Effect of prior anticoagulation therapy on outcomes of traumatic brain injury: A systematic review and meta-analysis

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Abstract. Anticoagulants are commonly prescribed for multiple conditions. However, their influence on traumatic brain injury (TBI) outcomes, especially mortality, is not clear. The present study aimed to explore the effect of prior anticoagulation treatment on the outcomes of TBI. PubMed, Embase, Cochrane Central Register of Controlled Trials, Scopus and CINAHL databases were systematically searched for studies on individuals diagnosed with TBI, with a subgroup on prior anticoagulation therapy. Outcomes of interest included overall mortality, in-hospital mortality, length of hospital and intensive care unit stay, need for neurosurgical intervention and discharge rate. Cohort and case-control studies, published up to September 2023, were examined. Analysis was performed using STATA version 14.2 software and the Newcastle Ottawa Scale was used for bias assessment. A total of 22 studies (102,036 participants) were included in the analysis. Patients with TBI with prior anticoagulation treatment showed a statistically higher overall mortality risk [odds ratio (OR): 1.967, 95% confidence interval (CI): 1.481-2.613]. Subgroup analyses revealed age-specific and TBI severity-specific variations. Prior anticoagulation treatment was associated with a 1.860-times higher rate of in-hospital mortality and a significantly increased likelihood of requiring neurosurgical intervention (OR: 1.351, 95%CI: 1.068-1.708). However, no significant difference was noted in lengths of hospital or ICU stays. Patients with TBI and prior anticoagulation therapy are at higher risk of overall and in-hospital mortality and have significantly higher likelihood of needing neurosurgical interventions. The results emphasized the need for tailored therapeutic approach and more comprehensive clinical guidelines. Future investigations on specific anticoagulant types and immediate post-TBI interventions could offer further insights.

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Introduction

Traumatic Brain Injury (TBI) is an acute neurological event that may lead to complications such as ischemia, edema and inflammatory responses and is associated with significant morbidity and mortality (1). TBI is considered a major cause of mortality and disability worldwide, with an estimated 10 million individuals affected annually and a significant socioeconomic burden (2).

Managing a patient with TBI is complex and this complexity is further accentuated in patients with concurrent anticoagulant therapy, routinely prescribed for atrial fibrillation, deep vein thrombosis, pulmonary embolism and certain cardiac diseases (3). With an aging population and the growing prevalence of cardiovascular diseases, the intersection of anticoagulation therapy and TBI is becoming increasingly commonplace in clinical practice (4).

Anticoagulant medications primarily work by interrupting the coagulation cascade, thereby preventing clot formation. However, in the event of trauma, especially TBI, this anticoagulated state can exacerbate intracranial hemorrhage (ICH) and potentially amplify the severity of injury (5). Expanding hematomas post-TBI are of particular concern, as they can lead to increased intracranial pressure and may affect cerebral perfusion. Therefore, outcomes of TBI in patients who receive anticoagulation therapy are potentially complicated by the need for the reversal of anticoagulation, timely surgical interventions and potential complications from hemorrhagic progression (6).

Several studies have explored the effect of prior anticoagulation on TBI outcomes with inconclusive results. While some studies report an amplified risk of adverse outcomes, including increased ICH, extended hospital stays and elevated mortality rates (5,7), others suggest that with meticulous management, outcomes in anticoagulated patients with TBI can be comparable to those of non-anticoagulated patients (6,8).

Nursing care plays a pivotal role in managing patients with TBI, especially those on anticoagulant therapy. The meticulous monitoring, timely interventions and patient education provided by nurses can influence patient outcomes, potentially reducing complications and promoting recovery. Recognizing and understanding the interplay between anticoagulation and TBI is, therefore, paramount for optimizing nursing care of these patients.

The current study aimed to critically evaluate the effect of prior anticoagulation therapy on outcomes post-TBI to provide clinicians and nurses with evidence-based guidance in managing this group of patients. It distinguished itself from prior analyses by incorporating a comprehensive, up-to-date dataset that included recent studies not previously evaluated.

Materials and methods

Study protocol registration. The study protocol is registered at PROSPERO, the number is CRD42023470867.

Eligibility criteria

Population. The analysis centered on studies that included individuals diagnosed with TBI, without restrictions based on age, gender, ethnicity, or geographical location.

Intervention group. Patients who had been on anticoagulation therapy prior to TBI (i.e., occurrence of TBI in patients who are actively taking anticoagulants at the time of injury).

Comparison group. This group consisted of patients with TBI who were not on anticoagulation therapy.

Outcomes. The primary objective was to compare the outcomes between patients with TBI with prior anticoagulation and those without, particularly focusing on overall mortality, in-hospital mortality, length of hospital stay, length of intensive care unit (ICU) stay, need for neurosurgical intervention and discharge rate.

Study design. The present study incorporated cohort and case-control studies written in English, from the commencement of database records up to September 2023. Peer-reviewed articles and grey literature were both evaluated to minimize publication bias.

Information sources. A comprehensive search was performed in PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com/search/), Cochrane Central Register of Controlled Trials (CENTRAL) (https://www.cochranelibrary.com/advanced-search), Scopus (https://www.scopus.com/search/) and CINAHL (https://www.ebsco.com/products/research-databases/cinahl-database) databases. Reference lists of relevant papers and reviews were also manually inspected. Authors were contacted as needed for additional data or to seek clarifications. Key words such as 'traumatic brain injury', 'anticoagulation', 'warfarin', 'direct oral anticoagulants' and 'outcomes' were integrated, leveraging both Medical Subject Headings (MeSH) and related keywords. Filters were applied for English language publications and to only include articles up to September 2023.

