Vincenzo G. Menditto*, Marco Moretti, Lucia Babini, Annalisa Mattioli, Andres Ramon Giuliani, Marina Fratini, Fabienne Yvonne Pallua, Elisa Andreoli, Cinzia Nitti, Susanna Contucci, Armando Gabrielli, Marco Bruno Luigi Rocchi and Giovanni Pomponio

Minor head injury in anticoagulated patients: performance of biomarkers S100B, NSE, GFAP, UCH-L1 and Alinity TBI in the detection of intracranial injury. A prospective observational study

https://doi.org/10.1515/cclm-2023-1169
Received October 18, 2023; accepted December 26, 2023; published online January 12, 2024

Abstract

Objectives: Data in literature indicate that in patients suffering a minor head injury (MHI), biomarkers serum levels could be effective to predict the absence of intracranial injury (ICI) on head CT scan. Use of these biomarkers in case of patients taking oral anticoagulants who experience MHI is very limited. We investigated biomarkers as predictors of ICI in anticoagulated patients managed in an ED.

Methods: We conducted a single-cohort, prospective, observational study in an ED. Our structured clinical pathway included a first head CT scan, 24 h observation and a second CT scan. The outcome was delayed ICI (dICI), defined as ICI on the second CT scan after a first negative CT scan. We assessed the sensitivity (SE), specificity (SP), negative predictive value (NNV) and positive predictive value (PPV) of the biomarkers S100B, NSE, GFAP, UCH-L1 and Alinity TBI in order to identify dICI.

Results: Our study population was of 234 patients with a negative first CT scan who underwent a second CT scan. The rate of dICI was 4.7 %. The NPV for the detection of dICI were respectively (IC 95 %): S100B 92.7 % (86.0–96.8 %,); ubiquitin C-terminal hydrolase-L1 (UCH-L1) 91.8 % (83.8–96.6 %); glial fibrillary protein (GFP) 100 % (83.2–100 %); TBI 100 % (66.4–100 %). The AUC for the detection of dICI was 0.407 for S100B, 0.563 for neuron-specific enolase (NSE), 0.510 for UCH-L1 and 0.720 for glial fibrillary acidic protein (GFAP), respectively.

Conclusions: The NPV of the analyzed biomarkers were high and they potentially could limit the number of head CT scan for detecting dICI in anticoagulated patients suffering MHI. GFAP and Alinity TBI seem to be effective to rule out a dCI, but future trials are needed.

Keywords: minor head injury; protein S100B; neuron-specific enolase (NSE); ubiquitin C-terminal hydrolase-L1 (UCHL-1); glial fibrillary acidic protein (GFAP); anticoagulated patients

***Corresponding author: Vincenzo G. Menditto**, MD, Emergency and Internal Medicine Department, Azienda Ospedaliero Universitaria delle Marche, Via Conca n.71, 60126 Ancona, Ancona, Italy, E-mail: vincenzogiannicola.menditto@ospedaliriuniti.marche.it. https://orcid.org/0000-0001-6231-2251
Marco Moretti and Lucia Babini, Medicina di Laboratorio, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy
Annalisa Mattioli, Andres Ramon Giuliani, Marina Fratini, Fabienne Yvonne Pallua, Elisa Andreoli, Cinzia Nitti and Susanna Contucci, Emergency and Internal Medicine Department, Azienda Ospedaliero Universitaria delle Marche, Ancona, Ancona, Italy
Armando Gabrielli, Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, Ancona, Italy
Marco Bruno Luigi Rocchi, Statistica Medica, Dipartimento di Scienze Biomolecolari, Università di Urbino, Urbino, Italy
Giovanni Pomponio, Clinica Medica, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy

Introduction

The optimal management of patients taking oral anticoagulants who experience minor head injury (MHI) is debated [1, 2]. CT scanning is generally recommended for such patients regardless of clinical presentation. However, it remains unclear whether such patients should then be hospitalized for observation or undergo a later second CT scan in order to identify delayed intracranial injury (dICI) [3–6].

