Predittori di esito nei pazienti con trauma cranico lieve in terapia con anticoagulanti

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dichiarazione di potenziale conflitto di interesse

- Non ha rapporti di consulenza con Aziende farmaceutiche e non ha ricevuto onorari o compensi per la partecipazione a convegni e/o congressi organizzati per presentare dati di specifici farmaci o dispositivi medici

- Negli ultimi 3 anni non ha ricevuto grants di ricerca

Predittori di esito nei pazienti con trauma cranico lieve in terapia con anticoagulanti

My background

TRAUMA/ORIGINAL RESEARCH

Management of Minor Head Injury in Patients Receiving Oral Anticoagulant Therapy: A Prospective Study of a 24-Hour Observation Protocol

Vincenzo G. Menditto, MD, Moira Lucidi, MD, Stefano Polonara, MD, Giovanni Pomponio, MD, Armando Gabrielli, MD
From the Emergency Department, Ospedali Riuniti di Ancona, Ancona, Italy (Menditto, Polonara), and the Department of Internal Medicine, Università Politecnica delle Marche, Ancona, Italy (Lucidi, Pomponio, Gabrielli).

Study objective: Patients receiving warfarin who experience minor head injury are at risk of intracranial hemorrhage, and optimal management after a single head computed tomography (CT) scan is unclear. We evaluate a protocol of 24-hour observation followed by a second head CT scan.

Methods: In this prospective case series, we enrolled consecutive patients receiving warfarin and showing no intracranial lesions on a first CT scan after minor head injury treated at a Level II trauma center. We implemented a structured clinical pathway, including 24-hour observation and a CT scan performed before discharge. We then evaluated the frequency of death, admission, neurosurgery, and delayed intracranial hemorrhage.

Results: We enrolled and observed 97 consecutive patients. Ten refused the second CT scan and were well during 30-day follow-up. Repeated CT scanning in the remaining 87 patients revealed a new hemorrhage lesion in 5 (6%), with 3 subsequently hospitalized and 1 receiving craniotomy. Two patients discharged after completing the study protocol with 2 negative CT scan results were admitted 2 and 8 days later with symptomatic subdural hematomas; neither received surgery. Two of the 5 patients with delayed bleeding at 24 hours had an initial international normalized ratio greater than 3.0, as did both patients with delayed bleeding beyond 24 hours. The relative risk of delayed hemorrhage with an initial international normalized ratio greater than 3.0 was 3.4 (95% confidence interval 4 to 49).

Conclusion: For patients receiving warfarin who experience minor head injury and have a negative initial head CT scan result, a protocol of 24-hour observation followed by a second CT scan will identify most occurrences of delayed bleeding. An initial international normalized ratio greater than 3 suggests higher risk. [Ann Emerg Med. 2012;59:451-455.]

Please see page 452 for the Editor's Capsule Summary of this article.

A podcast for this article is available at www.annemergmed.com.

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SEE EDITORIAL, P. 457.

INTRODUCTION

Background

The indications for computed tomography (CT) scanning in the setting of minor head injury have been the focus of substantial research.[1-3] Long-term oral anticoagulation has been identified as a significant risk factor for intracranial injury,[4-6] and CT scanning is generally recommended for such patients regardless of clinical presentation.[7-10,13] However, it remains unclear whether such patients should then be hospitalized for observation or undergo a later second CT scan.[2,3,11-15] Oral anticoagulant therapy is prescribed to prevent thromboembolic complications of atrial fibrillation, deep venous thrombosis, and surgically placed cardiac valves.[16]

Importance

A 2002 guideline from the European Federation of Neurological Societies recommends that all anticoagulated patients with minor head injury receive an initial CT scan, admission for a 24-hour period of close neurologic observation, and then a second CT scan before discharge. It remains controversial whether this protocol should apply to all anticoagulated patients with minor head injury or perhaps just those with advanced age, more significant trauma, or greater comorbidity or anticoagulation.[16-19]

Goals of This Investigation

We evaluated the incidence of delayed intracranial bleeding in anticoagulated patients after a minor head injury who were

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Minor head injury in anticoagulated patients: Outcomes and analysis of clinical predictors. A prospective study

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ABSTRACT
Background: The optimal management of patients taking oral anticoagulants who experience minor head injury (MHI) is unclear. The availability of validated protocols and reliable predictors of prognosis would be of great benefit. We investigated clinical factors as predictors of clinical outcomes and intracranial injury (ICI).
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 primary outcome was the occurrence of MHI related death or re admission to ED at day +30. The secondary outcome was the rate of delayed ICI (dICI), defined as second positive CT scan after a first negative CT scan. We assessed some clinical predictors derived from guidelines and clinical prediction rules as potential risk factors for the outcomes.
Results: 450 patients with a negative first CT scan who underwent a second CT scan composed our study population. The rate of the primary outcome was 4%. The rate of the secondary outcome was 4.7%. Upon univariate and multivariable analysis no statistically significant predictors for the outcomes were found.
Conclusions: Previous retrospective studies showed a lot of negative predictive factors for anticoagulated patients suffering a minor head injury, in our prospective study no clinical factors emerged as predictors of poor clinical outcomes and dICI. So, even if we confirmed a low rate of adverse outcomes, the best management of these patients in ED remains not so clear and future trials are needed.

1. Introduction

Best management of patients incurring in minor head injury (MHI) while undergoing chronic anticoagulation is a controversial and debated clinical problem [1-7]. Finding a point of equilibrium between caution and avoiding unnecessary radiological examinations and/or in-hospital observation is still a conundrum. In this context, the availability of validated protocols and reliable predictors of prognosis would be of great benefit, in particular, after a first CT-scan [8-11] it remains unclear whether such patients should then be hospitalized for observation and/or undergo a later second CT scan [12-15], given the increase of risk for intracranial injury (ICI; linked to anticoagulation [16,17].

A 2002 guideline from European federation of Neurological Societies (EFNS) recommends that all anticoagulated patients with MHI should receive an initial CT scan, admission for a 24-h period of close neurologic observation, and then a second CT scan before discharge [18]. In 2012, we tested this guideline on 87 patients receiving warfarin without intracranial lesions on a first CT scan, finding a rate of 6% of delayed ICI (dICI), defined as a second positive head CT scan after a first negative head CT scan [19]. Unfortunately, statistical power was insufficient to analyze multivariable predictors of ICI. Since then, some systematic reviews (SRs) [20-25] have been published, reporting a lower incidence of dICI (0.5–2%). However, most published studies were retrospective and did not report clinical data of the patients. A well-powered prospective cohort study is needed to estimate risk of dICI and identify clinical factors predictive of adverse outcomes.

We measured the incidence of death, admission in hospital, neurosurgery, re-admission to ED, dICI and ICI at the first or second CT in anticoagulated patients following a MHI, who were treated according to EFNS guidelines in our Emergency Department Observational Unit

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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

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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. The 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% (85.0–96.0%); glial fibrillary protein (GFP) 100% (93.2–100%); TBI 100% (96.4–100%). 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 (C-CHL-1); glial fibrillary acidic protein (GFAP); anticoagulated patients

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

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Giovanni Pomponio, Clinica Medica, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy

Journal of Clinical Medicine
MDPI
Review

Traumatic brain injury in patients under anticoagulant therapy: management in Emergency Department. A review.

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Abstract: For original research articles, systematic reviews and meta-analyses, the abstract should be an objective representation of the article and consist of about 250 words. It must not contain results that have not been substantiated in the main text and should not exaggerate the main conclusion. The abstract should be structured to contain the following headings. **Background/Objectives:** highlight the purpose of the study, introduce your research question(s), and the context surrounding them. **Methods:** describe the main methods or treatments applied, highlighting any unique characteristics of the participant/patient samples. Include any relevant preregistration numbers. Clinical trials should include details that CONSORT has identified as essential. **Results:** summarize the article's main findings. **Conclusions:** describe the main takeaways and interpretations of the study. For other article types, such as Reviews, a 200 word unstructured abstract should be included.

Keywords: keyword 1; keyword 2; keyword 3 (List three to ten pertinent keywords specific to the article yet reasonably common within the subject discipline.)

1. Background

1.1 Definition and epidemiology

Traumatic brain injury (TBI) is the alteration in the normal function of the brain provoked by crash, blow, jerk to the head, or penetrating injury [1]. It differs in severity from mild (mTBI), accounting for 80% of cases, to moderate (moTBI) and severe TBI (sTBI) [2]. The economic and social burden of TBI is substantial and multifaceted, encompassing both direct and indirect costs, approximately estimated around $400 billion annually [3], which impact individuals, families and society at large. Moreover, individuals with TBI frequently require immediate diagnostic workout and treatment in Emergency Department (ED) [4].

