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Full Length Article

# Intracranial bleeding risk after minor traumatic brain injury in patients on antithrombotic drugs

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ABSTRACT

*Background:* Intracranial haemorrhage (ICH) risk after minor traumatic brain injury (mTBI) in patients on antithrombotic treatment is unclear. We compared ICH rates in mTBI patients on single, double and no antithrombotic therapy. Antithrombotic drugs encompassed vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs) and antiplatelets. Secondary aim was to identify potential predictors of ICH.

*Methods:* We retrospectively analysed consecutive adults referred to our emergency department for mTBI. All clinical information was retrieved by patients' charts review. Patients were divided in 5 groups: 1) no antithrombotic users, 2) antiplatelet users, 3) vitamin K antagonist users, 4) direct oral anticoagulants users, and 5) double antithrombotic users.

*Results:* A total of 1846 patients were enrolled, mean age 71 years (IQR 46–83); 1222 (66.2%) were in group 1, 407 (22.0%) in group 2, 120 (6.5%) in group 3, 51 (2.7%) in group 4 and 46 (2.5%) in group 5. At entry, 1387 (75.1%) patients underwent brain CT, 787 (64.4%) in group 1, 387 (95.1%) in group 2, 119 (99.2%) in group 3 and 51 (100%) in group 4 and 43 (93.5%) in group 5. ICH was documented in 36 patients (4.6%; CI 95%: 3.2–6.3) in group 1, 22 (5.9%; CI 95%: 3.6–8.5) in group 2, 5 (4.2%; CI 95%: 1.4–9.5) in group 3, 2 (3.9%; CI 95%: 0.5–13.5) in group 4 and 3 (7.0%; CI 95%: 1.5–19.1) in group 5 ($p$-value for across groups comparison = 0.86). At multivariable analysis GCS < 15 (OR 7.95 CI 95%: 3.12–20.28), post-traumatic amnesia (OR 6.49; CI 95%:3.57–11.82), vomiting (OR 4.45 CI 95%:1.47–13.50), clinical signs of cranial fractures (OR 8.41 CI 95%: 2.12–33.33), scalp lesions (OR 2.31 CI 95%: 1.09–4.89), but none of antithrombotic drugs were independently associated with ICH.

*Conclusion:* mTBI-related ICH rate was similar in patients with and without antithrombotic use. Potential predictors of ICH can be drawn from patients' clinical examination.

## 1. Introduction

Traumatic brain injury (TBI) is a major public health problem accounting for the main cause of emergency department attendance in developed countries [1–4]. It is an acute complex neurologic disorder with a wide spectrum of clinical manifestations, but most cases have a Glasgow Coma Scale (GCS) score of 13 or greater and are differently categorized as minimal, minor or mild TBI according to neurological features at Emergency Department (ED) entry [5,6]. Generally, these TBI forms have a favourable clinical course and prognosis. Overall, only a minority of cases ranging from 5% to 15% harbours an acute intracranial injury that can be reliably detected by CT which for the large majority are represented by intracranial haemorrhages [7]. Actually, this rate could be even lower considering that many patients suffering a mTBI do not search for health care. Urgent neurosurgery is needed in < 1% of cases [8–11]. The fear of missing such uncommon, but life-threatening brain damages entails a growing and unrestricted brain CT prescription not always justified by an actual clinical need [12,13]. To cope with this inefficient CT use, in the last two decades, a number of prediction models to select mTBI patients who would benefit from an emergency brain CT scan have been developed [14–20]. Yet, none of these models yielded fully generalizable results due to some methodological flaws, in particular concerning the definition of mTBI, inclusion criteria, outcome assessments, and study designs [8,21]. For instance, antithrombotic drugs users who experience a mTBI are a subset of patients for whom management evidence is lacking [19]. In particular,

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whether antithrombotic drugs are independently associated with an increased risk of bleeding after a mTBI, and whether this risk differs across antithrombotic classes is unknown.

The primary goal of our investigation was to comparatively assess intracranial bleeding prevalence after mTBI with a GCS score ≥ 13 in patients treated with vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), antiplatelets and in patients not receiving antithrombotic drugs. Secondary aim was to identify potential clinical predictors for intracranial bleeding complications related to a mTBI.

