postmortem brain tissue of patients aged 60 years old and more without dementia,  
14 were higher than those observed in younger patients. However, all S100B levels remained  
15 below those seen in Alzheimer's patients (25). In Alzheimer's disease, S100B overexpression  
16 is explained by the role played by activated astrocytes in the pathogenesis of  $\beta$ -amyloid plaques  
17 (26). In mice, overexpression has been reported to exacerbate cerebral amyloidosis, which may  
18 be a vicious circle (27). Several hypotheses can be formulated in order to explain S100B blood  
19 increase with aging (eFigure 1). First of all, increasing levels of  $\beta$ -amyloid plaques in the brain  
20 may stimulate S100B synthesis as an attempt to regenerate neuronal damage (28,29). It has  
21 been shown that S100B levels of older chronic schizophrenic patients are positively correlated  
22 with age and negatively with deficit symptoms. This suggests an impact of S100B in  
23 neuroplasticity and aging (28). Moreover, neuronal architecture is altered with increasing age  
24 while neuronal count does not change (30–33). A reduction in the complexity of dendrites  
25 arborization and dendritic length is observed, and spine numbers are also decreased (33,34). As



1 a result, astrocytes may be recruited for dendrites regrowth by releasing trophic factors  
2 (31,35,36) like S100B protein. Neuroinflammation characteristic of aging (“inflammaging”)  
3 may also activate astrocytes cells (35,37,38). Astrocyte reactivity may then lead to an  
4 exaggerated release of astrocytic biomarkers like GFAP (32,37) and potentially S100B.  
5 Astrocytes have a duality in their phenotype, neurotoxic or neuroprotective (37,39). While  
6 astrocytes lose their neuroprotective functions in Alzheimer's disease (37), molecular changes  
7 upon physiological aging are more complex. During normal aging, the impact of astrocyte  
8 activation and reactive gliosis may be neuroprotective at first (39). Experimental data from  
9 selected central nervous system (CNS) pathologies suggest that if not resolved in time, reactive  
10 gliosis can exert inhibitory effects on neuroplasticity and CNS regeneration (39), which is  
11 consistent with S100B effects. Nanomolar concentrations of S100B exert neurotrophic effects  
12 by stimulating neurite outgrowth and regulating survival of neurons whereas micromolar  
13 concentrations are neurotoxic for the neuronal environment (40). Another hypothesis for the  
14 increased S100B blood levels observed in older adults is an increased BBB permeability. A  
15 meta-analysis reported a significant increase in BBB permeability in old healthy subjects (n =  
16 238) when compared to younger healthy subjects (n = 213) (41). Increased S100B blood levels  
17 could also be linked to an extracerebral release since this protein is also expressed in other  
18 tissues such as skeletal muscle or bone tissue (8). A recent study showed an S100B increase in  
19 muscle cells in patients with sarcopenia (42). Another study showed higher S100B blood levels  
20 in patients with acute fractures without apparent cerebral injury (43,44). A higher incidence of  
21 sarcopenia and fractures in older people could also explain the S100B increase in this  
22 population (42,45). Furthermore, kidney function, which is known to decrease with age, may  
23 also contribute to the elevation of the S100B protein itself eliminated by the kidney (46,47).  
24 However, Jönsson *et al.* showed that the elimination of S100B was not affected by a moderate  
25 reduction of glomerular filtration (48). This could be explained by the low molecular weight of

1 S100B (21 kDa) allowing it to be easily filtered by the renal glomeruli. Lastly, in patients with  
2 end-stage renal disease, chronic inflammation and dysfunction of the BBB could increase the  
3 release of S100B by astrocytes and thus potentially explain the complication of cognitive  
4 impairment well known in these patients (49).