Managing traumatic brain injury in patients who are anticoagulated, principally for the prevention of ischemic stroke in atrial fibrillation and for the treatment of acute venous thromboembolism, presents unique challenges and requires careful consideration to balance the risks of bleeding with the risk of thrombosis. The high prevalence (up to 2.4%) of these patients among the adult population, makes it of great relevance to public health and the routine activities of emergency professionals [5]. The proportion of patients with TBI on oral anticoagulation (OAT) is steadily increasing and now it is estimated to be up to 38% [5], the prevalence of intracranial injury in this cohort has been reported between 5 and 20% [6]. For many years, vitamin K antagonists (VKAs) were the most widely used OAT [7], but now direct oral anticoagulants (DOAs), apixaban, edoxaban, rivaroxaban and dabigatran, are largely prescribed [8]. The most effective and safest management of

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Significative clinical outcomes

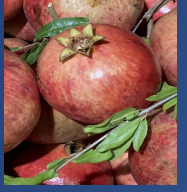
- Acute traumatic Intra-cranial Injury (ICI):
subdural, epidural, parenchymal hematoma, subarachnoid hemorrhage, cerebral contusion, depressed skull fracture minor lesions or minimal intracranial bleeding (minor lesions)

- Delayed ICI (dICI):
ICI occurred after > 24 hours (and after a negative first head CT scan, if done)

- death

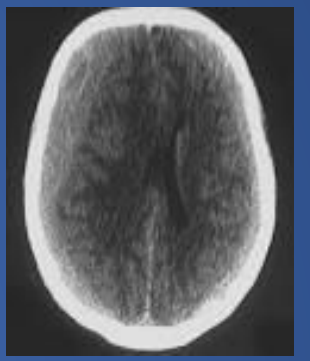
- operative neurosurgery

- MHI related re-admission to ED within 30 days from MHI



Actual management

+



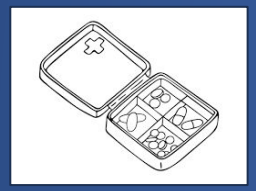
ICI

negative

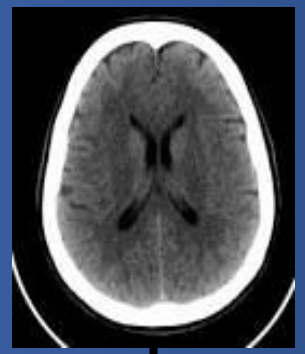
???

Options of management: always 2 CT scans

+



First CT scan

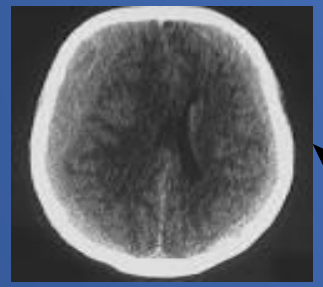


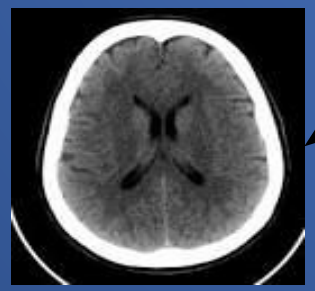
negative

Observation

Second CT scan

dICI



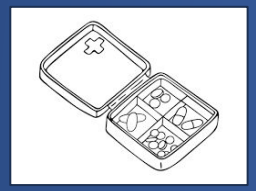


negative

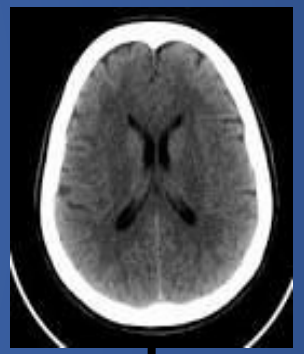
Discharge

Options of management: observation

+



First CT scan



negative

Observation

Symptons

NO

Discharge

???

dICI

Second CT scan

YES

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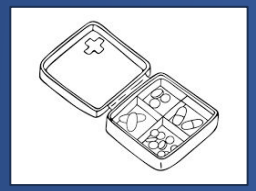
Options of management: one CT scan

+



First CT scan

negative

Discharge

???

dICI

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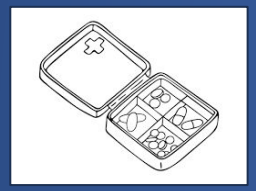
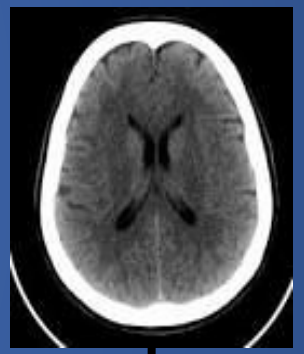
Options of management: predictors

+



First CT scan



negative

Predictors

Positive

NO

Discharge

???

dICI

YES

Second CT scan

The problem of the guidelines: the "sensitive" GLs

- ✔ European Federation of the Neurological Societies (EFNS) GLs:
  head CT scan: in case of normal CT, considering observation of 24 hours, consulting neurotrauma center and repeating CT scan

- ✔ Scandinavian GLs:
  head CT scan and 24 hours observation: in the case of neurological deterioration and/or GCS (≥2 points) repeating CT scan

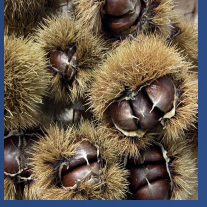
- ✔ 2023 NICE GLs:
  head CT scan: in case of absence of other injuries or high energy traumas (and supervision at home and low risk of further falls) then discharge

Vos PE, et al. Mild traumatic brain injury. Eur J Neurol. 2012;19(2):191-198
Undén J, et al. 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
Head injury: assessment and early management NICE Guideline, No. 232 London: National Institute for Health and Care Excellence (NICE); 2023 May 18. ISBN-13: 978-1-4731-5026-3

The problem of the guidelines: the "specific" GLs

- ✔ To date, there aren't specific guidelines on TBI patients on anticoagulants
- ✔ Only few studies focused specifically on recommendations regarding TBI :
  - An interdisciplinary group of Austrian experts
  - The Brain Injury GL (BIG): patients on warfarin are allocated to the most severe tertile (BIG3)

Wiegele M, et al.E. Diagnostic and therapeutic approach in adult patients with traumatic brain injury receiving oral anticoagulant therapy: an Austrian interdisciplinary consensus statement. Crit Care. 2019;23(1):62.
Gallagher SP, et al. Modified BRAIN INJURY GUIDELINE for pre-injury anticoagulation in traumatic brain injury: an opportunity to reduce healthcare resource utilization. J Trauma Acute Care Surg. 2024 Feb 1;96(2):240-246.



The problem of the Clinical Decision Rules: the "sensitive" CDRs

- ✔ No specific decision rule dedicated only to OAT patients with mTBI is currently available
- ✔ In the two main validated CDRs - the Canadian CT Head Rule (CCHR) and the New Orleans Criteria (NOC) OAT was an exclusion criterion

Stiell IG, et al. The Canadian CT Head Rule for patients with minor head injury. Lancet. 2001;357(9266):1391-1396.
Haydel MJ, et al. Indications for computed tomography in patients with minor head injury. N Engl J Med. 2000;343(2):100-105.
Alzuhairy AKA. Accuracy of Canadian CT Head Rule and New Orleans Criteria for Minor Head Trauma; a Systematic Review and Meta-Analysis. Arch Acad Emerg Med. 2020;8(1):e79.

The problem of the Clinical Decision Rules: the "specific" CDRs from retrospective studies

Clinical predictor	OAT	Only DOA
Post-traumatic amnesia	Cipriano, Turcato 2022	Turcato 2021
Signs of trauma above the clavicles	Cipriano, Turcato 2022	Cipriano, Turcato 2021, Park
Major dynamics	Turcato 2022	Turcato 2021, Park
Post-traumatic transitory loss of consciousness	Turcato 2022	Turcato 2021, Park
GCS score <15	Turcato 2022	Turcato 2021, Park
Post-traumatic headache	/	Turcato 2021, Park
Previous neurosurgery	/	Turcato 2021, Park
Post-traumatic vomiting	/	Park

Cipriano A, et al. Predictors of post-traumatic complication of mild brain injury in anticoagulated patients: DOACs are safer than VKAs. Intern Emerg Med. 2021;16(4):1061-1070
Turcato G, et al. Risk factors associated with intracranial bleeding and neurosurgery in patients with mild traumatic brain injury who are receiving direct oral anticoagulants. Am J Emerg Med. 2021;43:180-185
Park N, et al. Multi-centric study for development and validation of a CT head rule for mild traumatic brain injury in direct oral anticoagulants: the HERO-M nomogram. BMC Emerg Med. 2023;23(1):122
Turcato G, et al. Decision tree analysis for assessing the risk of post-traumatic haemorrhage after mild traumatic brain injury in patients on oral anticoagulant therapy. BMC Emerg Med. 2022;22(1):47

Predittori di esito nei pazienti con trauma cranico lieve in terapia con anticoagulanti

ARTICLE IN PRESS

TRAUMA/SYSTEMATIC REVIEW/META-ANALYSIS

Should Adults With Mild Head Injury Who Are Receiving Direct Oral Anticoagulants Undergo Computed Tomography Scanning? A Systematic Review

Gordon W. Fuller, MBChB, PhD*; Rachel Evans, MBBS; Louise Preston, PhD; Helen B. Woods, MSc; Suzanne Mason, PhD

*Corresponding Author. E-mail: g.fuller@sheffield.ac.uk.

Study objective: Patients receiving direct oral anticoagulant medications commonly undergo computed tomography head scanning after mild traumatic brain injury, regardless of symptoms or signs. International guidelines have noted a lack of evidence to support management decisions for such patients. This systematic review aims to identify, appraise, and synthesize the current evidence for the risk of adverse outcome in patients receiving direct oral anticoagulants after mild head injury.