## 2. Methods

### 2.1. Setting, participants and data collection

We carried out a single-center, retrospective cohort study involving all consecutive adult patients admitted to the ED of the Teaching Hospital of Varese, Italy, between January 2015 and September 2017 because of a mTBI. Patients were detected by querying ED medical electronic registry with the following descriptive diagnosis: minor TBI, minimal TBI, mild TBI, minor/minimal/mild TBI on anticoagulation therapy/VKA/DOACs and minor/minimal/mild TBI on antiplatelet therapy. We enrolled patients who fulfilled the following inclusion criteria: GCS score ranging from 13 to 15 upon ED presentation after a referred TBI and age over 18 years old. Patients receiving any regimen of low molecular weight heparin were excluded. From electronical clinical reports we collected patients baseline characteristics and TBI-related information. We tried to abstract all clinical variables that were taken into account as risk factors for mTBI-related ICH by major guidelines [14–20]. In detail, for each enrolled patient we reported age, sex, antithrombotic medication use (antiplatelet, VKA, DOAC), history of stroke/TIA/previous neurosurgical intervention, cerebral neoplastic lesion, serum INR value > 3, clinical suspicion and/or biochemical evidence of alcoholic intoxication. Antiplatelets included aspirin, ticlopidine, indobufen, clopidogrel, prasugrel, and ticagrelor. VKA included warfarin and acenocumarol. DOACs included apixaban, dabigatran, edoxaban and rivaroxaban. Double antithrombotic therapy included both a dual antiplatelet therapy and the association between an antiplatelet and an oral anticoagulant. Patients enrolled were subsequently divided into 5 groups, according to pre-TBI use of chronic antithrombotic agents: 1) no antithrombotic users; 2) single antiplatelet users; 3) vitamin K antagonist (VKA) users; 4) direct oral anticoagulants (DOACs) users; and 5) double antithrombotic users. TBI information included GCS score at ED entry, mechanism of injury and post-traumatic clinical manifestations. These latter encompassed loss of consciousness, amnesia, headache, seizures, any episode of vomiting, signs of basal skull fracture (hemotympanum, “panda” eyes, Battle's sign cerebrospinal fluid leakage from the ear or nose), focal neurologic deficits, presence of complicated contused lacerated wound (i.e. active bleeding wound and/or an extended to eye/ear/face/nasal pyramid wound), evidence of other lesions such as scalp ecchymosis and hematoma. Traumatic brain injury dynamic was defined critical when it was caused by ground-level fall from a height of more than three meters, ejection from a vehicle, vehicle overturning, death of a vehicle passenger, unseated motorcyclist from his bike and high-speed pedestrian/cyclist struck. All clinical information not reported in the ED report was assumed as negative.

The Emergency Department adopted a National guidance document drafted by a multidisciplinary workgroup (document published in Italian in a non-indexed journal) to drive the management of patients with TBI. According to this document, an urgent baseline CT scan was mandatory — for all patients with GCS 13 and 14. Conversely, traumatic brain injured patients with a GCS score of 15 were classified at low, intermediate and high risk for intracranial complications on the basis of pre- and post-TBI factors. Pre-TBI factors included alcohol and drugs intoxication, coagulopathies and anticoagulant treatments, epilepsy history and age older than 65 years. Post-TBI factors included worsening diffuse headache, loss of consciousness, vomiting, amnesia, post-traumatic seizure, trauma critical dynamic and skull fracture. Low risk for intracranial complications was defined by GCS score of 15 and no pre- and post-traumatic factors. In this case patients could be discharged without brain CT investigation. Intermediate risk for intracranial complications was defined by GCS score 15 and one of the following risk factors: retrograde amnesia, trauma critical dynamic, vomiting, suspicion for or ascertained alcohol intoxication, coagulopathies or anticoagulant treatments, worsening diffuse headache and epilepsy history. In this case a clinical observation for at least 6 h and a brain CT were suggested. In presence of coagulopathies or anticoagulant treatments a 24 h observation and a repeat CT were recommended. High risk for intracranial complications was defined by loss of consciousness and one of the following factors: headache, vomiting, post traumatic seizure, age older than 65 years with concomitant alcohol/drugs intoxication, amnesia, epilepsy or coagulopathies/anticoagulants treatments. In this case an urgent brain CT and a 24 h clinical observation were recommended. During observation a second CT was suggested if symptoms worsened or in presence of coagulopathies or anticoagulant treatments.

We reported all brain CT scan prescriptions by treating physicians after patients' clinical evaluation. We abstracted all radiological findings that were considered to be relevant for an acute intracranial bleeding lesion (bleeding contusion, acute subdural hematoma, epidural hematoma, intraparenchymal bleeding, subarachnoid haemorrhage and intraventricular haemorrhage). Given the retrospective design of the study, some patients did not undergo a brain CT because they were considered at low risk of bleeding by the treating physicians. The study was approved by the local Internal Review Board.

### 2.2. Statistical analysis

Descriptive statistics measures were used to describe baseline patient characteristics. All categorical variables were expressed as absolute (n) and relative frequencies (%). Age was reported both as median with interquartile range (IQR) and as categorical variable (more or < 65 years). We computed ICH prevalence according to the number of concomitant risk factors by distinguishing between patient baseline risk factors and trauma-related risk factors. We classified age older than 65 years, any ongoing antithrombotic treatment, history of epilepsy, history of TIA/stroke/neurosurgery, history of cerebral neoplasia and drug/alcohol intoxication as patient baseline risk factors; GCS score < 15, loss of consciousness, amnesia, vomiting, neurological signs, seizure, headache, clinical signs of skull fracture, complicated contused lacerated wound, other scalp lesions, critical dynamic as trauma-related risk factors. Cochran-Armitage trend test was applied to detect a significant increase of ICH prevalence with the number of risk factors.

Chi-square test was applied to test any difference in the baseline features between patients who did and did not undergo CT scan and to investigate a potential association between an acute intracranial bleeding complication and a pre-TBI ongoing antithrombotic monotherapy. Considering CT scanned patients, the proportion of CT positive for intracranial bleeding in each patient group, together with 95% confidence interval, was calculated. Univariate and multivariate logistic regression analysis was performed to examine patients clinical factors associated with an acute intracranial bleeding complication. Unadjusted and adjusted Odds Ratios together with 95% confidence interval were calculated. This analysis was performed twice. Once by considering the whole study population and in this case patients who did not undergo CT scan were assumed to have no intracranial bleeding complications; a second time by considering only patients who underwent brain CT. Two-tailed $p$-values < 0.05 were considered statistically significant. All statistical procedures were performed by using SAS v 9.4 software.

