Acta Neurochirurgica (2022) 164:97–105
https://doi.org/10.1007/s00701-021-05066-w

ORIGINAL ARTICLE - BRAIN TRAUMA

Are oral anticoagulants a risk factor for mild traumatic brain injury progression? A single-center experience focused on of direct oral anticoagulants and vitamin K antagonists

Giuseppe Maria Della Pepa[1] · Marcello Covino[2,3] · Grazia Menna[1] · Anna Maria Auricchio[1] · Filippo Maria Polli[1] · Alberto Manno[2] · Benedetta Simeoni[2] · Alessandro Olivi[1] · Francesco Franceschi[2]

Received: 23 June 2021 / Accepted: 8 November 2021 / Published online: 30 November 2021

Abstract

Background Mild traumatic brain injury (TBI) in anticoagulated patients is a common challenge for emergency departments because of lack of appropriate epidemiological data and huge management variability for those under oral anticoagulation therapy.

Given the discrepancies between guidelines, the aim of the present study was to quantify the association between oral anticoagulant therapy (either vitamin K antagonist (VKA) or direct oral anticoagulant (DOAC)) and the post-traumatic intracranial hemorrhage worsening compared to admission CT scan.

Methods We included all consecutive records of patients admitted to our emergency department for mild TBI as chief complaint and with a positive admission CT scan. After statistical univariate comparison, cause-specific hazard ratio (HR) and 95% confidence interval (CI) were determined with the use of Cox proportional hazard model.

Results In the study period, 4667 patients had a CT scan for mild TBI; 439 (9.4%) were found to have intracranial hemorrhage. Among these patients, 299 (68.1%) were prescribed observation and control CT: 46 (15.38%) were on anticoagulant therapy, 23 (50%) on VKA, and 23 (50%) on DOAC. In multivariate analysis, only oral anticoagulation therapy was significantly associated to an increased risk of intracranial hemorrhage progression (HR 2.58; 95% CI 1.411–4.703; $p = .002$ and HR 1.9; 95% CI 1.004–3.735; $p = .0048$ for VKA and DOAC, respectively). Surgery was due to isolated subdural hematoma in 87.5% of cases, to subdural hematoma associated with intraparenchymal hemorrhage in 9.38% and to intraparenchymal hemorrhage only in 3.12%; 13 cases (4.35%) deceased in intensive care unit.

Conclusions In our series, anticoagulation was associated to a significant increase in intracranial progression, leaving the question open as to what this implies in current clinical practice; subdural hematoma was the major finding associated to evolution and surgery. Against this background, further studies are needed to clarify patients' management and DOAC safety profile compared to VKA in mild TBI.

Keywords Mild traumatic brain injury · Oral anticoagulants · Direct oral anticoagulants · Aspirin · VKA

This article is part of the Topical Collection on *Brain trauma*

Giuseppe Maria Della Pepa and Marcello Covino are authors equally contributed to the manuscript.

✉ Grazia Menna
mennagrazia@gmail.com

[1] Institute of Neurosurgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Catholic University, 8, 00168 Rome, Italy

[2] Emergency Department, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

[3] Università Cattolica del Sacro Cuore, Rome, Italy

Abbreviations

CT	Computed tomography
DOAC	Direct oral anticoagulants
VKA	Vitamin K antagonist

Introduction

Traumatic brain injury (TBI) represents one of the most common causes of morbidity and mortality worldwide, with an estimated annual cost of 31 billion Euros in Europe only. Approximately 80% of all TBI are classified as mild TBI [12, 22].

Oral anticoagulation therapy is traditionally considered an independent risk factor for developing both immediate and delayed intracranial hemorrhage in all TBI patients [3, 13]. Narrowing it down to mild TBI, previous clinical studies have shown that immediate intracranial hemorrhage prevalence in patients under vitamin K antagonist (VKA) treatment ranged between 4.3 and 16%, while average post-traumatic intracranial complication rate for those under direct oral anticoagulants (DOAC) is still unclear due to lack of evidence [5, 19, 20].

Given the presence of discrepancies between different clinical guidelines approaches, it is our belief that identification of potential risk factors for intracranial hemorrhage worsening might lead to quicker and safer clinical decision-making in both emergency medicine and neurosurgical setting. Therefore, the primary endpoint of the present study was to assess the association between oral anticoagulation therapy (either VKA or DOAC) and the post-traumatic intracranial hemorrhage worsening in patients suffering from mild TBI.

Methods

Study design and setting

The present is an observational, cross-sectional study conducted in a large emergency department admitting about 77,000 patients per year, in a teaching urban hospital. Our institution is the referral center for several peripheral emergency departments, a major trauma center, and serves a metropolitan area. The study was conducted over a 3-year period: from 1st January 2016 to 31st December 2018.