Methods: A protocol was registered with PROSPERO and review methodology followed Cochrane Collaboration recommendations. Studies of adult patients with mild head injury (Glasgow Coma Scale score 13 to 15) and who were receiving direct oral anticoagulants that reported the risk of adverse outcome after the head injury were eligible for inclusion. A comprehensive range of bibliographic databases and gray literature was examined with a sensitive search strategy. Selection of eligible studies, data extraction, and risk of bias were evaluated independently by separate reviewers. A random-effects meta-analysis was used to provide a pooled estimate of the risk of adverse outcome. The overall quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation Working Group approach.

Results: A total of 4,886 articles were screened for inclusion, of which 7 cohort studies including 346 patients met inclusion criteria. All studies were at high or unclear risk of bias as a result of selection and information bias. Estimates of adverse outcome (any death, intracranial hematoma, or neurosurgery) ranged from 0.0% to 8.3%. A random-effects meta-analysis showed a weighted composite outcome risk of 3.7% (95% confidence interval 1.7% to 5.8%; I^2=3.3%). The overall quality of the body of evidence was low as a result of imprecision, indirectness, and risk of bias.

Conclusion: There are limited data available to characterize the risk of adverse outcome in patients receiving direct oral anticoagulants after mild traumatic brain injury. A sufficiently powered prospective cohort study is required to validly define this risk, identify clinical features predictive of adverse outcome, and inform future head injury guidelines. [Ann Emerg Med. 2018;■:1 10.]

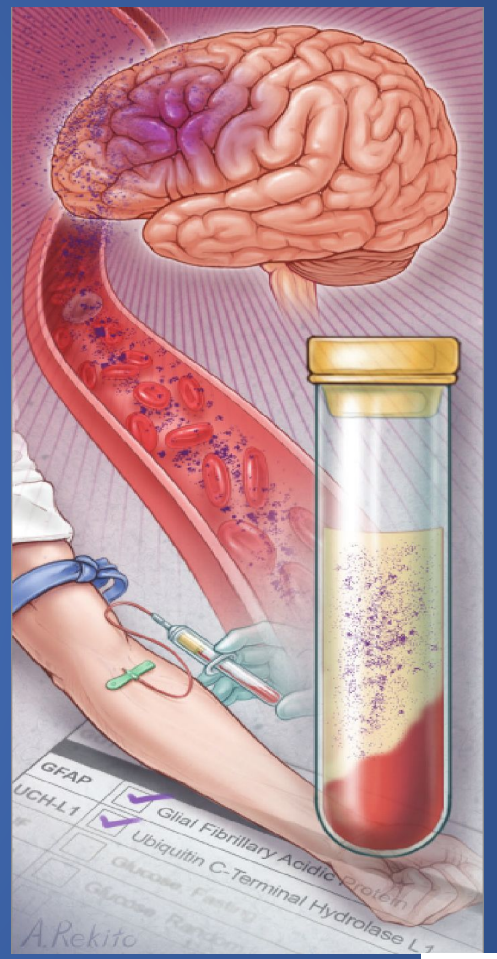
Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2018.07.020

HYPOTESIS

Could be possible to use BIOMARKERS for the RULE OUT of patients with MINOR HEAD INJURY on ANTICOAGULANT THERAPY ?



Voelker R. Taking a Closer Look at the Biomarker Test for Mild Traumatic Brain Injury. JAMA. 2018;319(20):2066-2067.

The origins

PROtein S (in) Emergency Room (of) Patients (with) Head Injury oN Anticoagulants: the PROSERPHINA STUDY

Ratto di Proserpina
Gian Lorenzo Bernini (Napoli 1598 - Roma 1680)
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Scope of the study

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Minor head injury in anticoagulated patients: Outcomes and analysis of clinical predictors. A prospective study

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ABSTRACT

Background: The optimal management of patients taking oral anticoagulants who experience minor head injury (MHI) is unclear. The availability of validated protocols and reliable predictors of prognosis would be of great benefit. We investigated clinical factors as predictors of clinical outcomes and intracranial injury (ICI).
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 primary outcome was the occurrence of MHI-related death or re-admission to ED at day 1-30. The secondary outcome was the rate of delayed ICI (dICI), defined as second positive CT scan after a first negative CT scan. We assessed some clinical predictors derived from guidelines and clinical prediction rules as potential risk factors for the outcomes.
Results: 450 patients with a negative first CT scan who underwent a second CT scan composed our 'study population'. The rate of the primary outcome was 4%. The rate of the secondary outcome was 4.7%. Upon univariate and multivariate analysis no statistically significant predictors for the outcomes were found.
Conclusions: Previous retrospective studies showed a lot of negative predictive factors for anticoagulated patients suffering a minor head injury. In our prospective study no clinical factors emerged as predictors of poor clinical outcomes and dICI. So, even if we confirmed a low rate of adverse outcomes, the best management of these patients in ED remains not so clear and future trials are needed.

1. Introduction

Best management of patients incurring in minor head injury (MHI) while undergoing chronic anticoagulation is a controversial and debated clinical problem [1–7]. Finding a point of equilibrium between caution and avoiding unnecessary radiological examinations and/or in hospital observation is still a conundrum. In this context, the availability of validated protocols and reliable predictors of prognosis would be of great benefit. In particular, after a first CT-scan [8–11], it remains unclear whether such patients should then be hospitalized for observation and/or undergo a later second CT scan [12–15], given the increase of risk for intracranial injury (ICI) linked to anticoagulation [16,17].

A 2002 guideline from European Federation of Neurological Societies (EFNS) recommends that all anticoagulated patients with MHI should receive an initial CT scan, admission for a 24-h period of close neurologic observation, and then a second CT scan before discharge [18]. In 2012, we tested this guideline on 87 patients receiving warfarin without intracranial lesions on a first CT scan, finding a rate of 6% of delayed ICI (dICI), defined as a second positive head CT scan after a first negative head CT scan [19]. Unfortunately, statistical power was insufficient to analyze multivariable predictors of ICI. Since then, some systematic reviews (SRs) [20–25] have been published, reporting a lower incidence of dICI (0.5–2%). However, most published studies were retrospective and did not report clinical data of the patients. A well-powered prospective cohort study is needed to estimate risk of dICI and identify clinical factors predictive of adverse outcomes.

We measured the incidence of death, admission in hospital, neurosurgery, re-admission to ED, dICI and ICI at the first or second CT in anticoagulated patients following a MHI, who were treated according to EFNS guidelines in our Emergency Department Observational Unit

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0735-6757/

The purpose of this study was the incidence of significative clinical outcomes in anticoagulated patients following a MHI, who were treated according to EFNS guidelines in our Emergency Department Observational Unit (EDOU). We prospectively assessed a number of well-known clinical predictors for poor clinical outcomes, ICI and dICI

Menditto VG, Moretti M, Babini L, Sampaolesi M, Buzzo M, Montillo L, Raponi A, Riccomi F, Marcosignori M, Rocchi M, Pomponio G. Minor head injury in anticoagulated patients: Outcomes and analysis of clinical predictors. A prospective study. Am J Emerg Med. 2024;76:105-11

Outcomes of the study

Primary outcome:
the cumulative rate of MHI-related death or MHI related re-admission to ED at day +30 in the study population

Secondary outcomes:
the rate of dICI in the study population
the rate of ICI (on the first or the second CT scan) and of MHI-related death or MHI related re-admission to ED at day +30 in all enrolled patients

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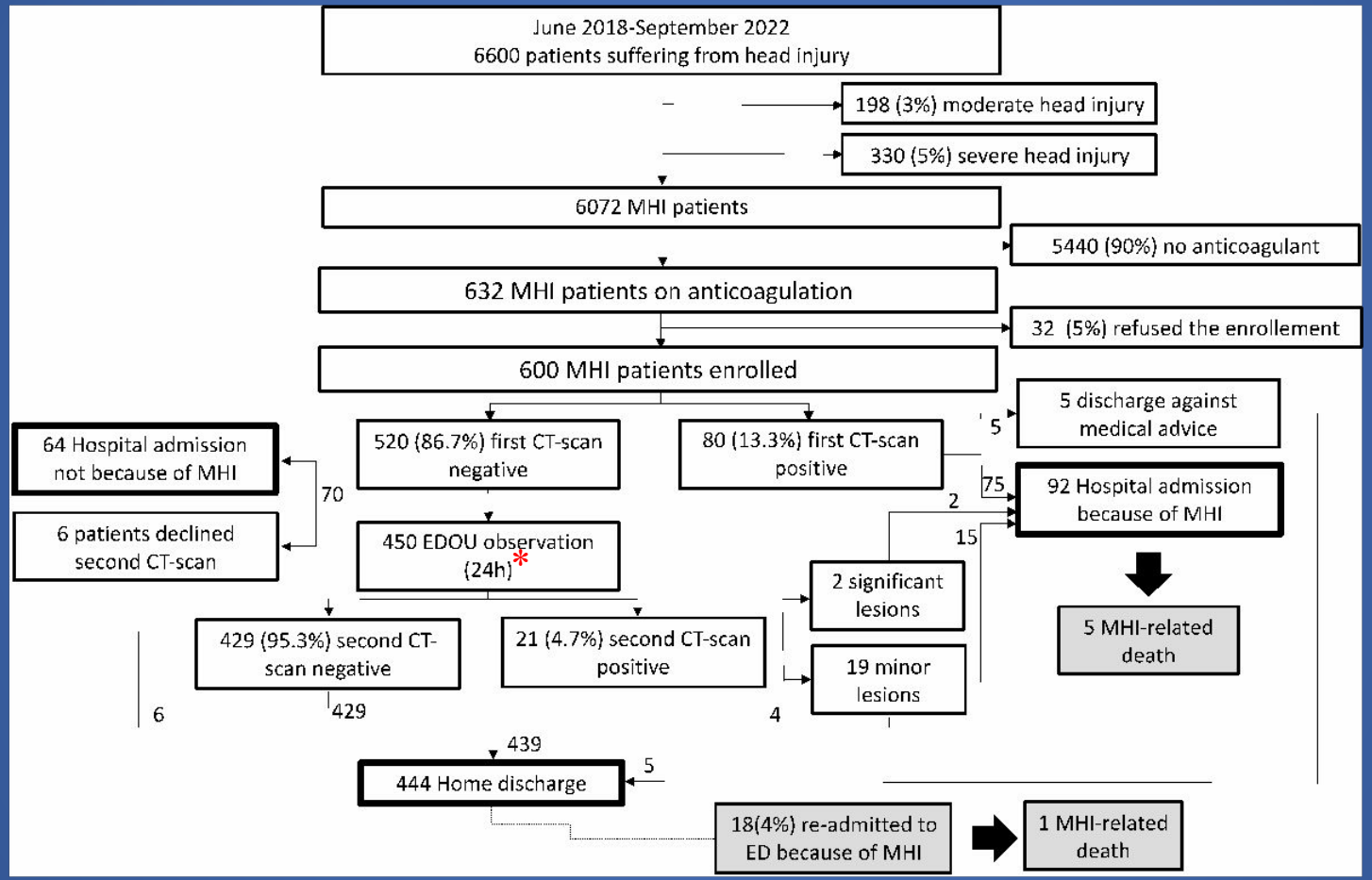
Results of the study