**Table 1**
Baseline clinical features of the overall study population and different patients' groups.

| | Study population | | No-antithrombotic use (Group 1) | | Antiplatelet use (Group 2) | | VKA use (Group 3) | | DOACs use (Group 4) | | Double antithrombotic use (Group 5) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Number of subjects | 1846 | 100.0 | 1222 | 100.0 | 407 | 100.0 | 120 | 100.0 | 51 | 100.0 | 46 | 100.0 |
| Minimal TBI | 1620 | 87.8 | 1056 | 86.4 | 365 | 89.7 | 109 | 90.8 | 47 | 92.2 | 43 | 93.5 |
| Mild TBI | 226 | 12.4 | 166 | 13.6 | 42 | 10.3 | 11 | 9.2 | 4 | 7.8 | 3 | 6.5 |
| Sex, male | 926 | 50.2 | 650 | 53.2 | 171 | 42.0 | 52 | 43.3 | 29 | 56.9 | 24 | 52.2 |
| Age > 65 years | 1042 | 56.5 | 463 | 37.9 | 115 | 95.8 | 376 | 92.4 | 46 | 90.2 | 42 | 91.3 |
| GCS score 15 | 1811 | 98.1 | 1193 | 97.6 | 402 | 98.8 | 120 | 100.0 | 50 | 98.0 | 46 | 100.0 |
| 14 | 29 | 1.6 | 23 | 1.9 | 5 | 1.2 | 0 | 0.0 | 1 | 2.0 | 1 | 2.0 |
| 13 | 6 | 0.3 | 6 | 0.5 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Loss of consciousness | 68 | 3.7 | 55 | 4.5 | 9 | 2.2 | 0 | 0.0 | 2 | 3.9 | 2 | 4.4 |
| Amnesia | 140 | 7.6 | 101 | 8.3 | 27 | 6.6 | 10 | 8.3 | 1 | 2.0 | 1 | 2.2 |
| Neurological signs | 15 | 0.8 | 10 | 0.8 | 3 | 0.7 | 1 | 0.8 | 0 | 0.0 | 1 | 2.2 |
| Seizure | 4 | 0.2 | 4 | 0.3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Headache | 31 | 1.7 | 25 | 2.1 | 5 | 1.2 | 1 | 0.8 | 0 | 0.0 | 0 | 0.0 |
| Vomiting | 30 | 1.6 | 22 | 1.8 | 5 | 1.2 | 1 | 0.8 | 0 | 0.0 | 2 | 4.4 |
| Clinical signs of cranial fracture | 12 | 0.7 | 6 | 0.5 | 3 | 0.7 | 0 | 0.0 | 1 | 2.0 | 2 | 4.4 |
| Complicated contused lacerated wound | 52 | 2.8 | 32 | 2.6 | 13 | 3.2 | 1 | 0.8 | 4 | 7.8 | 2 | 4.4 |
| INR > 3 | 36 | 2.0 | 1 | 0.8 | 0 | 0.0 | 30 | 25.0 | 0 | 0.0 | 5 | 10.9 |
| Critical dynamic | 37 | 2.0 | 31 | 2.5 | 4 | 1.0 | 0 | 0.0 | 2 | 3.9 | 0 | 0.0 |
| History of epilepsy | 29 | 1.6 | 22 | 1.8 | 5 | 1.2 | 2 | 1.7 | 0 | 0.0 | 0 | 0.0 |
| Previous stroke/TIA/neurosurgery | 98 | 5.3 | 41 | 3.4 | 40 | 9.8 | 11 | 9.2 | 3 | 5.9 | 3 | 6.5 |
| Drug/alcohol intoxication | 76 | 4.1 | 68 | 5.6 | 5 | 1.2 | 1 | 0.8 | 1 | 2.0 | 1 | 2.2 |
| History of cerebral neoplasia | 10 | 0.5 | 7 | 0.6 | 2 | 0.5 | 1 | 0.8 | 0 | 0.0 | 0 | 0.0 |
| Other scalp lesions | 1207 | 65.4 | 766 | 62.7 | 283 | 69.5 | 85 | 70.8 | 38 | 74.5 | 35 | 76.1 |
| First CT prescription | 1387 | 75.1 | 787 | 64.4 | 387 | 95.1 | 119 | 99.2 | 51 | 100.0 | 43 | 93.5 |
| Second CT prescription | 412 | 22.3 | 135 | 11.1 | 131 | 32.2 | 86 | 71.7 | 29 | 54.9 | 28 | 60.9 |

