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*Review Article*

# Association of ABCB1 gene polymorphisms with aspirin or clopidogrel resistance in ischemic stroke: a meta-analysis

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**Abstract:** Objective: Ischemic stroke (IS) is a major public health concern worldwide. In this study, we aimed to investigate the relationship between *ABCB1* gene polymorphisms and antiplatelet resistance in patients with IS. Methods: We performed a comprehensive search of the PubMed, China National Knowledge Infrastructure, Web of Science, and WANFANG databases for articles published until February 2024. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to measure the association between *ABCB1* polymorphisms and antiplatelet resistance in patients with IS. All the statistical analyses were performed using STATA version 11.0. Results: Eleven studies containing 2,228 cases and 2,556 controls met the inclusion criteria. Our results showed that aspirin resistance in patients with IS was significantly correlated with the polymorphism of *ABCB1* rs1045642 (Allele model: OR=1.5, 95% CI [1.10, 2.05], P=0.010; Homozygote model: OR=2.02, 95% CI [1.01, 4.05], P=0.047; Heterozygote model: OR=1.37, 95% CI [0.91, 2.08], P=0.132; Dominant model: OR=1.75, 95% CI [1.09, 2.81], P=0.021; Recessive model: OR=1.61, 95% CI [1.01, 2.57], P=0.045). Meanwhile, we found that *ABCB1* rs1045642 polymorphism might be significantly associated with clopidogrel resistance in IS (A. Homozygote model: OR=3.35, 95% CI [1.99, 5.63], P=0.000; B. Heterozygote model: OR=0.81, 95% CI [0.54, 1.21], P=0.895; C. Dominant model: OR=1.41, 95% CI [0.59, 3.36], P=0.435; D. Recessive model: OR=3.43, 95% CI [2.14, 5.51], P=0.000). Conclusion: This meta-analysis suggests a potential link between *ABCB1* rs1045642 polymorphism and resistance to clopidogrel or aspirin in patients with IS.

**Keywords:** ABCB1 gene, aspirin, clopidogrel, ischemic stroke, resistance

## Introduction

Stroke is the third leading cause of loss of life and the second leading cause of death worldwide due to disability [1]. Moreover, recent clinical studies have observed a trend of ischemic stroke in younger individuals. The dysfunction caused by ischemic stroke places a significant burden on patients' families and contributes to substantial healthcare costs at the national level. Antithrombotic therapy is very important in the prevention of stroke [2]. Aspirin and clopidogrel are recognized as effective drugs for the prevention of cerebrovascular diseases [3]. Unfortunately, despite prolonged use of aspirin or clopidogrel, some patients still experience thrombotic events called aspirin or clopidogrel treatment failure [4]. The mechanism of antiplatelet drug resistance remains unclear and may be related to a variety of factors, such as drug dose, drug bioavailability, drug interaction, and genetic factors. However, research on antiplatelet drug resistance and gene polymorphisms has gained increasing attention in recent years [5-7].

The *ABCB1* gene is located on chromosome 7p21 and more than 50 nucleotide polymorphisms have been reported. One of these mutations is a C-to-T mutation at position 3435 of exon 26, which does not change the amino acid

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sequence of ABCB1 and is reportedly related to the expression and function of *ABCB1* [8]. Several researchers have found that the C3435T polymorphism is associated with altered *ABCB1* expression levels, while other studies have found no effect of this polymorphism on *ABCB1* expression or function [9].

There is limited data on the relationship between *ABCB1* polymorphisms and the development of ischemic stroke or antiplatelet resistance in these patients [10-21]. Kim et al. [11] found that the *ABCB1* rs1128503 polymorphism was related to the development of ischemic stroke in a Korean population, while Liu et al. [16] reported no association between the *ABCB1* rs1128503 polymorphism and the development of ischemic stroke. Hu et al. [18] reported a significant association between *ABCB1* polymorphisms and clinical response to clopidogrel treatment. Wang et al. [15] and Su JF et al. [12] reported that, based on platelet aggregation in Chinese ischemic stroke patients receiving clopidogrel treatment, the *ABCB1* C3435T polymorphism was not associated with clopidogrel response. Moreover, several studies found a significant association between *ABCB1* C3435T polymorphism and aspirin response in ischemic patients [10, 14, 21].

However, the universality of these studies is confined by the small sample sizes and limited statistical abilities. The purpose of this meta-analysis was to collect case-control studies to assess the relationship between *ABCB1* gene polymorphisms and IS susceptibility, as well as the association between the *ABCB1* gene polymorphism and antiplatelet resistance in patients with IS.

## Materials and methods

### *Search strategy*

Four electronic databases (PubMed, Web of science, China National Knowledge Infrastructure, and WANFANG databases) were searched up to February 2024, and the search strategy was as follows: (abcb1[All Fields] OR ("atp binding cassette transporter, subfamily b, member 1"[MeSH Terms] OR "p glycoprotein"[All Fields])) AND (("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "apoplexy"[All Fields]) OR (("ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischemic"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) OR ("cerebral infarction"[MeSH Terms] OR ("cerebral"[All Fields] AND "infarction"[All Fields]) OR "cerebral infarction"[All Fields]) OR ("brain infarction"[MeSH Terms] OR ("brain"[All Fields] AND "infarction"[All Fields]) OR "brain infarction"[All Fields])) AND (("polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields]) OR ("Socioaffect Neurosci Psychol"[Journal] OR "snp"[All Fields]) OR variant [All Fields] OR ("mutation"[MeSH Terms] OR "mutation"[All Fields])). At the same time, a manual search for reference lists of reviews was conducted. This meta-analysis only included the published full-text studies in English or Chinese. Regarding the duplicate samples contained in some publications, only the most recent or comprehensive studies were included in this meta-analysis. The PRISMA checklist is provided as Supplementary Table 1.