* study population

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Results of the study

Characteristic	Value
Demographic characteristics	*n* = 450
Age years mean (SD)	82.1 (8.7)
Sex No. (%)	
M	218 (48.4)
F	232 (51.6)
GCS No. (%)	
15	445 (98.9)
14	5 (1.1)
Comorbidities No. (%)	
Coagulopaty	2 (0.4)
Hypertension	329 (73.1)
Previous TIA/stroke	45 (10)
Chronic liver disease	5 (1.1)
Renal insufficiency	207 (46)
Diabetes mellitus	88 (19.5)
Active cancer	27 (6)
Epilepsy	24 (5.3)
History No. (%)	
Previous neurosurgery intervention	5 (1.1)
Previous endocranic bleeding	8 (1.7)
Previous endocranic post-traumatic bleeding	7 (1.5)
Anticoagulant No. (%)	
VKA	134 (29.8)
DOA	316 (70.2)
Dabigatran	26 (5.6)
Rivaroxaban	101 (22.4)
Apixaban	135 (30)
Edoxaban	55 (12.2)
Anticoagulant therapy onset month mean (SD)	49.6 (57.8)
Indication for anticoagulant therapy No. (%)	
Atrial fibrillation	380 (84.4)
Thromboembolic disease	40 (8.9)
Valvular disease	30 (6.7)
Time between onset of symptoms and enrollment hours mean (SD)	8.1 (3.7)

Management (action)	Value
Anticoagulant withdrawal No. (%)	376 (83.5)
Plasma infusion No. (%)	1 (0.2)
Prothrombin complex infusion No. (%)	0 (0)
Vitamin K infusion No. (%)	33 (7.3)
Tranexamic acid infusion No. (%)	1 (0.2)
Embolization No. (%)	0 (0)
Neurosurgery No. (%)	0 (0)
Time between 1st and 2nd CT scan hours mean (SD)	27 (6.9)
ED discharge No. (%)	433 (96)
ED discharge against medical advice No. (%)	0 (0)
Hospital admission because of MHI No. (%)	17 (3.7)
Day of anticoagulant renewall mean (SD)*	2.6 (4.2)

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Results of the study

- In the study population
  30-day overall mortality: 2%
  primary outcome: 4% (95% CI: 2.2–5.8%) 1 MHI related death and 18 MHI related readmission
  dICI: 4.7% (95% CI: 2.7–6.6%)
  No patients required operative neurosurgery

- In the enrolled population:
  30-day overall mortality: 2.5%
  MHI-related death or MHI related readmission: 5.8% (95% CI: 4.0–7.7%)
  ICI: 16.8% (95% CI: 13.8–19.8%)
  No patients required operative neurosurgery

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Results of the study

Clinical predictors: prevalence in the study population.

Clinical predictors	Study population No. (%; 95% CI)
Concomitant antiplatelet therapy	22 (4.9; 2.9–6.9)
Mechanism of injury	
Accidental	330 (73.3; 69.2–77.4)
Syncope	82 (18.2; 14.7–21.8)
Unclear	37 (8.2; 5.7–10.8)
Physical evidence of trauma above clavicles	334 (74.2; 70.2–78.3)
INR > 3 (in case of VKA)	33/132 (25.0; 17.6–32.4)
Inappropriate anticoagulant dosage (in case of DOA)	16/315 (5.1; 2.7–7.5)
Post-traumatic severe headache	2 (0.4; 0.0–1.1)
Loss of consciousness	15 (3.3; 1.7–5.0)
Post-traumatic vomiting	8 (1.8; 0.6–3.0)
Post-traumatic amnesia	10 (2.2; 0.9–3.6)
Subsequent neurologic deterioration	11 (2.4; 1.0–3.9)

- Univariate and multivariate logistic analysis could not identify any clinical factor alone or in combination as independent predictors for the primary outcome
- Only post-traumatic severe headache (OR: 5.10; 95% CI: 1.26–20.75; p = 0.02) and post-traumatic vomiting (OR: 3.44; 95% CI: 1.20–9.89; p = 0.02) correlated with ICI on the first or the second head CT scan

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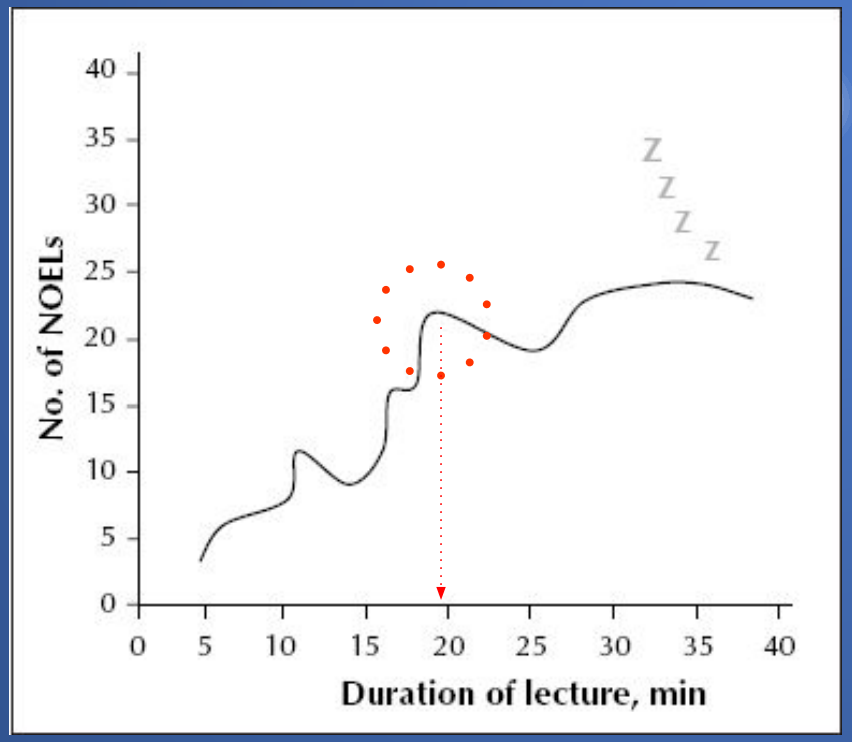
Lezioni scientifiche: il rischio di perdere l'attenzione degli astanti

CMAJ • DEC. 7, 2004; 171 (12)

Incidence of and risk factors for nodding off at scientific sessions

Kenneth Rockwood, David B. Hogan, Christopher J. Patterson; for the Nodding at Presentations (NAP) Investigators



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Incidence of and risk factors for nodding off at scientific sessions

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Table 1: Risk factors for nodding off at lectures

Factor	Odds ratio (and 95% CI)
Environmental	
Dim lighting	1.6 (0.8–2.5)
Warm room temperature	1.4 (0.9–1.6)
Comfortable seating	1.0 (0.7–1.3)
Audiovisual	
Poor slides	1.8 (1.3–2.0)
Failure to speak into microphone	1.7 (1.3–2.1)
Circadian	
Early morning	1.3 (0.9–1.8)
Post prandial	1.7 (0.9–2.3)
Speaker-related	
Monotonous tone	6.8 (5.4–8.0)
Tweed jacket	2.1 (1.7–3.0)
Losing place in lecture	2.0 (1.5–2.6)

Note: CI = confidence interval.

