Neurocrit Care (2023) 38:812–820
https://doi.org/10.1007/s12028-022-01671-4

NEUROCRITICAL CARE SOCIETY

REVIEW ARTICLE

Risk Factors for Anticoagulant-Associated Intracranial Hemorrhage: A Systematic Review and Meta-analysis

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Abstract

Background: Anticoagulant-associated intracranial hemorrhage has a high mortality rate, and many factors can cause intracranial hemorrhage. Until now, systematic reviews and assessments of the certainty of the evidence have not been published.

Methods: We conducted a systematic review to identify risk factors for anticoagulant-associated intracranial hemorrhage. The protocol for this systematic review was prospectively registered with PROSPERO (CRD42022316750). All English studies that met the inclusion criteria published before January 2022 were obtained from PubMed, EMBASE, Web of Science, and Cochrane Library. Two researchers independently screened articles, extracted data, and evaluated the quality and evidence of the included studies. Risk factors for intracranial hemorrhage were used as the outcome index of this review. Random or fixed-effect models were used in statistical methods. I^2 statistics were used to evaluate heterogeneity.

Results: Of 7322 citations, we included 20 studies in our analysis. For intracranial hemorrhage, moderate-certainty evidence showed a probable association with race, Glasgow Coma Scale, stroke, leukoaraiosis, cerebrovascular disease, tumor, atrial fibrillation, previous bleeding, international normalized ratio, serum albumin, prothrombin time, diastolic blood pressure, and anticoagulant. Low-certainty evidence may be associated with age, cerebral microbleeds, smoking, alcohol intake, platelet count, and antiplatelet drug. In addition, we found very low-certainty evidence that there may be little to no association between the risk of intracranial hemorrhage and hypertension and creatinine clearance. Leukoaraiosis, cerebral microbleeds, cerebrovascular disease, and international normalized ratio are not included in most risk assessment models.

Conclusions: This study informs risk prediction for anticoagulant-associated intracranial hemorrhage and informs guidelines for intracranial hemorrhage prevention and future research.

Keywords: Anticoagulation, Intracranial hemorrhage, Risk factor, Predict, Prognosis, Meta-analysis

Introduction

Anticoagulants, such as warfarin and rivaroxaban, are widely used to prevent and treat venous thromboembolism. They also reduce the risk of ischemic stroke, especially among patients with atrial fibrillation [1]. The most feared complication of anticoagulation is intracranial hemorrhage (ICH) because it is responsible for most of the death and disability attributable to anticoagulant-associated bleeding [2]. ICH is also called cerebral

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hemorrhage. All-cause ICH in the anticoagulated population occurs at a rate of 0.2–1.0% per year [3–5]. A burning clinical question is how to reliably predict which patients are at a high risk of ICH if anticoagulated and which factors reliably predict the risk of ICH caused by anticoagulants. For example, one factor identified by most studies is advancing age [6, 7]. Therefore, it is necessary to accurately predict the bleeding risk of patients, which will help physicians weigh the benefits and risks of anticoagulant drugs and reduce the occurrence of ICH.

The risk assessment model (RAM) for anticoagulant-associated ICH consists of multiple predictors. Risk for specified end points can be obtained based on the relevant predictors to inform recommendations for strata of patients [8]. In the clinical treatment or medication decisions, we can apply relevant models for risk prediction to reduce the occurrence of ICH. Therefore, establishing and using an anticoagulant-associated ICH model is crucial.

RAMs are currently available for patients on anticoagulant therapy, which can be scored and stratified according to risk factors. Although these models can prevent ICH to some extent, most of them were developed using existing data that were not based on a systematic review of all potential risk factors [9]. However, model development requires a systematic review to determine the importance of risk factors [9]. Predictors included in existing models were not comprehensive, and effect sizes of the risk factors were not subjected to meta-analysis, which may reduce the model's predictive power.

Therefore, this review included studies of anticoagulant-associated intracerebral hemorrhage models and risk factors to conduct a systematic review and meta-analysis of risk factors for intracerebral bleeding that may inform treatment, future guideline recommendations, and the development of RAMs.

Method

Search Strategy

The protocol for this systematic review was prospectively registered with PROSPERO (CRD42022316750). Data were reviewed from four databases: PubMed, EMBASE, Web of Science, and the Cochrane Library. Studies in English published before January 2022 were included. The groups of search keywords included were the following: (1) anticoagulant OR anticoagulant drugs OR anticoagulant agents OR anticoagulant therapy; (2) intracerebral hemorrhage OR ICH OR cerebral hemorrhage OR hemorrhagic infarction OR subarachnoid hemorrhage OR subdural hemorrhage OR epidural hemorrhage; and (3) prediction model OR predict* OR risk prediction OR risk factor. A detailed search strategy is presented in Supplemental Material 1.