## 3. Results

A total of 1916 patients were referred to our ED for a mTBI during the study period. We excluded 48 patients because they were younger than 18 years, 18 because they were receiving different LMWH dose, and 4 because GCS score was missing. Ultimately, 1846 patients fulfilled the inclusion criteria of our analysis. The median age was 71 years (IQR 46–83) and 926 (50.1%) patients were males. A critical TBI dynamic was described in 37 (2.0%) cases. At ED entry, 1811 (98.1%) patients had a GCS score 15, 29 (1.6%) had a GCS score 14 and 6 (0.3%) had a GCS score 13. We included 1222 (66.2%) patients in group 1 (no antithrombotic therapy prior to the index event), 407 (22.0%) in group 2 (one antiplatelet agent), 120 (6.5%) in group 3 (VKAs), 51 (2.8%) in group 4 (DOACs) and 46 (2.5%) in group 5 (double antithrombotic therapy). Complete patients' characteristics at ED initial evaluation are detailed in Table 1. An urgent CT was performed in 787 (64.2%) patients of group 1, in 387 (95.1%) patients of group 2, in 119 (99.2%) patients of group 3, in 51 (100%) patients of group 4 and in 43 (93.5%) patients of group 5. Baseline characteristics of patients who did and did not undergo brain CT scan are shown in Table 2. Among patients who underwent brain CT, 68 (4.9% CI 95%: 3.9–6.2) had acute intracranial bleeding: 36 (4.6%; 95% CI: 3.2–6.3) in group 1, 22 (5.7%; 95% CI: 3.6–8.5) in group 2, 5 (4.2%; 95% CI: 1.4–9.5) in group 3, 2 (3.9%; 95%: 0.5–13.5) in group 4 and 3 (7.0%; 95%CI: 1.5–19.1) in group 5. Intracranial bleeding prevalence was similar among patient groups (Chi-square $p$-value = 0.86) (Table 3). ICH prevalence increased as the number of overall concurrent risk factors increased (Fig. 1, Cochran-Armitage Trend test $p$-value < 0.0001). This trend was confirmed when we only considered the number of trauma-related risk factors (Fig. 2, Fig. 3, Cochran-Armitage Trend test $p$-value < 0.0001). An INR value greater than three was documented in 2 out of 5 cases of intracranial bleeding on VKAs. None of the intracranial bleeding lesions required a neurosurgical treatment. Overall, only 1 patient died. He belonged to group 4 and was on dabigatran. At ED physical examination he reported bleeding leakage from the right ear and brain CT scan documented a parenchymal and subarachnoid bleeding. A second brain CT was repeated in 412 (22.3%) patients and a delayed bleeding was diagnosed in 3 cases (0.7%), two of whom belonged to group 2, one to group 1.

At multivariable analysis performed in the whole study population, the following clinical characteristics were independently associated with acute intracranial bleeding complications: GCS < 15 (OR 7.95 CI 95%: 3.12–20.28), post traumatic amnesia (OR 6.49; CI 95%: 3.57–11.82), vomiting (OR 4.45 CI 95%: 1.47–13.50), clinical signs of cranial fractures (OR 8.41 CI 95%: 2.12–33.33), and evidence of other clinical scalp lesions (OR 2.31 CI 95%: 1.09–4.89). Treatment with single antiplatelet (OR = 1.93 CI 95%: 0.98–3.80), VKAs (OR = 1.58 CI 95%: 0.55–4.54), DOACs (OR = 1.54 CI 95%: 0.33–7.16) or double antithrombotic drugs (OR = 2.11 CI 95%: 0.51–8.67) was not significantly associated with an increased risk of intracranial bleeding (Table 4). These findings, with the exception for the variable “other scalp lesions”, were confirmed at the multivariable analysis performed by considering only patients who underwent CT scan (Table 5).

## 4. Discussion

Clinical decision making in the acute setting after mTBI with GCS equal or > 13 is a controversial topic. Evidence-based data are not comprehensive to model a reliable assessment strategy for all patients and, as a result, the need of CT investigation to rule out intracranial bleeding is ultimately left to treating physicians' clinical judgement. In this defective background, inadequate data are available for some patient groups, such as those receiving antithrombotic treatment. In the attempt to tackle this unmet clinical need, we retrospectively assessed patients with and without chronic antithrombotic therapy that were referred to our ED for a mTBI during the study period. A non-negligible proportion of these traumatic events, accounting for about 30%, occurred in patients on chronic antithrombotic therapy. In clinical practice, patients suffering mTBI while on anticoagulation or on antiplatelet drugs are automatically deemed to be at high risk of bleeding, regardless of their baseline and post-traumatic clinical features. In fact, all anticoagulant and antiplatelet users (from 95.1% to 100%) were

**Table 2**
Comparison of baseline characteristics among patients who underwent or not CT.

| | Study population | | CT not performed | | CT performed | | *p*-Value* |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Number of subjects | 1846 | 100.0 | 459 | 100.0 | 1387 | 100.0 | |
| Sex, male | 926 | 50.1 | 260 | 56.6 | 666 | 48.0 | ***0.001*** |
| Age > 65 years | 1042 | 56.5 | 78 | 17.0 | 964 | 69.5 | ***< 0.0001*** |
| GCS score < 15 | 35 | 1.9 | 0 | 0.0 | 35 | 2.5 | ***0.001*** |
| Loss of consciousness | 68 | 3.7 | 5 | 1.1 | 63 | 4.5 | ***0.001*** |
| Amnesia | 140 | 7.6 | 9 | 2.0 | 131 | 9.4 | ***< 0.0001*** |
| Neurological signs | 15 | 0.8 | 0 | 0.0 | 15 | 1.1 | ***0.03*** |
| Seizure | 4 | 0.2 | 0 | 0.0 | 4 | 0.3 | 0.25 |
| DOACs use | 51 | 2.8 | 0 | 0.0 | 51 | 3.7 | ***< 0.0001*** |
| VKA use | 120 | 6.5 | 1 | 0.2 | 119 | 8.6 | ***< 0.0001*** |
| Antiplatelet use | 407 | 22.1 | 20 | 4.4 | 387 | 27.9 | ***< 0.0001*** |
| Double antithrombotic therapy | 46 | 2.5 | 3 | 0.7 | 43 | 3.1 | ***0.004*** |
| Headache | 31 | 1.7 | 4 | 0.9 | 27 | 2.0 | 0.12 |
| Vomiting | 30 | 1.6 | 2 | 0.4 | 28 | 2.0 | ***0.02*** |
| Clinical signs of cranial fracture | 12 | 0.7 | 0 | 0.0 | 12 | 0.9 | ***0.05*** |
| Complicated contused lacerated wound | 52 | 2.8 | 8 | 1.7 | 44 | 3.2 | 0.11 |
| Critical dynamic | 37 | 2.0 | 3 | 0.7 | 34 | 2.5 | ***0.02*** |
| History of epilepsy | 29 | 1.6 | 5 | 1.1 | 24 | 1.7 | 0.34 |
| Previous stroke/TIA/neurosurgery | 98 | 5.3 | 4 | 0.9 | 94 | 6.8 | ***< 0.0001*** |
| Drug/alcohol intoxication | 76 | 4.2 | 13 | 2.8 | 63 | 4.5 | 0.11 |
| History of cerebral neoplasia | 10 | 0.5 | 0 | 0.0 | 10 | 0.7 | 0.07 |
| Other lesions | 1207 | 68.1 | 263 | 57.3 | 944 | 68.1 | ***< 0.0001*** |

