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Association between *CES1* rs2244613 and the pharmacokinetics and safety of dabigatran: Meta-analysis and quantitative trait loci analysis

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Objective: To date, the influence of the carboxylesterase 1 (*CES1*) rs2244613 genotype on the pharmacokinetics (PKs) and safety of dabigatran remains controversial. Hence, a systematic review was performed to study the association between *CES1* rs2244613 genotype and the PKs and safety of dabigatran and *CES1* relative expression.

Methods: In addition to the three English databases (Web of Science, PubMed, and Embase), two Chinese databases (CNKI and Wanfang) were thoroughly revised. The mean differences (MD) and corresponding 95% confidence intervals (CI) were applied to evaluate the differences in PKs between the *CES1* rs2244613 genotype. Odds ratio (OR) was used to study the risk for bleeding events between the *CES1* rs2244613 genotypes. Subsequent expression quantitative trait loci (eQTL) analyses were performed to evaluate genotype-specific expressions in human tissues.

Results: Ten studies (n = 2,777) were included. *CES1* rs2244613 G allele carriers exhibited significantly lower dabigatran trough concentrations compared to T allele carriers (MD: −8.00 ng/mL; 95% CI: −15.08 to −0.92; p = 0.03). The risk for bleeding events was significantly lower in carriers of the G allele compared to T allele carriers (OR: 0.65; 95% CI: 0.44–0.96; p = 0.03). Subsequent eQTL

analysis showed significant genome-wide expressions in two human tissues, whole blood ($p = 5.1 \times 10^{-10}$) and liver ($p = 6.2 \times 10^{-43}$).

Conclusion: Our meta-analysis indicated a definite relation between the *CES1* rs2244613 genotype and tolerability variations or pharmacokinetic fluctuations. The carriers of T allele showed higher dabigatran concentrations; therefore, they would benefit from a dose reduction.

Systematic review registration: [https://inplasy.com/inplasy-2022-6-0027/], identifier [NPLASY202260027].

KEYWORDS

***CES1*, rs2244613, polymorphism, dabigatran, pharmacokinetics, safety, QTL**

Introduction

Direct oral anticoagulants (DOACs) are the first alternative to vitamin K antagonists (VKAs) (1). They specifically target a single coagulation protein, including thrombin or coagulation factor Xa. Compared with traditional anticoagulants, the convenience and safety of DOACs is well documented (2). Dabigatran is a representative drug of DOACs widely used to treat atrial fibrillation and pulmonary embolism (3). It is administered as a prodrug–dabigatran etexilate–which is rapidly hydrolyzed into dabigatran, the active moiety, by means of esterases, such as carboxylesterase 1 (*CES1*) and *CES2*. Hepatic *CES1* mainly catalyzes the conversion of the prodrug dabigatran etexilate to dabigatran, while the intestinal *CES2* enzyme plays a compensatory role when *CES1* is inhibited (4). This is the reason why we chose *CES1* as the subject of this study.

CES1 is a crucial liver enzyme that conduces to the metabolism of drugs containing ester moieties, including dabigatran etexilate or the M1 metabolite (5, 6). As to treatment for atrial fibrillation, *CES1* polymorphism may also affect clopidogrel pharmacological metabolism in the body. Up to 85% of the clopidogrel prodrug entering the body is rapidly hydrolyzed into inactive metabolites under the catalysis of *CES1*, and only 15% of the clopidogrel can exert drug effects. What's more, *CES1* is related to the development of many other thrombotic diseases like venous thromboembolism through regulating the pharmacokinetics of multiple anticoagulants (7, 8).

Single nucleotide polymorphisms (SNPs) in the *CES1* gene may lead to interindividual differences in dabigatran pharmacokinetics (PKs), which may affect the metabolism and bioavailability of this drug. In addition, although the tolerability of dabigatran is better than that of VKAs, some serious adverse clinical events such as bleeding or thrombosis may occur.

Due to interindividual variability in PKs, bleeding or thrombotic events may occur in patients taking dabigatran. However, the conclusions of the existing studies on the association between the *CES1* SNPs and drug concentration and bleeding risk are controversial due to their small sample sizes (4, 9–11). For instance, *CES1* rs2244613 G allele was related to a reduction in the trough concentration of dabigatran in patients compared to the T allele, and with a reduced risk of bleeding (12, 13). However, Shi et al. (14) observed that this gene locus was unrelated to dabigatran concentration and clinical outcome.

Thence, a systematic review and meta-analysis were conducted with existing studies on the application of dabigatran in atrial fibrillation, cardioembolic stroke, knee arthroplasty, and other diseases. This study explores the relationship between the *CES1* rs2244613 variant and patient's plasma concentration and bleeding risk and determines its clinical relevance to guide individualized dabigatran prescription further.

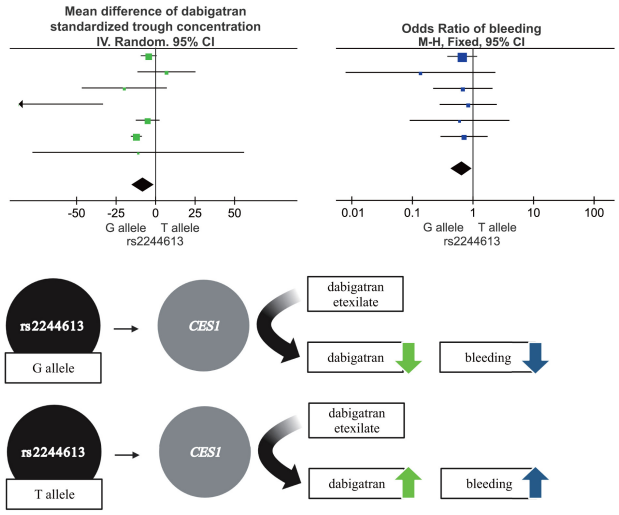
Materials and methods

We performed this study in the light of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (**Supplementary Table 1**) (15). We have registered our detailed protocol for this systematic review on INPLASY (registration number: INPLASY202260027), and it is available in full on inplasy.com[1].