Study Selection

Studies were selected independently by two researchers and checked to prevent potential errors. A third independent researcher resolved disputes arising in the process of study selection. Studies that met the following criteria were included: (1) use of anticoagulant drugs (e.g., warfarin, rivaroxaban); (2) comparison between the ICH group and the non-ICH group; and (3) the outcome index was risk factors or predictors. Studies that met the following criteria were excluded: (1) patients with ICH treated with nonanticoagulant drugs; (2) no access to data (including no data related to the risk factors in the study, the study was in the design or recruitment stage, no permission to use the data had been granted, or contacted the corresponding author but no reply had been received).

Data Extraction

Data were extracted independently by two researchers and checked to prevent potential errors. A third independent researcher resolved disputes arising in the process of data extraction. The data extracted included the name of the first author, year of publication, time frame, population and their demographics (e.g., sample size, number of centers, age, and sex), study design (e.g., cohort or case–control), type of prediction model study (development, validation, and impact), outcomes, and measures of association (e.g., odds ratio [OR] or risk ratio or hazard ratio, 95% confidence interval [CI], and *P* value).

Quality Assessment

Risk of Bias Assessment

We assessed the risk of bias in the included studies by using the Prediction Study Risk of Bias Assessment Tool for RAM studies [10] and the Quality in Prognosis Studies tool for prognostic factor studies [11–13].

Certainty of Evidence Assessment

We assessed the certainty of the evidence for each risk factor per outcome based on the GRADE approach [14]. The approach considers the following domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. We developed evidence profiles and rated the overall certainty of evidence as high, moderate, and low or very low, depending on the grading of the individual domains [14]. We narratively described the strength of the association by using the terms "there is," "there probably is," or "there may be," depending on whether the quality of the evidence was "high," "moderate," or "low/very low," respectively.