Bold and italics emphases for underlying variables with a statistically significant p- value.
* Chi-square test for association.

investigated by brain CT scan. Conversely, physicians were more likely to adopt a selective strategy for CT use among patients not receiving antithrombotic treatment. In about one-third of group 1 subjects, intracranial bleeding was ruled out without performing imaging tests. Factors driving the decision to request CT scan included GCS < 15, post-traumatic amnesia, age older than 65 years, male sex, loss of consciousness, the presence of neurological signs, post-traumatic vomiting, critical dynamic of trauma and a previous history of stroke/TIA/neurosurgical intervention (Table 2). By using this strategy based on clinical gestalt, the prevalence of intracranial bleeding was 4.9% (CI 95%: 3.9–6.2) and was similar between patients receiving single or double antithrombotic drugs and patients not receiving antithrombotic drugs who were considered at increased risk of post-traumatic bleeding. The prevalence of intracranial bleeding observed in this study is similar to that reported in the general population suffering mTBI [7]. Such low incidence of intracranial bleeding calls for a more structured patient selection and questions the common concept that patients on antithrombotic treatment are at high risk independently of other risk factors. This is in particular relevant to drive the decision to perform a second CT scan after an initial period of clinical observation. To date, the role of antiplatelets in predicting intracranial adverse outcomes related to mTBI is unclear. Antiplatelet use does not figure within the variables panel of the main decision-aids [14–20]. Despite the lack of good quality evidence, Scandinavian Guidelines refer antiplatelet medication as a selective criterion for CT use in patients with GCS score 14–15 and aged > 65 years [22]. A recent meta-analysis concluded that pre-injury anti-platelet therapy is a potential risk factor for intracranial haemorrhage but pointed out the high heterogeneity among the reviewed studies [23]. Moreover, the impact of aspirin monotherapy on post-traumatic intracranial bleedings lacks of evidence. As regards anticoagulant agents, different international guidelines, such as the 2014 updated NICE recommendations [19], CHIP prediction Rule [17], National Emergency X-Radiology Utilisation Study criteria [16], American College of Emergency clinical policy [8] and European Federation of Neurological Societies recommendations [18] advise head CT scanning in all warfarin users. However, these recommendations rely on low quality evidences stemmed from small retrospective studies [24,25]. More recently the AHEAD study challenged a routine CT scanning of these patients, advocating the key role of GCS score and neurological symptoms to stratify their risk of intracranial adverse outcome [26]. To the best of our knowledge, the bleeding risk related to a mTBI in patients with a double antithrombotic therapy has not never been systematically investigated.

Our results endorse the potential predicting role of some clinical criteria not only in patients on VKA, but also in those receiving antiplatelets and DOACs as well as in non-antithrombotic users. In our cohort of patients, the core variables associated with an increased intracranial bleeding risk were GCS score < 15, post-traumatic amnesia, post-traumatic vomiting and clinical signs of basal skull fracture. Of note, this set of elements can be directly and easily derived from the

**Table 3**
Intracranial bleedings documented by brain CT in different patients' groups.

| | Group 1 | | Group 2 | | Group 3 | | Group 4 | | Group 5 | | *p*-Value* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | |
| Patients | 1222 | 100.0 | 407 | 100.0 | 120 | 100.0 | 51 | 100.0 | 46 | 100.0 | |
| TAC performed | 787 | 64.4 | 387 | 95.1 | 119 | 99.2 | 51 | 100.0 | 43 | 93.5 | |
| TAC results | | | | | | | | | | | |
| Negative for intracranial bleeding | 751 | 95.4 | 365 | 94.3 | 114 | 95.8 | 49 | 96.1 | 40 | 93.0 | 0.86 |
| Positive for intracranial bleeding | 36 | 4.6 | 22 | 5.7 | 5 | 4.2 | 2 | 3.9 | 3 | 7.0 | |
| EXACT CI 95% for proportion | | 3.2–6.3 | | 3.6–8.5 | | 1.4–9.5 | | 0.5–13.5 | | 1.5–19.1 | |

* Chi-square test for association.