Scope of the study

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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

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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 (NPV) 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

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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

The purpose of this study was to assess the reliability of S100B, NSE, GFAP, UCH-L1 and Brain Trauma Indicator™ (BTI) plasma test as negative predictive tools for delayed intra-cranial injury (dICI) after MHI in patients on OAT

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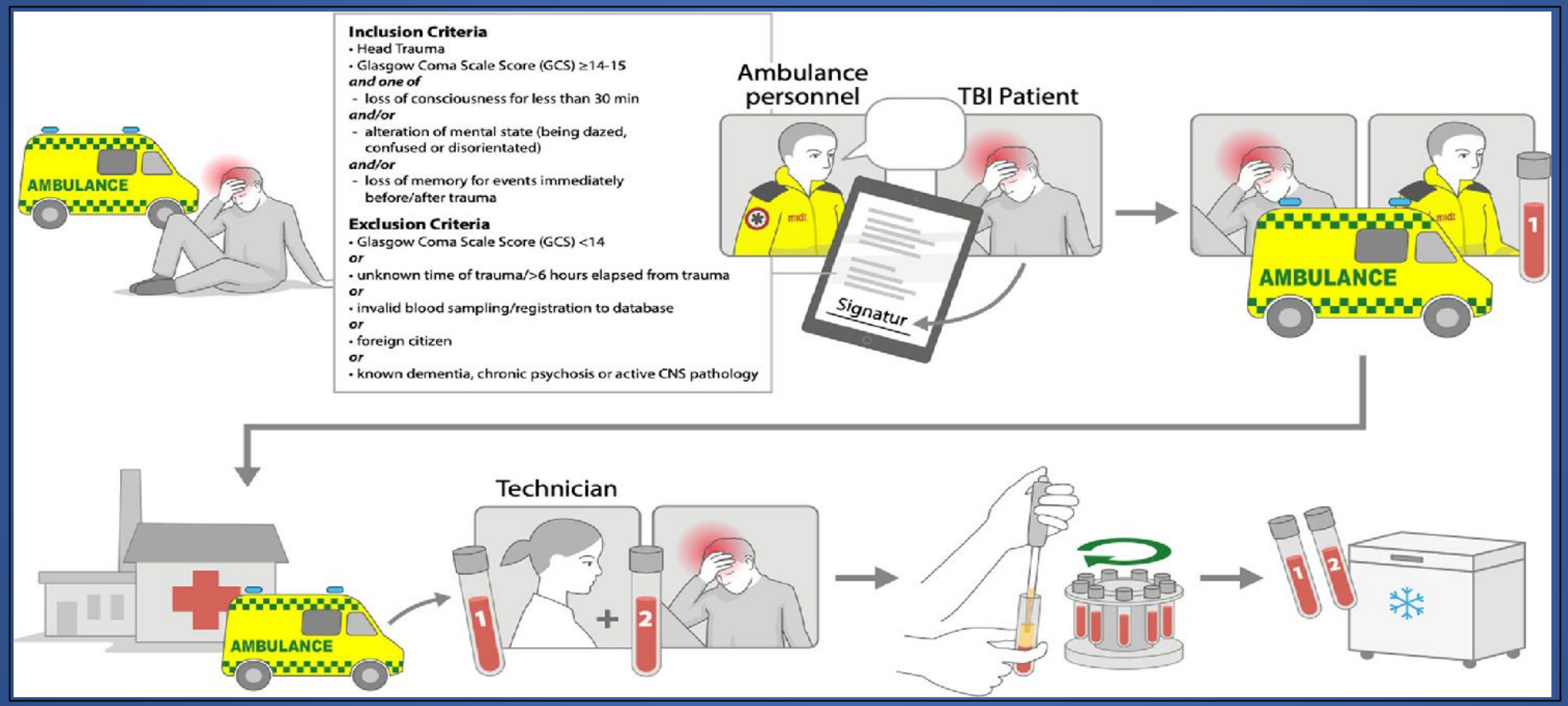
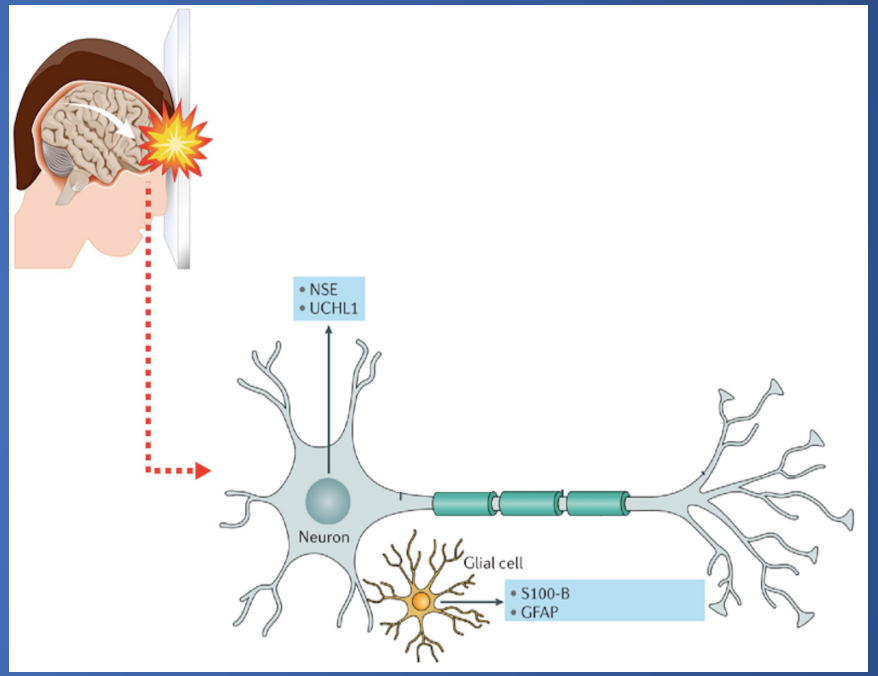
The scenario



Brain damage biomarkers

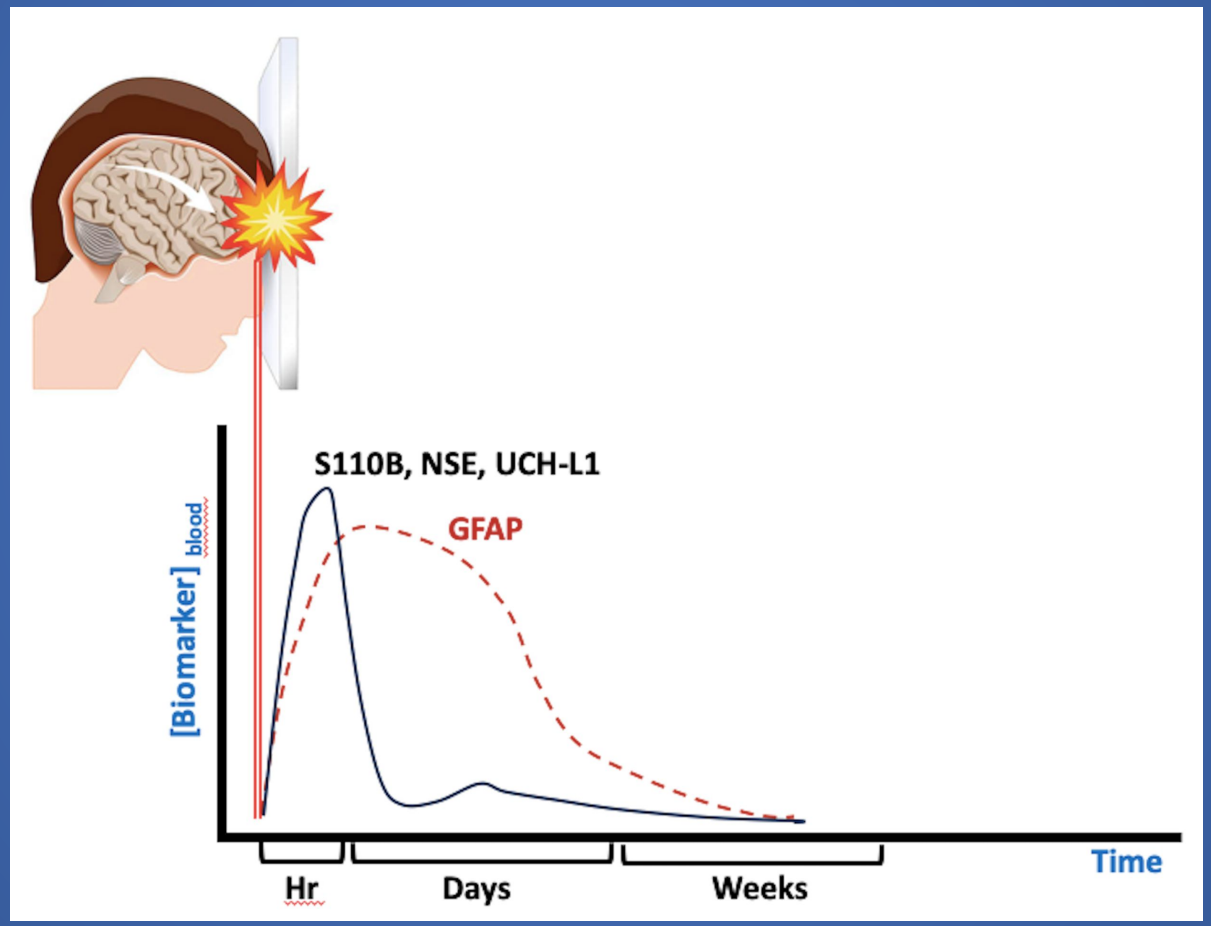
Six commonly investigated blood biomarkers:

1. S100 calcium binding protein B (S100B) [astrocytes, glia and Schwann cells]
2. glial fibrillary acidic protein (GFAP) [astrocytes]
3. ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) [neurons]
4. neuron specific enolase (NSE) [neurons]
5. neurofilament light chain (NF-L) [neurons]
6. tau protein [neurons]



Kevin K et al. (2018) An update on diagnostic and prognostic biomarkers for traumatic brain injury, Expert Review of Molecular Diagnostics, 18:2, 165-180

Brain damage biomarkers



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Methods: biomarkers

Biomarker	Limit of quantification (LoQ)	Range	Cut-off
S100B	0.02 µg/mL	0.005 - 39 µg/mL	0.105 µg/mL
NSE	0.225 ng/mL	0.075 - 300 ng/mL	14.7 ng/mL
GFAP	6.1 pg/mL	3.2 - 42000 pg/mL	35 pg/mL
UCH-L1	26.3 pg/mL	18.3 - 25000 pg/mL	400 pg/mL

The BTI plasma test (BTI) reported "not elevated" if the concentrations of both GFAP and the UCH-L1 are below their respective cut-offs

Performance measures of the study

The performance measures (ROULE OUT) of the biomarkers for the detection of dICI and ICI were:
- sensitivity (SE), specificity (SP)
- positive predictive value (PPV) and negative predictive value (NPV)

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value for biomarkers' serum level to maximize sensitivity and NPV

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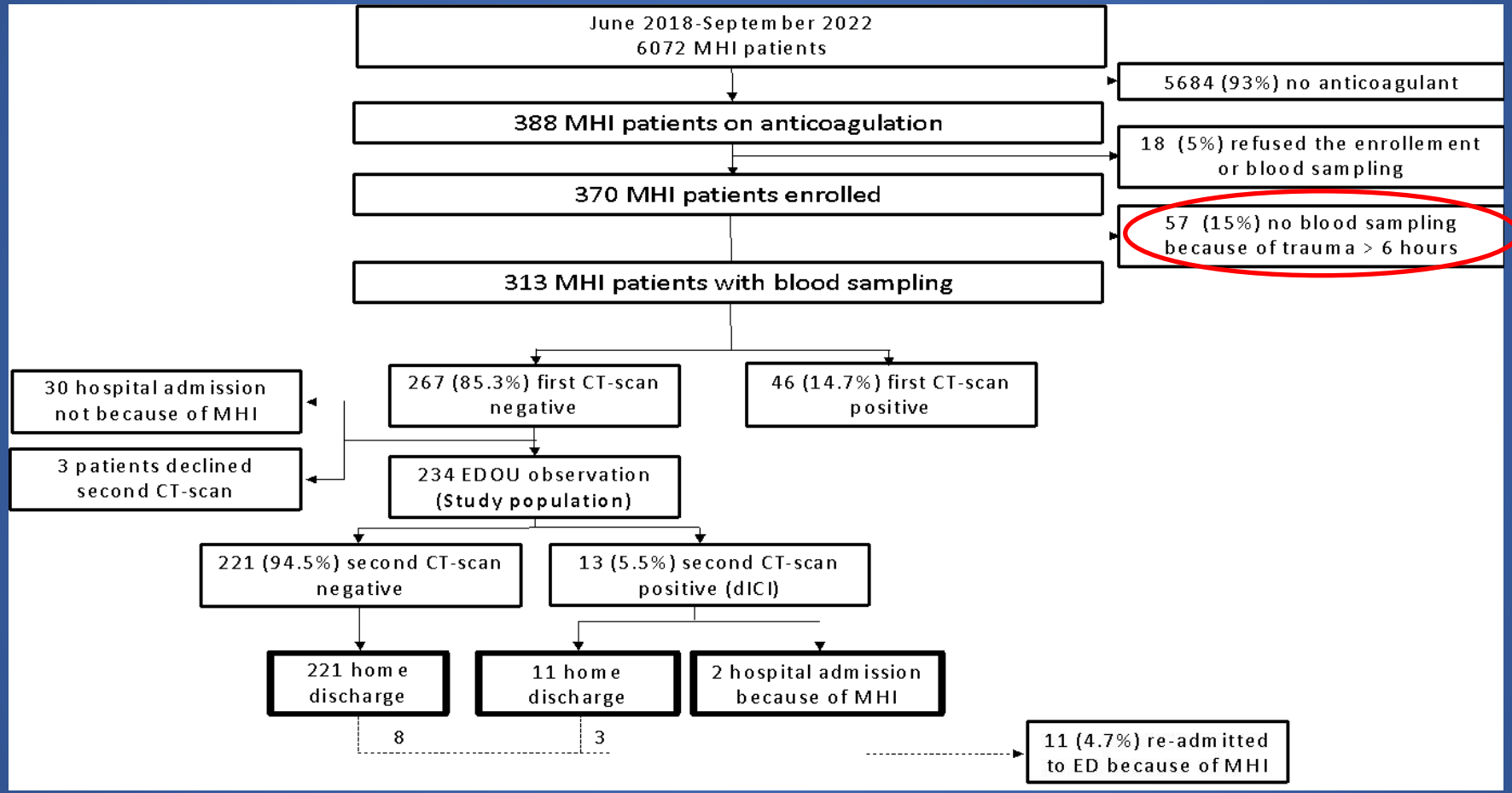
Results of the study



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Results of the study

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)

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Results of the study

Biomarker	Beyond the cut-off (%)	Sensibility % (95% CI)	Specificity % (95% CI)	VPN % (95% CI)	VPP % (95% CI)
S100B	53	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	36	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	59	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	88	100 (63.0-100)	12.3 (7.7-18.3)	100 (83.2-100)	5.3 (2.1-10.2)
BTI	95	100 (63.1-100)	5.5 (2.6-10.2)	100 (66.4-100)	4.9 (2.2-9.5)

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Results of the study

- 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 a NPV of 100.0% (95% CI: 94.9%—100.0%)

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Results of the study

- The NPV and PPV of UCH-L1 for the identification of ICI on first or second CT scan were 84.5% (95% CI 75-91.5%) and 21% (95% CI 14.5-29%), respectively
- The NPV and PPV of GFAP for the identification of ICI on first or second CT scan were 95.8% (95% CI 79-99.9%) and 20.7% (95% CI 15.2-27.1%), respectively
- The NPV and PPV of BTI for the identification of ICI on first or second CT scan were 90.9% (95% CI 58.7-99.8%) and 19.4% (95% CI 14.2-25.5%), respectively

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Discussion

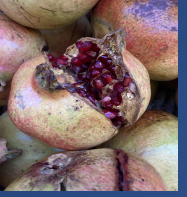
- ✔ Many studies evaluated mTBI in anticoagulated patients, but they are retrospective; our study, as a recent cohort by Uccella et al., showed data from prospective cohort
- ✔ We confirmed that the risk of ICI after mTBI in anticoagulated patients is not neglectable (13%) and similar to that reported in a recent sytematic review (9.4%) by Karamian et al.
- ✔ We didn't find that DOAs were associated with a reduced risk of ICI compared to the use of VKAs as presented in a recent sytematic review (OR of 0.44) by Santing et al.
- ✔ We presented for the first time data about the performance of 4 brain damage biomarkers in anticoagulated patients after a mTBI, in a moment in which only one study concerning S100B was available

Karamian A, et al. Incidence of intracranial bleeding in mild traumatic brain injury patients taking oral anticoagulants: a systematic review and meta-analysis. J Neurol. 2024 doi: 10.1007/s00415-024-12424-y
Uccella L, et al. Use of the Canadian CT head rule for patients on anticoagulant/anti-platelet therapy presenting with mild traumatic brain injury: prospective observational study. Front Neurol. 2024 doi: 10.3389/fneur.2024
Kobeissy F, et al. The game changer: UCH-L1 and GFAP-based blood test as the first marketed in vitro diagnostic test for mild traumatic brain injury. Expert Rev Mol Diagn. 2024;24(1-2):67-77
Santing JAL, et al. Mild Traumatic Brain Injury in Elderly Patients Receiving Direct Oral Anticoagulants: A Systematic Review and Meta-Analysis. J Neurotrauma. 2022;39(7-8):458-72