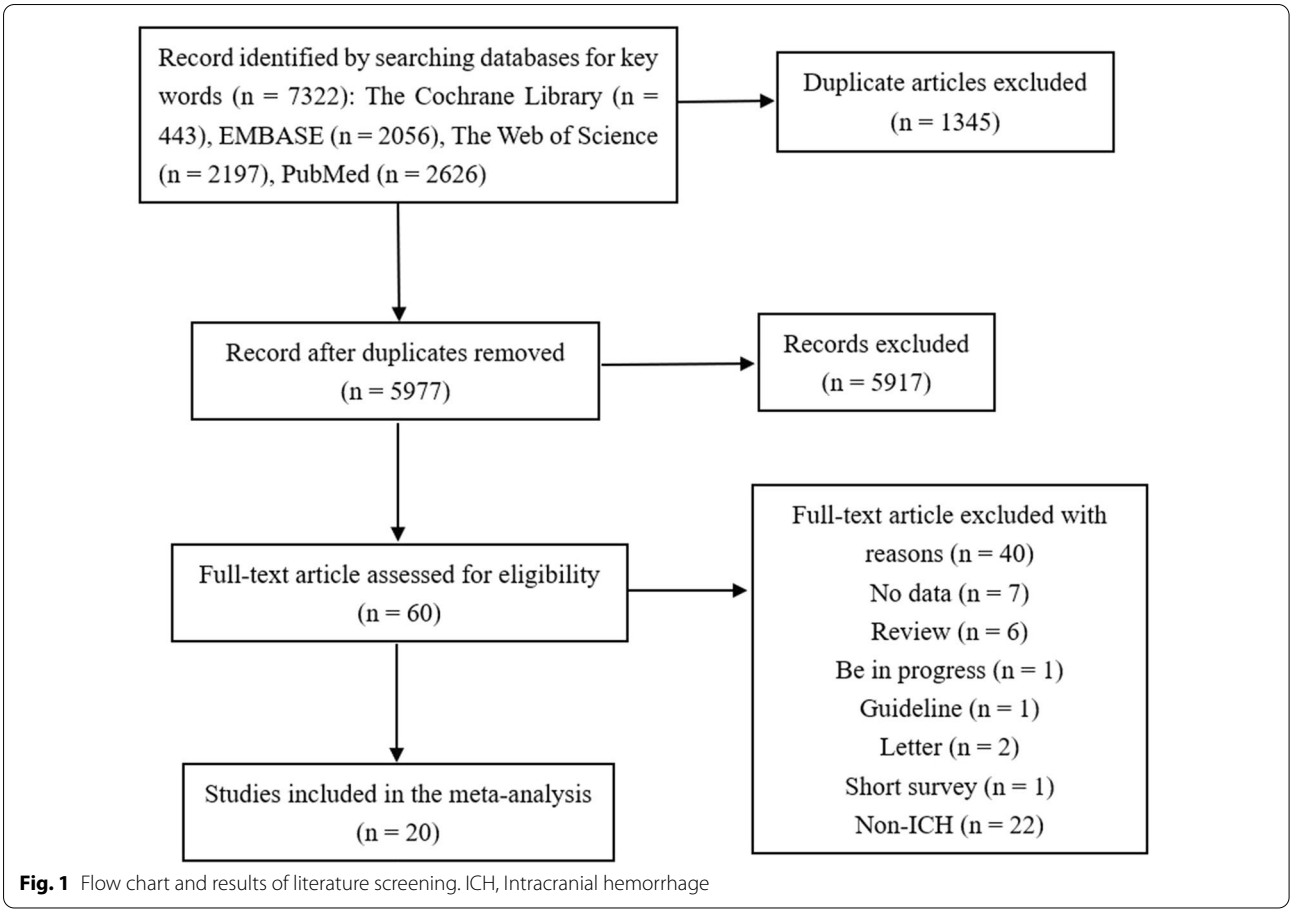

Fig. 1 Flow chart and results of literature screening. ICH, Intracranial hemorrhage

Statistical Analysis

We standardized each risk factor by log transformation [15]. In studies that reported the measure of association as hazard ratio or risk ratio, we converted them to ORs by using the baseline risk reported in the studies [16, 17]. We conducted a meta-analysis of associations by using the generic inverse variance-based method to produce an overall measure of association. The statistical indicators were OR and 95% CI. The χ^2 test was used to test the heterogeneity of results. If $P \geq 0.1$ and $I^2 \leq 50\%$, the fixed-effect model was used for meta-analysis. The random-effect model was used when $P < 0.1$ and $I^2 > 50\%$. To explore the stability of the results, we conducted a sensitivity analysis by eliminating studies one by one. We used the Review Manager 5.3 software for meta-analysis.

Results

The Characteristics of Included Studies

A total of 7322 articles were retrieved based on the search criteria. After screening, 20 articles met the inclusion criteria and were analyzed [18–37]. The flow chart and results of the screening are shown in Fig. 1. Supplemental Table 1 describes the characteristics of the included studies reporting on the outcomes of ICH. Five were prediction model development studies [18–22] and 15 were risk factor studies [23–37]. Fourteen studies were cohorts [18–22, 24–26, 29, 31–33, 36, 37], eight of which were multicenter [18–22, 24, 29, 33]; six were case–control studies [23, 27, 28, 30, 34, 35], two of which were multicenter [30, 35]. Most of the patients were between 60 and 80 years old, and most of them were women. Among the 20 studies, the populations of four studies were patients who had a stroke [18, 23, 33, 37], three were patients with atrial fibrillation [27, 35, 36], five were patients with atrial fibrillation who had a stroke [19, 24, 29, 30, 32], two were in patients with brain injury [22, 25], one was in a patient with venous thromboembolism [21], and five were in patients with anticoagulant therapy of unknown etiology [20, 26, 28, 31, 34].

Risk of Bias Assessment

The risk of bias was serious across all identified studies, each presenting risk of bias in at least one domain or item (Supplemental Table 4). Among the 20 included studies, 12 were retrospective, which may have introduced

classification bias [18, 21, 22, 24–28, 30, 31, 34, 36]. Certainty in evidence was downgraded for imprecision, given that the CI suggests that there may be no association. One of the five prediction model studies and four of the 15 risk factors studies did not clearly describe appropriate outcome measurement [22, 25, 31, 34, 35]. Supplemental Tables 2 and 3 provide detailed judgments for each risk of bias domain criteria.

Analysis of Risk Factors of Anticoagulant-Associated ICH

Investigated were 52 candidate risk factors for ICH from 20 studies. Supplemental Table 2 provides the evidence profile for risk factors of anticoagulant-associated ICH. Supplemental Figs. (sFigs.) 1–52 provides the forest plots of the meta-analysis of each risk factor. In addition, we summarize and group (statistically significant vs. non-statistical significant) the different certainty-risk factors into a new table to permit easy reading. Please see Supplemental Table 5 for details.