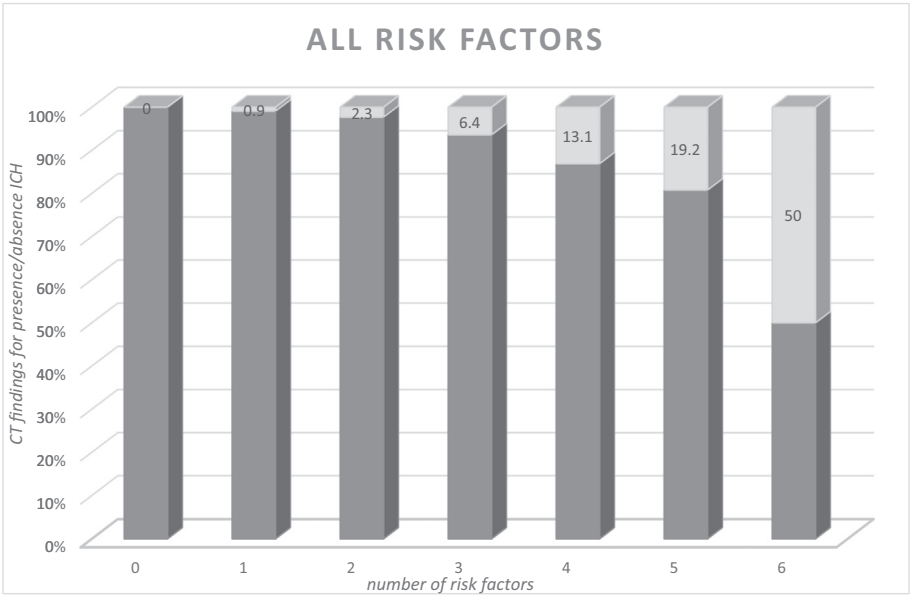


**Fig. 1.** ICH prevalence according to patients' risk factor numbers. (Light grey = prevalence of CT positive for ICH; dark grey = CT negative for ICH).

initial structured clinical examination of patient, as recommended by the good clinical practice, without need of information from witnesses of the traumatic event. Ultimately, patient clinical assessment could conceal the meaningful elements to drive the best management of all patients suffering a mTBI with a resulting GCS score equal or > 13.

In the interpretation of our findings, some strengths and limitations deserve to be taken into account. The major strength of our study is of methodological nature. First, in agreement with the recommendations for improving data standardisation in TBI research [21], we clearly defined our study population focusing on all mTBI forms with a resulting GCS score equal or greater than thirteen. Due to the retrospective collection of data, some clinical confounders might have not been consistently documented in medical record. For instance, we could not draw information about conscious state of patients with a GCS score 13–14 in absence of the three separate values of eye, verbal and motor response. Likewise, it was not possible to detail patients baseline bleeding risk and their comorbidities burden. Also, this is a single center study and the relatively small sample size of patient subgroups could have underpowered our study and affected our outcomes, precluding us from drawing definitive conclusions. This explains the wide confidence intervals of our exact esteems. As a result, our findings must be considered with caution as hypothesis generating and requiring confirmation. A possible underestimation of acute intracranial bleeding cannot be excluded as we assumed the absence of acute intracranial bleeding lesions in patients not undergoing CT scan. Moreover, some potential delayed intracranial bleedings may have not been captured, given the lack of a systematic follow-up period for patients after their discharge from the hospital. However, this is expected to be rather infrequent. Finally, we considered both DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) and antiplatelets (aspirin, clopidogrel, indobufen, ticagrelor, prasugrel, ticlopidine) as drugs classes without evaluating the effect of individual molecules in multivariate analysis.

In summary, antithrombotic therapy based on VKAs, DOACs and/or antiplatelets does not appear to independently increase the bleeding

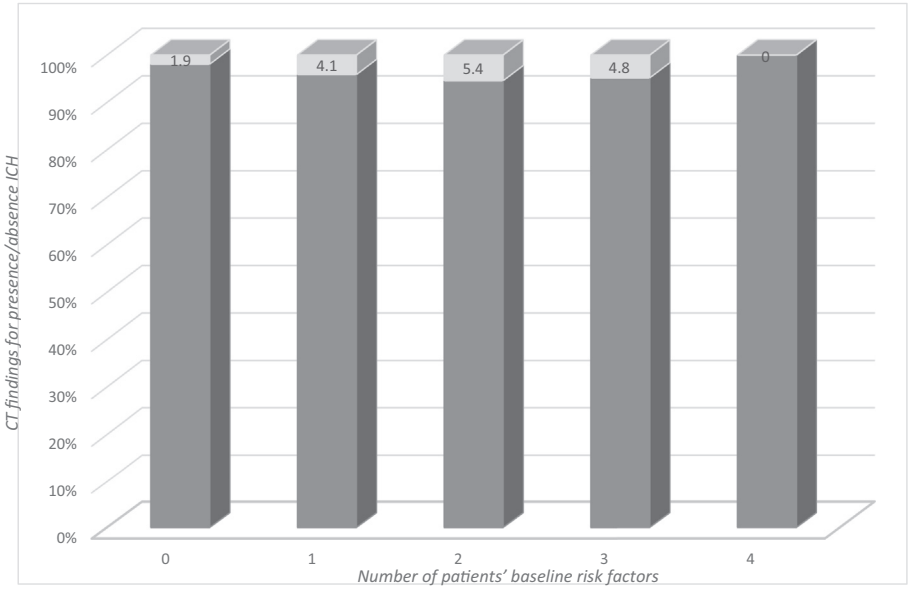


**Fig. 2.** ICH prevalence according to patients' baseline risk factor numbers. (Light grey = prevalence of CT positive for ICH; dark grey = CT negative for ICH).

