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Risk factors for anticoagulant-associated gastrointestinal hemorrhage: a systematic review and meta-analysis

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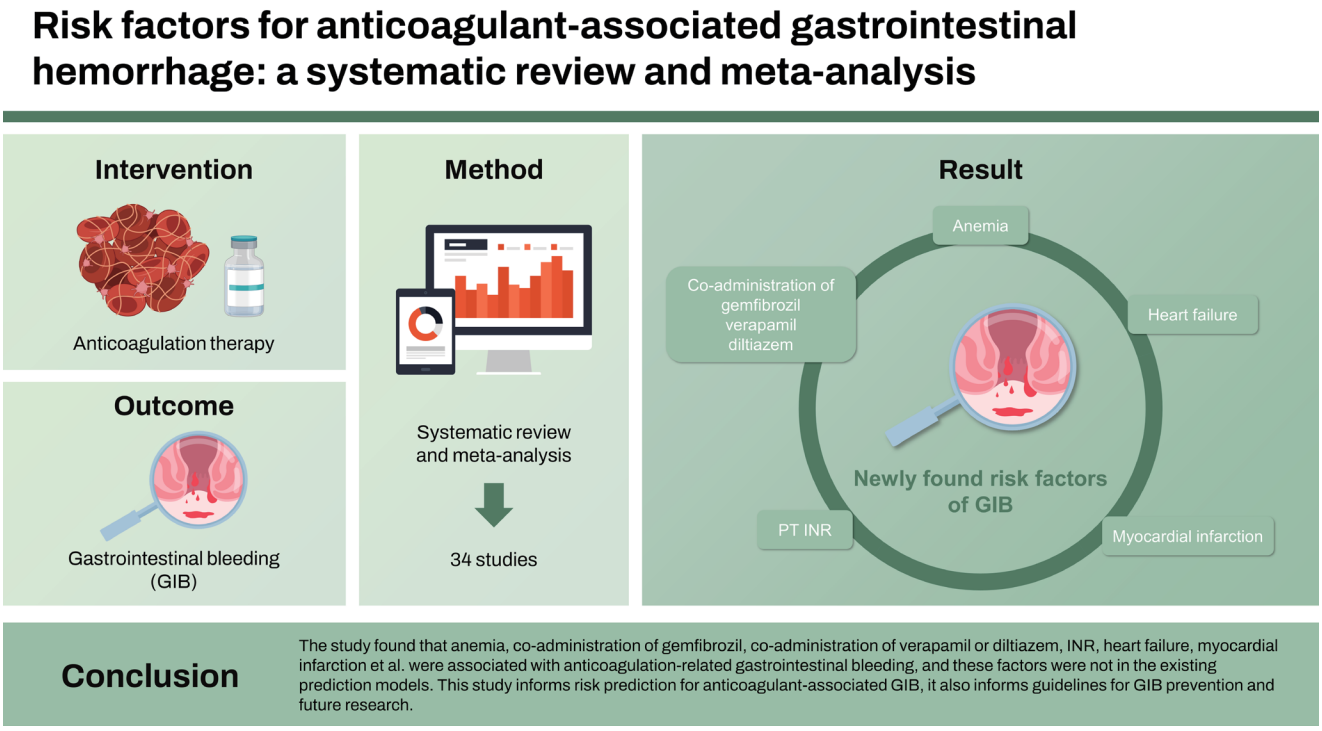

Background/Aims: There may be many predictors of anticoagulation-related gastrointestinal bleeding (GIB), but until now, systematic reviews and assessments of the certainty of the evidence have not been published. We conducted a systematic review to identify all risk factors for anticoagulant-associated GIB to inform risk prediction in the management of anticoagulation-related GIB.

Methods: A systematic review and meta-analysis were conducted to search PubMed, EMBASE, Web of Science, and Cochrane Library databases (from inception through January 21, 2022) using the following search terms: anticoagulants, heparin, warfarin, dabigatran, rivaroxaban, apixaban, DOACs, gastrointestinal hemorrhage, risk factors. According to inclusion and exclusion criteria, studies of risk factors for anticoagulation-related GIB were identified. Risk factors for anticoagulant-associated GIB were used as the outcome index of this review.