Literature search

A structured search of three English databases (Web of Science, PubMed, and Embase) and two Chinese databases (CNKI and Wanfang) was performed on 16 April 2022. The search terms we applied are as follows: ('novel oral anticoagulant' or 'new oral anticoagulant' or 'direct oral anticoagulant' or 'target-specific oral anticoagulant' or NOAC or DOAC or TSOAC or dabigatran) and (*CES1* or 'carboxylesterase 1' or carboxylesterase-1) and ('dabigatran concentration' or bleeding) and (polymorph* or variant* or mutation* or genotyp* or phenotyp* or haplotyp* or SNP or rs2244613).

1 https://inplasy.com/inplasy-2022-6-0027/



GRAPHICAL ABSTRACT

Data selection and collection

With duplicate studies removed, two researchers (Li and Qiu) excluded irrelevant studies independently, according to the titles and abstracts and assessed the full-text articles for further inclusion. When inconsistencies occur, a team meeting was held with extra researchers, and a consensus would be finally reached.

In the step of data extraction, a predesigned form to obtain information from the included studies was used, which mainly comprised of basic data (including title, author, date, and sample size) and outcome variables (including means and standard bias for dabigatran plasma levels and the number of bleeding events). Then the means and standard deviations was estimated according to Wan's method and presented the continuous outcomes in the form of medians and interquartile ranges (16).

Quality assessment

The Newcastle–Ottawa scale (NOS) tool, which is based on three domains including the selection of exposed and unexposed subjects (0–4 points), comparability of study groups (0–2 points), and outcome assessment (0–3 points), was used to evaluate the quality of the research (17).

Statistical analysis

The Review Manager software (version 5.3) and STATA software (version 12.0) were used. The MD, OR and 95% CI were used to evaluate the strength of the association. A total of five genetic models were implemented to make an assessment on the association between *CES1* rs2244613 and dabigatran PKs and safety, including: homozygote model (GG vs. TT), heterozygote model (GT vs. TT), dominant model (GG + GT vs. TT), recessive model (GG vs. GT + TT), and allele comparison (G vs. T). The Q and I^2 statistics were used to evaluate the heterogeneity degree (18). The selection of fixed-effects or random-effects model was based on the degree of heterogeneity (19). $I^2 < 50\%$ was considered to low heterogeneity, $50 \leq I^2 < 75\%$ was considered to moderate heterogeneity and $I^2 \geq 75\%$ was considered to significant heterogeneity. If $I^2 < 50\%$ and p value > 0.1, the fixed-effects model would be used. If $I^2 \geq 50\%$ or $P \leq 0.1$, the random-effects model would be used. Multiple populations were enrolled in the present meta-analysis. Therefore, we performed subgroup analysis and evaluated the impact of *CES1* rs2244613 on the dabigatran pharmacokinetics and safety based on diverse ethnicities. To validate the credibility of outcomes in this meta-analysis, a sensitivity analysis was performed to identify potentially influential studies. Furthermore, funnel plot and Egger's test were applied to detect publication bias (20). The funnel plot depends on whether the points on both sides are symmetric, which indicates a possible publication bias. And Egger's test depends on the Student's t-test ($p < 0.05$ suggests a publication bias).

Genotype quantitative trait loci analysis for rs2244613 in human tissues

We assessed the genotype-specific expression of *CES1* in 49 human tissues by *cis*-expression quantitative trait loci (*cis*-eQTL) and splicing quantitative trait loci (sQTL) analysis through the Genotype-Tissue Expression (GTEx) portal[2]

2 https://gtexportal.org/home/

(21). Violin plots of the genotype-specific expression were constructed to visualize normalized gene expressions between three variant genotypes (GG, GT, and TT).

Results

Search results and patient characteristics

Fifty four studies were included after the preliminary search, 35 of which remained after removing duplicates. Of 25 removed after full text revision, three were reviews, seven were case reports, six for evaluating other clinical outcomes, and nine for not providing extractable data (**Supplementary Figure 1**). Finally, ten studies (8, 12, 13, 22–28) involving 2,777 subjects were included: **Table 1** summarizes the characteristics of them. The earliest year of included literature is 2013, and the latest year is 2021.

Seven of the included works analyzed the trough plasma concentration of dabigatran in patients with different genotypes, and nine analyzed the bleeding risk. Six of them were conducted with a Caucasian population and four with Asian populations. All publications were evaluated by NOS and scored above seven points.

Association between *CES1* rs2244613 and the trough plasma concentration of dabigatran

Meta-analysis showed a statistically significant difference between trough plasma concentrations of dabigatran and rs2244613 genotype. In summary, the *CES1* rs2244613 G allele was related to a lower trough plasma concentration of dabigatran when compared with T allele. The following MDs were observed for each model: GG vs. TT, MD = −58.29 ng/mL, 95% CI: −98.64 to −17.94, P = 0.005, I^2 = 98%; GT vs. TT: MD = −10.14 ng/mL, 95% CI: −13.21 to −7.07, P < 0.00001, I^2 = 0%; GG + GT vs. TT: MD = −12.56 ng/mL, 95% CI: −15.59 to −9.52, P < 0.00001, I^2 = 0%; GG vs. GT + TT: MD = −44.86 ng/mL, 95% CI: −79.84 to −9.87, P = 0.01, I^2 = 98%; G vs. T: MD = −8.00 ng/mL, 95% CI: −15.08 to −0.92, P = 0.03, I^2 = 68% (**Figure 1**).

Significant heterogeneity was found for the homozygote model (I^2 = 98%, **Figure 1**), for the recessive model (I^2 = 98%, **Figure 1**), and for the allele contrast model (I^2 = 68%, **Figure 1**). The heterogeneity was lower in Asian population in the homozygote model (I^2 = 58%, **Figure 2**), recessive model (I^2 = 67%, **Figure 2**), and allele contrast model (I^2 = 53%, **Figure 2**).

TABLE 1 Characteristics of studies included in the systematic review and meta-analysis.