Demographic Factors

We found moderate-certainty evidence that there is probably an association between the risk of ICH and race (OR, 1.24; 95% CI, 1.13–1.35; $I^2=31\%$; $P<0.0001$) [19, 20]. Subgroup analysis showed that Asian American (OR, 1.22; 95% CI, 1.08–1.38; $I^2=31\%$; $P=0.001$) [19, 20] and Black race (OR, 1.52; 95% CI, 1.21–1.91; $I^2=57\%$; $P=0.0004$) [19, 20] were statistically significant. See sFig. 1 for details. We found low-certainty evidence that there may be an association between the risk of ICH and age (OR, 1.50; 95% CI, 1.20–1.88; $I^2=88\%$; $P=0.0004$) [18, 19, 21, 27, 30, 34, 35]. See sFig. 2 for details.

Functional Factors

We found moderate-certainty evidence that there is probably an association between the risk of ICH and Townsend score (OR, 1.14; 95% CI, 1.10–1.17; $I^2=0\%$; $P<0.0001$) [20] (see sFig. 3 for details), immobility (OR, 1.99; 95% CI, 1.40–2.83; $P=0.0001$) [21] (see sFig. 4 for details), Glasgow Coma Scale (OR, 3.32; 95% CI, 1.19–9.23; $P=0.02$) [22] (see sFig. 5 for details), and HAS-BLED Score (OR, 1.58; 95% CI, 1.15–2.19; $P=0.005$) [36] (see sFig. 6 for details).

Medical Illness and Patient History Factors

We found moderate-certainty evidence that there is probably an association between risk of ICH and the following: posttraumatic loss of consciousness (OR, 7.35; 95% CI, 2.19–24.64; $P=0.001$) [22] (see sFig. 7 for details), posttraumatic amnesia (OR, 3.96; 95% CI, 1.57–9.99; $P=0.004$) [22] (See sFig. 8 for details), major dynamics (OR, 6.26; 95% CI, 1.89–20.66; $P=0.003$) [22] (see sFig. 9 for details), visible trauma above the clavicles (OR, 3.38; 95% CI, 1.20–9.53; $P=0.02$) [22] (see sFig. 10 for details), posttraumatic headache (OR, 4.17; 95% CI, 1.10–15.78; $P=0.04$) [22] (see sFigu. 11 for details), stroke (OR, 1.43; 95% CI, 1.02–2.00; $P=0.04$) [19] (see sFig. 12 for details), initial infarction location [posterior circulation infarction (PCI)] (OR, 2.28; 95% CI, 1.33–3.91; $P=0.003$) [24] (see sFig. 13 for details), leukoaraiosis (OR, 2.56; 95% CI, 1.60–4.10; $I^2=60\%$; $P<0.0001$) [23, 30, 35] (see sFig. 14 for details), basal ganglia perivascular spaces (OR, 9.75; 95% CI, 2.45–38.89; $P=0.001$) [29] (see sFig. 15 for details), cerebrovascular disease (OR, 2.30; 95% CI, 1.50–3.54; $I^2=0\%$; $P=0.0001$) [28, 34] (see sFig. 16 for details), risk of fall (OR, 1.43; 95% CI, 1.16–1.76; $I^2=0\%$; $P=0.0008$) [35] (see sFig. 17 for details), M1 middle cerebral artery occlusion (OR, 8.67; 95% CI, 1.42–52.94; $P=0.02$) [37] (see sFig. 18 for details), and absence of collateral flow (OR, 17.40; 95% CI, 2.69–112.55; $P=0.003$) [37] (see sFig. 19 for details). We found low-certainty evidence that there may be an association between the risk of ICH and cerebral microbleeds (OR, 8.52; 95% CI, 1.46–49.65; $I^2=66\%$; $P=0.02$) [31–33]. See sFig. 20 for details.

We found low-certainty evidence that there may be an association between the risk of ICH and smoking (OR, 1.60; 95% CI, 1.30–1.97; $I^2=97\%$; $P<0.0001$) [20]. Subgroup analysis showed that former smokers (OR, 1.08; 95% CI, 1.00–1.16; $I^2=51\%$; $P=0.04$) [20] and current smokers (OR, 1.83; 95% CI, 1.59–2.11; $I^2=87\%$; $P<0.0001$) [20] were statistically significant. See sFig. 21 for details. We found low-certainty evidence that there may be an association between the risk of ICH and alcohol intake (OR, 1.17; 95% CI, 1.02–1.34; $I^2=91\%$; $P=0.03$) [20]. Subgroup analysis showed that light alcohol intake (OR, 0.91; 95% CI, 0.83–1.00; $I^2=74\%$; $P=0.05$) [20] and moderate alcohol intake (OR, 1.04; 95% CI, 0.96–1.12; $I^2=0\%$; $P=0.33$) [20] were not statistically significant. However, severe alcohol intake (OR, 1.80; 95% CI, 1.44–2.26; $I^2=60\%$; $P<0.0001$) [20] was statistically significant. See sFig. 22 for details.