Study records

Data management. EndNote X9 was utilized for managing and categorizing the identified articles. After the elimination of duplicate entries, the remaining studies were systematically evaluated for relevance.

Selection process. Two separate reviewers preliminary reviewed titles and abstracts of identified studies and full texts of potentially eligible articles were examined. Any disparities in selection were resolved through discussion between the two reviewers. The present study was planned and executed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 protocol (9).

Data collection process. The two reviewers independently extracted critical data using pre-established format. The extracted data included study details, participant demographics, details of anticoagulation therapy and outcome measures. Information pertaining to the funding source and possible conflicts of interest were also recorded.

Risk of bias assessment. The Newcastle Ottawa Scale (NOS) was used for the evaluation of the risk of bias within the incorporated studies (10). The NOS assesses potential biases across three major domains: selection, comparability and outcome. Studies are scored (0-9) based on the risk of bias, with higher scores indicating lower risk of bias. Each study was individually evaluated using the NOS and any discrepancies between the reviewers in scoring were reconciled through discussion between the two reviewers. The aggregate scores provided an overview of the overall quality and potential biases inherent in the included studies.

Data synthesis. STATA version 14.2 (StataCorp LP). was used for statistical analysis. Meta-analysis was performed when studies exhibited adequate homogeneity. Using a random-effects model, pooled effect sizes i.e., odds ratio (OR) with 95% confidence interval (CI) were determined. I^2 statistic was used to assess heterogeneity among the included studies (11). In cases of high heterogeneity, subgroup analyses were executed based on variables such as severity of TBI and patient age. Publication bias assessment was conducted by funnel plots and Egger's regression test for outcomes having at least 10 studies (11). The consolidated findings were visualized using forest plots.

Results

Search results. Initial literature search of databases identified 2,184 records. Of them, 732 duplicates were removed. Of the remaining 1,452 records, 1,355 were excluded (reasons included details on how differences in participant characteristics, outcome measures and exposure types influenced the exclusion of records from our analysis) and 97 full-text articles were assessed for eligibility. Finally, 22 studies met the inclusion criteria (i.e., studies on patients with TBI, covering all ages, ethnicities, locations and both sexes, comparing those on anticoagulation therapy at injury time to those who were not, focusing on mortality rates, hospital and ICU stay lengths, neurosurgical intervention need and discharge rates, using cohort and case-control studies in English up to September 2023, including peer-reviewed and grey literature; Fig. 1) (5,12-32).

Characteristics of the included studies. General characteristics of included studies are summarized in Table I. Most studies were from the USA, spanning from 2001-2023 and evaluated the impact of various anticoagulants, [warfarin, direct oral anticoagulants (DOAC) and vitamin K antagonists] on patients with TBI. Multiple study designs were present, with retrospective cohort studies being most prevalent. The sample sizes varied significantly, ranging from a 48 to 57,056. Age groups mainly included older adults (18 to ≥65 years). While several

Table I. Characteristics of included studies.

First author(s), year	Country	Type of anticoagulant	Study design	Sample size	Age group of the study participants	Inclusion of participants based on Severity of TBI	Follow up duration	Mean age (in years)	Sex distribution Male/Female	Risk of bias	(Refs.)
Ahmed *et al*, 2009	USA	Warfarin/ heparin	Retrospective cohort	68	≥18 years	All TBI	NR	OAC=74.6 No OAC=77.9	OAC=2/3 No OAC=33/30	Low	(32)
Batey *et al*, 2018	USA	Warfarin, DOAC	Retrospective cohort	700	≥65 years	All TBI	In-hospital outcomes	OAC=81 No OAC=81	OAC=83/94 No OAC=235/288	High	(15)
Bazzi *et al*, 2023	USA	Warfarin, DOAC	Retrospective	1,591	≥18 years	All TBI	In-hospital outcomes	OAC=76.13 No OAC=50.12	OAC= 92/47 No OAC=836/346	Low	(16)
Beynon *et al*, 2015	Germany	Phenprocourmon, rivaroxaban	Retrospective cohort	48	≥65 years	Mild TBI	In-hospital outcomes	OAC=72.4 No OAC=60	OAC=6/5 No OAC=15/22	High	(25)
Della Pepa *et al*, 2022	Italy	DOAC	Retrospective	301	>18 years	Mild TBI	In-hospital outcomes	OAC=84 No OAC=80	OAC=9/14 No OAC=137/116	Low	(13)
Fakhry *et al*, 2021	USA	Warfarin, rivaroxaban	Retrospective	33,710	≥65 years	All TBI	In-hospital outcomes	OAC=NR No OAC=NR	OAC= NR No OAC=NR	High	(12)
Fortuna *et al*, 2008	USA	Warfarin	Retrospective cohort	279	≥50 years	All TBI	In-hospital outcomes	OAC=78.3 No OAC=66.4	OAC=NR No OAC=NR	High	(27)
Gavrila Laic *et al*, 2023	Belgium	DOAC	Retrospective cohort	1,371	≥65 years	All TBI	1 month	OAC=NR No OAC=NR	OAC= NR No OAC=NR	High	(19)
Grandhi *et al*, 2015	USA	Warfarin	Retrospective cohort	719	≥65 years	All TBI	In-hospital outcomes	OAC=80.2 No OAC=79.8	OAC=NR No OAC=NR	Low	(24)
Hon 2016 *et al*, 2016	USA	Warfarin	Case control study	1,400	≥22 years	All TBI	In-hospital outcomes	OAC=77.1 No OAC=76.7	OAC=346/354 No OAC=372/328	High	(30)

Table I. Continued.