References	Country	Ethnicity	Sample size	Mean age (Years)	Men/Women	BMI (Kg/m^2)	Dosage regimen	Treatment Indication	NOS
Paré et al. (13)	Canada	Caucasian	1694	71.8	1163/531	29.1	110 mg Bid 150 mg Bid	AF	7
Sychev et al. (8)	Russia	Caucasian	60	62	2/58	35.3	220 mg	Knee replacement	7
Meshcherykov et al. (22)	Russia	Caucasian	72	64.89	35/37	NA	150 mg Bid	AF	7
Xu (23)	China	Asian	113	60.81	68/45	NA	110 mg Bid 150 mg Bid	AF	7
Tomek et al. (24)	Czechia	Caucasian	110	70.2	54/56	NA	NA	Cardioembolic stroke	7
Sychev et al. (12)	Russia	Caucasian	96	75	39/57	29.7	110 mg Bid 150 mg Bid	AF	7
Ji et al. (25)	China	Asian	198	63.3	120/78	23.9	110 mg Bid	AF	7
Lähteenmäki et al. (26)	Finland	Caucasian	340	69.8	178/162	NA	110 mg Bid 150 mg Bid	Multiple diseases	9
Zheng et al. (27)	China	Asian	80	64.5	43/37	23.8	NA	AF	7
Xiang (28)	China	Asian	14	61.5	10/4	24	NA	AF	7

BMI, body mass index; NOS, Newcastle–Ottawa scale; NA, not available; AF, atrial fibrillation; Bid, twice daily; Multiple diseases include vascular disease, stroke/cerebral infarction or atherosclerosis in (pre-)cerebral arteries, atrial Fibrillation, pulmonary embolism, phlebitis and thrombophlebitis, portal vein thrombosis, and other venous embolism and thrombosis.

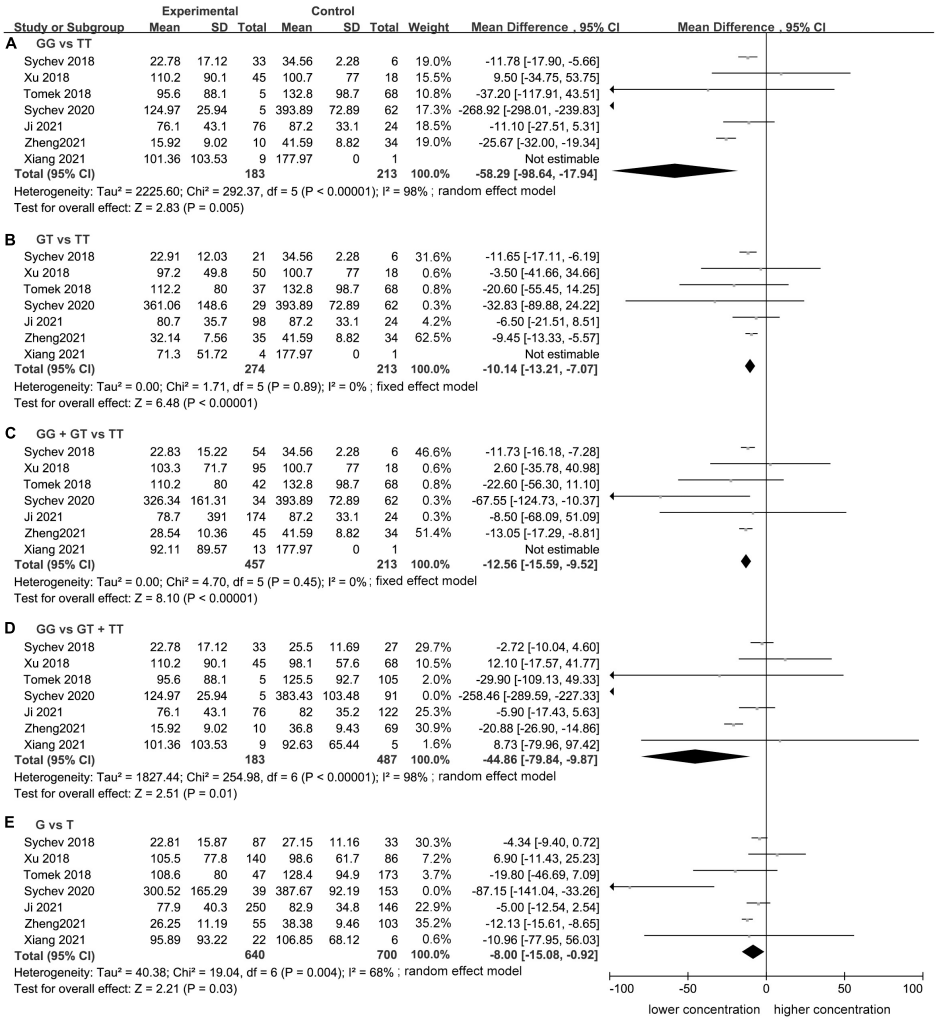


FIGURE 1
Forest plots comparing dabigatran trough concentrations across rs2244613 genotype polymorphism of the carboxylesterase 1 (*CES1*) gene: **(A)** homozygote model, **(B)** heterozygote model, **(C)** dominant model, **(D)** recessive model, and **(E)** allelic model.

No single study could not influence the overall results qualitatively, indicating robustness and reliability of our results (**Figure 3**).

No publication bias was observed, as funnel plots (**Figure 4**) were relatively symmetrical.

Association between *CES1* rs2244613 and the risk of bleeding

Meta-analysis showed a statistically significant difference between the risk of developing bleeding and rs2244613 genotype. In summary, the *CES1* rs2244613 G allele was related to a lower risk of developing any bleeding when compared with T allele. The following ORs were observed for each model: GG vs. TT, OR = 0.84, 95% CI: 0.40–1.77, $P = 0.65$, $I^2 = 40\%$; GT vs. TT: OR = 0.70, 95% CI: 0.40–1.24, $P = 0.22$, $I^2 = 0\%$; GG + GT vs. TT: OR = 0.64, 95% CI: 0.52–0.78, $P < 0.0001$, $I^2 = 0\%$; GG vs. GT + TT: OR = 0.53, 95% CI: 0.31–0.92, $P = 0.02$, $I^2 = 0\%$; G vs. T: OR = 0.65, 95% CI: 0.44–0.96, $P = 0.03$, $I^2 = 0\%$ (**Figure 5**).

No publication bias was observed, as funnel plots (**Figure 6**) were relatively symmetrical.