We found moderate-certainty evidence that there is probably an association between risk of ICH and the following: diabetes (OR, 4.03; 95% CI, 1.34–12.08; $P=0.01$) [29] (see sFig. 23 for details), esophageal varices (OR, 2.40; 95% CI, 1.30–4.45; $I^2=68\%$; $P=0.005$) [20] (see sFig. 24 for details), chronic liver disease or pancreatitis (OR, 2.09; 95% CI, 1.78–2.45; $I^2=0\%$; $P<0.0001$) [20] (see sFig. 25 for details), tumor (OR, 2.65; 95% CI, 1.30–5.39; $I^2=84\%$; $P=0.007$) [21, 35] (see sFig. 26 for details), anemia (OR, 1.54; 95% CI, 1.07–2.22; $P=0.02$) [21] (see sFig. 27 for details), hyperlipidemia (OR, 2.66; 95% CI, 1.96–3.61; $P<0.0001$) [35] (see sFig. 28 for details), atrial fibrillation (OR, 1.26; 95% CI, 1.09–1.47; $I^2=52\%$; $P=0.002$) [20] (see sFig. 29 for details), congestive heart

failure (OR, 0.56; 95% CI, 0.40–0.78; $P=0.0007$) [35] (see sFig. 30 for details), previous bleeding (OR, 1.35; 95% CI, 1.22–1.50; $I^2=60\%$; $P<0.0001$) [20, 21] (see sFig. 31 for details), distal deep vein thrombosis (OR, 0.39; 95% CI, 0.16–0.95; $P=0.04$) [21] (see sFig. 32 for details), peripheral artery disease (OR, 2.18; 95% CI, 1.50–3.17; $P<0.0001$) [35] (see sFig. 33 for details), and cardiogenic embolism (OR, 18.13; 95% CI, 2.60–126.43; $P=0.003$) [37] (see sFig. 34 for details). We found very low-certainty evidence that there may be little to no association between the risk of ICH and hypertension (OR, 1.16; 95% CI, 0.99–1.37; $I^2=78\%$; $P=0.07$) [20, 28, 32]. See sFig. 35 for details.

Laboratory and Physical Examination Factors

We found moderate-certainty evidence that there is probably an association between the risk of ICH and international normalized ratio (INR) (OR, 3.53; 95% CI, 1.98–6.28; $I^2=65\%$; $P<0.0001$) [25–28, 32]. Subgroup analysis showed that there is probably an association between the risk of ICH and high INR (OR, 4.69; 95% CI, 2.41–9.11; $I^2=63\%$; $P<0.0001$) [25–28, 32]. However, there may be little to no association between the risk of ICH and therapeutic INR (OR, 1.83; 95% CI, 0.43–7.75; $I^2=73\%$; $P=0.41$) [25, 26] and subtherapeutic INR (OR, 2.23; 95% CI, 0.61–8.11; $P=0.22$) [25]. See sFig. 36 for details. We found moderate-certainty evidence that there is probably an association between risk of ICH and serum albumin (OR, 1.40; 95% CI, 1.12–1.74; $P=0.003$) [19] (see sFig. 37 for details), prothrombin time (OR, 3.18; 95% CI, 1.79–5.65; $I^2=60\%$; $P<0.0001$) [21, 31, 34] (see sFig. 38 for details), diastolic blood pressure (DBP) (OR, 1.17; 95% CI, 1.01–1.36; $P=0.04$) [19] (see sFig. 39 for details), estimated glomerular filtration rate (eGFR) (OR, 1.95; 95% CI, 1.04–3.66; $P<0.04$) [18] (see sFig. 40 for details), infarct volume (OR, 1.10; 95% CI, 1.06–1.14; $P<0.0001$) [18] (see sFig. 41 for details), moderate/severe white matter hyperintensities (OR, 6.28; 95% CI, 1.62–24.34; $P=0.008$) [33] (see sFig. 42 for details), and vitamin E (OR, 3.50; 95% CI, 1.74–7.06; $I^2=0\%$; $P=0.0005$) [36] (see sFig. 43 for details). We found low-certainty evidence that there may be an association between the risk of ICH and platelet count (OR, 1.49; 95% CI, 1.11–2.00; $I^2=94\%$; $P=0.008$) [19–21]. See sFig. 44 for details. In addition, we found very low-certainty evidence that there may be little to no association between the risk of ICH and creatinine clearance (CrCl) (OR, 1.48; 95% CI, 0.68–3.23; $I^2=93\%$; $P=0.33$) [21, 35]. See sFig. 45 for details.