First author(s), year	Country	Type of anticoagulant	Study design	Sample size	Age group of the study participants	Inclusion of participants based on Severity of TBI	Follow up duration	Mean age (in years)	Sex distribution Male/Female	Risk of bias	(Refs.)
Karni *et al*, 2001	USA	Warfarin	Retrospective cohort	273	≥65 years	All TBI	NR	OAC=70 No OAC=70.3	OAC=8/8 No OAC =102/155	Low	(31)
Krueger *et al*, 2020	USA	Warfarin, rivaroxaban	Retrospective	111	>18 years	All TBI	In-hospital outcomes	OAC=NR No OAC =NR	OAC=NR No OAC =NR	Low	(21)
Nederpelt *et al*, 2022	Nether-lands	DOAC	Prospective	1,724	≥65 years	All TBI	In-hospital outcomes	OAC=83 No OAC=81	OAC=33/23 No OAC=602/635	Low	(29)
O'Donohoe *et al*, 2022	Australia	Warfarin, DOAC, apixaban, dabigatran, rivaroxaban	Retrospective	81	≥65 years	Moderate and severe TBI	1 month	OAC=82.4 No OAC =75.34	OAC=13/12 No OAC=31/25	Low	(28)
Peck *et al*, 2014	USA	Warfarin	Retrospective cohort	312	≥55 years	All TBI	In-hospital outcomes	OAC=78.7 No OAC=74.9	OAC= 20/19 No OAC=140/133	High	(5)
Pieracci *et al*, 2007	USA	Warfarin	Retrospective cohort	225	≥65 years	All TBI	NR	OAC=80.6 No OAC=79.2	OAC= 17/23 No OAC=77/108	Low	(14)
Posti *et al*, 2022	Finland	DOAC, vitamin K antagonist	Retrospective	57,056	≥18 years	All TBI	1 month	OAC=78.9 No OAC=61.4	OAC=2067/1986 No OAC=29439/23037	High	(17)
Prexl *et al*, 2018	Austria	Pheonprocoumon/ DOAC	Retrospective cohort	145	≥60 years	All TBI	NR	OAC=80.3 No OAC=73.2	OAC= 29/36 No OAC=48/32	Low	(26)
Rønning *et al*, 2021	Norway	DOAC, vitamin K antagonist	Retrospective	830	≥65 years	All TBI	1 month	OAC=81 No OAC=73	OAC= 106/66 No OAC=195/165	High	(18)
Senft *et al*, 2009	Germany	Phenprocoumon	Retrospective cohort	107	≥21 years	All TBI	6 months	OAC=72.4 No OAC=59.9	OAC= 6/5 No OAC =NR	High	(20)

Table I. Continued.

First author(s), year	Country	Type of anticoagulant	Study design	Sample size	Age group of the study participants	Inclusion of participants based on Severity of TBI	Follow up duration	Mean age (in years)	Sex distribution Male/Female	Risk of bias	(Refs.)
Tollefsen *et al*, 2018	Norway	Warfarin	Retrospective cohort	141	≥50 years	Moderate and Severe TBI	6 months	OAC=73.2 No OAC=63.7	OAC=14/6 No OAC=80/41	High	(22)
Wettervik *et al*, 2021	Sweden	Vitamin K antagonist	Retrospective	844	≥15 years	All TBI	6 months	OAC=NR No OAC =NR	OAC=NR No OAC =NR	Low	(23)

DOAC, direct oral anticoagulants; NR, not reported; OAC, oral anticoagulants; TBI, traumatic brain injury.

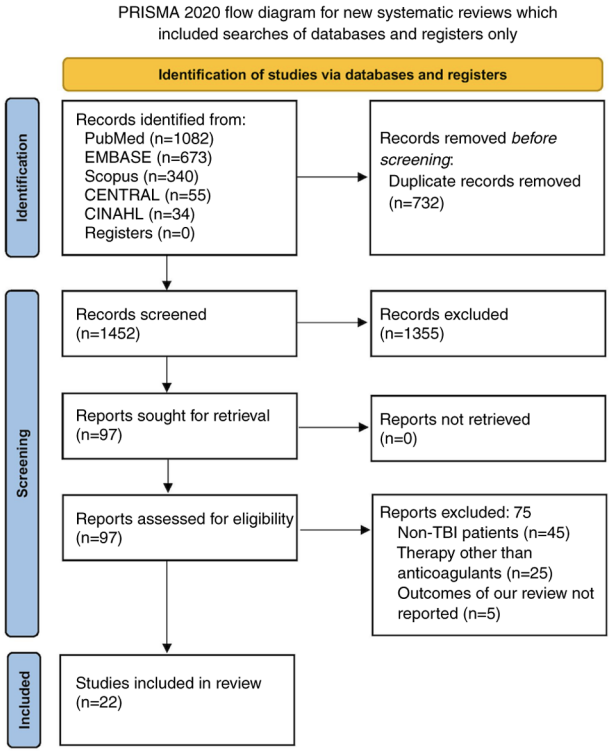

Figure 1. Search strategy.

studies reported data of TBI with various severities, some had specific focus groups such as mild or moderate to severe TBI. The mean age of participants varied across studies. DOAC users were typically older (average age of 70-84 years). Sex distributions exhibited diversity, with some studies showing a slight male predominance. Of 22 included studies, 11 had a high risk of bias, constituting ~42% of the total studies assessed (Table I).

Overall mortality. Risk of overall mortality in patients with TBI with and without prior anticoagulant therapy was reported in all 22 included studies. The pooled OR was 1.967 (95% CI 1.481-2.613), with a significant test for the overall effect (z=4.673, P<0.001), indicating a statistically higher risk of overall mortality in patients with TBI with prior anticoagulant therapy (Fig. 2). The heterogeneity among the included studies was notably high with a Cochran's Q value of 214.57 (df=21; P<0.001) and an I^2 statistic of 90.2%, suggesting that 90.2% of the total variation in study estimates was due to heterogeneity rather than chance. Funnel plot indicated no significant publication bias (Fig. S1).