To prevent unnecessary imaging, multiple clinical predictors have been developed to identify those who are at risk of having ICI or dICI, but they are self-reporting or non-specific [7]. Recent progresses in understanding the pathophysiology of brain injury are raising new hopes to have reliable predictors for ICI. Following MHI, axonal shearing and cellular disruption

cause the release of brain-damage biomarkers from neurons, such as neuron-specific enolase (NSE), ubiquitin C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain protein and from astrocytes, such as glial fibrillary acidic protein (GFAP) and S100B protein (S100B) [8–10]. Data indicate that biomarkers serum levels could be effective to predict the absence of ICI on head CT scan [10–18]. Moreover, the kinetic profile of NSE, UCH-L1, GFAP and S100B, characterized by an early response to bleeding, seems particularly adapt to a prognostic biomarker in anticoagulated patients with head trauma [11, 12]. In 2018 serum measurement of GFAP in combination with ubiquitin UCH-L1 was cleared by the Food and Drug Administration (FDA) for clinical use to identify patients with MHI as having likely to have ICI on head CT within 12 h from trauma [12]. Moreover, dosage of S100B was incorporated into the Scandinavian Neurotrauma Guidelines [19] and, more recently, testing of S100B, UCH-L1 and GFAP was proposed, with a strong agreement among the experts, by the French Society of Emergency Medicine [20], aiming to limit the request for head CT scans. Adding biomarkers to current recommendations could therefore reduce the need for CT examination and save costs. To date, there are no published studies on the role of dosing NSE, GFAP or UCH-L1serum levels in anticoagulated patients with MHI and only one study concerning S100B [21] is available. We explored potential role of measuring S100B, NSE, GFAP and UCH-L1 serum levels as predictive tools for dICI.

Materials and methods

Study design

We performed a prospective observational study at Azienda Ospedaliero-Universitaria delle Marche in Ancona, Italy, a level II trauma centre with an annual ED census of 57,000. The study protocol was approved by the local Ethics Committee (Ethics Committee for Clinical Trials, Ancona, Italy, #2018-41). Patients or their legal representatives provided written informed consent to participate. The study was conducted according to Declaration of Helsinki. The study was funded by the Italian National Health System. The kits for biomarkers determination were provided by Roche and Abbott. We followed the 'Standards for Reporting Diagnostic Accuracy (STARD)' 2015 checklist [22].

Study setting and population

Since January 2018 to June 2022, we enrolled a cohort of adult consecutive patients with MHI, defined as a head injury presenting a Glasgow Coma Scale (GCS) score of 14–15, regardless of the presence of history of loss of consciousness. Other inclusion criteria were: 1. head trauma occurred <12 h before ED access; 2. current use of oral anticoagulation therapy, Vitamin K antagonists (VKAs) or direct oral anticoagulants (DOAs), taken for at least one week before the injury; 3. absence of acute traumatic ICI (see below) on a first head TC scan performed within 6 h from the injury. We excluded patients who have an Injury Severity Score (ISS)>15 [23]. Investigators screened two electronic databases (Galileo Emergency and Pacs Web) and verified that all eligible patients had been included. All patients underwent a first head CT scan (non-contrast) within 6 h from the injury; results were interpreted by the neuro-radiologist on duty. Subsequently, all patients who did not need admission in specialized wards were put into EDOU, where they received a neurologic examination every 4–6 h for 24 h. Afterwards, a second CT-scan was proposed to all patients before discharge. Our study population was characterized by: 1. absence of ICI (see below) on of a first head TC scan; 2. a second CT-scan before discharge.

Data collection

The ED physicians in charge for the patient, trained by the principal investigators, recorded inclusion/exclusion criteria, demographics, GCS, mechanism of injury, associated injuries, sensory or motor deficits, type and dose of anticoagulant and indication for, international normalised ratio (INR), concomitant antiplatelet therapy, death or operative neurosurgery, re-admission to ED, using a dedicated data collection form at bedside. The investigators made a follow-up phone call to all patients 30 days after discharge [24].

Measurement of serum biomarkers

We collected serum for S100B and NSE since April 2020 and for UCH-L1 and GFAP since March 2021. Venous blood samples were collected within 6 h after injury and frozen to −20 °C [25]. We assessed S100B, NSE, GFAP and UCH-L1 serum levels. S100B and NSE serum levels were determined by Elecsys® electrochemiluminescence immunoassays (ECLIA) on a Cobas e601 system (Roche Diagnostics, Meylan, France). GFAP and UCH-L1 serum levels were determined by Abbott CMIA assays on an Alinity i platform (Abbott, Chicago, IL, USA). The cut-offs for S100B, UCH-L1 and GFAP were 0.105 µg/L, 400 pg/mL and 35 pg/mL respectively, as specified by the manufacturers and chosen to maximize sensitivity and negative predictive value (NPV). NSE, the cut-off for NSE was set at 14.7 ng/mL, as reported in literature [11]. Cut-points are detailed in Table 1. The Alinity TBI test was defined positive if GFAP or UCH-L1 or both concentrations were above their respective cut-offs.