Decisions on the management

Management decisions were made according to Italian National Guidelines on TBI [18] and EFNS Guidelines on mild TBI [23]. Either way, mild TBI patients' management is based on the probability of developing neurosurgical complications (developmental risk) and the absence or the presence of one or more pre-existing or consequential risk factors resulting from the trauma.

In agreement with EFNS guidelines, and depending on the presence or absence of risk factors, we defined developmental risk and stratified clinical management as follows:

Low risk (EFNS category 0): Patients oriented in time and space (GCS 15) or space-oriented (GCS 15) patients without pre-existing or consequential risk factors; in these cases, patients were either discharged home or observed.
Intermediate risk (EFNS categories 1 and 2): In the absence of other risk factors, patients with any of the following criteria were included: GCS 15, loss of consciousness < 30 min, post-traumatic amnesia < 1, high-risk trauma dynamics (pedestrian struck, passenger thrown out of the car, fall from more than 1 m), vomiting, suspected or confirmed alcohol or drug abuse, coagulopathy or therapy with anticoagulants, severe or worsening headache not limited to the point of impact, history of epilepsy; in these cases, admission CT scan was performed.
High risk (EFNS category 3): GCS of 14–15, loss of consciousness < 30 min, post-traumatic amnesia < 1 h, with one or more of the following risk factors: headache, vomiting, age over 65 with pre-existing (such as alcohol and drug intoxication) or consequential risk factors, continuative amnesia, epilepsy, focal neurological deficits, coagulopathy, therapy with oral with oral anticoagulants, high-risk trauma dynamics; also in these cases, admission CT scan was performed.

Further decisions (repeat CT, surgery) were made on the basis of admission CT scan findings; in cases of a negative CT, a second scan was repeated if coagulation disorders were present or in case of polytrauma.

Patients' selection and data extraction.

We performed an automatized search of the emergency department electronic clinical records based on admission and discharge diagnosis.

We included in the study all consecutive records of patients admitted to our emergency department for mild TBI as chief complaint who, after a first positive CT scan at admission, had indication to observation and repeated a CT scan 24 h later.

Mild TBI was defined as TBI with Glasgow Coma Score (GCS) ≥ 13, loss of consciousness < 30 min, and post-traumatic amnesia < 24 h.

We excluded from analysis:

- Patients undergoing immediate surgery after intra-cranial hemorrhage diagnosis;
- Trauma not classified as mild TBI;
- Patients < 18 years of age;
- Pregnant women;
- Patients with a known history of inherited coagulation disease;
- Patients without a first CT scan evaluation in our emergency department;
- Patients that were negative for intra-cranial hemorrhage at first CT scan assessment.

For all patients included, we extracted the following data by manually reviewing the clinical records:

- Demographics, including sex and age at the admission;
- Anticoagulant therapy at time of injury (VKA or DOAC);

- Antiplatelet drug therapy (aspirin or clopidogrel);
- Presence of comorbidities (history of neoplasia, neurodegenerative diseases, cerebrovascular diseases, thrombocytopenia, alcohol abuse, and epilepsy)
- Neurological and physical examination data at admission and during observation period (amnesia > 30 min, loss of consciousness, post-traumatic epilepsy, worsening headache)

Radiological features evaluation

Axial CT images were acquired at 2.5 mm slices on a 64-slide CT scan (Revolution CT, GE Healthcare) and retrospectively analyzed. CT was considered positive if any kind of acute intra-cranial bleeding (regardless of the amount) was found, including subarachnoid hemorrhage, subdural hematoma, epidural hematoma, intra-parenchymal hemorrhage, and intraventricular hemorrhage.

From a radiological point of view, lesion worsening was considered if:

- An increase in subdural, epidural, and intraventricular hematoma thickness was reported at control CT scan—intended as the follow-up CT scan after the one performed at the time of admission. Given lack of evidence, this was the method of choice to establish lesion worsening [8, 24].
- An increase in intraparenchymal hemorrhage volume (cm^3) was identified. ABC/2 formula, corrected for hemorrhage's shape, was employed to estimate intraparenchymal hemorrhage size and assess possible volume variations (delta volume, cm^3) [9, 10].

Routine anticoagulated patient management

Notwithstanding the CT scan findings and according to our institutional protocol, VKA patients with significative intracranial hemorrhage were administered Human Protombin Complex (Protoplex 20 mg/kg) along with vitamin K. Other anticoagulated patients (including those under DOAC) were administered human plasma. Aspirin and other antiplatelet agents were always suspended during observation period.

Statistical analysis

Continuous variables were reported as median (interquartile range). Categorical variables were reported as absolute number (%). Statistical univariate comparison with respect of primary study endpoint was assessed by Mann–Whitney *U* test for continuous variables, and chi-square test (with Yates correction or Fisher test, as appropriate) for categorical variables.