The subgroup analysis based on the age included 14 studies involving 40,558 participants aged ≥50 years. The OR for mortality in anticoagulated patients with TBI of this age group was 1.776 (95% CI 1.249-2.525), a statistically significant finding compared with patients with no prior anticoagulation treatment (z=3.199; P=0.001).

A subgroup analysis based on the severity of TBI was then performed. The subgroup analysis of patients with mild TBI included three studies with a total of 32,795 participants. The pooled OR for mortality in patients with TBI with prior anticoagulant therapy compared with those without was 1.498

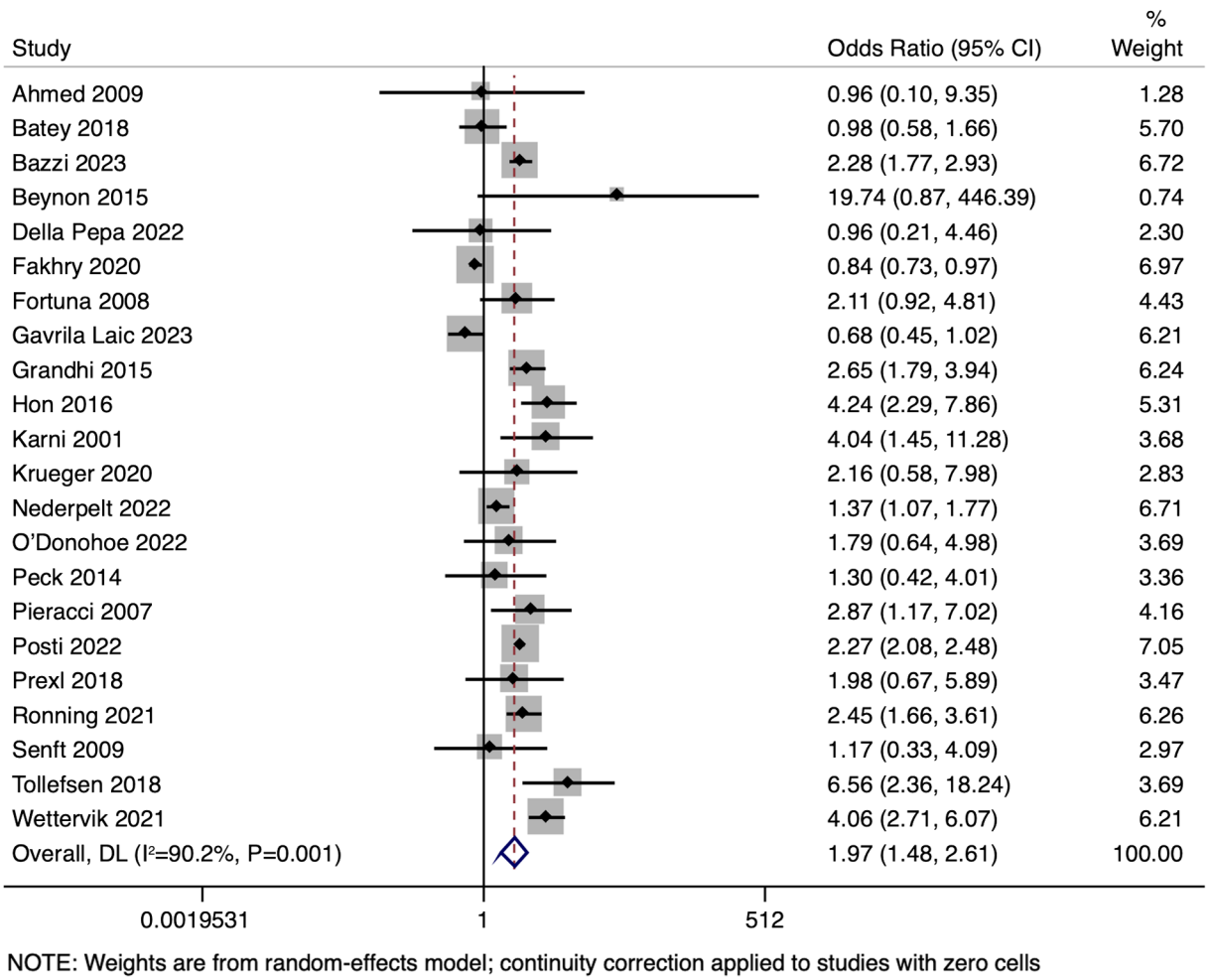

Figure 2. Forest plot showing the difference in overall mortality between patients with traumatic brain injury with prior anticoagulation therapy and those without anticoagulation therapy. CI, confidence interval.

(95% CI 0.633-3.541). This result was not statistically significant (z=0.920; P=0.358). This suggested that in patients with mild TBI, prior anticoagulant therapy does not significantly influence the risk of overall mortality.

The analysis focusing on patients with moderate TBI included two studies, with the pooled OR of 2.660 (95% CI 0.150-47.111). This result was not statistically significant (z=0.667, P=0.505).

The subset analysis for patients with severe TBI included pooled data from two studies. The combined OR for mortality in this subgroup of patients with TBI who received prior anticoagulant therapy was 0.667 (95% CI 0.470-0.948). This result was statistically significant (z=-2.255, P=0.024), indicating that among patients with severe TBI, prior anticoagulant therapy is associated with a decreased risk of overall mortality.