Take home messages

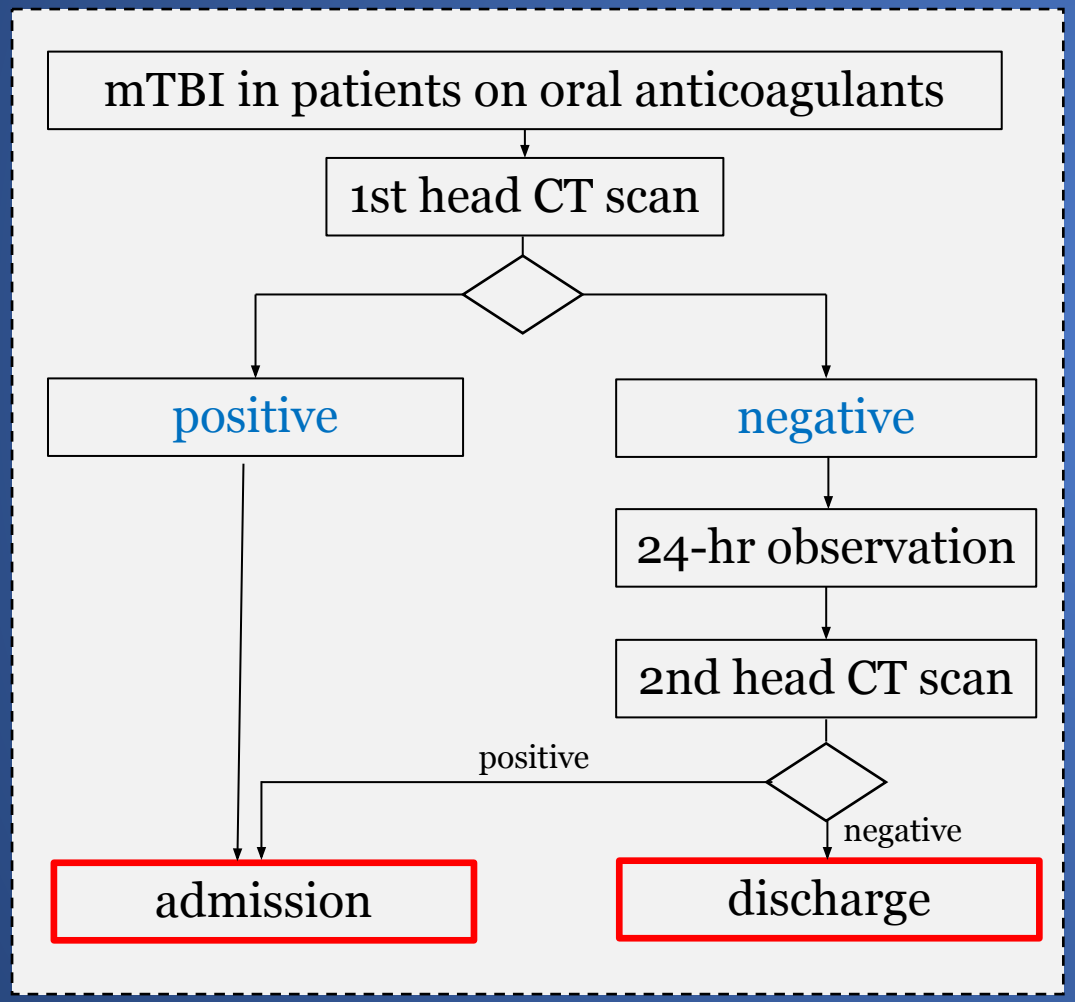
- ✔ Managing TBI in patients who are anticoagulated presents unique challenges and requires careful consideration to balance the risks of bleeding with the risk of thrombosis
- ✔ We confirmed that the mortality and the need of neurosurgery were low in anticoagulated patients after a mTBI, however the community of clinicians have not yet reached a consensus on the 'acceptable' risk threshold
- ✔ One of the most controversial issue is the selection of those patients who really benefit from prolonged observation and repeat CT scan: checking a combination of clinical predictors and biomarkers, such as GFAP, after a first negative CT scan, could be effective and reduce unnecessary resource wasting, without missing dICI

Menditto VG et al. 2024 Traumatic Brain Injury in Patients under Anticoagulant Therapy: Management in Emergency Department. A Review. In Press