Quantitative trait loci analysis of rs2244613 in human tissues

Out of the total 49 genotypic *cis*-eQTL results for rs2244613, only one *cis*-eQTLs reached a genome-wide significance threshold in **Figure 7A** ($p = 5.1 \times 10^{-10}$ in whole blood tissue). Genome-wide *cis*-eQTLs were upregulated in whole blood tissues in **Figure 7B** (slope = 0.30). Compared to TT

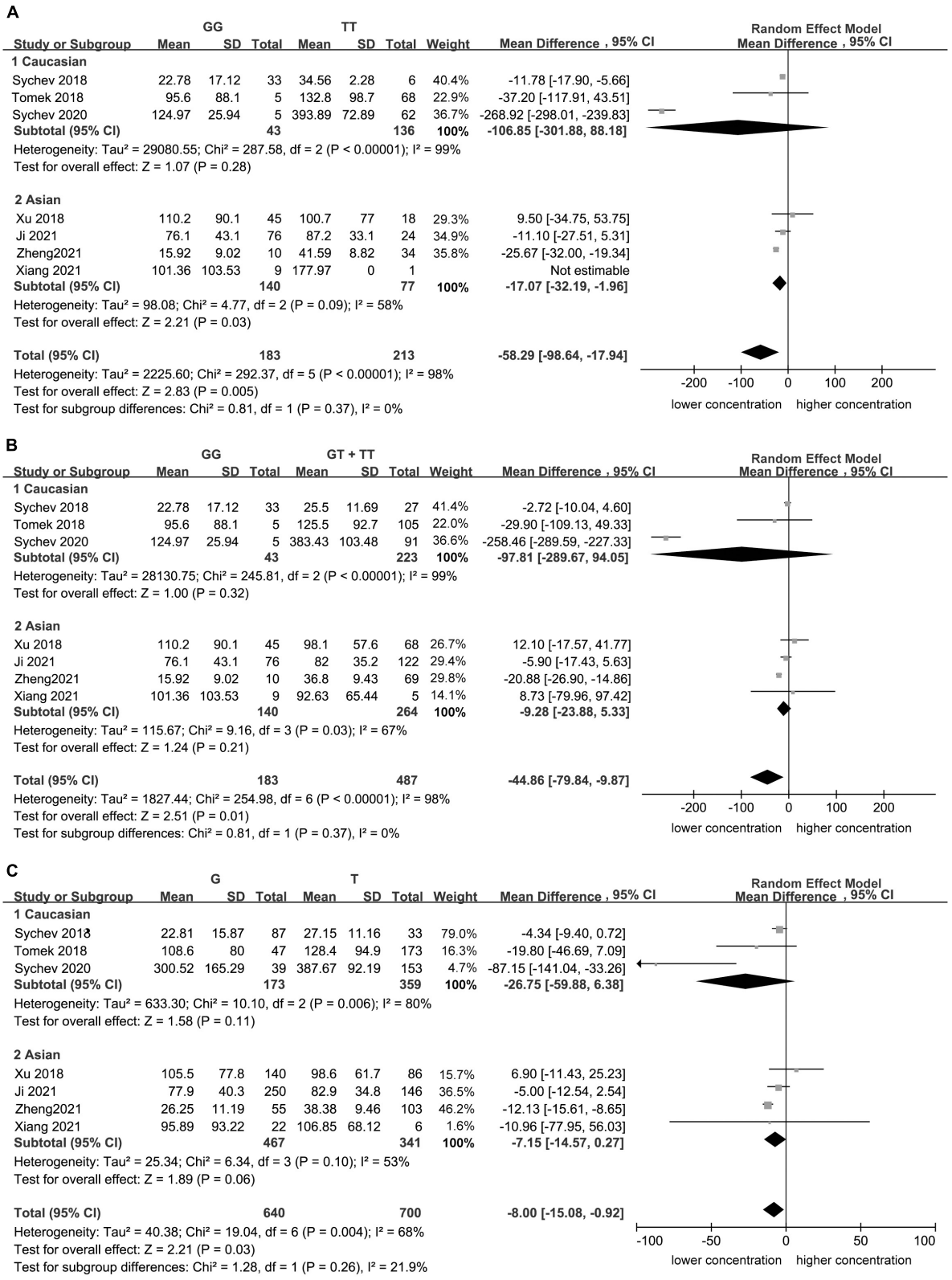


FIGURE 2
Subgroup analyses for the association between carboxylesterase 1 (*CES1*) rs2244613 polymorphism and the trough plasma concentration of dabigatran: **(A)** homozygote model, **(B)** recessive model, and **(C)** allelic model.