Cranial CT examinations

ICI on CT scan was classified as subdural, epidural, parenchymal hematoma, subarachnoid hemorrhage, cerebral contusion, depressed skull fracture or minimal intracranial bleeding (minor lesions) [26]. The same lesions on the second CT were defined as dICI.

Table 1: Limit of quantification (LoQ) and range of the biomarkers used in the study.

Biomarker	Limit of quantification (LoQ)	Range
S100B	0.02 µg/L	0.005–39 µg/L
NSE	0.225 ng/mL	0.075–300 ng/mL
GFAP	6.1 pg/mL	3.2–42,000 pg/mL
UCH-L1	26.3 pg/mL	18.3–25,000 pg/mL

Statistical analysis

In our analysis there was no estimate of sample size. Therefore, conclusions regarding the performance of biomarkers have to be considered exploratory. The continuous variables were compared using either the Student's t-test or the Mann–Whitney U-test, as appropriate. The categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) of the biomarkers' blood level for the detection of dICI were estimated in the study population. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value for biomarkers' serum level to maximize sensitivity and NPV. Cohen's k statistics were calculated to assess interrater agreement for the biomarkers' positivity. Altman's scale was used for assessing the strength of agreement demonstrated by k statistics: <0.20 poor, 0.21 to 0.39 fair, 0.40 to 0.59 moderate, 0.60 to 0.79 good, and 0.80 to 1.0 very good. A significance level of alpha=0.05 will be used for all the statistical analyses. We analysed our data using SPSS (version 13).

Results

A total of 370 patients were screened during the study period (Figure 1). 57 venous blood samples were not collected because the injury had occurred more than 6 h before clinical observation. Of the rest 313 patients, 46 patients had first head CT scan positive and 33 patients did not undergo a second CT scan because of admission to specialized wards due to reasons other than MHI (30 patients) or because of refusal to undergo a second CT scan (3 patients).

234 patients were our study population. General characteristics (51 % female, aged 81.7 ± 9.3 y (mean, SD)) of the study population are reported in Table 2. The mean time between the MHI and the blood sample was 2.2 ± 1.4 h. The rate of dICI was 5.5 % (95 % CI: 2.7–6.6 %) (13 patients, 11 minor lesions). No patients underwent to neurosurgery nor died because of MHI within 30 days after MHI. The overall 30 day mortality was 2.6 % (6/234 patients). 11 patients (4.7 %) were readmitted to ED within 30 days after the discharge because of consequences of MHI and all were discharged from ED (Figure 1).

Within the study population, S100B and NSE were available for 234 patients and UCH-L1/GFAP (and Alinity TBI) for 171 patients, respectively. We found serum levels going beyond the cut-off in the 53 % of cases for S100B, 36 % for NSE, 59 % for UCH-L1 and 88 % for GFAP (Table 3); Alinity TBI was positive in 162/171 samples (95 %). SE, SP, PPV and NPV for the detection of dICI are shown in Table 4. Interestingly, by using the cut-off values suggested by producers, the NPV and PPV of S100B was 92.7 % (95 % CI: 56.0–96.8 %) and 4.0 % (95 % CI: 1.3–9.1 %) respectively, the NPV and PPV of UCH-L1 was 96.9 % (95 % CI: 91.4–99.4 %) and 4 % (95 % CI: 1.3–9.1 %) and the NPV and PPV of GFAP was 100 % (95 % CI:

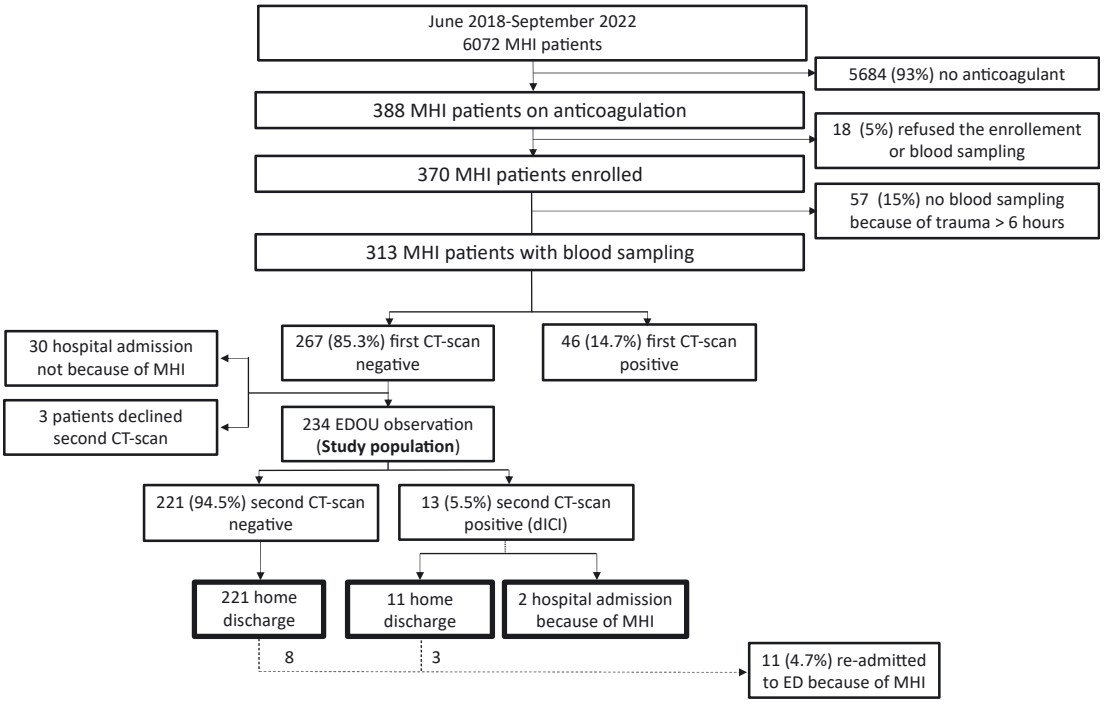

Figure 1: Flow diagram of the selection and study group with the overall prevalence of abnormal head CT scan findings and clinical outcomes. MHI, minor head injury; EDOU, emergency department observation unit.

Table 2: Demographic and clinical characteristics of the study population.

Characteristic	Value
Demographic characteristics	n=234
Age, years, mean, SD	81.7 (9.3)
Sex, n (%)	
M	115 (50.8)
F	119 (49.2)
GCS, n (%)	
15	231 (98.7)
14	3 (1.3)
Comorbidities, n (%)	
Coagulopathy	1 (0.4)
Hypertension	167 (71.4)
Previous TIA/stroke	22 (9.4)
Chronic liver disease	1 (0.4)
Renal insufficiency	108 (46.1)
Diabetes mellitus	49 (20.9)
Active cancer	17 (7.2)
Epilepsy	11 (4.7)
History, n (%)	
Previous endocranic post-traumatic bleeding	7 (1.5)
Concomitant antiplatelet therapy	10 (4.3)
Anticoagulant, n (%)	
VKA	75 (32.0)
DOA	159 (68.0)
Dabigatran	13 (5.6)
Rivaroxaban	47 (20.1)
Apixaban	71 (30.3)
Edoxaban	28 (12.0)
Indication for anticoagulant therapy, n (%)	
Atrial fibrillation	195 (83.3)
Thromboembolic disease	22 (9.4)
Valvular disease	17 (7.3)
Time between trauma and blood sampling	
hours mean, SD	2.2 (1.4)
Mechanism of injury, n (%)	
Accidental	166 (70.9)
Syncope	48 (20.6)
Not clear	20 (8.5)
Time between 1th and 2nd CT hours mean, SD	26 (6.1)

83.2–100 %) and 5.3 % (95 % CI: 2.3–10.2 %), respectively. The NPV and PPV of Alinity TBI was also 100 % (95 % CI: 66.4–100 %) and 4.9 % (95 % CI: 2.1–9.5 %), respectively.

Moreover, SE and NPV of GFAP/UCH-L1 were similar in patients <65 years and in those >65 year (p=0.5525 and p>0.9999, respectively). SP was significantly lower in elderly patients (13.1 vs. 44.2 %; p<0.0001) and decreased stepwise with older age. Compared to younger patients, elderly patients with negative head CT also had a significantly higher serum levels of GFAP (38.6 vs. 16.2 pg/mL; p<0.0001) and of UCH-L1 (347.4 vs. 232.1 pg/mL; p<0.0001).