5 TBI results in astrocyte release of S100B, which may itself contribute to brain damage.  
6 Herrmann *et al.* showed, on a group of patients with mTBI, that increased posttraumatic  
7 concentrations of S100B help to identify the patients with a risk of long term  
8 neuropsychological dysfunction (50). In addition, S100B appears to be an important and useful  
9 predictor of functional outcome in moderate-to-severe TBI (51). An increase of S100B in  
10 traumatic brain conditions (micromolar levels) may contribute to brain damage by promoting  
11 inflammatory activities in astrocytes that cause neuronal dysfunction (52,53). This observation  
12 is all the more relevant because older people have an exaggerated astrocytic reactivity with  
13 higher basal levels of S100B, which explains why post-traumatic concentrations more easily  
14 reach micromolar levels. Perhaps this is why the TBI can contribute to dementia (54). Aging  
15 also seems to alter the mechanisms of cerebral compensation, plasticity and cerebral re-  
16 organization of the brain (55). Moreover, older patients often have more difficulty making the  
17 required psychological adjustments to the traumatic event. Globally, S100B levels could in part  
18 explain the less favourable outcome for elderly patients (55).

19 Finally, we questioned the effect of Alzheimer's disease and other dementias on S100B  
20 concentrations. As expected, median S100B concentrations are significantly different between  
21 patients with dementia (0.301  $\mu\text{g/L}$ ) and others (0.207  $\mu\text{g/L}$ ) ( $p < 0.001$ ). The high rate of  
22 dementia among patients over 90 years of age ( $\sim 41.0\%$ ) in our study population is consistent  
23 with the estimated prevalence of dementia in France (56). In 2018, 40.8% of people over 90  
24 years old had dementia (56). In our cohort, the optimal threshold of 0.15  $\mu\text{g/L}$  would have  
25 avoided 20% of CCT-scans in people over 90 years old against 10% with the routine threshold

1 of 0.10 µg/L. The exclusion of patients with dementia could enable a 25% CCT scans reduction  
2 instead of 20% when these were included. Although there is no statistically significant  
3 difference between the two values ( $p = 0.32$ ), a 25% specificity is closer to the one in average  
4 adult populations (~ 30%) and the AUC for this subgroup is not significant. In addition, we  
5 obtain lower specificity values in dementia patients compared to our whole cohort. For patients  
6 aged 90 years and over, the specificity falls from 20% to 13%. Once again, the difference is not  
7 significant ( $p = 0.16$ ), which proves the necessity for a new study focused on dementia patients  
8 to reevaluate optimal thresholds.

9 Recently, similar studies in older patients have also shown a reduced specificity of serum Glial  
10 Fibrillary Acidic Protein (GFAP) (23,57) and Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-  
11 L1) (23). Only Tau protein has been shown to have equivalent specificity performance between  
12 different age-groups (57). Another study, presenting data on GFAP and Neurofilament Light  
13 (NFL) levels in the cerebrospinal fluid of healthy participants, showed an increase in both  
14 biomarkers with increasing age (58). Finally, these data point to the influence of older age on  
15 candidate mTBI biomarkers. As for S100B, thresholds' adjustment will be necessary in older  
16 patients' management. Due to the retrospective nature of the study, we were unable to measure  
17 any brain biomarkers other than S100B. These assays will be the subject of future work.

18 **One of the limitations of the study was the lack of direct ascertainment of intracranial lesions**  
19 **in some patients. Moreover,** clinical data on dementia was collected retrospectively, and the  
20 etiology of dementia could not be identified for all patients. Some information (such as the time  
21 between the trauma and the blood sample) provided by patients with dementia may be  
22 questionable. **In addition,** future work will be required to achieve a better pathophysiological  
23 understanding of blood S100B increase in older patients. Finally, the retrospective nature of the  
24 study limited us in collecting data such as co-morbid conditions (e.g. chronic kidney disease,

1 estimated glomerular filtration rate (eGFR) reduction, sarcopenia, recent bone fractures) or  
2 medication intake (glucocorticoids, other anti-inflammatory drugs, ...).