In-hospital mortality. A total of 10 studies with 39,358 participants reported data on in-hospital mortality. The pooled OR of 1.860 (95% CI: 1.216-2.843) indicated that the risk of in-hospital mortality was significantly higher in anticoagulated patients with TBI compared with the control group (z=2.864; P=0.004; Fig. 3). Significant heterogeneity was observed among the included studies, with an I^2 value of 89.0% and Cochran's Q of 81.65 (P<0.0001). Funnel plot indicated potential publication bias with Egger's significance level of P=0.080 (Fig. S2).

Need for neurosurgical intervention. A total of nine studies, encompassing 94,517 participants, evaluated the need for neurosurgical intervention. The pooled OR was 1.351 (95% CI: 1.068-1.708; P=0.012), suggesting a statistically significant increased likelihood of requiring neurosurgical intervention in patients with TBI with prior anticoagulant therapy (Fig. 4). Notably, significant heterogeneity was observed across the studies (I^2=72.4%; P<0.001).

Discharge rate. In six studies involving 37,158 participants that reported data on the discharge rates, the combined OR was 0.639 (95% CI: 0.285-1.437; P=0.279), indicating no significant difference in the discharge rates (Fig. 5). There was substantial heterogeneity among the studies with an I^2 value of 98.1% (P<0.001).

Length of hospital stay. A total of 12 studies with 63,405 participants assessed the length of hospital stay in patients with TBI with and without prior anticoagulant therapy. The pooled weighted mean difference was -0.897 days (95% CI: -1.873-0.079, P=0.072), indicating a non-significant decrease in hospital stay for patients

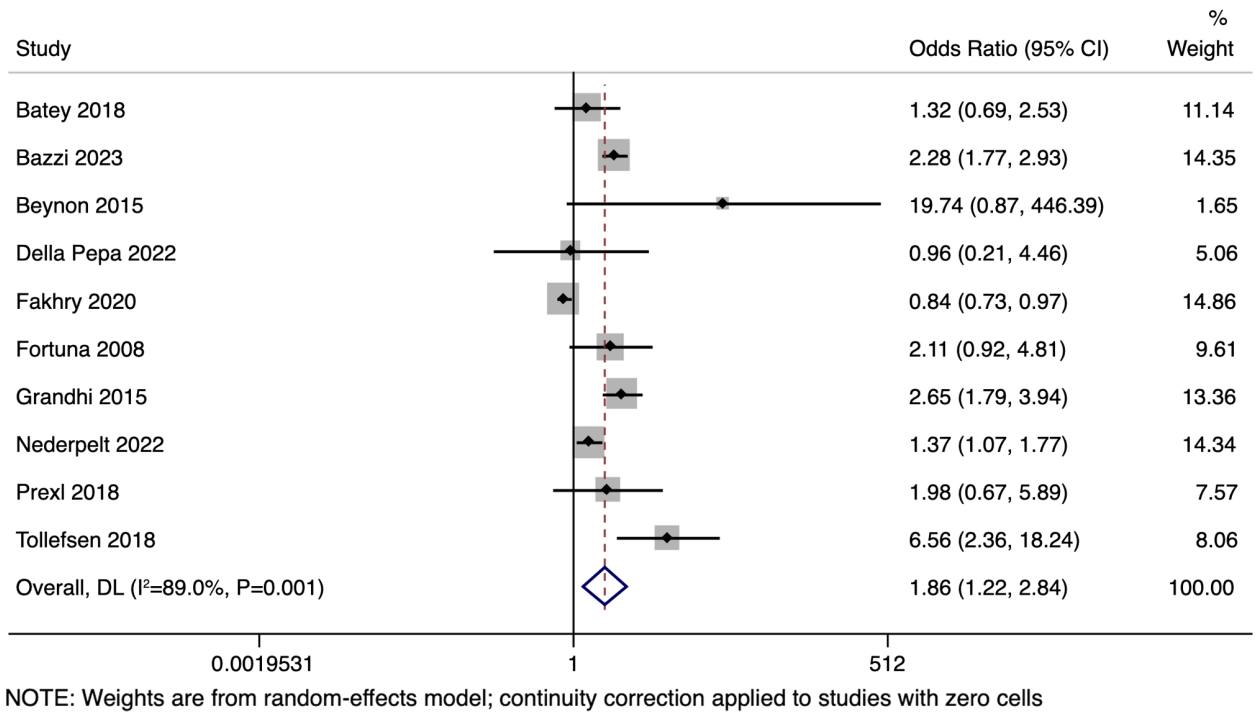

Figure 3. Forest plot showing the difference in in-hospital mortality between patients with traumatic brain injury with prior anticoagulation therapy and those without anticoagulation therapy. CI, confidence interval.