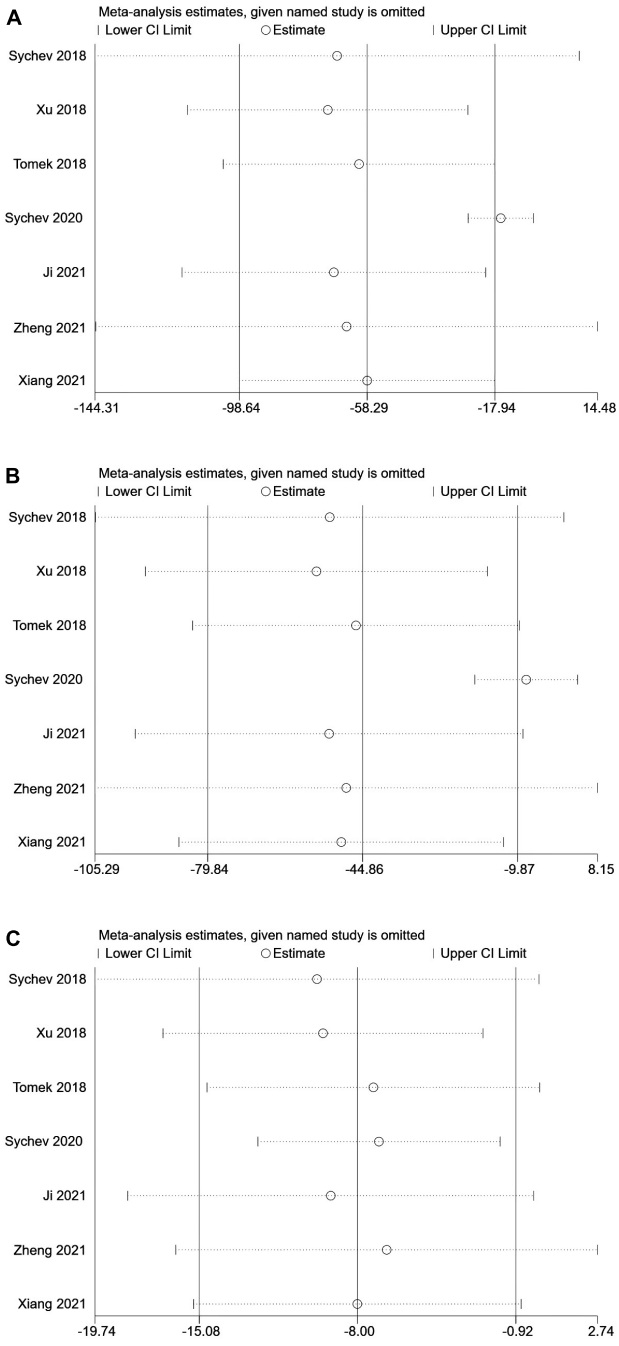


FIGURE 3
Sensitive analysis of carboxylesterase 1 (*CES1*) rs2244613 polymorphism and the trough plasma concentration of dabigatran: **(A)** homozygote model, **(B)** recessive model, and **(C)** allelic model.

allele patients, the expression of *CES1* was significantly lower in GG. sQTLs showed genome-wide significance in seventeen tissues ($p < 5 \times 10^{-8}$) in **Figure 7C** and **Supplementary Figure 2**. Particularly, finding the *cis*-eQTL and sQTLs genotypes implicated the rs2244613 variant as a transcriptional regulatory factor.

Discussion

Our study comprehensively explored the application of dabigatran in atrial fibrillation, cardioembolic stroke, and knee replacement, and other diseases to explore the relationship between *CES1* rs2244613 and dabigatran PKs and bleeding risk.

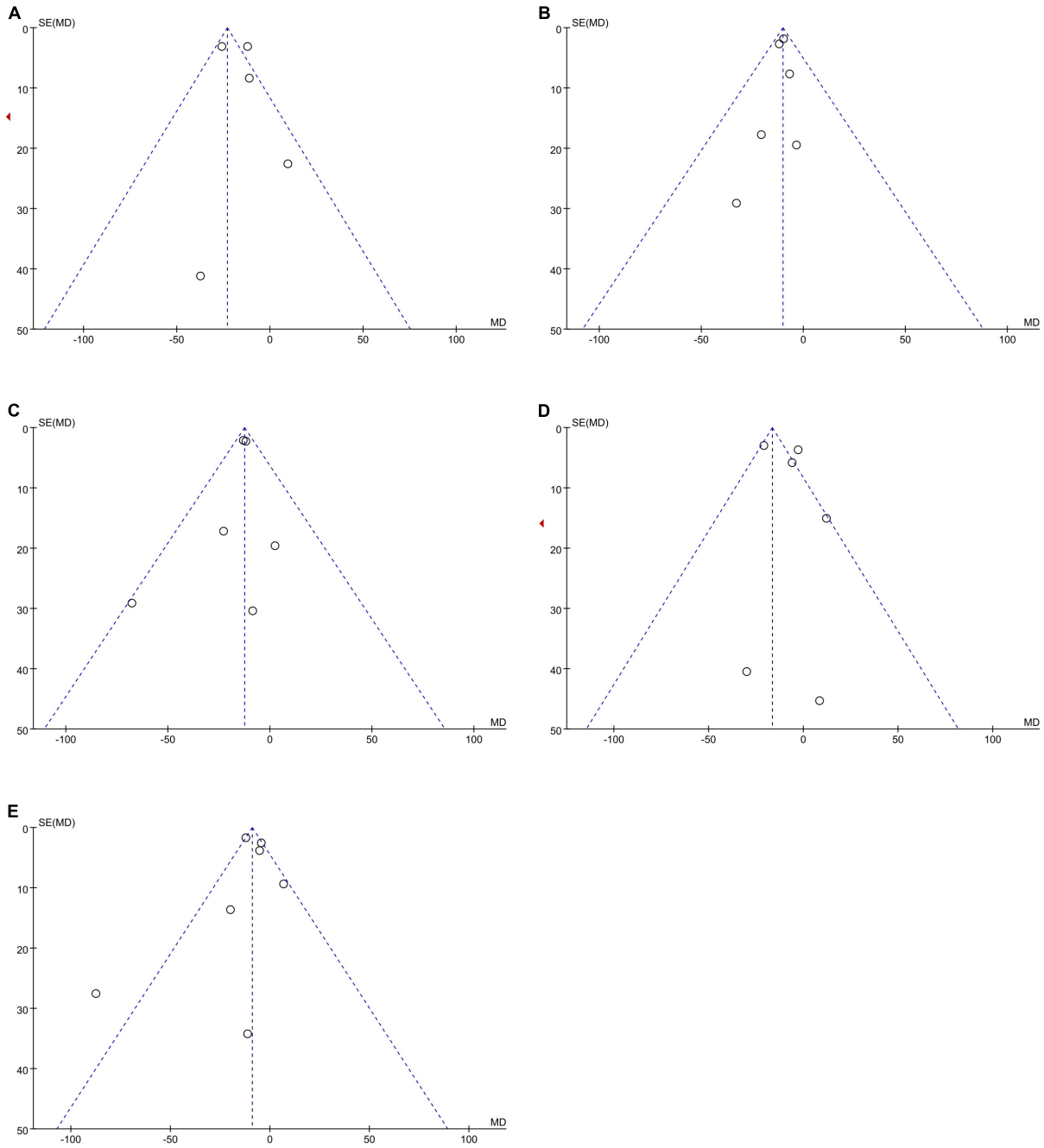


FIGURE 4
Funnel plots to assess the publication bias related to the dabigatran trough concentrations: **(A)** homozygote model, **(B)** heterozygote model, **(C)** dominant model, **(D)** recessive model, and **(E)** allelic model.