Significant variables at univariate analysis were entered into a multivariate logistic regression model to identify independent risk factors for intra-cranial hemorrhage worsening. Association of risk factors to intra-cranial hemorrhage worsening was expressed as odds ratio (OR) (95% confidence interval). For better odds estimation and model fitting, continuous variables were categorized as dichotomous parameters (i.e., low/high). For each variable, the optimal dividing cut-off was obtained by Youden's index, performing a receiver operating characteristic (ROC) curve analysis with respect to association with intra-cranial hemorrhage worsening. A two-sided p value ≤ 0.05 was considered significant. Data were analyzed by SPSS v25® (IBM, Armonk, NY, USA).

Statement of ethics

The study was conducted in accordance with the principles expressed in the Declaration of Helsinki and its later amendments and approved by local institutional review board. Being a retrospective analysis based on a digital anonymized database, patient's informed consent was waived.

Results

A total of 8615 consecutive patients with age ≥ 18 years were evaluated in our emergency department for mild TBI in the study period, of which 4667 (54.2%) were prescribed admission CT scan. A total of 439 (9.4%) reported a positive CT scan for intra-cranial hemorrhage; 299 (68.1%) of them were prescribed clinical observation and control CT: 160 (53.5%) were males with median age of 76 years (Fig. 1).

Detailed additional therapy, clinical evaluation at admission, clinical history, radiological features, and clinical outcomes are reported in Table 1.

In the study cohort, 46 patients (15.38%) were on anticoagulant therapy. Among them, 23 (50%) were on VKA and 23 (50%) on DOAC. Among the 23 on DOAC, 4 (17.4%) were on Dabigatran, 9 (39.13%) on Apixaban, 9 (39.13%) on Rivaroxaban, and 1 (4.34%) on Edoxaban.

Ninety-four patients (31.4%) reported lesion worsening at second CT scan. Twenty-four (25.5%) of them were under oral anticoagulant therapy, specifically 13 (12.8%) under VKA and 11 (11.7%) under DOAC.

Overall, 32 (10.7%) underwent surgery due to isolated subdural hematoma (87.5%), subdural hematoma associated with intraparenchymal hemorrhage (9.38%), and intraparenchymal hemorrhage only (3,12%); 13 (4.35%) deceased in intensive care unit.

Table 2 reports factors associated to lesion worsening at univariate analysis. A statistically significant association ($p \leq 0.05$) emerged for the following variables: age (years)

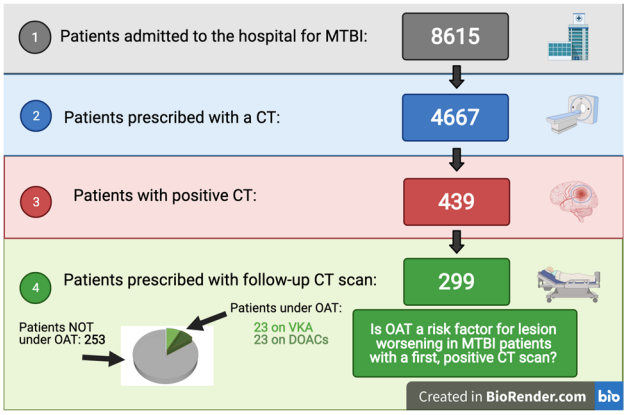

Fig. 1 The figure shows patients' selection process. A total of 8615 consecutive patients with age ≥ 18 years were evaluated for MTBI in the study period. Among them, 4667 (54.2%) were prescribed a CT scan. In 439 (9.4%), CT scan was positive for intracranial hemorrhage; of these, 299 (68.1%) were prescribed clinical observation and control CT. In this study cohort, 46 patients were on anticoagulant therapy, with 23 on VKA and 23 on DOAC (MTBI mild traumatic brain injury, CT computerized tomography, OAT oral anticoagulant treatment, VKA vitamin K antagonist, DOAC direct oral anticoagulant)—Created with BioRender.com

($p = < 0.001$); VKA anticoagulant therapy ($p = 0.004$); anticoagulant therapy, either VKA or DOAC ($p = 0.001$); amnesia > 30 min ($p = 0.016$); presence of subdural hemorrhage at first CT ($p = 0.005$).

The relationship between the aforementioned variables and lesion worsening was analyzed using the Cox proportional hazard model (Fig. 2). Patients on anticoagulation therapy had a significantly higher probability of lesion worsening compared to those not on anticoagulation (OR 2.58; 95% CI 1.411–4.703; $p = 0.002$ and OR 1.9; 95% CI 1.004–3.735; $p = 0.005$ for VKA and DOAC, respectively): our analysis identified anticoagulation therapy as the only significant factor affecting the treatment outcome; no other variable showed a significant association.