3 In conclusion, S100B levels are considerably affected by age. At the routine threshold (0.10  
4  $\mu\text{g/L}$ ), its clinical utility is very limited by a poor specificity leading to only a small decrease in  
5 CCT scanning. Adjustment of the S100B threshold is necessary in older patients' management.  
6 An optimal 0.15  $\mu\text{g/L}$  threshold is particularly interesting for patients over 80 years of age with  
7 a  $\sim 30\%$  CCT scans reduction, which is comparable to the CCT scans reduction allowed in  
8 relatively younger adults. To validate the accuracy of our results, a future prospective study will  
9 be needed.

#### 10 **Conflict of Interest**

11 The authors have no conflicts.

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14

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1 **TABLE LEGENDS**

2 **Table 1: S100B concentration levels according to age.**

3 IQR: interquartile range; max: maximum; min: minimum. These data include the entire  
4 population (CCT performed or not) (n = 1172).

5 **Table 2: Population characteristics according to age.**

6 AT : antiplatelet treatment; CCT: cranial computed tomography; CCT+:  $\geq 1$  intracerebral  
7 lesion; F: females; h: hours; IQR: interquartile range; LC: loss of consciousness; M: males;  
8 max: maximum; min: minimum; RA: retrograde amnesia; †: time between trauma and sample;  
9 \*: *p* value of a multivariate model including gender.

10 **Table 3: Analysis of sensitivity (SE), specificity (SP), positive predictive value (PPV) and**  
11 **negative predictive value (NPV) for the two thresholds tested on the three age categories.**

12 AUC: area under ROC curve; yo: years old; \*: Optimal threshold (keeping 100% SE): 0.11  
13  $\mu\text{g/L}$  for patients aged 65 to 80, 0.15  $\mu\text{g/L}$  for patients aged 80 to 90, and 0.15  $\mu\text{g/L}$  for patients  
14 aged 90 years and over; †: Comparison of the specificity obtained at the 0.10  $\mu\text{g/L}$  threshold to  
15 that obtained at the optimal threshold.

1 **Table 1:** S100B concentration levels according to age

2

Age-group (years old)	n	S100B median, µg/L (min; max; IQR)		p value
<b>65-69</b>	138	0.183 (0.032; 4.18; 0.090-0.381)	0.184 (0.029; 7.74; 0.103-0.360)	< 0.001
<b>70-74</b>	160	0.187 (0.038; 3.77; 0.105-0.360)		
<b>75-79</b>	178	0.182 (0.029; 7.74; 0.109-0.343)		
<b>80-84</b>	239	0.235 (0.035; 5.40; 0.129-0.468)	0.255 (0.032; 8.97; 0.129-0.474)	
<b>85-89</b>	252	0.266 (0.032; 8.97; 0.128-0.486)		
<b>90-94</b>	154	0.317 (0.039; 3.52; 0.168-0.608)	0.318 (0.039; 4.68; 0.178-0.609)	
<b>≥ 95</b>	51	0.331 (0.086; 4.68; 0.179-0.700)		

3

4 IQR: interquartile range; max: maximum; min: minimum.

5 These data include the entire population (CCT performed or not) (n = 1172).

1 **Table 2:** Population characteristics according to age

	65-79 years old n = 476	80-89 years old n = 491	≥ 90 years old n = 205	p value
<b>Age median, years</b> (min; max; IQR)	73.5 (65.0; 79.9; 69.4-76.9)	85.1 (80.0; 89.9; 82.9-87.4)	92.9 (90.0; 105.1; 91.2-94.9)	< 0.001
<b>Sex ratio M/F</b>	1.1	0.7	0.5	< 0.001
<b>Median time<sup>†</sup>, h</b> (min; max; IQR)	1.7 (0.3; 3.0; 1.2-2.2)	1.5 (0.2; 3.0; 1.2-2.0)	1.7 (0.3; 3.0; 1.3-2.0)	0.413
<b>S100B median, µg/L</b> (min; max; IQR)	0.184 (0.029; 7.74; 0.103-0.360)	0.255 (0.032; 8.97; 0.129-0.474)	0.318 (0.039; 4.68; 0.178-0.609)	< 0.001*
<b>%S100B+</b> threshold of 0.10 µg/L	76.1	82.9	90.2	< 0.001*
<b>%S100B+</b> optimal threshold	72.7	67.8	81.0	< 0.001*
<b>CCT+ (%)</b>	n = 18 (1.5%)	n = 30 (2.6%)	n = 15 (1.3%)	0.11
<b>Risk factor</b>				
- RA (%)	n = 49 (4.2%)	n = 27 (2.3%)	n = 20 (1.7%)	0.017
- LC (%)	n = 233 (19.9%)	n = 151 (12.9%)	n = 44 (3.8%)	< 0.001
- AT (%)	n = 272 (23.2%)	n = 386 (32.9%)	n = 165 (14.1%)	< 0.001
- ≥ 2 (%)	n = 71 (6.1%)	n = 67 (5.7%)	n = 24 (2.0%)	0.532