We also analyzed the performance of the biomarkers to detect a dICI in the two subtypes of anticoagulated patients, VKA group and DOACs' group: the VPN (95 % CI) was respectively 96.8 % (89.0–99.3 %) vs. 91.0 % (85.2–94.8 %) for S100B, 94.2 % (85.6%-98.0) vs. 95.9 % (91.2–98.3 %) for NSE, 100.0 % (90.2–100.0 %) for UCH-L1 and 100 % (90.2–100.0 %) vs. 100 % (96.3–100.0 %) for both GFAP and TBI.

The best concordance between biomarkers was found between G-FAP and Alinity TBI (K=0.591).

The AUC was >0.50 (0.720) only for GFAP. ROC curve analysis showed an optimal cut-off for GFAP for the detection of dICI of 67 pg/mL providing a sensitivity of 100.0 % (95 % CI: 63.1–100.0 %), a specificity of 43.6 % (95 % CI: 35.8–51.5 %) and an NPV of 100.0 % (95 % CI: 94.9–100.0 %).

In all screened patients with available blood sampling (n=313), the performance [VPN (95 % CI)] for detecting ICI on the first head CT scan was: 86.9 % (82.5–90.3 %) for S100B, 84.3 % (79.7–88.1 %) for NSE, 88.1 % (82.8–91.9 %) for UCH-L1, 95.8 % (92.0–97.9 %) for GFAP and 90.9 % (86.1–94.2 %) for TBI.

Discussion

Previous studies have shown the efficacy of brain biomarkers serum levels to discriminate patients regarding the presence or absence of ICI on an initial CT scan after an MHI

Table 3: Results of biomarkers' values in the subgroup of patients with head CT positive (CT+) and head CT negative (CT−) in the study population.

Value	S100B n=234	NSE n=234	UCH-L1 n=171	G-FAP n=171	TBI n=171
CT+					
Median (IGR)	0.08 (0.06–0.20) µg/L	12.3 (6.3–16.7) ng/mL	502.7 (259.7–729.1) pg/mL	116.8 (70.4–295.3) pg/mL	na
Positive, n (%)	5 (38)	6 (46)	5 (62)	8 (100)	8 (100)
Negative, n (%)	8 (62)	7 (54)	3 (38)	0 (0)	0 (0)
CT−					
Median (IGR)	0.12 (0.06–0.25) µg/L	10.5 (5.5–17.5) ng/mL	425.5 (280.3–695.5) pg/mL	70.9 (48.1–111.4) pg/mL	na
Median, n (%)	120 (54)	78 (39)	96 (59)	143 (88)	154 (94)
Negative, n (%)	101 (46)	143 (61)	70 (41)	20 (12)	9 (6)

S100B, S100B protein; NSE, neuron-specific enolase; UCH-L1, ubiquitin C-terminal hydrolase-L1; GFAP, glial fibrillary acidic protein.

Table 4: Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of S100B protein (S100B), Neuron-specific enolase (NSE), Ubiquitin C-terminal hydrolase-L1 (UCH-L1), Glial fibrillary acidic protein (GFAP) and TBI for the detection of dICI in the study population.

Biomarker	Sensitivity, % (95 % CI)	Specificity, % (95 % CI)	NPV, % (95 % CI)	PPV, % (95 % CI)
S100B	38.5 (13.9–68.4)	45.7 (39.0–52.5)	92.7 (86.0–96.8)	4.0 (1.3–9.1)
NSE	46.1 (19.1–74.9)	39.4 (32.54–46.57)	91.8 (83.8–96.6)	4.8 (1.8–10.1)
UCH-L1	62.5 (24.5–91.5)	44.4 (37.7–51.3)	96.9 (91.4–99.4)	4.0 (1.3–9.1)
GFAP	100 (63.0–100)	12.3 (7.7–18.3)	100 (83.2–100)	5.3 (2.1–10.2)
TBI	100 (63.1–100)	5.5 (2.6–10.2)	100 (66.4–100)	4.9 (2.2–9.5)

[9, 11–15]. To date, indeed, there are no published studies on the role of dosing NSE, GFAP or UCH-L1serum levels in anticoagulated patients with MHI and only one study concerning S100B [21] is available. We tested and compared, for the first time, the performance of 4 brain biomarkers to detect dICI in this setting of patients.