Discussion

The aim of the study was to quantify how being under oral anticoagulant therapy (either VKA or DOAC) represents a risk factor for lesion worsening in mild TBI patients, after a positive CT scan at admission. Our data demonstrated that anticoagulation was associated to a significant risk for intra-cranial hemorrhage progression (OR 2.58 and 1.9; for VKA and DOAC, respectively), leaving the question open as to what this implies in current clinical practice.

What do we know

Mild TBI is a common condition in emergency department: improving its management is a clear goal of neuro-traumatological research. Worldwide increase in life expectancy has reshaped mild TBI patient demographics, increasing the number of affected elderlies as well. This population subgroup often suffers from a high number of comorbidities for which it is being treated with as many drugs: it has been calculated that about 6% of those aged 65–74 and 10% of those over 75 years are on anticoagulant therapy.

DOAC are increasingly replacing warfarin as anticoagulants of choice, as they do not require monthly monitoring and have shorter half-lives, lower risks of fatal bleeding, and fewer drug and food interactions [13]. However, their behavior in mild TBI, and in general in post-traumatic intracranial bleeding, remains unclear as evidences are unclear on the topic [5, 19, 20]. The same goes for progressive intracranial hemorrhage risk after mild TBI and positive admission CT, as proved again by the lack of consensus in guidelines [1, 6, 11, 15, 16, 18, 23].

Due to paucity of evidence, considerable efforts are required to increase the number and quality of research on the topic.

Where do we stand

The study tries to bring attention on a subset of mild TBI patients of particular interest for the neurosurgeon, due to their variable clinical course and their controversial management.

While for mild TBI with absent/significant alterations at CT scan, management is de facto straightforward (observation\surgery); in mild TBI patients under oral anticoagulant therapy and with positive admission CT scan, treatment is more on a case-by-case basis. This is especially true since VKA are being progressively replaced by DOAC, and for the latter, evidence is scarce.

In our series of 299 mild TBI patients with positive admission CT scan, roughly one-third reported lesion worsening; of them, 70 patients were in non-anticoagulated group and 23 in oral anticoagulation group (Table 2). Twenty-three patients (50%) among those on anticoagulant therapy assumed DOAC and 23 (50%) were on VKA. Eleven patients (47.8%) under DOAC group and 13 (56.5%) on VKA showed a progressive intracranial hemorrhage (OR 2.58 and 1.9; for VKA and DOAC, respectively). Our data are relevant and in line with those from large registry studies, which displayed higher efficacy and lower major bleeding rates for DOAC compared to VKAs [14].

While bearing in mind our retrospective data acquisition, with consequent lack of standardized follow-up, we believe

Table 1 Baseline patient in study cohort characteristics, comorbidities, clinical presentation, and outcome. Data are presented separately for patients with no anticoagulant therapy, patients on VKA, or DOAC