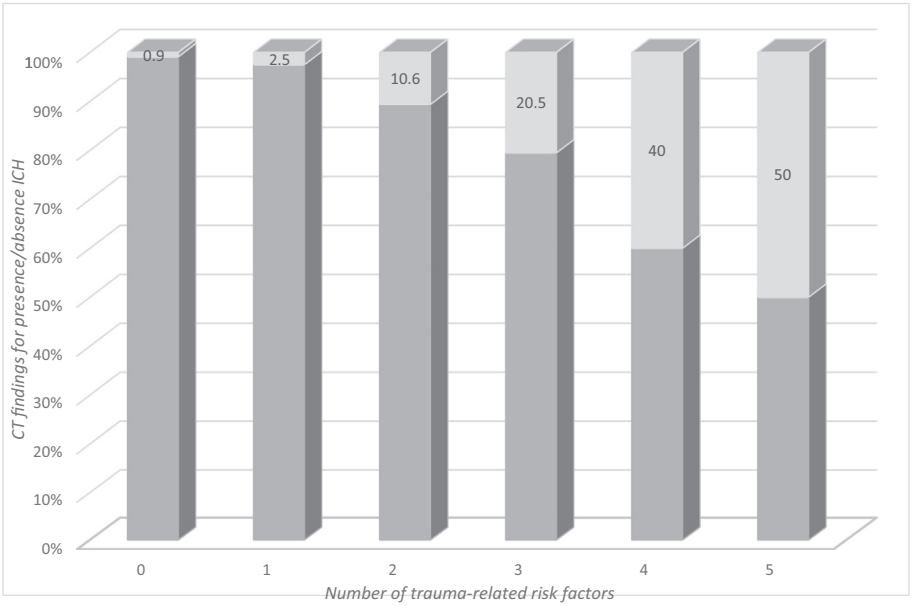


**Fig. 3.** ICH prevalence according to trauma-related risk factors number. (Light grey = prevalence of positive CT for ICH; dark grey = prevalence of negative CT for ICH).

**Table 4**
Association between patients' clinical findings and intracranial bleedings. Logistic regression model, overall sample.

| | | N | Positive CT | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|---|---|
| | | | n | % | OR | CI 95% | OR | CI 95% |
| Antithrombotic drug | None | 1222 | 36 | 3.0 | 1.0 | Ref | 1.0 | Ref |
| | Antiplatelet | 407 | 22 | 5.4 | **1.88** | **1.09–3.24** | 1.93 | 0.98–3.80 |
| | VKA | 120 | 5 | 4.1 | 1.43 | 0.55–3.72 | 1.58 | 0.55–4.54 |
| | DOACs | 49 | 2 | 3.9 | 1.35 | 0.32–5.75 | 1.54 | 0.33–7.16 |
| | Double therapy | 46 | 3 | 7.0 | 2.30 | 0.68–7.76 | 2.11 | 0.51–8.67 |
| Age (years) | < 65 | 804 | 19 | 2.4 | 1.0 | Ref | 1.0 | Ref |
| | ≥65 | 1042 | 49 | 4.7 | **2.04** | **1.19–3.50** | 1.89 | 0.92–3.87 |
| Sex | Female | 920 | 32 | 3.5 | 1.0 | Ref | 1.0 | Ref |
| | Male | 926 | 36 | 3.9 | 1.12 | 0.69–1.82 | 1.13 | 0.65–1.97 |
| GCS score | 15 | 1811 | 57 | 3.2 | 1.0 | Ref | 1.0 | Ref |
| | < 15 | 35 | 11 | 31.4 | **14.1** | **6.59–30.19** | **7.95** | **3.12–20.28** |
| Loss of consciousness | No | 1778 | 63 | 3.5 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 68 | 5 | 7.4 | 2.16 | 0.84–5.56 | 1.31 | 0.42–4.04 |
| Amnesia | No | 1706 | 43 | 2.5 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 140 | 25 | 17.9 | **8.41** | **4.96–14.26** | **6.49** | **3.57–11.82** |
| Neurological signs | No | 1831 | 67 | 3.7 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 15 | 1 | 6.7 | 1.88 | 0.24–14.51 | 1.04 | 0.09–11.56 |
| Seizure | No | 1842 | 68 | 3.7 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 4 | 0 | 0.0 | NE | | NE | |
| Headache | No | 1815 | 67 | 3.7 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 31 | 1 | 3.2 | 0.87 | 0.12–6.47 | 1.11 | 0.13–0.43 |
| Vomiting | No | 1816 | 61 | 3.4 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 30 | 7 | 23.3 | **8.76** | **3.62–21.19** | **4.45** | **1.47–13.50** |
| Clinical signs of cranial fracture | No | 1834 | 63 | 3.4 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 12 | 5 | 41.7 | **20.1** | **6.20–65.0** | **8.41** | **2.12–33.33** |
| Complicated contused lacerated wound | No | 1794 | 64 | 3.6 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 52 | 4 | 7.7 | 2.26 | 0.79–6.44 | 1.01 | 0.28–3.61 |
| Critical dynamic | No | 1809 | 62 | 3.4 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 37 | 6 | 16.2 | **5.45** | **2.20–13.55** | 3.03 | 0.96–9.60 |
| History of epilepsy | No | 1817 | 66 | 3.6 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 29 | 2 | 6.9 | 2.0 | 0.46–8.44 | 2.46 | 0.51–11.79 |
| Previous stroke/TIA/neurosurgery | No | 1748 | 62 | 3.6 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 98 | 6 | 6.1 | 1.77 | 0.75–4.21 | 1.57 | 0.61–4.09 |
| Drug/alcohol intoxication | No | 1770 | 65 | 3.7 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 76 | 3 | 4.0 | 1.10 | 0.33–3.51 | 1.13 | 0.30–4.25 |
| History of cerebral neoplasia | No | 1836 | 68 | 3.7 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 10 | 0 | 0.0 | NE | | NE | |
| Scalp lesions | No | 639 | 9 | 1.4 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 1207 | 59 | 4.9 | **3.60** | **1.77–730** | **2.31** | **1.09–4.89** |

Bold emphasis for underlying OR and CI of the variables associated with intracranial bleedings accordinbg to univariate and multivariate regression models.
CT findings different from bleedings are not considered; NE = not estimable.