The NPV of S100B and of NSE in our study population, 92.7 and 91.8 % respectively, are slightly low compared to NPV found in the literature in studies about non-anticoagulated patients [10, 17, 18, 27]. David et al. [21] reported an NPV of S100B serum level of 94.3 % using a cut-off value of 0.105 µg/mL in a prospective study involving 308 patients with mild head trauma while they were under antithrombotic medication, of whom 30 % were taking oral anticoagulants. More recently, Rogan et al. [10] conducted a multicentre prospective observational study included adult patients with MHI injury, of whom 25 % were taking oral anticoagulants. The NPV was 97.3 % (95 % CI 84.2 %–99.6 %) and the AUC was 0.73. Those results are slightly to moderately better than ours. However, both the studies analyzed the potential of S100B protein as a negative predictive marker for ICI at the first CT scan, while in our study we tested the biomarkers as predictive markers for dICI. Moreover, previous studies showed that S100B and UCHL1 had a good accuracy for detecting CT positivity among young adults only, but not middle-aged or older adults [28, 29]. Data about performance of NSE across age-categories still lack. These observations highlight some of the challenges of the use of brain biomarkers in older adults who may have multiple preexisting neurological disorders, such as dementia [30, 31]. Decrements in SP and increased serum values in elderly patients suggest that special deference may be warranted for those patients [28]. We found similar difference in performance of the biomarkers between elderly and younger patients, but these results need to be confirmed because elderly patients (age> 65 years) constituted the 96 % of our cohort (83 % with age>75 years).

The most important finding from our data is an NPV of GFAP and Alinity TBI of 100 % for the diagnosis of dICI using the cut-offs specified by the manufacturers. Moreover, we found a superiority of GFAP over S100B, NSE and UCHL1 for discriminating dICI in patients of both the VKA and DOAC group and even for discriminating CT positive from CT negative in patients presenting within traumatic brain injury at a first head CT scan (with lower VPN). Our data confirm some prior findings [28, 32, 33]. However, the wide 95 % CIs (83.2–100 % and 66.4–100 %, respectively) somewhat hampers clinical fallout of our results. At present, a multicenter validation is currently in progress [*ClinicalTrials.gov, 2017, NCT03280485], but very few clinical data are available [34]. Our data, if adequately confirmed in future studies, might suggest the utility of GFAP, Alinity TBI or a combination of biomarkers after a first negative CT scan in order to screen which patient should undergo 24 h-observation and a second CT scan. This strategy may reduce the need to repeat CT scan by approximately 5 %. Since MHI in older anticoagulated people has a relatively high prevalence, this percentage could be of special importance regarding the radiation-associated health risks, financial burden and ED overcrowding. Using the hypothetical cut-off of 67 pg/mL, 40 % of samples of the study population would be negative for GFAP, with a result similar to that recently reported by Ahmadi et al. [35]. This finding could give a more significant improvement to MHI management in elderly patients under antithrombotic therapy. Indeed, our results might to be considered as hypothesis, given the inadequate sample size and wide confidence intervals. Moreover, the lower limit of CI is too low to be acceptable to most practicing clinicians. Our results worth further investigation in a well powered prospective study.

Lastly, FDA approved the i-STAT® System handheld device for rapid measurement of plasma-based GFAP and UCH-L1 [36]. Since values measured using i-STAT and core laboratory platform seem to be strongly correlated [37], then this assay could be implemented for rapid assessment of GFAP.

Limitations

Limitations of our study are the following: 1. the monocentric nature of our study, conducted in a II-level academic hospital, could increase the risk of selection bias; 2. samples

for biomarkers were not available for all patients because we have been collecting serum only since April 2020 for S100B and NSE and since March 2021 for UCH-L1 and GFAP; 3. we didn't estimate the sample size needed to determine clinically useful test characteristics, therefore, our study is exploratory rather than definitive; 4. results cannot be applied to patients in concomitant antiplatelet therapy; 5. compliance with anticoagulation was not reported and, given the inability to measure the degree of anticoagulation with DOAs, we cannot exclude that some patients were on sub-therapeutic dosages. However, we evaluated whether the dosage of the drug was theoretically appropriate for patients on DOAs and recorded INR for patients on VKAs.

Conclusions

In conclusion, brain-damage plasma biomarkers, such as S100B and GFAP, appear promising in predicting intracranial lesion during the observation period after a first normal CT-scan in anticoagulated patients with MHI. In particular, GFAP and Alinity TBI showed an NPV of 100 % for detecting dICI. These findings are worth future dedicated trials.