	No Anticoagulation n° 253	VKA n° 23	DOAC n° 23	*p*
Baseline characteristics				
Age (years)	80 (69–85)	86 (80–89)	84 (78–88)	0.008
Sex (male)	137 (54.2)	9 (39.1)	14 (60.9)	0.293
Therapy				
ASA	36 (14.2)	1 (4.3)	1 (4.3)	0.180
Clopidogrel	17 (6.7)	0	1 (4.3)	0.405
ASA + Clopidogrel	3 (1.2)	0	1 (4.3)	0.380
Clinical evaluation				
High or mild risk	149 (58.9)	17 (73.9)	17 (73.9)	0.157
Amnesia > 30 min	44 (17.4)	1 (4.3)	3 (13.0)	0.243
Loss of consciousness	68 (26.9)	3 (13.0)	8 (34.8)	0.226
Post-traumatic epilepsy	8 (3.2)	0	0	0.474
Worsening headache	20 (7.9)	1 (4.3)	3 (13.0)	0.546
Clinical history				
Malignancy	18 (7.1)	1 (4.3)	2 (8.7)	0.838
Neurodegenerative disease	42 (16.6)	2 (8.7)	5 (21.7)	0.477
Cerebrovascular disease	24 (9.5)	2 (8.7)	1 (4.3)	0.711
Thrombocytopenia	5 (2.0)	0	0	0.630
Alcohol abuse	8 (3.2)	0	0	0.474
Epilepsy	5 (2.0)	0	1 (4.3)	0.573
Radiological features				
Timing of control CT (hours)	17 (11–24)	17 (9–24)	18 (11–23)	0.856
Skull fractures	19 (7.5)	3 (13.0)	0	0.232
Multiple lesions (≥ 2)	27 (10.7)	1 (4.3)	2 (8.7)	0.612
Subdural hemorrhage	137 (54.2)	9 (39.1)	12 (52.2)	0.384
Sub-arachnoid hemorrhage	147 (58.1)	9 (39.1)	15 (65.2)	0.153
Epidural hemorrhage	6 (2.4)	0	0	0.573
Intra-ventricular hemorrhage	16 (6.3)	2 (8.7)	1 (4.3)	0.832
Intra-parenchymal hemorrhage	74 (29.2)	7 (30.4)	8 (34.8)	0.855
Intra-parenchymal hemorrhage Location				
- Frontal	32 (43.3)	3 (42.8)	3 (37.5)	
- Parietal	8 (10.8)	1 (14.3)	2 (25)	
- Occipital	3 (4.05)	1 (14.3)	1 (12.5)	
- Temporal	22 (29.7)	1 (14.3)	2 (25)	
- Basal ganglia	3 (4.05)	1 (14.3)	0	
- Brainstem	3 (4.05)	0	0	
- Posterior cranial fossa	3 (4.05)	0	0	
Intra-ventricular hemorrhage	16 (6.3)	2 (8.7)	1 (4.3)	0.832
Lesion Volume cm^3 (initial)	0.35 (0.10–2.25)	0.01 (0.10–0.90)	1.17 (0.29–5.65)	0.237
Lesion Volume cm^3 (evolution)	4.15 (1.40–6.00)	1.40 (0.30–2.30)	1.40 (0.20–2.65)	0.853
Radiological outcome				
Lesion worsening	70 (27.7)	13 (56.5)	11 (47.8)	0.004
• Increased number	27 (10.7)	8 (34.8)	6 (26.1)	0.001
• Increased volume	57 (22.5)	10 (43.5)	8 (34.8)	0.046
Clinical outcome				
Surgery	29 (11.5)	2 (8.7)	1 (4.3)	0.543
- Isolated SDH	28 (96.5)	0	0	
- SDH in association with other patterns	0	2 (100)	1 (100)	
- Intra-parenchymal hemorrhage (IPH)	1 (3.5)	0	0	

Table 1 (continued)

	No Anticoagulation n° 253	VKA n° 23	DOAC n° 23	*p*
Deceased	11 (4.3)	2 (8.7)	0	0.352
Deceased or surgery	40 (15.8)	4 (17.4)	1 (4.3)	0.321
Length of hospital stay (days)	7.9 (4.8–12.9)	7.6 (5.9–8.9)	9.0 (5.6–9.0)	0.712

Table 2 Factor associated to lesion worsening at univariate analysis

	Lesion stable or reduced *n* 205	Lesion worsened *n* 94	*p*
Age (years)	81 (70–86)	81 (73–87)	< 0.001
Sex (male)	106 (51.7)	54 (57.4)	0.356
Therapy			
VKA	10 (4.9)	13 (13.8)	0.004
DOAC	12 (5.9)	11 (11.7)	0.078
Either VKA or DOAC	22 (10.7)	24 (25.5)	0.001
ASA	29 (14.1)	9 (9.6)	0.270
Clopidogrel	12 (5.9)	6 (6.4)	0.858
ASA + Clopidogrel	3 (1.5)	1 (1.1)	0.780
Clinical evaluation			
High and mild risk	131 (63.9)	52 (55.3)	0.157
Amnesia > 30 min	40 (19.5)	8 (8.5)	0.016
Loss of consciousness	58 (28.3)	21 (22.3)	0.278
Post-traumatic epilepsy	6 (2.9)	2 (2.1)	0.691
Worsening headache	19 (9.3)	5 (5.3)	0.243
Clinical history			
Malignancy	15 (7.3)	6 (6.4)	0.769
Neurodegenerative disease	35 (17.1)	14 (14.9)	0.636
Cerebrovascular disease	20 (9.8)	7 (7.4)	0.518
Thrombocytopenia	2 (1.0)	3 (3.2)	0.165
Alcohol abuse	5 (2.4)	2 (2.1)	0.920
Epilepsy	4 (2.8	1 (4.3)	0.573
Radiological findings			
Timing of control CT (hours)	17 (11–24)	21 (10–24)	0.670
Skull fracture	13 (6.3)	9 (9.6)	0.320
Multiple lesions (≥ 2)	17 (8.3)	13 (13.8)	0.139
Subdural hemorrhage	97 (47.3)	61 (64.9)	0.005
Sub-arachnoid hemorrhage	124 (60.5)	47 (50.0)	0.089
Epidural hemorrhage	6 (2.9)	0	0.182
Intra-parenchymal hemorrhage	63 (30.7)	26 (27.7)	0.590
Intra-ventricular hemorrhage	14 (6.8)	5 (5.3)	0.619
Outcome			
Surgery	8 (3.9)	24 (25.5)	< 0.001
Deceased	7 (3.4)	6 (6.4)	0.243
Deceased or surgery	15 (7.3)	30 (31.9)	< 0.001

that our findings are of relevance and confirm the need for further research.