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Results: We included 34 studies in our analysis. For anticoagulant-associated GIB, moderate-certainty evidence showed a probable association with older age, kidney disease, concomitant use of aspirin, concomitant use of the antiplatelet agent, heart failure, myocardial infarction, hematochezia, renal failure, coronary artery disease, helicobacter pylori infection, social risk factors, alcohol use, smoking, anemia, history of sleep apnea, chronic obstructive pulmonary disease, international normalized ratio (INR), obesity et al. Some of these factors are not included in current GIB risk prediction models. such as anemia, co-administration of gemfibrozil, co-administration of verapamil or diltiazem, INR, heart failure, myocardial infarction, etc.

Conclusions: The study found that anemia, co-administration of gemfibrozil, co-administration of verapamil or diltiazem, INR, heart failure, myocardial infarction et al. were associated with anticoagulation-related GIB, and these factors were not in the existing prediction models. This study informs risk prediction for anticoagulant-associated GIB, it also informs guidelines for GIB prevention and future research.

Keywords: Gastrointestinal hemorrhage; Risk factor; Predict; Meta-analysis

INTRODUCTION

Anticoagulants including heparin, low molecular heparin, fondaparinux, warfarin and novel oral anticoagulants (NOACs) are effective against acute or chronic thromboembolic complications [1-3]. Anticoagulants increase the risk of bleeding while exerting their antithrombotic effect. The annual rate of major bleeding in patients taking warfarin is reported to be as high as 8%, with gastrointestinal bleeding (GIB) being the most common [4]. The incidence of GIB during antithrombotic therapy with vitamin K antagonists (VKAs) ranges from 1.5% to 4.5% [5,6] and may result in a 10–15% short-term mortality rate [7-9]. And with millions of patients currently receiving anticoagulation therapy worldwide, it is necessary to accurately predict the risk of GIB associated with anticoagulants.

The risk assessment models (RAMs) for anticoagulation-related GIB consists of a combination of multiple predictors. Risk for specific endpoints can be obtained based on relevant predictors, thus providing recommendations for patient stratification [10].

Although these models can prevent GIB to some extent, most were developed using existing data rather than based on a systematic review of all potential risk factors [11]. The risk factors included in existing models are not comprehensive and may reduce the predictive power of the model. Therefore, this review conducts a systematic review and meta-analysis of risk factors for GIB that may inform anticoagulation therapy, future guideline recommendations, and the development of RAMs.

METHODS

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [12]. The protocol for this systematic review was prospectively registered with PROSPERO (CRD 42022340867).

Patient and public involvement

No patient involved.

Search strategy

Data were reviewed from four databases: PubMed, EMBASE, Web of Science, and the Cochrane Library. Studies in English published before January 21, 2022 were included. To ensure a comprehensive literature search, we also identified additional studies by searching the reference list of the literature.

Supplementary Material 1 provides detailed descriptions of the search strategy.

Study selection

Studies that met the following criteria were included: Use of anticoagulants (e.g., heparin, VKAs, NOACs); Comparison between the GIB group and the non-GIB group; The outcome index was risk factors or predictors.

Studies that met the following criteria were excluded: Patients with GIB treated with non-anticoagulant medications; Incomplete data (including data related to risk factors not obtained, a study in design or recruitment phase, permission

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to use data not obtained, the corresponding author contacted but not responded to).

Data extraction

For all identified studies, RAMs, and prognostic factor studies, 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), outcomes and measures of association (e.g., odds ratio [OR] or risk ratio [RR] or hazard ratio [HR], 95% confidence interval [CI] and *p* value). GIB was defined as a reduction in the Hb level ≥ 2 g/dL, or transfusion of at least 2 units of blood.