**Table 5**
Association between patients' clinical findings and intracranial bleedings. Logistic regression model, only patients with CT performed.

| | | N | CT positive | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|---|---|
| | | | n | % | OR | CI 95% | OR | CI 95% |
| Antithrombotic drug | None | 787 | 36 | 4.6 | 1.0 | Ref | 1.0 | Ref |
| | Antiplatelet | 387 | 22 | 5.7 | **1.26** | **0.73–2.17** | 1.70 | 0.87–3.33 |
| | VKAs | 119 | 5 | 4.2 | 0.92 | 0.35–2.38 | 1.33 | 0.47–3.77 |
| | DOACs | 49 | 2 | 3.9 | 0.85 | 0.20–3.64 | 1.28 | 0.28–5.88 |
| | Double therapy | 43 | 3 | 6.7 | 1.57 | 0.46–5.30 | 1.84 | 0.46–7.44 |
| Age (years) | < 65 | 423 | 19 | 4.5 | 1.0 | Ref | 1.0 | Ref |
| | ≥65 | 964 | 49 | 5.1 | 1.14 | 0.66–1.96 | 1.38 | 0.67–2.83 |
| Sex | Female | 721 | 32 | 4.4 | 1.0 | Ref | 1.0 | Ref |
| | Male | 666 | 36 | 5.4 | 1.23 | 0.76–2.01 | 1.15 | 0.66–2.00 |
| GCS score | 15 | 1352 | 57 | 4.2 | 1.0 | Ref | 1.0 | Ref |
| | < 15 | 35 | 11 | 31.4 | **10.4** | **4.86–22.30** | **6.69** | **2.67–16.77** |
| Loss of consciousness | No | 1324 | 63 | 4.8 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 63 | 5 | 7.9 | 1.73 | 0.67–4.45 | 1.10 | 0.36–3.37 |
| Amnesia | No | 1256 | 43 | 3.4 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 131 | 25 | 19.1 | **6.65** | **3.91–11.32** | **5.62** | **3.07–10.26** |
| Neurological signs | No | 1372 | 67 | 4.9 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 15 | 1 | 6.7 | 1.39 | 0.18–10.74 | 0.92 | 0.09–9.92 |
| Seizure | No | 1383 | 68 | 4.9 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 4 | 0 | 0.0 | NE | | NE | |
| Headache | No | 1360 | 67 | 4.9 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 27 | 1 | 3.7 | 0.74 | 0.10–5.55 | 0.91 | 0.10–8.02 |
| Vomiting | No | 1359 | 61 | 4.5 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 28 | 7 | 25.0 | **7.10** | **2.90–17.33** | **4.33** | **1.43–3.11** |
| Clinical signs of cranial fracture | No | 1375 | 63 | 4.6 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 12 | 5 | 41.7 | **14.89** | **4.59–48.18** | **7.36** | **1.88–28.91** |
| Complicated contused lacerated wound | No | 1343 | 64 | 4.8 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 44 | 4 | 9.1 | 2.0 | 0.69–5.76 | 1.04 | 0.30–3.60 |
| Critical dynamic | No | 1353 | 62 | 4.6 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 34 | 6 | 17.7 | **4.46** | **1.78–11.17** | 2.38 | 0.76–7.48 |
| History of epilepsy | No | 1363 | 66 | 4.8 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 24 | 2 | 8.3 | 1.79 | 0.41–7.76 | 2.15 | 0.45–10.25 |
| Previous stroke/TIA/neurosurgery | No | 1293 | 62 | 4.8 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 94 | 6 | 6.4 | 1.36 | 0.57–3.22 | 1.47 | 0.57–3.77 |
| Drug/alcohol intoxication | No | 1324 | 65 | 4.9 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 63 | 3 | 4.8 | 0.97 | 0.30–3.17 | 0.96 | 0.26–3.58 |
| History of cerebral neoplasia | No | 1377 | 68 | 4.9 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 10 | 0 | 0.0 | NE | | NE | |
| Scalp lesions | No | 443 | 9 | 2.0 | 1.0 | Ref | 1.0 | Ref |
| | Yes | 944 | 59 | 6.3 | **3.22** | **1.58–6.54** | 2.20 | 1.03–4.68 |

Bold emphasis for underlying OR and CI of the variables associated with intracranial bleedings according to univariate and multivariate regression models. Positive TAC for other than intracranial bleeding was not considered; NE = not estimable.

risk after a mTBI. Other clinical predictors need to be taken into account to stratify intracranial bleeding risk in order to identify all high-risk subjects who would benefit from a CT scan after acute mTBI irrespective of any concomitant antithrombotic therapy. A such tailored management strategy might turn out as a more cost-effective and rationale approach that would limit unnecessary radiation exposures for patients and, at the same time, workload and costs for hospitals [27]. This could also drive the optimal time of observation of these patients and the need for a second CT scan. Future studies are warranted to confirm our preliminary results and to derive a clinical prediction rule to drive physicians decision-making in all patients sustaining a mTBI.

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