In particular, it should be noted how in non-anticoagulated patients, lesions worsening was more related to an increase in volume compared increment in number, approximately in a 2:1 ratio. Conversely, in patients under VKA or DOAC, this ratio is 4:3 and 5:4, respectively (Table 2). These findings suggest:

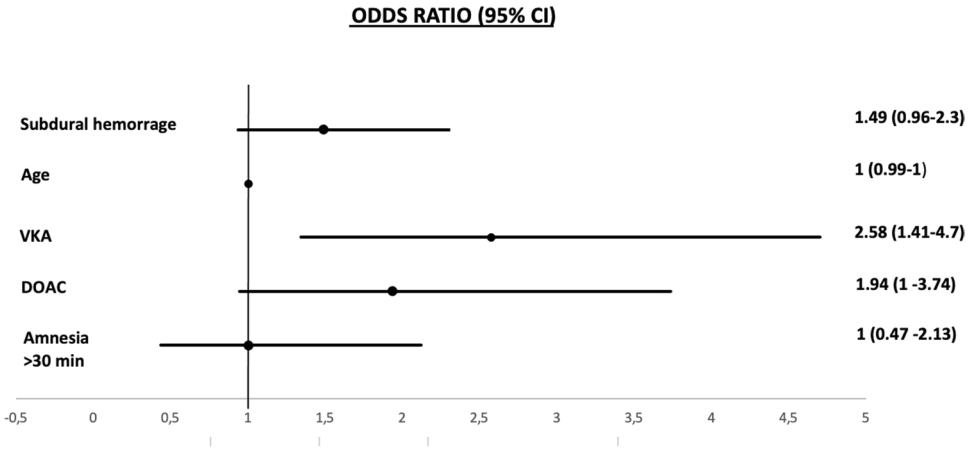

Fig. 2 The odds ratio quantifies the associations with lesion progression with 95% confidence interval. (VKA, vitamin K antagonist; DOAC, direct oral anticoagulant)

- in non-anticoagulated patients, the presence of a single lesion which keeps bleeding, resulting in a subsequent volume increase;
- in patients under oral anticoagulation therapy, the presence of multiple, close, and small lesions which, due to persistent bleeding, will result in the formation of single, bigger lesion.

The need for additional research is true also for those variables often associated to radiological lesions' worsening, such as age, prolonged amnesia, and presence of subdural hematoma [2, 4, 21], since significant ($p < 0.05$) at univariate analysis in our series.

An additional consideration is related to the use of single or dual antiplatelet therapy (aspirin or clopidogrel or aspirin + clopidogrel). Against this background, a recent meta-analysis showed that patients with mild TBI on antiplatelet therapy have a slighter increased risk of post-traumatic intracranial hemorrhage compared to patients not on antiplatelet therapy, but this higher risk is not coupled with the need to perform admission CT, if there are no additional risk factors. In our series, antiplatelet therapy was not associated to an increased rate of ICH progression at follow-up CT. This emphasizes the paucity of data on antiplatelet therapy and the need for CT scan evaluation and monitoring in patients with mild TBI [5].

What is next

Quantifying whether and how patients on oral anticoagulant therapy are more prone to intra-cranial hemorrhage worsening could be relevant to personalize management in terms of overall treatment strategy.

It is known that the role of routinely repeated CT scan in case of complicated mild TBI is debatable, especially due to a very low predicting yield in quantifying the need for delayed surgical intervention [17]. Due to the increased risk of lesion worsening in anticoagulated patients, it could be interesting to evaluate the accuracy of serial neurological examination versus a second CT scan (as performed in this case), after positive findings at admission. Given the increased number of anticoagulated patients suffering from MTBI, reserving a second CT scan examination only to those with neurological worsening or with specific risk factors (subdural hemorrhage) will allow to safely monitor these patients with lower costs and more effective resource utilization.

In our series, mild TBI patients' requiring surgery were those reporting isolated subdural hematoma, subdural hematoma associated with other patterns, and intraparenchymal hemorrhage, in descending order (Table 1). The overall need for neurosurgical intervention was 10–7%, and it was higher in the non-anticoagulated (11.5%), compared to the anticoagulated group (6.5%).

In other words, despite a statistical association between lesion progression and being under oral anticoagulation therapy, in absolute terms, this association was not clinically relevant, as demonstrated by the overall lower surgery rates in oral anticoagulated group.

Surgery was mostly addressed for subdural hematoma (subdural hematoma alone in 87.5%, associated to intraparenchymal hemorrhage in 9.38%), whereas intraparenchymal hemorrhage was significant and required surgery only in a minority of cases (3.12%). Thus, from our analysis, if a subdural hematoma is present at first CT, it should be considered a risk for neurological and radiological evolution, and hence, patients should be closely monitored as evolution towards surgery in this subset in not negligible.