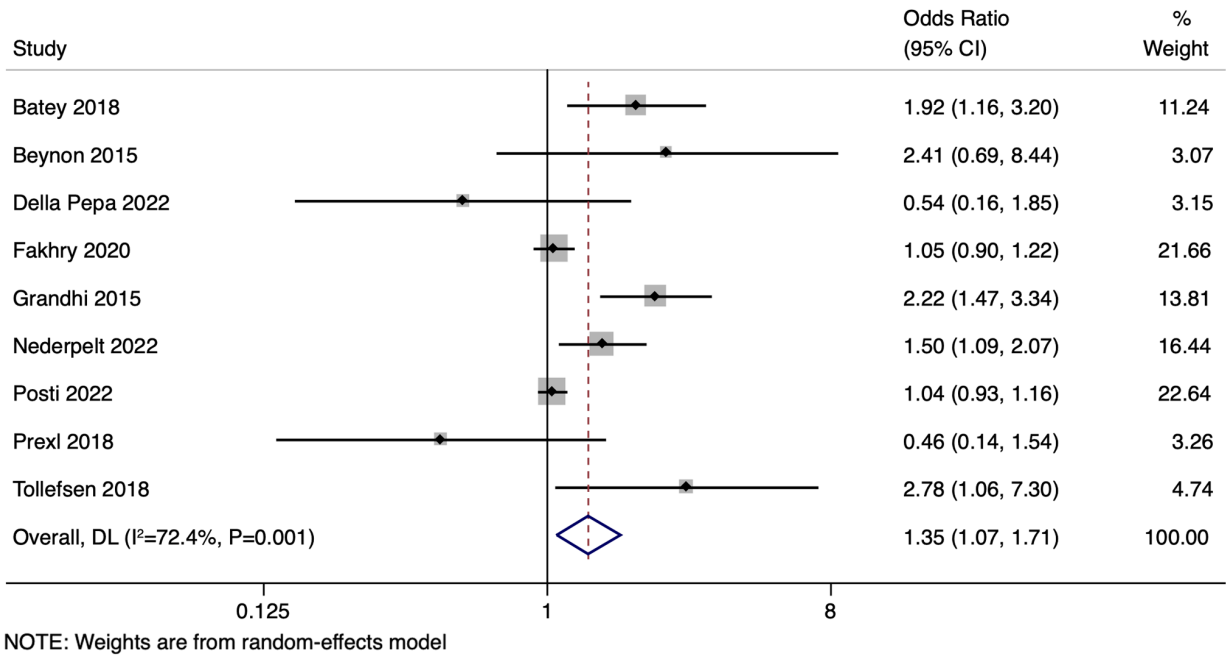

Figure 4. Forest plot showing the difference in need for neurosurgical intervention between patients with traumatic brain injury with prior anticoagulation therapy and those without anticoagulation therapy. CI, confidence interval.

with TBI with prior anticoagulant therapy (Fig. 6). Significant heterogeneity was present among the studies (I^2=99.4%; P<0.001). Funnel plot showed no publication bias (Fig. S3).

Length of ICU stay. A total of five studies, with a total of 4,823 participants, assessed the length of the ICU stay. The pooled weighted mean difference was 0.303 days (95% CI: -0.405-1.011, P=0.402), indicating no significant difference in the length of the ICU stay (Fig. 7). Notably, there was substantial heterogeneity across the studies (I^2=97.7%; P<0.001), suggesting variations in study outcomes or methodologies.

Discussion

The present comprehensive meta-analysis encompassing 102,036 participants provided vital insights into the clinical

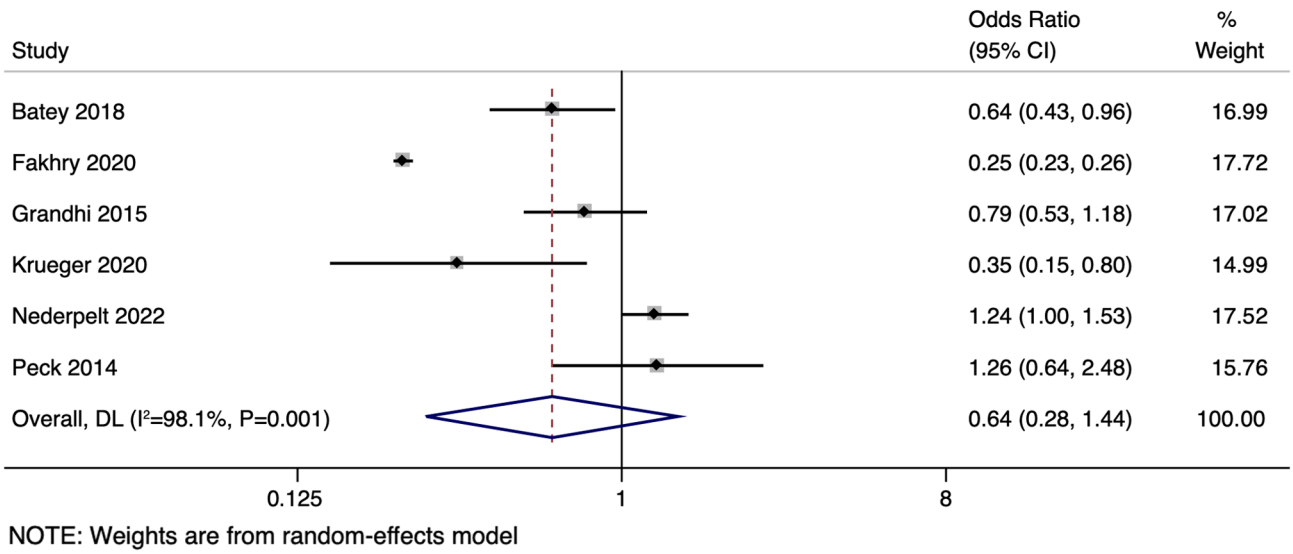

Figure 5. Forest plot showing the difference in discharge rate between patients with traumatic brain injury with prior anticoagulation therapy and those without anticoagulation therapy. CI, confidence interval.