Research ethics: The study protocol was approved by the local Ethics Committee (Ethics Committee for Clinical Trials, Ancona, Italy, #2018-41). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no conflict of interest.
Research funding: None declared.
Data availability: The raw data can be obtained on request from the corresponding author.

References

1. Garra G, Nashed AH, Capobianco L. Minor head trauma in anticoagulated patients. Acad Emerg Med 1999;6:121–4.
2. Li J, Brown J, Levine M. Mild head injury, anticoagulants, and risk of intracranial injury. Lancet 2001;357:771–2.
3. Haydel MJ, Preston CA, Mills TJ, Luber S, Blaudeau E, DeBlieux PM. Indications for computed tomography in patients with minor head injury. N Engl J Med 2000;343:100–5.
4. Fabbri A, Servadei F, Marchesini G, Dente M, Iervese T, Spada M, et al. Which type of observation for patients with high-risk mild head injury and negative computed tomography? Eur J Emerg Med 2004;11:65–9.
5. Menditto VG, Lucci M, Polonara S, Pomponio G, Gabrielli A. Management of minor head injury in patients receiving oral anticoagulant therapy: a prospective study of a 24-hour observation protocol. Ann Emerg Med 2012;59:451–5.
6. Hadwe SE, Assamadi M, Barrit S, Giannis D, Haidich AB, Goulis DG, et al. Delayed intracranial hemorrhage of patients with mild traumatic brain injury under antithrombotics on routine repeat CT scan: a systematic review and meta-analysis. Brain Inj 2022;36:703–13.
7. Turcato G, Zaboli A, Bonora A, Ricci G, Zannoni M, Maccagnani A, et al. Analysis of clinical and laboratory risk factors of post-traumatic intracranial hemorrhage in patients on direct oral anticoagulants with mild traumatic brain injury: an observational multicenter cohort. J Emerg Med 2023;64:1–13.
8. Hier DB, Obafemi-Ajayi T, Thimgan MS, Olbricht GR, Azizi S, Allen B, et al. Blood biomarkers for mild traumatic brain injury: a selective review of unresolved issues. Biomark Res 2021;9:70.
9. Ghaith HS, Nawar AA, Gabra MD, Abdelrahman ME, Nafady MH, Bahbah EI, et al. A literature review of traumatic brain injury biomarkers. Mol Neurobiol 2022;59:4141–58.
10. 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.
11. Mussack T, Biberthaler P, Kanz KG, Heckl U, Gruber R, Linsenmaier U, et al. Immediate S-100B and neuron-specific enolase plasma measurements for rapid evaluation of primary brain damage in alcohol-intoxicated, minor head-injured patients. Shock 2002;18: 395–400.
12. Bazarian JJ, Biberthaler P, Welch RD, Lewis LM, Barzo P, Bogner-Flatz V, et al. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. Lancet Neurol 2018;17:782–9.
13. Welch RD, Ayaz SI, Lewis LM, Unden J, Chen JY, Mika VH, et al. Ability of serum glial fibrillary acidic protein, ubiquitin C-Terminal Hydrolase-L1, and S100B to differentiate normal and abnormal head computed tomography findings in patients with suspected mild or moderate traumatic brain injury. J Neurotrauma 2016;33:203–14.
14. Mondello S, Sorinola A, Czeiter E, Vámos Z, Amrein K, Synnot A, et al. Blood-based protein biomarkers for the management of traumatic brain injuries in adults presenting to emergency departments with mild brain injury: a living systematic review and meta-analysis. J Neurotrauma 2021;38:1086–106.
15. Amoo M, Henry J, O'Halloran PJ, Brennan P, Husien MB, Campbell M, et al. S100B, GFAP, UCH-L1 and NSE as predictors of abnormalities on CT imaging following mild traumatic brain injury: a systematic review and meta-analysis of diagnostic test accuracy. Neurosurg Rev 2022;45: 1171–93.
16. Blais Lécuyer J, Mercier É, Tardif PA, Archambault PM, Chauny JM, Berthelot S, et al. S100B protein level for the detection of clinically significant intracranial haemorrhage in patients with mild traumatic brain injury: a subanalysis of a prospective cohort study. Emerg Med J 2021;38:285–9.
17. Rogan A, Sik A, Dickinson E, Patel V, Peckler B, McQuade D, et al. Endorsed by ACEM Emergency Department Epidemiology Network. 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 2023;40:159–66.