Conversely, intraparenchymal hemorrhage in the oral anticoagulated group showed an increased risk of radiological worsening; however, this did not correspond to an increased requirement for surgery, mirroring the observation that those patients display a tendency towards confluence of rather small and close contusions not resulting into an increase of mass signs.

With reference to the HR, analyzing the subgroups of anticoagulated patients, those under DOAC have a relatively lower risk of radiological or clinical worsening comparing to those on VKA. However, it should be acknowledged that the relatively small sample of patients undergoing DOAC in our populations could affect the reliability of this figure.

Furthermore, despite our analysis being focused on the need for closer patients' monitoring given an increased risk of radiological and clinical worsening, the points mentioned above remark the need for further study to elucidate the actual relationship between lesions' progression and need for surgery.

Limitations

In our series, there was a considerable use of CT scan in mild TBI patients, which arises from a combination of different factors: our institution is the referral center of several peripheral emergency department; the overall median age of patients referring to our emergency department is high; many patients were under concomitant anticoagulation therapy.

Moreover, the absolute number of progressive intra-cranial hemorrhage observed in oral anticoagulation subgroup was low, which prevent us to give conclusive clues on the differences between patients on VKA or DOAC.

In addition to this, the mean age of our study population was 76 year, therefore prone to ground falls and usually present with significant pre-injury comorbidities and treatment, further impacting their recovery [7].

Finally, our study was retrospective in nature, provided that the intrinsic nature of mild TBI makes a different, perspective, analysis arduous.

Conclusions

Due to lack evidence, there is a huge management variability for anticoagulated patients suffering from MTBI and with a positive CT scan at admission. The main finding of present study is that anticoagulation, including both DOAC and VKA, was associated to a significant increase in intracranial hemorrhage progression, leaving the question open as to what this implies in current clinical practice: further studies and larger cohorts of subjects are needed to clarify their management and the safety profile of DOAC compared to VKA.

Author contribution Giuseppe Maria Della Pepa and Marcello Covino contributed to the study conception and design. Data collection was performed by Grazia Menna, Annamaria Auricchio, Alberto Manno, and Benedetta Simeoni. Data analysis was performed by Marcello Covino. The first draft of the manuscript was written by Giuseppe Maria Della Pepa and Grazia Menna. Filippo Maria Polli, Alessandro Olivi, and Francesco Franceschi supervised the work. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The dataset that supports the findings of this study are available from the corresponding author, G.M, upon reasonable request.

Declarations

Ethics approval Ethical approval was waived by the local Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate Being a retrospective analysis based on a digital anonymized database, patient's informed consent was waived.

Consent for publication Additional informed consent regarding publishing their data was obtained by all individual participants. The author transfers the publication rights and warrant that her contribution is original and that she has full power to make this grant. The author signs for and accepts responsibility for releasing this material on behalf of any and all co-authors.

Conflict of interest The authors declare no competing interests.

References

1. 2019 surveillance of head injury: assessment and early management (NICE guideline CG176). National Institute for Health and Care Excellence (UK), London; September 5, 2019
2. Bittencourt-Villalpando M, van der Horn HJ, Maurits NM, van der Naalt J (2020) Disentangling the effects of age and mild traumatic brain injury on brain network connectivity: a resting state fMRI study [published online ahead of print, 2020 Dec 22]. Neuroimage Clin. 29:102534. https://doi.org/10.1016/j.nicl.2020.102534
3. Brewer ES, Reznikov B, Liberman RF et al (2011) Incidence and predictors of intracranial hemorrhage after minor head trauma in patients taking anticoagulant and antiplatelet medication. J Trauma 70(1):E1–E5. https://doi.org/10.1097/TA.0b013e3181e5e286
4. Draper K, Schönberger M (2008) Functional outcome 10 years after traumatic brain injury: its relationship with demographic, injury severity, and cognitive and emotional status. J Int Neuropsychol Soc 14(2):233–242. https://doi.org/10.1017/S1355617708080272
5. Fiorelli EM, Bozzano V, Bonzi M et al (2020) Incremental risk of intracranial hemorrhage after mild traumatic brain injury in patients on antiplatelet therapy: systematic review and meta-analysis. J Emerg Med 59(6):843–855. https://doi.org/10.1016/j.jemermed.2020.07.036
6. Grandhi R, Harrison G, Voronovich Z et al (2015) Preinjury warfarin, but not antipatelet medications, increases mortality in elderly traumatic brain injury patients. J trauma Acute Care Surg 78:614–621
7. Hecht JP, LaDuke ZJ, Cain-Nielsen AH, Hemmila MR, Wahl WL (2020) Effect of Preinjury oral anticoagulants on outcomes following traumatic brain injury from falls in older adults. Pharmacotherapy 40(7):604–613. https://doi.org/10.1002/phar.2435
8. Hu TT, Yan L, Yan PF, Wang X, Yue GF (2016 Jan) Assessment of the ABC/2 method of epidural hematoma volume measurement