2,777 patients in 10 articles were included. We found that the bleeding risk of patients taking dabigatran with GG and GT genotypes was significantly lower than that of patients with TT genotype; the bleeding risk of patients with GG genotype was remarkably lower than that of patients with GT + TT genotypes. Moreover, the bleeding risk is lower in patients carrying the G allele compare to T allele carriers. Additionally, we consistently observed that the trough concentrations of dabigatran were notably lower in the G compared to the T allele. Therefore, we conclude that *CES1* rs2244613 affects dabigatran plasma concentration and ADR incidence. Moreover, the effect of *CES1* rs2244613 on the trough concentrations of dabigatran varied among ethnicities, which is consistent with previous works (29).

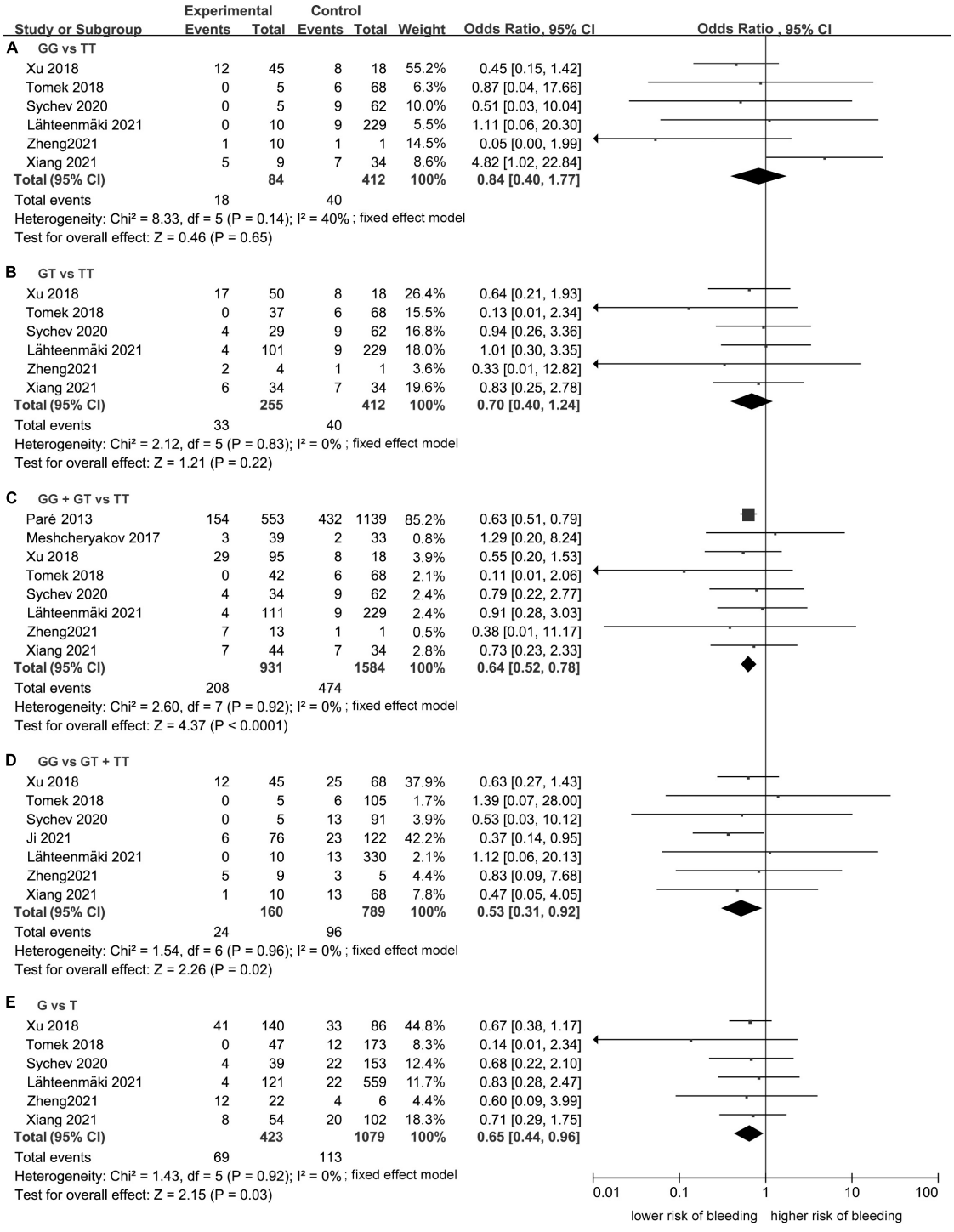


FIGURE 5
Forest plots comparing the risk of developing any bleeding event across rs2244613 genotype polymorphism of the carboxylesterase 1 (*CES1*) gene: **(A)** homozygote model, **(B)** heterozygote model, **(C)** dominant model, **(D)** recessive model, and **(E)** allelic model.

Mammalian CES belong to the α, β-hydrolase-fold protein superfamily, which can be divided into five categories in accordance with the homology of the amino acid sequences (*CES1* – *CES5*). Both *CES1* and *CES2* are mainly involved in the metabolism of human drugs, and *CES1* is mostly found in the human liver (27, 28, 30, 31). Once dabigatran etexilate enters