18. Skogseid IM, Nordby HK, Urdal P, Paus E, Lilleaas F. Increased serum creatine kinase BB and neuron specific enolase following head injury indicates brain damage. Acta Neurochir 1992;115:106–11.
19. 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.
20. Prise en charge des patients presentant un traumatisme crânien leger de l'adulte [Management of patients suffering from mild traumatic brain injury] RPP-TCL-2022.pdf - SFMU. https://www.sfmu.org/upload/consensus/RPP-TCL-2022.pdf [Accessed 30 Jan 2023].
21. 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.
22. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. Stard 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;28:h5527.
23. Baker SP, O'Neil B, Haddon W, Long WB. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14:187–96.
24. Jones J, Clark W, Bradford J, Dougherty J. Efficacy of a telephone follow-up system in the emergency department. J Emerg Med 1988;6:249–54.
25. 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.
26. Fuller GW, Evans R, Preston L, Woods HB, Mason S. Should adults with mild head injury who are receiving direct oral anticoagulants undergo computed tomography scanning? A systematic review. Ann Emerg Med 2019;73:66–75.
27. Seidenfaden SC, Kjerulff JL, Juul N, Kirkegaard H, Møller MF, Münster AB, et al. Diagnostic accuracy of prehospital serum S100B and GFAP in patients with mild traumatic brain injury: a prospective observational multicenter cohort study – "the PreTBI I study". Scand J Trauma Resuscitation Emerg Med 2021;29:75.
28. Gardner RC, Puccio AM, Korley FK, Wang KKW, Diaz-Arrastia R, Okonkwo DO, et al. Effects of age and time since injury on traumatic brain injury blood biomarkers: a TRACK-TBI study. Brain Commun 2022;5:fcac316.
29. Ward MD, Weber A, Merrill VD, Welch RD, Bazarian JJ, Christenson RH. Predictive performance of traumatic brain injury biomarkers in high-risk elderly patients. J Appl Lab Med 2020;5:91–100.
30. Oris C, Bouillon-Minois JB, 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 A Biol Sci Med Sci 2021;76:1471–9.
31. Asken BM, Elahi FM, La Joie R, Strom A, Staffaroni AM, Lindbergh CA, et al. Plasma Glial Fibrillary Acidic Protein levels differ along the spectra of amyloid burden and clinical disease stage. J Alzheimers Dis 2020;78:265–76.
32. Czeiter E, Amrein K, Gravesteijn BY, Lecky F, Menon DK, Mondello S, et al. Blood biomarkers on admission in acute traumatic brain injury: relations to severity, CT findings and care path in the CENTER-TBI study. EBioMedicine 2020;56:102785.
33. Mastandrea P, Mengozzi S, Bernardini S. Systematic review and cumulative meta-analysis of the diagnostic accuracy of glial fibrillary acidic protein vs. S100 calcium binding protein B as blood biomarkers in observational studies of patients with mild or moderate acute traumatic brain injury. Diagnosis 2021;9:18–27.
34. Richard M, Lagares A, Bondanese V, de la Cruz J, Mejan O, Pavlov V, et al. BRAINI investigators. Study protocol for investigating the performance of an automated blood test measuring GFAP and UCH-L1 in a prospective observational cohort of patients with mild traumatic brain injury: European BRAINI study. BMJ Open 2021;11:e043635.
35. Ahmadi S, Roshdi Dizaji S, Babahajian A, Alizadeh M, Sarveazad A, Yousefifard M. Serum glial fibrillary acidic protein in detecting intracranial injuries following minor head trauma; a systematic review and meta-analysis. Arch Acad Emerg Med 2023;11:e9.
36. DA. 510(k) Substantial equivalence determination decision summary for the Abbott Laboratories i-STAT TBI Plasma cartridge with the i-STAT Alinity System; 2021. https://www.accessdata.fda.gov/cdrh_docs/reviews/K201778.pdf [Accessed 30 Jun 2023].
37. Korley FK, Datwyler SA, Jain S, Sun X, Beligere G, Chandran R, et al. Comparison of GFAP and UCH-L1 measurements from two prototype assays: the Abbott i-STAT and ARCHITECT assays. Neurotrauma Rep 2021;2:193–9.