2 AT : antiplatelet treatment; CCT: cranial computed tomography; CCT+: ≥ 1 intracerebral  
3 lesion; F: females; h: hours; IQR: interquartile range; LC: loss of consciousness; M: males;  
4 max: maximum; min: minimum; RA: retrograde amnesia; †: time between trauma and sample;  
5 \*: p value of a multivariate model including gender.

- 1 **Table 3:** Analysis of sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) for the two thresholds
- 2 tested on the three age categories.

	AUC (95% CI)	Threshold of 0.10 µg/L				Optimal threshold*				p value <sup>†</sup>
		SE (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)	SE (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)	
<b>All patients</b>	0.71 (0.66-0.76)	100 (94.3-100)	19.7 (17.4-22.1)	6.6 (5.1-8.4)	100 (98.3-100)	/	/	/	/	/
<b>65-79 yo</b>	0.71 (0.61-0.82)	100 (81.5-100)	<b>24.9</b> (21.0-29.1)	5.0 (3.0-7.7)	100 (96.8-100)	100 (81.5-100)	<b>28.4</b> (24.3-32.8)	5.2 (3.1-8.1)	100 (97.2-100)	<b>&lt; 0.001</b>
<b>80-89 yo</b>	0.75 (0.68-0.82)	100 (88.4-100)	<b>18.2</b> (14.8-22.1)	7.4 (5.0-10.4)	100 (95.7-100)	100 (88.4-100)	<b>34.3</b> (29.9-38.8)	9.0 (6.2-12.6)	100 (97.7-100)	<b>&lt; 0.001</b>
<b>≥ 90 yo</b>	0.55 (0.45-0.65)	100 (78.2-100)	<b>10.5</b> (6.6-15.8)	8.1 (4.6-13.0)	100 (83.2-100)	100 (78.2-100)	<b>20.5</b> (15.0-27.0)	9.0 (5.2-14.5)	100 (91.0-100)	<b>&lt; 0.001</b>

- 3 AUC: area under ROC curve; yo: years old; \*: Optimal threshold (keeping 100% SE): 0.11 µg/L for patients aged 65 to 80, 0.15 µg/L for patients
- 4 aged 80 to 90, and 0.15 µg/L for patients aged 90 years and over; †: Comparison of the specificity obtained at the 0.10 µg/L threshold to that
- 5 obtained at the optimal threshold.