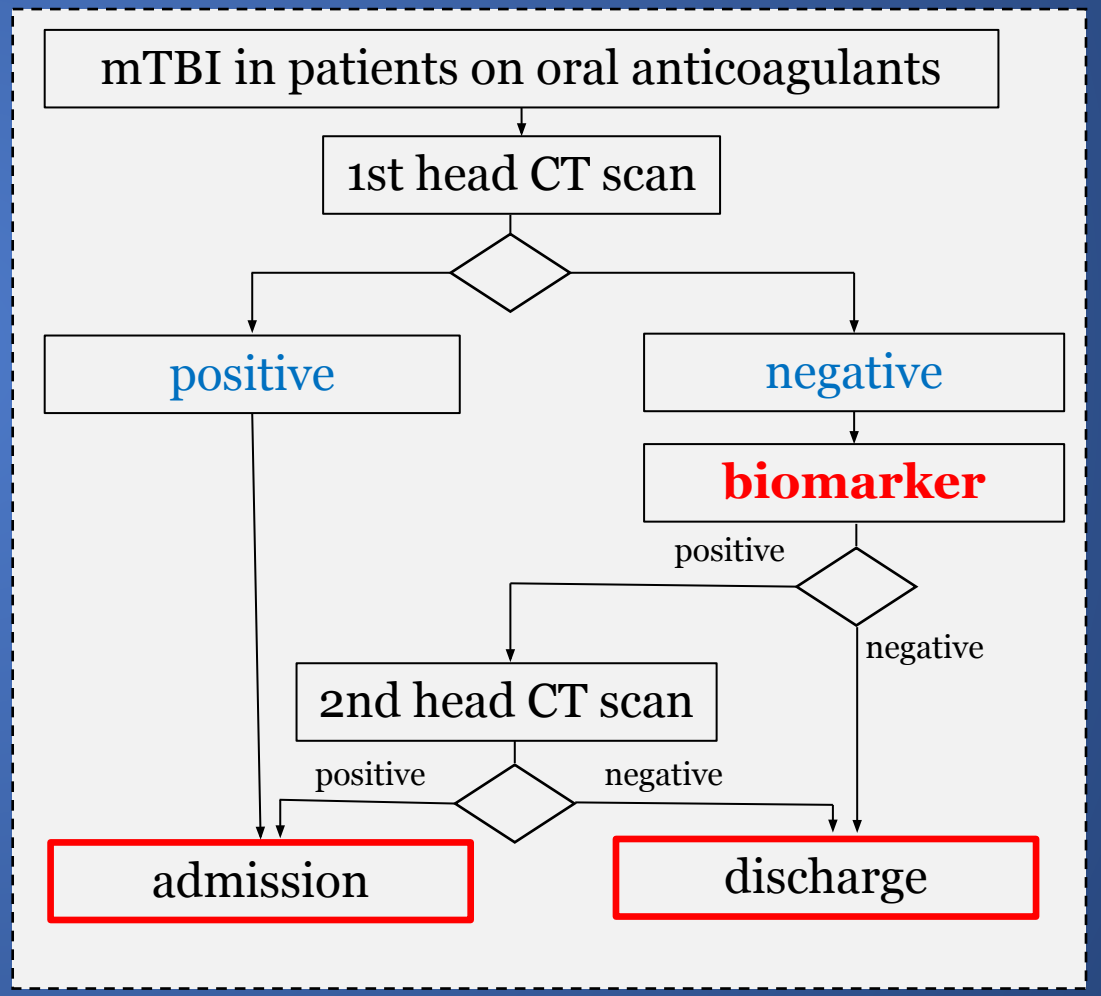


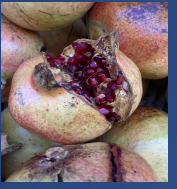
Future perspectives

Before inclusion of the biomarker



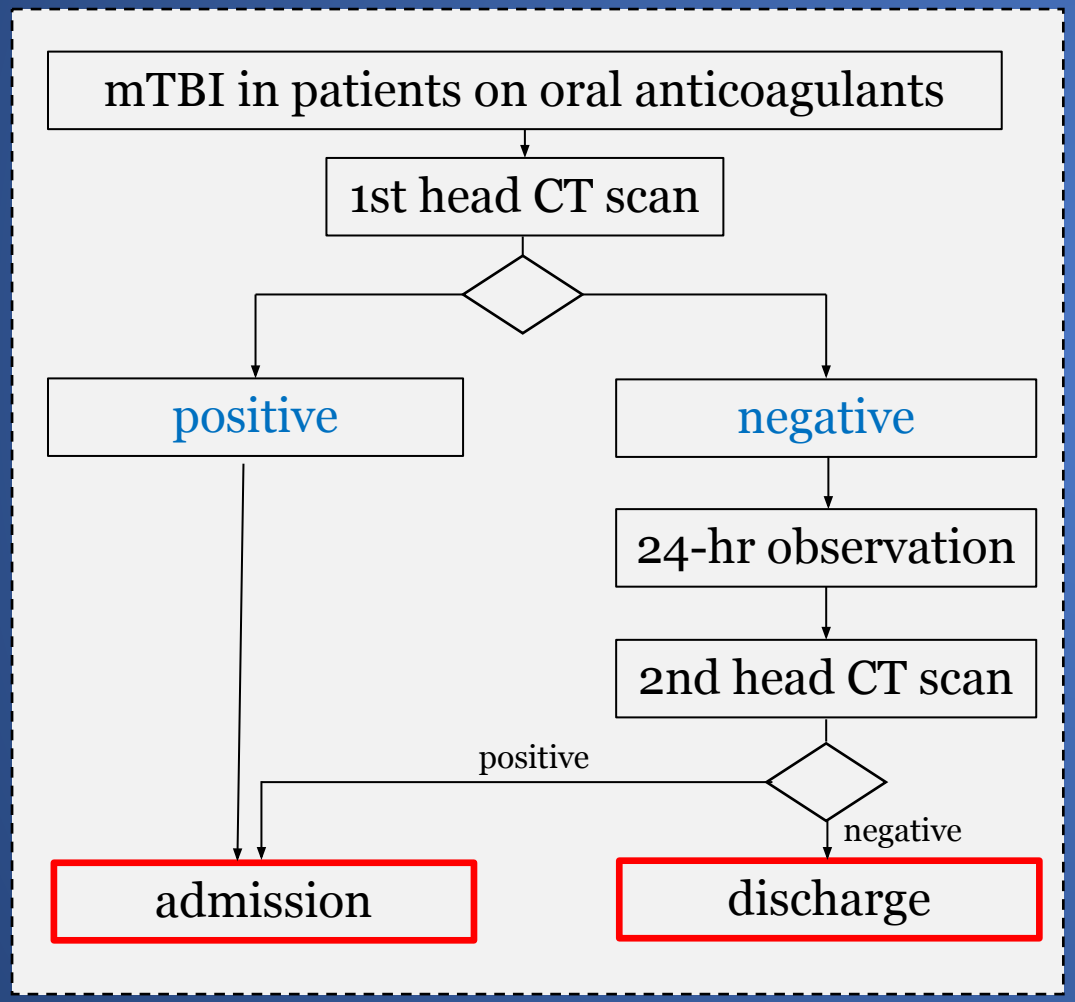
With the inclusion of the biomarker



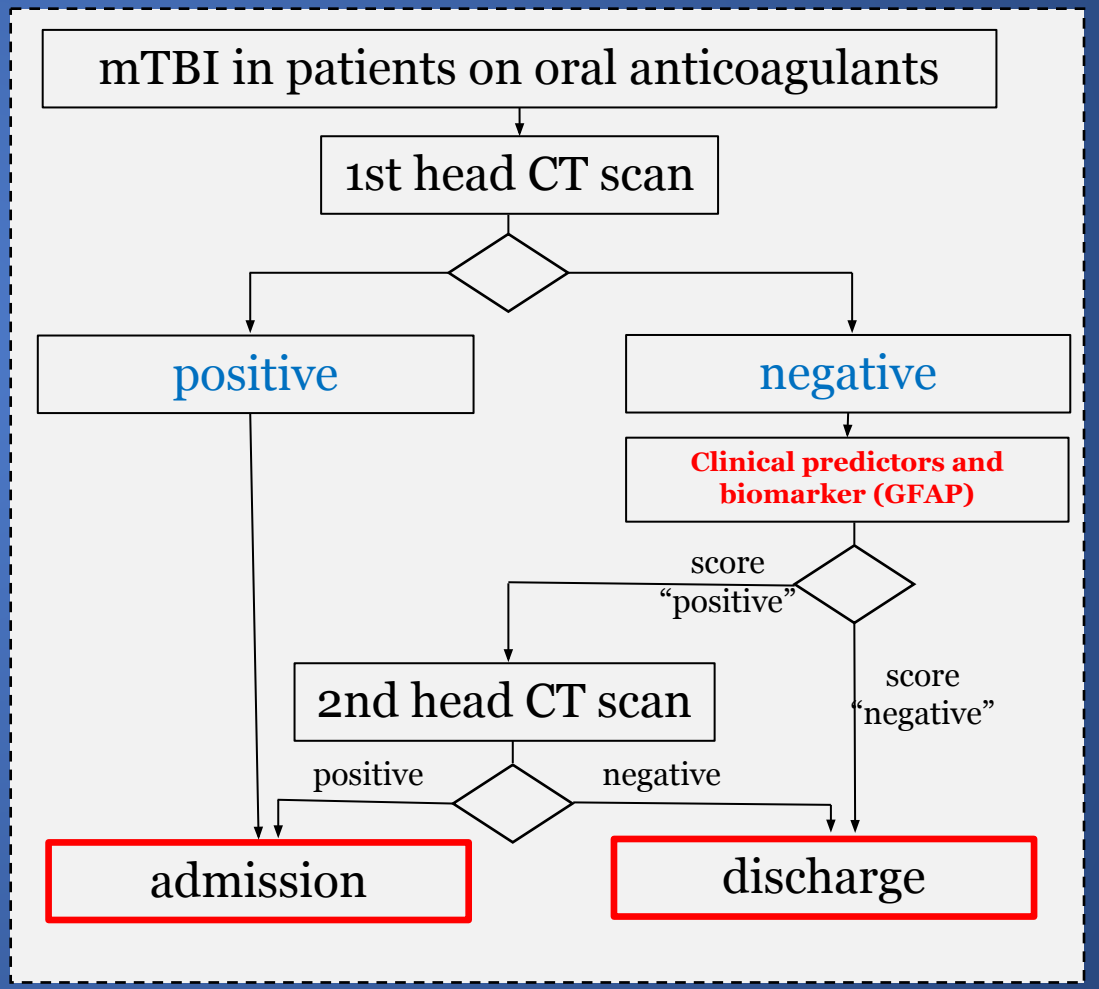


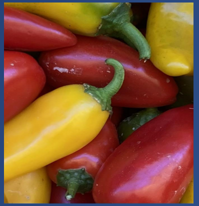
Future perspectives

Before inclusion of the biomarker



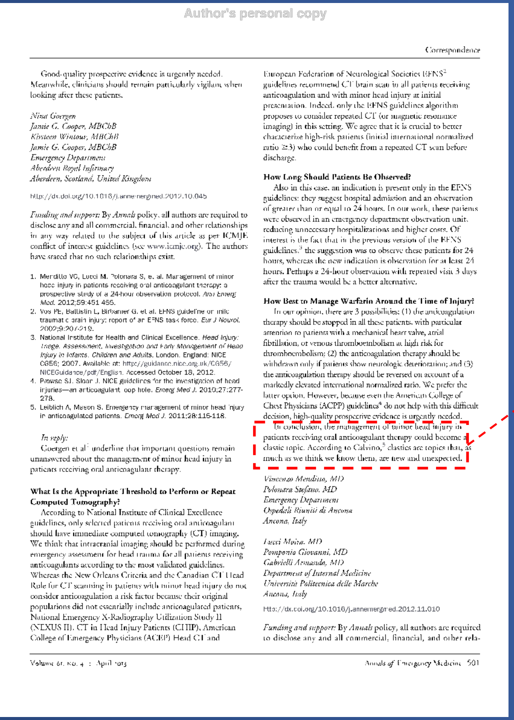
With the inclusion of the predictors





Predittori di esito nei pazienti con trauma cranico lieve in terapia con anticoagulanti

Conclusion



Good-quality prospective evidence is urgently needed. Meanwhile, clinicians should remain particularly vigilant when looking after these patients.

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In reply:

Goergen et al[1] underline that important questions remain unanswered about the management of minor head injury in patients receiving oral anticoagulant therapy.

What Is the Appropriate Threshold to Perform or Repeat Computed Tomography?

According to National Institute of Clinical Excellence guidelines, only selected patients receiving oral anticoagulant should have immediate computed tomography (CT) imaging. We think that intracranial imaging should be performed during emergency assessment for head trauma for all patients receiving anticoagulants according to the most validated guidelines. Whereas the New Orleans Criteria and the Canadian CT Head Rule for CT scanning in patients with minor head injury do not consider anticoagulation a risk factor because their original populations did not essentially include anticoagulated patients, National Emergency X-Radiography Utilization Study II (NEXUS II), CT in Head Injury Patients (CHIP), American College of Emergency Physicians (ACEP) Head CT and European Federation of Neurological Societies EFNS[2] guidelines recommend CT brain scan in all patients receiving anticoagulation and with minor head injury at initial presentation. Indeed, only the EFNS guidelines algorithm proposes to consider repeated CT (or magnetic resonance imaging) in this setting. We agree that it is crucial to better characterize high-risk patients (initial international normalized ratio ≥3) who could benefit from a repeated CT scan before discharge.

How Long Should Patients Be Observed?

Also in this case, an indication is present only in the EFNS guidelines: they suggest hospital admission and an observation of greater than or equal to 24 hours. In our work, these patients were observed in an emergency department observation unit, reducing unnecessary hospitalizations and higher costs. Of interest is the fact that in the previous version of the EFNS guidelines,[3] the suggestion was to observe these patients for 24 hours, whereas the new indication is observation for at least 24 hours. Perhaps a 24-hour observation with repeated visit 3 days after the trauma would be a better alternative.

How Best to Manage Warfarin Around the Time of Injury?

In our opinion, there are 3 possibilities: (1) the anticoagulation therapy should be stopped in all these patients, with particular attention to patients with a mechanical heart valve, atrial fibrillation, or venous thromboembolism at high risk for thromboembolism; (2) the anticoagulation therapy should be withdrawn only if patients show neurologic deterioration; and (3) the anticoagulation therapy should be reversed on account of a markedly elevated international normalized ratio. We prefer the latter option. However, because even the American College of Chest Physicians (ACPP) guidelines[4] do not help with this difficult decision, high-quality prospective evidence is urgently needed.

In conclusion, the management of minor head injury in patients receiving oral anticoagulant therapy could become a classic topic. According to Calvino,[5] classics are topics that, as much as we think we know them, are new and unexpected.

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In conclusion, the management of minor head injury in patients receiving oral anticoagulant therapy could become a classic topic. According to Calvino, classics are topics that, as much as we think we know them, are new and unexpected.

Calvino I. Perchè leggere i classici ? 1991

XIII congresso nazionale simeu GENOVA 30 MAG - 1 GIU 2024

Menditto 31-5-2024

THANK YOU FOR YOUR ATTENTION

Hands

I observe them, and hold them. When words are not enough, they always convey pain and suffering, often a struggle, and at times hope.
I share them with you so they can speak to you too

Le osservo, le stringo e, quando le parole non sono efficaci, mi affido a loro per capire
mi descrivono sempre la sofferenza ed il dolore, spesso la lotta ed a volte mi confidano la speranza
le condivido perché parlino anche a voi

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