as compared to computer-assisted planimetric analysis. Biol Res Nurs 18(1):5–11. https://doi.org/10.1177/1099800415577634 (**Epub 2015 Mar 23 PMID: 25802386**)
9. Huttner HB, Steiner T, Hartmann M et al (2006) Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. Stroke 37(2):404–408. https://doi.org/10.1161/01.STR.0000198806.67472.5c
10. Kothari RU, Brott T, Broderick JP et al (1996) The ABCs of measuring intracerebral hemorrhage volumes. Stroke 27(8):1304–1305. https://doi.org/10.1161/01.str.27.8.1304
11. Marshall S, Bayley M, McCullagh S et al (2015) Updated clinical practice guidelines for concussion/mild traumatic brain injury and persistent symptoms. Brain Inj 29(6):688–700. https://doi.org/10.3109/02699052.2015.1004755
12. Peeters W, van den Brande R, Polinder S et al (2015) Epidemiology of traumatic brain injury in Europe. Acta Neurochir (Wien) 157(10):1683–1696. https://doi.org/10.1007/s00701-015-2512-7
13. Pieracci FM, Eachempati SR, Shou J, Hydo LJ, Barie PS (2007) Use of long-term anticoagulation is associated with traumatic intracranial hemorrhage and subsequent mortality in elderly patients hospitalized after falls: analysis of the New York State Administrative Database. J Trauma 63(3):519–524. https://doi.org/10.1097/TA.0b013e31812e519b
14. Prexl O, Bruckbauer M, Voelckel W, Grottke O, Ponschab M, Maegele M, Schöchl H (2018 Mar 27) The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. Scand J Trauma Resusc Emerg Med 26(1):20. https://doi.org/10.1186/s13049-018-0487-0.PMID:29580268; PMCID:PMC5870487
15. Silverberg ND, Iaccarino MA, Panenka WJ et al (2020) Management of concussion and mild traumatic brain injury: a synthesis of practice guidelines. Arch Phys Med Rehabil 101(2):382–393. https://doi.org/10.1016/j.apmr.2019.10.179
16. Stiell IG, Wells GA, Vandemheen K et al (2001) The Canadian CT Head Rule for patients with minor head injury. Lancet 357(9266):1391–1396. https://doi.org/10.1016/s0140-6736(00)04561-x
17 Stippler Nagesh M, Patel KR, Mishra A, Yeole U, Prabhuraj AR, Shukla D (2019) Role of repeat CT in mild to moderate head injury: an institutional study. Neurosurg Focus. 1;47(5):E2. https://doi.org/10.3171/2019.8.FOCUS19527
18. Trattamento del Trauma Cranico minore e severo - Linee guida nazionali di riferimento (Italian Consensus on MTBI treatment - SINCH)
19. Trevisi G, Scerrati A, Peppucci E, DeWaure C, Anile C, Mangiola A (2018) What is the best timing of repeated CT scan in mild head trauma with an initially positive CT scan? World Neurosurg 118:e316–e322. https://doi.org/10.1016/j.wneu.2018.06.185
20. Turcato G, Zannoni M, Zaboli A et al (2019) Direct oral anticoagulant treatment and mild traumatic brain injury: risk of early and delayed bleeding and the severity of injuries compared with vitamin K antagonists. J Emerg Med 57(6):817–824. https://doi.org/10.1016/j.jemermed.2019.09.007
21. Van Ornam J, Pruitt P, Borczuk P (2019) Is repeat head CT necessary in patients with mild traumatic intracranial hemorrhage. Am J Emerg Med 37(9):1694–1698. https://doi.org/10.1016/j.ajem.2018.12.012
22. Vos PE, Alekseenko Y, Battistin L et al (2012) Mild traumatic brain injury. Eur J Neurol 19(2):191–198. https://doi.org/10.1111/j.1468-1331.2011.03581.x
23. Vos PE, Battistin L, Birbamer G et al (2002) EFNS guideline on mild traumatic brain injury: report of an EFNS task force. Eur J Neurol 9(3):207–219. https://doi.org/10.1046/j.1468-1331.2002.00407.x
24. Won SY, Zagorcic A, Dubinski D, et al. Excellent accuracy of ABC/2 volume formula compared to computer-assisted volumetric analysis of subdural hematomas. PLoS One. 2018;13(6):e0199809. Published 2018 Jun 26. https://doi.org/10.1371/journal.pone.0199809