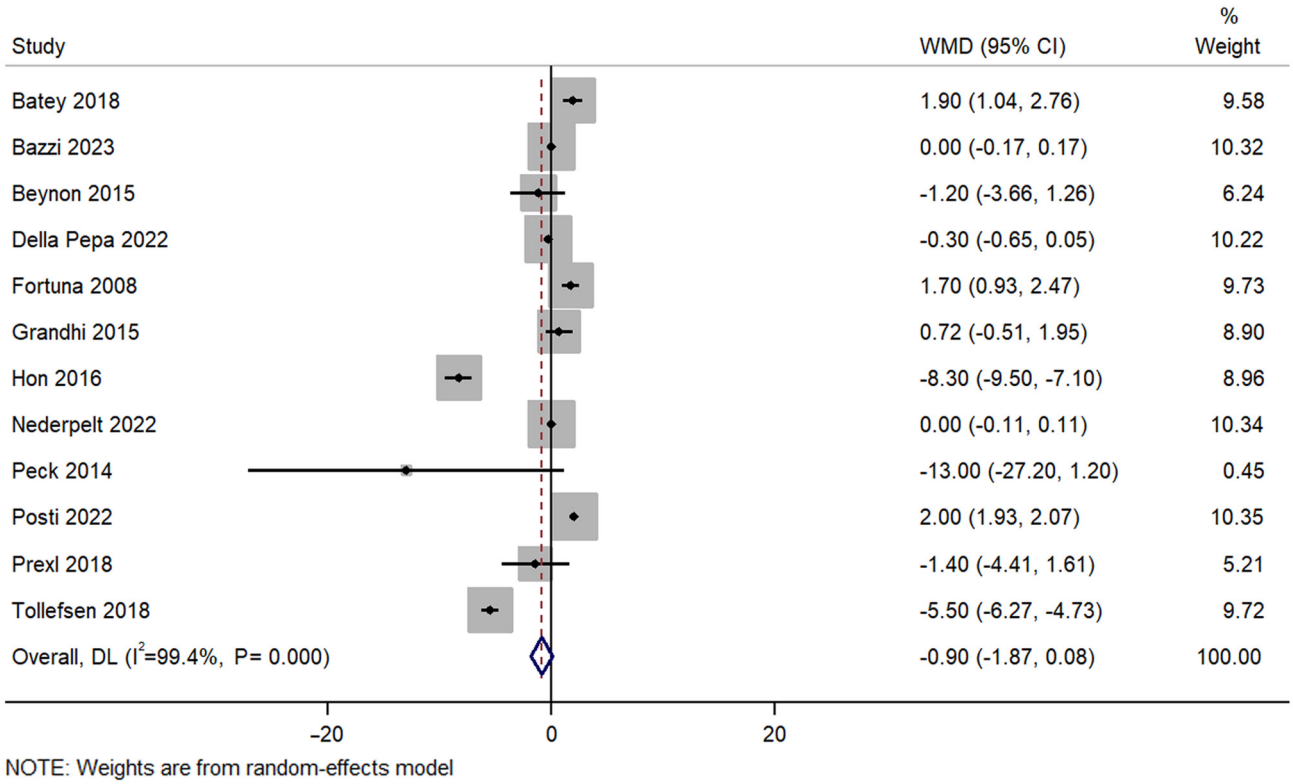

Figure 6. Forest plot showing the difference in length of hospital stay between patients with traumatic brain injury with prior anticoagulation therapy and those without anticoagulation therapy. WMD, weighted mean difference; CI, confidence interval.

implications of prior anticoagulant therapy on traumatic brain injury (TBI) outcomes. The central finding indicated that patients with TBI with a history of anticoagulant therapy experience a higher risk of overall and in-hospital mortality and have higher likelihood of requiring neurosurgical intervention, compared with patients without a history of anticoagulation therapy. However, the present review demonstrated that this increased mortality risk does not translate into longer hospital or ICU stays. It is suggested that this could be attributed to the timely and efficient interventions that are currently in place in trauma centers.

The results of the present review are consistent with previous reports on the subject. Lim *et al* (33) undertook a similar meta-analysis and found that anticoagulant therapy had detrimental outcomes in patients who sustained a TBI. A previous review has also indicated that, while anticoagulant therapy posed a risk, the prognosis was largely dictated by other factors such as age, injury severity and comorbidities (33).

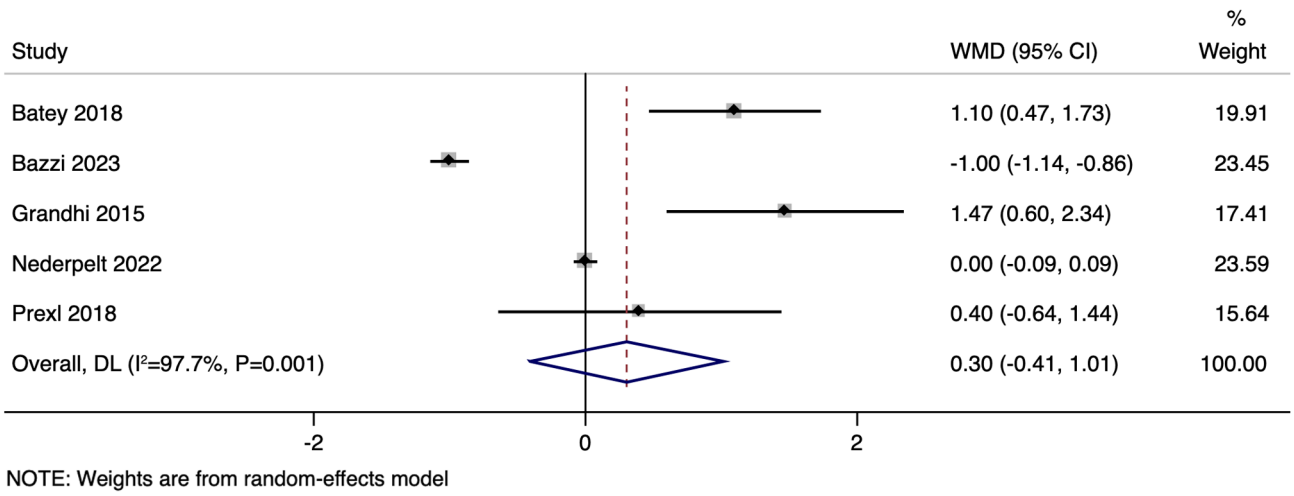

Figure 7. Forest plot showing the difference in length of intensive care unit stay between patients with traumatic brain injury with prior anticoagulation therapy and those without anticoagulation therapy. WMD, weighted mean difference; CI, confidence interval.