Medication Factors

We found moderate-certainty evidence that there is probably an association between the risk of ICH and the duration of oral anticoagulant (OAC) therapy (OR, 3.85; 95% CI, 1.66–8.96; $I^2=0\%$; $P=0.002$) [28] (see sFig. 46 for details), anticoagulants (OR, 3.88; 95% CI, 2.08–7.24; $I^2=0\%$; $P<0.0001$) [20] (see sFig. 47 for details), presence of a prosthetic heart valve (OR, 2.10; 95% CI, 1.20–3.67; $P=0.009$) [34] (see sFig. 48 for details), antidepressants (OR, 1.34; 95% CI, 1.27–1.41; $P<0.0001$) [20] (see sFig. 49 for details), anticonvulsants (OR, 2.12; 95% CI, 1.83–2.46; $P<0.0001$) [20] (see sFig. 50 for details), and low doses (given according to label or not) (OR, 0.43; 95% CI, 0.32–0.58; $P<0.0001$) [35] (see sFig. 51 for details). We found low-certainty evidence that there is probably an association between the risk of ICH and antiplatelet drugs (OR, 1.42; 95% CI, 1.18–1.70; $I^2=85\%$; $P=0.0002$) [20, 35]. See sFig. 52 for details.

Sensitivity Analysis

Sensitivity analysis was conducted by eliminating studies one by one. There were no significant changes in the outcome except for previous bleeding, leukoaraiosis, cerebral microbleeds, cerebrovascular disease, alcohol intake, CrCl, and antiplatelet drugs, indicating that most of the results were stable.

Discussion

Summary of Findings

We evaluated 52 risk factors for anticoagulant-associated ICH. We identified several statistically significant predictors such as race, Townsend score, immobility, Glasgow Coma Scale, HAS-BLED Score, posttraumatic loss of consciousness, posttraumatic amnesia, major dynamics, visible trauma above the clavicles, posttraumatic headache, stroke, initial infarction location (PCI), leukoaraiosis, basal ganglia perivascular spaces, cerebrovascular disease, risk of fall, M1 middle cerebral artery occlusion, absence of collateral flow, diabetes, esophageal varices, chronic liver disease or pancreatitis, tumor, anemia, hyperlipidemia, atrial fibrillation, congestive heart failure, previous bleeding, distal deep vein thrombosis, peripheral artery disease, cardiogenic embolism, INR, serum albumin, prothrombin time, DBP, eGFR, infarct volume, moderate/severe white matter hyperintensities, vitamin E, duration of OAC therapy, anticoagulant, presence of a prosthetic heart valve, antidepressants, anticonvulsants, and low doses (given according to label or not), which are supported by moderate certainty of the evidence.

We also found low-certainty evidence that there may be an association between the risk of ICH and age, cerebral microbleeds, smoking, alcohol intake, platelet count, and antiplatelet drug. However, we found very low-certainty evidence that there may be little to no association between the risk of ICH and hypertension and CrCl. Therefore, in addition to anticoagulant therapy that can affect ICH, other risk factors such as immobility, risk of

falls, smoking, alcohol intake, diabetes, anemia, hyperlipidemia, INR, DBP, vitamin E, duration of OAC therapy, antiplatelet drugs, presence of a prosthetic heart valve, antidepressants, anticonvulsants, and low doses (given according to label or not) should also be paid attention to during treatment as a way to reduce the occurrence of ICH.

Implications for Practice

Our study identified candidate risk factors for ICH, such as age, race, previous bleeding, hypertension, tumor, platelet count, prothrombin time, CrCl, and antiplatelet drugs, that have been considered in the analysis of some developed and widely used RAMs in daily practice, such as PANWARDS, QBleed, and RIETE [19–21]. However, based on our meta-analysis results, some factors that we identified as having a possible association with ICH were not included or considered in the development of most of the RAMs, such as leukoaraiosis, cerebral microbleeds, cerebrovascular disease, and INR.