Quality assessment

Risk of bias assessment

We assessed the risk of bias in the included studies by using the Prediction model Risk Of Bias Assessment Tool (PROBAST) for RAM studies and the Quality in Prognosis Studies (QUIPS) tool for prognostic factor studies [13-15].

Certainty of evidence assessment

We performed an assessment of the certainty of the evidence for each of the prognostic factors per outcome based on the GRADE approach. 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 [16].

Statistical analysis

We standardized each risk factor by log transformation and unifying the direction of the predictors. In studies that reported the measure of association as a HR or RR, we converted them to OR using the baseline risk reported in the studies [17,18]. We used the Review Manager 5.3 software for meta-analysis. The statistical indicators were OR and 95% CI. The chi-square test (χ^2) 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 $I^2 > 50\%$.

RESULTS

The characteristics of included studies

Our search identified 13,042 citations, of which we included 114 studies for full-text assessment. Finally, 34 articles fulfilled the inclusion criteria and were included in this study. Figure 1 is a PRISMA flowchart. Supplementary Table 1 describes the characteristics of the included studies reporting on the outcomes of GIB. Thirty-three studies were risk factor studies [19-50,51]. One study was a prediction model development study [52]. Twnety-seven studies were cohorts [19-21,23-25,27-29,31,34,36-49,51,52]: 1 of which was prospective cohort [40], 26 of which were retrospective cohorts [19-21,23-25,27-29,31,34,36-39,41-49,51,52]. Two studies were case-control studies [26,32], 5 were randomized controlled trials (RCTs) [22,30,33,35,50]. Among the 34 studies, the populations of 23 studies were only stroke patients [19-22,25,27-37,39-41,43,44,47,50], the composition of the population indications in the remaining 11 studies included atrial fibrillation, venous thromboembolism, pulmonary embolism, deep vein embolism, and stroke [23,24,26,38,42,45,46,48,49]. Most patients were between 50 and 80 years old, and most were male.

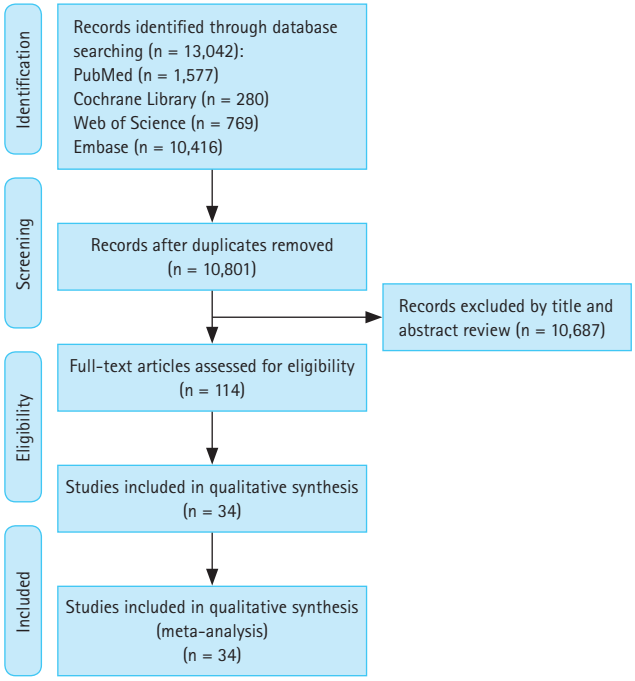

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart.

Risk of bias assessment

The risk of bias was serious across all identified studies, each presenting risk of bias in at least 1 domain or item (Supplementary Table 2). Among the 34 included studies, 26 were retrospective, which may have introduced classification bias [19-21,23-25,27-29,31,34,36-49,51,52]. We detected evidence of publication bias through visual assessment of asymmetry of the funnel plot for each pooled predictor in those that included at least 10 studies (Supplementary Table 2). Certainty in evidence was downgraded for imprecision, given that the CI suggests that there may be no association. 2 of the 33 risk factors studies did not clearly describe appropriate outcome measurement [37,38]. Supplementary Table 3 and 4 provide detailed judgments for each risk of bias domain criteria.