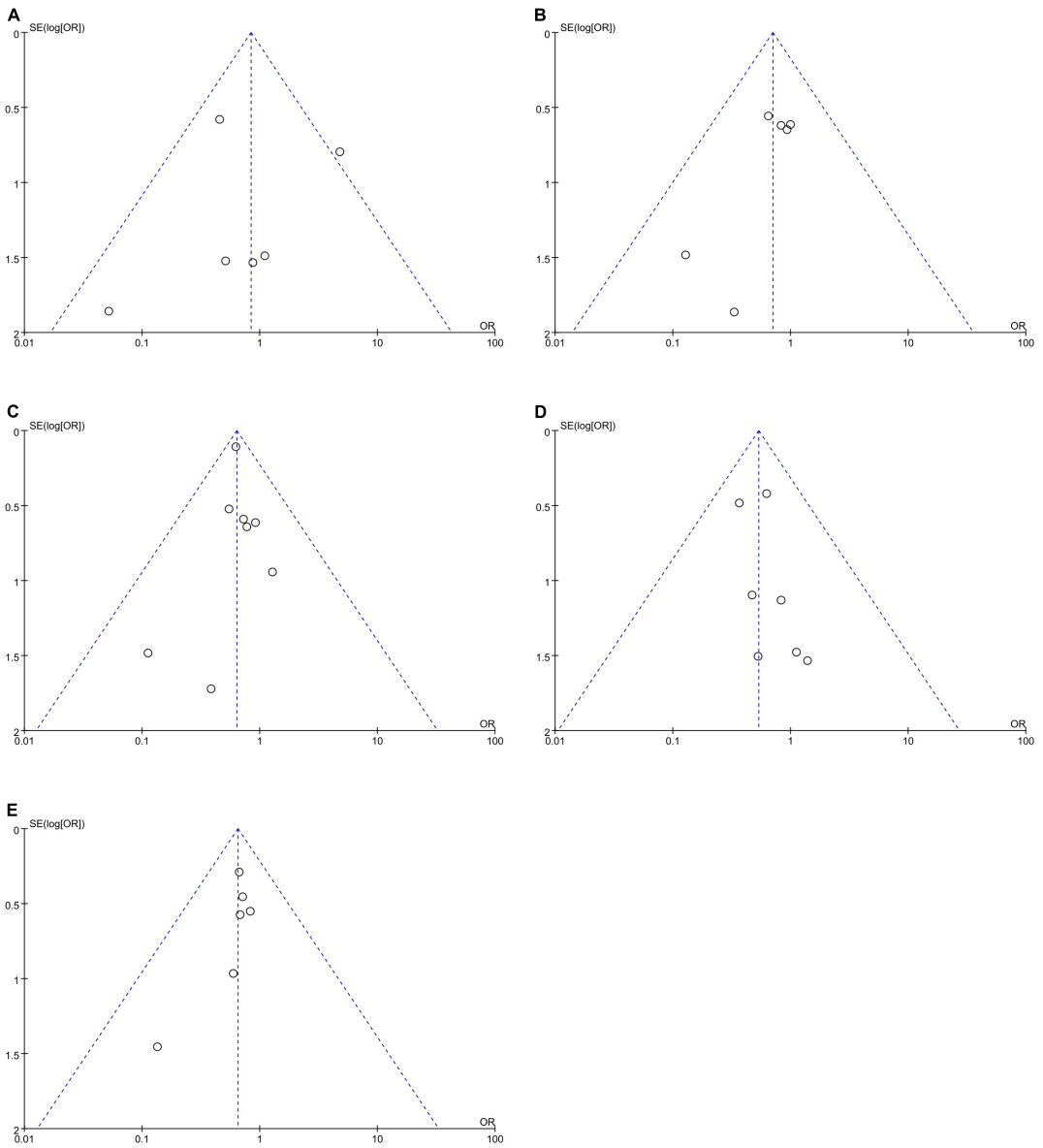


FIGURE 6
Funnel plots to assess the publication bias related to the risk of bleeding: **(A)** homozygote model, **(B)** heterozygote model, **(C)** dominant model, **(D)** recessive model, and **(E)** allelic model.

the body, it must be hydrolyzed at two separate sites to form an active thrombin inhibitor. First, in the intestine, the carbamate group is hydrolyzed by *CES2*, while *CES1* hydrolyses the ethyl ester part. After that, it can be converted into dabigatran, which has metabolic activity (5, 14). Then it binds to the specific site of thrombin, inhibiting thrombin activity and preventing fibrin formation, thereby exerting an anticoagulant effect (14).

In fact, apart from *CES1* and *CES2*, there are some other genes encoding enzymes [e.g., UDP-glucuronosyltransferase gene (*UGT*) and cytochrome P450 gene (*CYP*)] and genes encoding transporters [e.g., ATP binding cassette subfamily gene (*ABC*) and solute carriers' family gene (*SLC*)]. After oral administration, dabigatran binds to plasma proteins and is catalyzed by three UGTs (UGT1A9, UGT2B7, and UGT2B15) to form acyl glucuronic acid isomers, of which UGT2B15 contains the strongest effect. Particularly, dabigatran 1-O-acylglucuronide, a metabolite of dabigatran, exhibited anticoagulant activity comparable to the parent drug (32). In addition, cytochrome P450 (CYP2D6 and CYP3A5) may metabolize dabigatran after CES esterase's converting dabigatran to the active moiety. Dabigatran is mainly excreted unchanged in urine (85%) and remains in feces (9). Genes