1 **FIGURE LEGENDS**

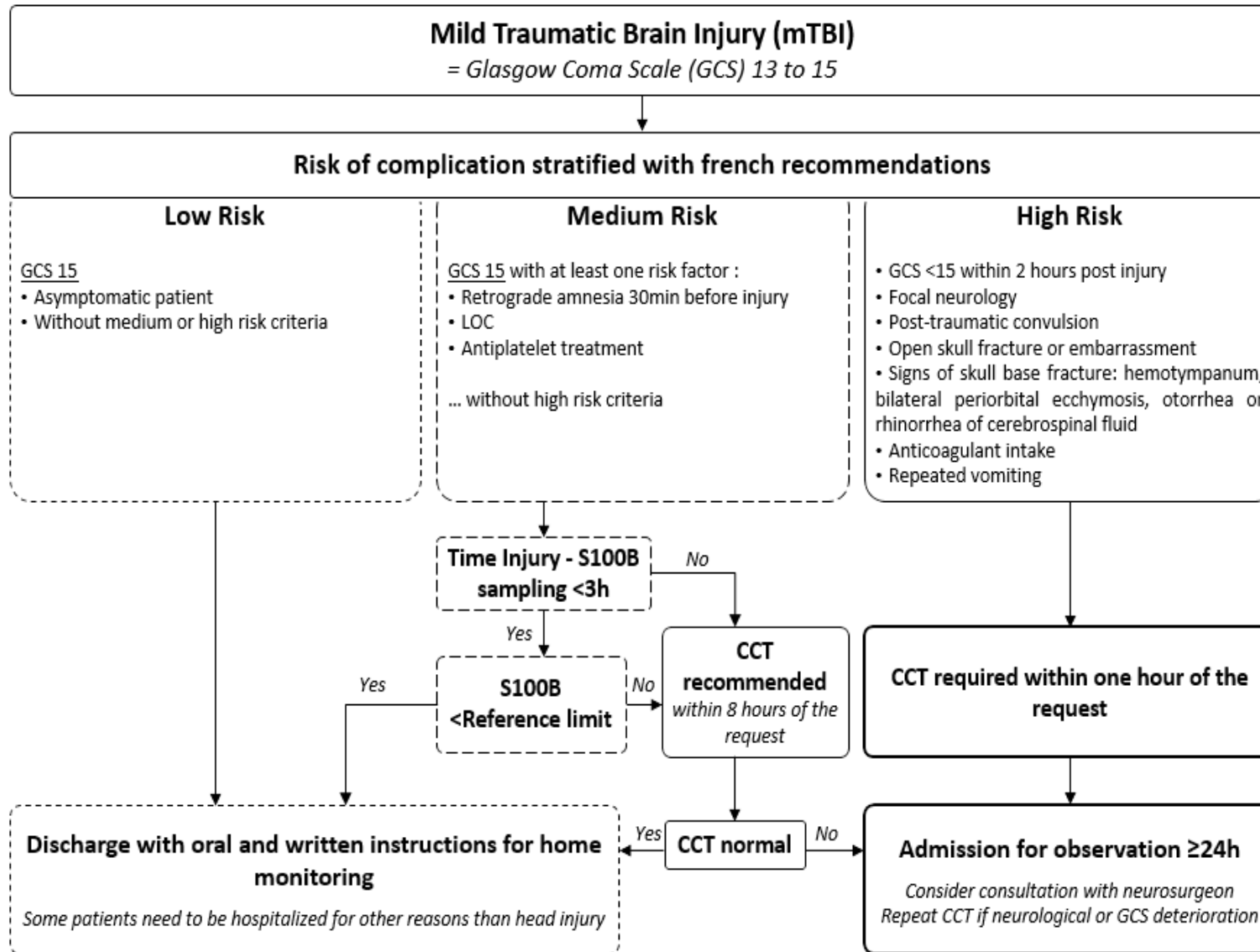
2 **Figure 1: Decision algorithm for patients' management with mild traumatic brain injury**  
3 **(mTBI) at the Clermont-Ferrand Emergency Department. The reference threshold is**  
4 **internationally defined as 0.10 µg/L for adults.**

5 CCT: Cranial Computed Tomography; GCS: Glasgow Coma Scale; h: hours; LOC: Loss Of  
6 Consciousness.

7 **Figure 2: Flow chart of patients included, S100B protein results and CCT results.**

8 CCT: Cranial Computed Tomography; GCS: Glasgow Coma Scale; mTBI: mild Traumatic  
9 Brain Injury; S100B-: serum concentrations below the cutoff ( $< 0.10 \mu\text{g/L}$ ); S100+: serum  
10 concentrations above the cutoff ( $\geq 0.10 \mu\text{g/L}$ );  $\emptyset$  CCT: CCT not performed.

Figure 1



**Figure 2**