Analysis of risk factors of anticoagulant-associated gastrointestinal bleeding

Investigated were 48 candidate risk factors for GIB from 34 studies. Supplementary Table 2 provides the evidence profile for anticoagulant-associated GIB risk factors. Supplementary Figure (S1-S48) provides the forest plots of the meta-analysis of each of the risk factors.

Demographic factors

We found moderate-certainty evidence that there is probably an association between risk of GIB and older age (OR, 1.95; 95% CI, 1.36–2.79) [19,23,24,28,33,36,45,47], age growth (age per year increase; OR, 1.03; 95% CI, 1.01–1.06; age increase per five years; OR, 1.11; 95% CI, 1.06–1.17) [40,50,51], and obesity (weight > 120 kg; OR, 1.44; 95% CI, 1.01–2.05) [25]. We found low-certainty evidence that there may be little to no association between risk of GIB and sex (male vs. female; OR, 0.95; 95% CI, 0.72–1.26) [20,26,28,36,39,40,47].

Functional factors

There was moderate-certainty evidence for a probable association between the risk of GIB and any international normalized ratio (INR) (OR, 2.43; 95% CI, 1.30–4.53) [24,41]. We found very-low-certainty evidence that there may be little to no association between the risk of GIB and Has-Bled-Score (≥ 3; OR, 1.20; 95% CI, 0.06–22.63) [19,41].

Medical illness and patient history factors

We identified moderate-certainty evidence for an association between the risk of GIB and kidney disease (OR, 1.69; 95% CI, 1.24–2.31) [19,36,45,46,52], cirrhosis (OR, 6.24; 95% CI, 2.63–14.83) [24,52], liver failure (OR, 7.01; 95% CI, 4.78–10.27) [26], and heart failure (HF) (OR, 1.30; 95% CI, 1.14–1.49) [28,36,46]. Subgroup analysis showed that congestive HF (OR, 1.29; 95% CI, 1.06–1.57) [28,36] and chronic HF (OR, 1.31; 95% CI, 1.09–1.58) [46] were statistically significant. We found moderate-certainty evidence that there is probably an association between the risk of GIB and history of bleeding (OR, 3.26; 95% CI, 1.86–5.73) [28], myocardial infarction (OR, 2.23; 95% CI, 1.12–4.43) [28], renal failure (OR, 3.18; 95% CI, 1.44–6.99) [34,47], coronary artery disease (OR, 1.36; 95% CI, 1.10–1.69) [36], *Helicobacter pylori* infection (OR, 4.75; 95% CI, 1.93–11.68) [36], anemia (OR, 1.48; 95% CI, 1.10–1.98) [36,50], history of sleep apnea (OR, 1.60; 95% CI, 1.22–2.10) [50], psychiatric illness, defined as schizophrenia, affective psychosis, paranoia, or other nonorganic psychosis (OR, 1.20; 95% CI, 1.03–1.39) [46], venous thromboembolism including deep vein thrombosis (OR, 1.21; 95% CI, 1.02–1.44) [36,46].

Furthermore, we identified low-certainty evidence that there may be little to no association between the risk of GIB and peripheral vascular disease including peripheral artery disease (OR, 2.33; 95% CI, 0.66–8.20) [28,36], mechanical valve implantation (OR, 1.97; 95% CI, 0.43–9.07) [45], liver disease (OR, 1.31; 95% CI, 0.99–1.74) [46], diabetes (OR, 1.08; 95% CI, 0.96–1.21) [36,46], and chronic obstructive pulmonary disease (OR, 2.01; 95% CI, 0.69–5.83) [50,52].

We found very-low-certainty evidence that there may be an association between the risk of GIB and history of peptic ulcer/GIB (OR, 5.26; 95% CI, 2.76–10.05) [19,23,24,28,30,39,41,45,47,48,50-52].