The present results further confirm these finding, underlining the complexity and multifaceted nature of TBI outcomes. While Lim *et al* (33) and other previous studies have laid the groundwork, the present research contributed novel insights by examining the latest data and incorporating a broader range of variables. This comprehensive approach underscored the multifactorial nature of TBI prognosis and offered a more granular perspective on the role of anticoagulation in TBI outcomes. The present findings serve as a pivotal resource for clinicians and nurses, providing an updated, evidence-based framework to guide decision-making and optimize patient care in this challenging clinical scenario.

It might be hypothesized that the pathogenesis of the increased mortality rates in patients with TBI with prior anticoagulant therapy is multifaceted. Anticoagulants diminish the coagulation capability of blood, potentially leading to exacerbated post-injury bleeding (34). It is conceivable that such therapy may worsen cerebral microbleeds, making the brain more susceptible to neuronal damage post-TBI. These microbleeds can activate a cascade of inflammatory processes detrimental to brain tissue (35). The presence of anticoagulants may also further disrupt the delicate balance between pro-coagulant and anticoagulant factors that is affected by TBI. Additionally, increased bleeding can lead to reduced cerebral perfusion, aggravating secondary brain injury complications such as ischemia, elevated intracranial pressure, herniation, or even diffuse axonal injury (36). Moreover, there is a potential risk of drug-drug interactions that might arise when patients with TBI on anticoagulants are administered other medications during their hospital stay (37).

The observed increase in mortality rates among patients with TBI with prior anticoagulant therapy demands a comparative analysis with other clinical conditions. In a recent observational study, patients with acute cardiovascular events on anticoagulants had slightly higher mortality rates (38). Therefore, it is plausible that this phenomenon is not restricted to TBI and there are more universal risks associated with anticoagulant therapy. One aspect that demands further investigation is the timely withdrawal or reversal of anticoagulation post-TBI. Some anticoagulants have reversal agents or antidotes which, when administered promptly, might mitigate the hemorrhagic risks. However, the exact timing, dosage and potential side effects of these antidotes remain to be elucidated (39).

Notably, the present study revealed that patients with severe TBI showed improved survival rates when on prior anticoagulants. This counterintuitive finding may be attributed to several factors. One possible explanation is the 'anticoagulant paradox,' where certain anticoagulants may offer neuroprotective effects due to their influence on cerebral blood flow and inflammation (40). Additionally, patients on long-term anticoagulant therapy often receive more rigorous medical monitoring, which could lead to quicker TBI diagnosis and treatment. It is also possible that the profile of patients on anticoagulants differs significantly from those not on such therapy, including factors such as improved overall health management and quicker access to medical care. Further research is needed to explore these hypotheses and understand the underlying mechanisms.

Early mobilization and rehabilitation are paramount for TBI recovery. Delays due to complications associated with anticoagulant therapy might compromise functional recovery and long-term quality of life. The nursing perspective in TBI care is multifaceted, addressing not just immediate medical needs but also holistic well-being. Nurses play a critical role in patient education, ensuring that patients with TBI and their families are well-informed about the implications of anticoagulant therapy. They are often the first to notice subtle changes in a patient's condition, making their role in monitoring patients with TBI on anticoagulants crucial.

The present meta-analysis had several strengths. The inclusion of a large number of participants across multiple studies ensures a diverse and representative sample, thus enhancing the external validity of our findings. Additionally, the rigorous methodology and subgroup analyses ensured robust and consistent results.

Nevertheless, the present study had several limitations. The significant heterogeneity among studies might be reflective of varying definitions of TBI severity, different anticoagulant classes, or differing healthcare standards

across regions. There is the absence of detailed information on long-term neurological outcomes and the specific use of reversal agents in the present study. This is indeed a limitation as it would have provided deeper insights into the recovery trajectory and management strategies post-TBI for patients on anticoagulants. Future studies should aim to include comprehensive data on neurological impairments over the long term and the effects of using reversal agents in the treatment protocol. Another notable limitation of the analysis is the inability to conduct a detailed comparison between patients on DOACs compared with Warfarin, as well as an separate analysis of various DOACs. This limitation stems from the composition of the dataset, which predominantly included studies focusing on a combination of DOAC and Warfarin therapies, or Warfarin alone. The prevalence of Warfarin use, often in isolation or combined with other drugs, in the existing literature limits the capacity for a more nuanced subgroup analysis.

The findings of the present meta-analysis suggest that trauma centers might need to revisit their protocols for managing patients with TBI with a history of anticoagulant use. Implementing a universal algorithm that encompasses rapid diagnostics, timely drug reversal and vigilant monitoring might improve outcomes. Furthermore, interdisciplinary collaborations involving neurologists, hematologists and trauma surgeons could foster comprehensive patient-centered care.

Future studies could focus on the specific classes of anticoagulants as different anticoagulants may carry varying risks. Future prospective studies are needed to establish more definitive causality. Additionally, focusing on specific TBI severity subgroups could provide more granular insights into which patients are most at risk.

The present meta-analysis underscores the heightened risk of adverse outcomes, such as in-hospital and overall mortality and higher need for neurosurgical interventions in patients with TBI with prior anticoagulant therapy. The results provided insights for informed clinical decisions and identify areas warranting further research.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LP conceived and designed the study. LP and JH collected the data and performed the literature search. LP was involved in the writing of the manuscript. LP and JH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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