First, most studies consistently report advancing age as one of the most important risk factors [6, 38]. Several studies have shown that increasing age is associated with a greater risk for serious hemorrhagic complications [39–41]. The proportion of patients found to be anticoagulated excessively has generally ranged from 6 to 38% of patients admitted with OAC-related ICH [42, 43]. Therefore, older patients should reduce the anticoagulation intensity (for example, the dose should be reduced). Moreover, we also found that both smoking and alcohol intake may be related to ICH, which is consistent with the results of a previous study [44]. The possible mechanism is that vascular endothelium's function decreases and blood vessels' fragility increases [45], making ICH more likely to occur. However, we found that only severe alcohol intake could lead to ICH. Small or moderate alcohol intake does not cause ICH, which may be related to the fact that alcohol can soften blood vessels. Therefore, patients should quit smoking in life, and moderate drinking may be beneficial to their health.

We found that immobility ≥ 4 days may be related to ICH. Immobility may cause varicose veins or venous thrombosis of lower limbs, which may cause ICH due to anticoagulation treatment. Patients should get out of bed and walk more to reduce the risk of bleeding caused by immobility. In addition, older patients have a higher risk for falls [46], which may place them at higher risk for ICH. Our study also concluded that a high fall risk might also be associated with intracerebral hemorrhage. Therefore, patients should exercise moderately, preferably accompanied by their families, and try to avoid falling.

Diabetes is a risk factor for ICH in our study, presumably by the effect of high glucose on the microcirculation, which enhances the effect of ischemic injury and damage to the blood–brain barrier [47]. Further, we found that a history of hyperlipidemia was a risk factor for ICH, as identified by Tong and colleagues [48]. Therefore, patients should pay attention to diet in life, avoid high sugar and fat intake, and control basic diseases.

Our findings of a higher risk of anticoagulant-associated ICH in patients with a history of stroke are consistent with other observational studies and schema for predicting an increased risk of major bleeding among anticoagulated individuals in other populations [49, 50]. This may be related to the destruction of the blood–brain barrier by stroke, thus increasing the incidence of bleeding [51]. Atrial fibrillation is closely related to stroke, which is also considered an important risk factor for ICH [52, 53]. Saposnik et al. [54] suggested that the adverse effects of atrial fibrillation were attributable to large areas of low perfusion and low recanalization, resulting in increased infarct volume and ICH severity. The results of our research are roughly the same as those above. We also found an interesting result that congestive heart failure may be a protective factor for ICH. The lower risk of ICH in patients with a history of congestive heart failure (CHF) may reflect a hypercoagulable heart failure state [55].

We found that there is probably an association between the risk of ICH and an INR above the therapeutic range, which aligns with previous publications [56, 57]. Intracerebral hemorrhages seem to be more severe at a higher INR. Two studies found the proportion of over-anticoagulated patients to be significantly higher among patients with ICH than in control patients (33% vs. 5%, $P<0.001$; and 10% vs. 3%, $P=0.04$) [58]. Therefore, it is of the utmost importance to consider the accuracy of diagnosis and the strength of indication before starting OAC therapy. The need for regular monitoring of OAC therapy is, of course, self-evident. Each indicator's lowest effective target INR should be recommended [59–61].

Other findings from this study are the association of declining platelet count and albumin with an increased risk of ICH, which is consistent with Hankey et al. [19]. A reduced platelet count below 210×109/L was associated with an increased hazard of ICH. The higher risk of ICH with declining serum albumin may reflect that warfarin and rivaroxaban are highly protein-bound [55]. Therefore, clinicians should closely monitor the value of serum albumin and platelet count and use human serum albumin and thrombopoietin when necessary to prevent the increased risk of ICH.

The findings of elevated blood pressure are consistent with other observational studies and schema for predicting an increased risk of ICH among anticoagulated individuals in other populations [62, 63]. Therefore, patients

should control their blood pressure within 140/90 mm Hg (older patients within 150 mm Hg) to prevent ICH caused by hypertension.

Previous reports suggest that renal failure is associated with higher bleeding rates in patients with atrial fibrillation [64]. It is also known that patients with end-stage renal disease on hemodialysis are prone to thrombosis and bleeding. One of the potential ways that renal failure increases bleeding risk is through the secondary dysfunction of platelets ("uremic platelets") [65]. Although the underlying mechanism of the dysfunction is poorly understood and little data exist on milder renal dysfunction, we should pay attention to the renal function of patients in clinical work, such as GFR and ClCr, to prevent ICH caused by renal function damage.