Laboratory and physical examination factors

There was moderate certainty evidence of a probable association between the risk of GIB and creatinine level (per 1 mg/dL increase; OR, 1.38; 95% CI, 1.09–1.74) [40] and diastolic BP (decrease to < 80 mmHg; OR, 1.10; 95% CI, 1.05–1.16) [50]. We identified low-certainty evidence that there may be an association between the risk of GIB and creatinine clearance (< 60 mL/min; OR, 1.06; 95% CI, 1.01–1.12) [50].

Medication factors

We found moderate-certainty evidence that there is probably an association between the risk of GIB and concomitant use of aspirin (OR, 2.07; 95% CI, 1.17–3.66)

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[22,23,26,27,47] and concomitant with non-steroidal anti-inflammatory drugs (NSAIDs) (OR, 2.37; 95% CI, 1.61–3.50) [26,39,43,47]. Subgroup analysis showed that combination of paracetamol (OR, 1.47; 95% CI, 1.35–1.60) [26] and combination of COX-2 inhibitor (OR, 1.97; 95% CI, 1.59–2.40) [26] were statistically significant. We found moderate-certainty evidence that there is probably an association between the risk of GIB and antiplatelet therapy (OR, 1.45; 95% CI, 1.11–1.90) [19,27,36,39,42,47,48,50,51], concomitant use of dronedarone (OR, 1.29; 95% CI, 1.04–1.62) [29], concomitant use of CYP3A4 or P-glycoprotein inhibitors (OR, 1.47; 95% CI, 1.15–1.88) [31], combination of digoxin (OR, 1.50; 95% CI, 1.19–1.88) [36], combination of gemfibrozil (OR, 2.29; 95% CI, 1.61–3.25) [38], combination of verapamil or diltiazem (OR, 2.33; 95% CI, 1.82–2.98) [44], and long-term acetylsalicylic acid (ASA) use at screening (OR, 1.47; 95% CI, 1.26–1.72) [50].

However, low-quality evidence showed that there may be little to no association between the risk of GIB and combination of clopidogrel (OR, 2.37; 95% CI, 1–5.65) [19], combination of corticosteroid (OR, 2.14; 95% CI, 0.98–4.72) [19,41], combination of thienopyridines (OR, 2.37; 95% CI, 0.75–7.44) [47].

We identified low-certainty evidence that there may be an association between the risk of GIB and concomitant use of oral glucocorticoid (OR, 1.83; 95% CI, 1.30–2.59) [32].

Other factors

There was moderate-certainty evidence of a probable association between risk of GIB and social risk factors, defined as lack of housing, inadequate housing, inadequate material resources, persons living alone, no other household member able to render care, or non-compliance with medical treatment (OR, 1.29; 95% CI, 1.12–1.48) [46]. We also identified moderate-certainty evidence that there is probably an association between risk of GIB and alcohol use (OR, 3.46; 95% CI, 2.30–5.19) [26,36] and smoking (OR, 1.26; 95% CI, 1.18–1.35) [26,50], anticoagulant treatment time (≤ 100 d; OR, 4.94; 95% CI, 2.66–9.17) [47-49], and substance abuse, defined as alcohol dependence, drug dependence, or non-dependent abuse, excluding tobacco use disorder (OR, 1.41; 95% CI, 1.07–1.87) [46].

We identified low-certainty evidence that there may be an association between the risk of GIB and dabigatran 150 mg twice daily (OR, 1.53; 95% CI, 1.39–1.69) [21,35].

DISCUSSION

We evaluated 48 risk factors for anticoagulant-associated GIB. We also identified several statistically significant predictors, such as social risk factors, alcohol consumption, smoking, co-administration of aspirin, co-administration of NSAIDs, renal disease, cirrhosis, liver failure, INR, older age, age growth, obesity (weight > 120 kg) et al., which supported by moderate certainty of the evidence.