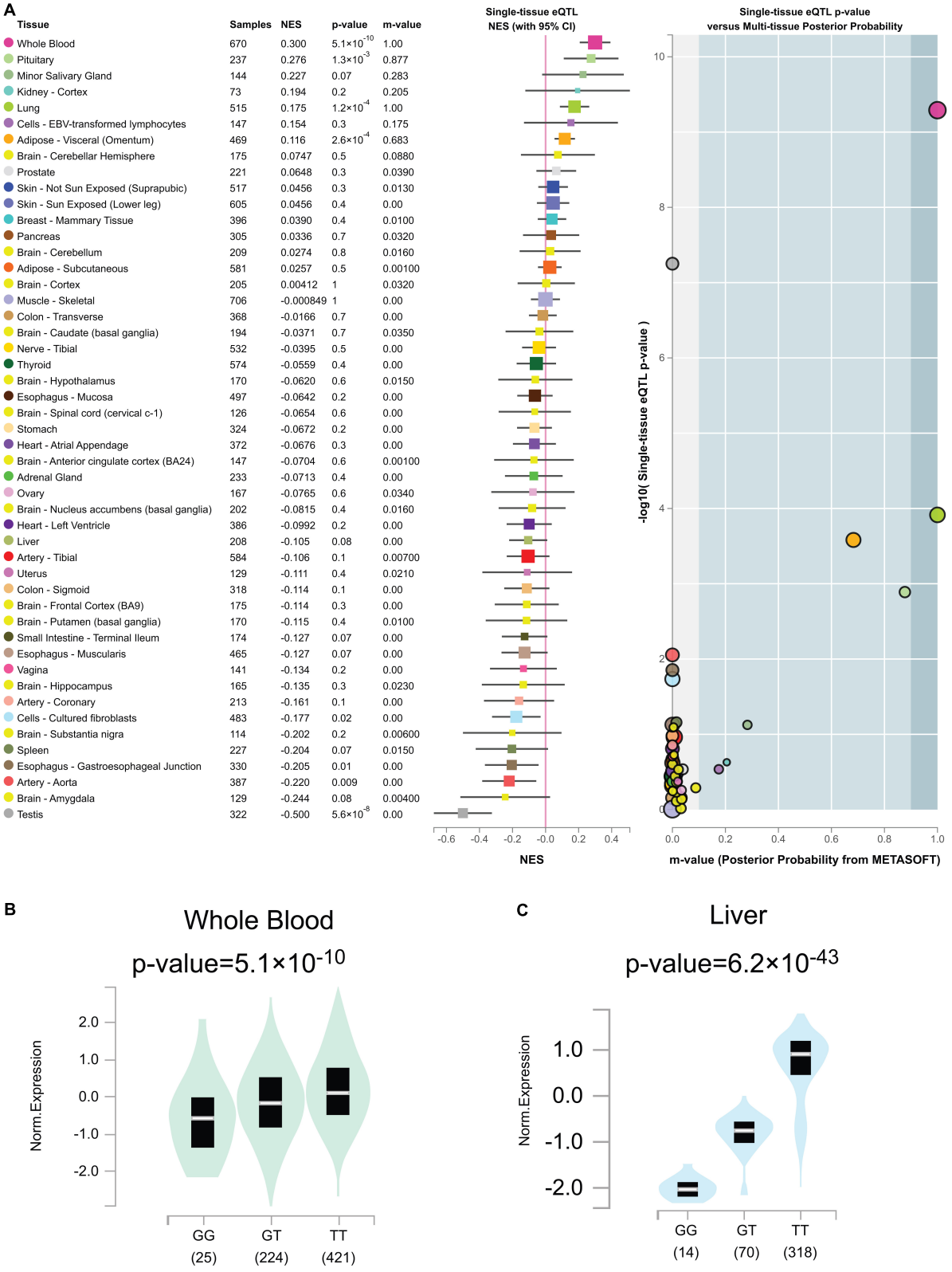


FIGURE 7
(A) Genotype *cis*-expression quantitative trait loci analysis for rs2244613 in 49 human tissues was obtained from the GTE database. **(B)** Violin plots of allele-specific *cis*-eQTLs according to rs2244613 genotypes in whole blood tissue in the Genotype-Tissue Expression (GTEx) dataset. **(C)** Violin plots of allele-specific splicing quantitative trait loci (sQTL) according to rs2244613 genotypes in liver tissue in the GTEx dataset.

encoding transporters are also reported. P-glycoprotein (P-gp) is a classical transporter encoded by the *ABCB1* gene, and dabigatran is one of its substrates. The gene polymorphism of *ABCB1* is considered being related to the pharmacokinetics and drug safety of dabigatran, and has been widely confirmed (33). In addition, SLC family transporters are also involved in the metabolism of dabigatran. For example, studies have shown that the *SLC22A1* mutant haplotype has higher t_{max} and $t_{1/2}$ with dabigatran than heterozygous and wild types, resulting in differences in the pharmacokinetics and safety of dabigatran among users of different genotypes (9).

High interindividual variability in plasma levels of dabigatran was reported, and the coefficient of variation of up to 30% for systemic exposure (34). Genetic variations in drug-metabolizing enzymes, receptors, and transporters have been identified as a major cause of interindividual variability in drug response, potentially leading to differences in responsiveness and adverse reactions to dabigatran therapy among individuals with different genotypes (35). Presently, thousands of SNPs are described in the *CES1* gene, such as rs8192935, rs71647871, and rs2244613 (36). The allele frequency of *CES1* rs2244613 was previously reported to be different in Chinese vs. Caucasian populations, with a G allele prevalence of 61.1% and 15.3–28.3%, respectively. Furthermore, *CES1* rs2244613 G allele was previously associated with reduced trough concentrations and a decreased bleeding risk rather than peak drug concentrations (4, 13, 25, 37). Another study of patients with atrial fibrillation who received oral dabigatran also concluded that the *CES1* SNP rs2244613 was remarkably in association with dabigatran trough concentrations (38). In summary, most conclusions in post researches are consistent with ours, except Xu et al. As a meta-analysis, our study has a large sample size and employs data on dabigatran in a variety of disease populations, only for the drug dabigatran rather than a specific disease, so it has a comparatively high reliability. The reason for the large discrepancy between Xu's research conclusions and ours may be the limitation of their sample size.

This study still has the following limitations. First, the results of our study indicate that SNPs may directly affect the bleeding risk of dabigatran through an internal mechanism and may indirectly influence the occurrence of adverse events by changing the concentration. The specific mechanisms acquire further basic research. Secondly, this study did not control other factors except genotypes, and the heterogeneity cannot be ignored. Thirdly, the blood concentration of dabigatran used in this study is from a single test rather than the average concentration of multiple tests, which may exist to some extent by chance. Fourthly, we have not analyzed other variants within *CES1* and *CES2*, meta-analysis of other variants will be done in the follow-up.

Conclusion

In summary, patients carrying at least one *CES1* rs2244613 G allele are associated with decreased dabigatran trough concentrations and lower bleeding risk compared to non-carriers (i.e., with the T/T genotype). This work is of great relevance as it will help eventually in the guidance and individualization of dabigatran prescription.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

XZ, ZZhai, and CW had full access to all the data in the study and took responsibility for the content of the manuscript. HW and ZZhang conceived and designed the study. HL and YQ integrated data, analyzed the data, and wrote the manuscript. GF provided methodological support. YZ, PZ, PY, and A-LV participated in editing of the manuscript. All authors were involved in the revision of the manuscript for important intellectual content and approved the final version.

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Conflict of interest

HW was employed by the Shenzhen Zaozhidao Technology Co., Ltd., and A-LV was employed by the VTT Technical Research Centre of Finland Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.959916/full#supplementary-material

SUPPLEMENTARY FIGURE 1
PRISMA flow diagram.

SUPPLEMENTARY FIGURE 2
Violin plots of allele-specific sQTLs according to rs2244613 genotypes in 17 human tissues in the GTEx dataset.

SUPPLEMENTARY TABLE 1
PRISMA checklist.

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