Most reports dealing with OAC-related ICH have discussed the impact of the duration of therapy on the risk of bleeding. One opinion is that the risk of an ICH is increased in the first months after starting OAC therapy [66, 67]. In addition, other cohort studies have found that recently starting OAC treatment (≤ 3 months) increases the risk of any bleeding [68, 69]. The findings from our study are entirely in keeping with the mentioned view. We found that there is probably an association between the risk of ICH and the duration of OAC therapy (≤ 12 months). This may indicate a "healthy patient" effect: patients who are perceived to be at the greatest risk of sustaining an ICH may be taken off OAC therapy prematurely. Therefore, family members and doctors should pay more attention to the bleeding risk of patients in the first few months or even a year of OAC treatment, observe whether patients have symptoms such as headache or vomiting, make regular outpatient follow-ups to adjust the dosage, and control other risk factors, such as hypertension and hyperlipidemia, to reduce the incidence of ICH.

The interactions between drugs are very complex. Different drugs may interact to cause adverse reactions. Quantifying the absolute risk of bleed for an individual receiving anticoagulation treatment is important. So, clinicians should monitor high-risk patients to help reduce their risk. For example, this could be achieved by modifying known risk factors for bleed, including avoiding the use of concurrent drugs known to increase the risk of bleeding, such as nonsteroidal anti-inflammatory drugs and antidepressants [70].

There is some uncertainty about aspirin's impact on the risk of sustaining an OAC-related ICH. One review claimed that aspirin would double the risk of intracerebral bleeding, regardless of dose [71]. However, in two case–control studies, aspirin in its usual prophylactic dose did not significantly increase the risk of intracerebral bleeding [72, 73]. The results of this study are roughly the same as those of the first view. Aspirin is an antiplatelet drug and a nonsteroidal anti-inflammatory drug, increasing the risk of ICH to a certain extent. Therefore, the use of aspirin in anticoagulant therapy should be carefully measured.

Strengths

Our study followed rigorous methods, conducted extensive searches, duplicate and independent screening, and data extraction, and assessed the certainty of evidence based on a structured framework. In addition, we conducted sensitivity analyses to determine the stability of the results. The greatest advantage is the comprehensiveness of the study results, which may have some clinical significance in preventing the occurrence of anticoagulant-associated ICH.

Limitations and Challenges

Because most of the studies included in this review were retrospective, classification and recall bias may lead to potential limitations. In addition, potential limitations of the included studies related to the inconsistency and variability across eligibility criteria in the original studies and variability in study design, study type, sample size, and definitions of the risk factors. Therefore, more rigorous, large-scale studies are needed to confirm our findings, and further analysis is necessary to provide a more reliable basis for clinical work.

Implications for Future Research

Researchers can reevaluate existing models by incorporating additional risk factors to create a more refined clinical prediction model. Considering the small number of studies included in this study, the model's developers may need to properly consider and further investigate all the risk factors we identified to support adequate model development and improvements for clinical practice.

Conclusions

This systematic review identified all reported risk factors for ICH associated with anticoagulant drugs. Some of these factors are not included in current ICH risk prediction models. Our findings will help inform experts in developing population-based guidelines and accurate, user-friendly RAMs to better guide individual patient prophylactic management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12028-022-01671-4.

Abbreviations

ICH: Intracranial hemorrhage; RAM: Risk assessment model; OR: Odds ratio; RR: Risk ratio; HR: Hazard ratio; CI: Confidence interval; PROBAST: The Prediction Study Risk of Bias Assessment Tool; QUIPS: The Quality in Prognosis Studies tool; AF: Atrial fibrillation; VTE: Venous thromboembolism; GCS: Glasgow Coma Scale; BGPVS: Basal ganglia perivascular spaces; MCA: Middle cerebral artery; DVT: Deep vein thrombosis; INR: International normalized ratio; PT: Prothrombin time; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; CrCl: Creatinine clearance; OAC: Oral anticoagulant.

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Author contributions
All authors made a substantial contribution to the concept and design of the study, interpreted the data, and reviewed the article. ZZW and CJN initiated the study. ZZW, CJN, QJF, and MFX performed data extraction and analyses and drafted the first version of the article. CJN, LMN, and ZJH critically reviewed the article and revised it. The final manuscript was approved by all authors.

Source of support
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest
The authors declare that they have no conflicts of interest.

Ethical approval/informed consent
We confirm adherence to ethical guidelines. This article does not contain any studies with human participants or animals performed by any of the authors.

Publisher's Note

Received: 19 August 2022 Accepted: 21 December 2022
Published: 20 January 2023

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