Therefore, in addition to anticoagulation therapy, which can affect GIB, other risk factors should also be noted. We can intervene in undesirable behaviors such as drinking and smoking through behavior-based education, minimize the combination of drugs such as aspirin, NSAIDs, antiplatelet drugs, verapamil or diltiazem, and anticoagulants, and actively treat kidney disease, cirrhosis, liver failure, and HF to reduce the occurrence of GIB.

Our study identified candidate risk factors for GIB, such as age, smoking, alcohol consumption, the combination of aspirin, the combination of NSAID, antiplatelet therapy, diabetes, cirrhosis, peripheral vascular disease, renal disease, etc. These risk factors have been considered in the analysis of some developed and widely used RAMs in daily practice, such as New Score, RIETE Score, Cuschieriet al. Score, and de Groot et al. Score [52-55]. However, some factors that we identified as having a probable association with GIB, based on our meta-analysis results, were not included or considered in the development of most of the RAMs, such as history of sleep apnea, co-administration of CYP3A4 or P-glycoprotein antagonists, co-administration of digoxin, co-administration of gemfibrozil, co-administration of verapamil or diltiazem, INR, HF, myocardial infarction, long-term ASA use at screening. This deserves our special concern. In addition, we found that antiplatelet theapy was associated with GIB risk. This observation was opposite to Nawarawong et al.'s study [42]. Antiplatelet theapy showed no association with GIB risk in their study. We believe that such reverse causation, given the study design, may be plausible. However, given the small sample size, the finding warrants further investigations in primary studies.

We found that dabigatran dose 150 mg is associated with GIB, which is an interesting point. Of note, in a previous meta-analysis by our research team, a higher risk of GIB with dabigatran than with warfarin had been demonstrated [56]. This result should draw clinicians' attention to the possible benefit of monitoring patients' risk of GIB after administra-

tion of dabigatran 150 mg.

In our meta-analyses, proton pump inhibitor (PPI) use decreased the risk of GIB by half (HR, 0.5), which closely reflects the findings of Ray et al. [57], who reported that PPI use was associated with a substantial reduction in the risk of warfarin-related upper GIB (HR, 0.76). Although PPI therapy was not included in either the HAS-BLED score, ATRIA score or ORBIT score, PPI use is an important means of preventing GIB in the long term.

We also did subgroup analyses to explore the sources of heterogeneity in history of peptic ulcer/GIB (I^2 = 97%). Subgroup analysis by population, design type, sample size, and study quality showed that retrospective cohort studies were the main cause of heterogeneity, with little heterogeneity in the RCT group.

The greatest advantage of our study is the comprehensiveness of the study results, which may have some clinical significance in preventing the occurrence of anticoagulant-associated GIB.

The study also has some limitations. Since 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. For example, in our study, 22 studies included only atrial fibrillation indications, while others 11 studies included venous thromboembolism, pulmonary embolism, deep vein embolism, and stroke in addition to atrial fibrillation. In anticoagulation, different populations will influence the choice of drug as well as the dose and duration of drug therapy and significantly affect the outcome of GIB in each study. Study effect OR value is closely related to outcomes, and we found significant differences in OR value for the same variables across studies. Of note, the process of meta-analysis may cause variables that were originally risk factors to become nonsignificant, or even to become protective factors.

Research may be needed to reevaluate existing RAMs, as the developers of the models may not have been able to use the variables we identified, given the limitations in the existing databases. However, full development or improvement of a RAM that supports clinical practice requires further investigation of all the prognostic factors we identified in our study. Therefore, more rigorous and large-scale studies are needed to confirm our findings, and further analysis is necessary to provide a more reliable basis for clinical work.

KEY MESSAGE

1. In this systematic review, we identified all reported risk factors for anticoagulation-associated GIB (e.g., alcohol consumption, smoking, co-administration of aspirin).
2. Some risk factors not included in current GIB risk prediction models (e.g., anemia, history of sleep apnea, co-administration of digoxin).
3. Our findings will help inform experts in developing population-based guidelines and accurate, user-friendly RAMs to guide individual patient management better.

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