### *Inclusion and exclusion criteria*

Qualified studies met the following inclusion criteria: 1) evaluation of *ABCB1* polymorphism and ischemic stroke; 2) case-control studies or cohort study design; 3) sufficient data for calculating *ABCB1* genotypes in the case and control groups; and 4) genotype distribution of the control groups in Hardy-Weinberg equilibrium (HWE). The exclusion criteria were as follows: 1) studies with overlapping data from other studies; 2) the number of wild-type genotypes or alleles not available; and 3) editorials, reviews, comments, and abstracts. Two independent investigators reviewed all the articles to determine their eligibility. Any disagreement between the two investigators was resolved through consultation.

### *Data extraction and quality assessment*

We extracted the following information from each study: name of the first author, publication year, country of population, number of cases and controls, genotyping methods, genotype and allele distributions, and Hardy-Weinberg equilibrium (HWE) results. Two researchers used the Newcastle-Ottawa Quality Assessment Scale (NOS) to evaluate the quality of each study [9].

### *Statistical analysis*

The correlation between *ABCB1* gene polymorphisms and antiplatelet resistance was evaluated by unadjusted odds ratios (OR) and 95%

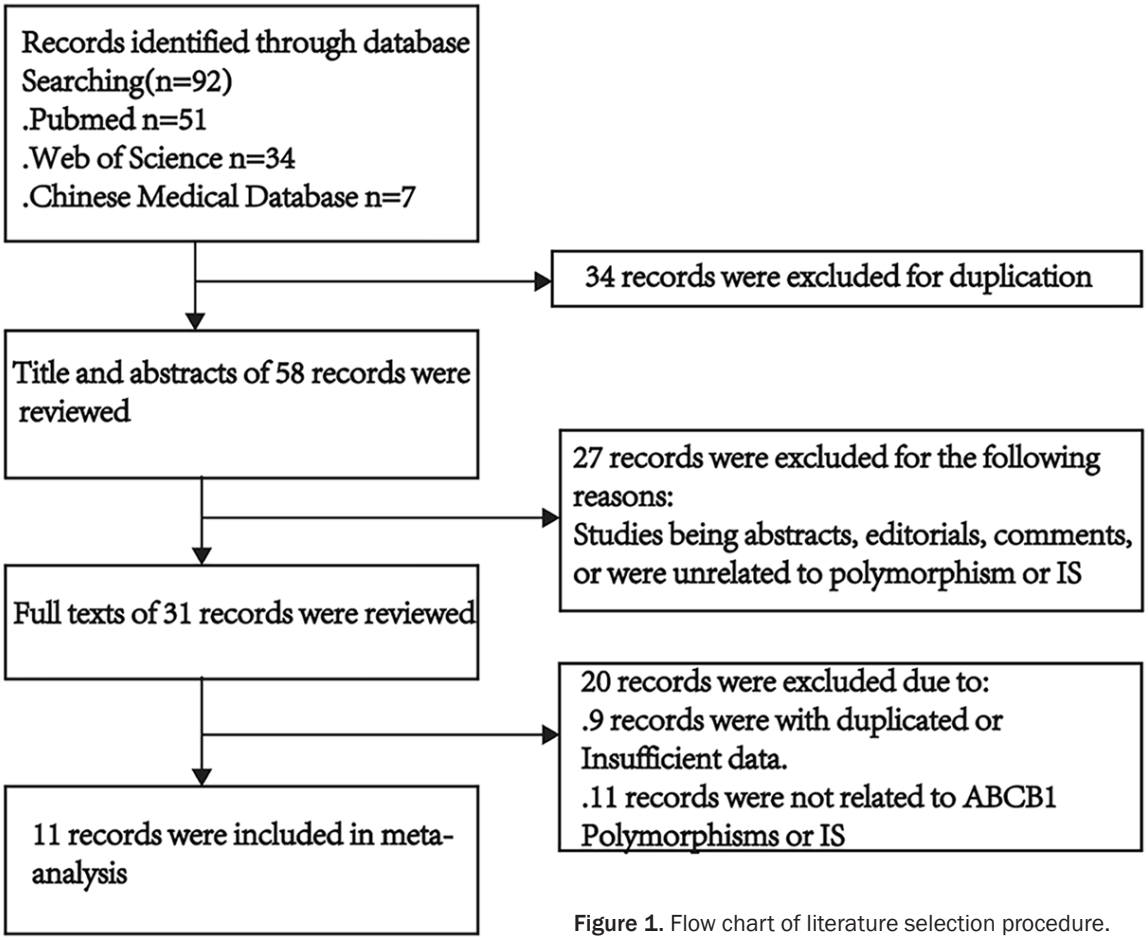


**Figure 1.** Flow chart of literature selection procedure.

confidence intervals (CIs). The quantitative meta-analysis was performed using STATA version 11.0 (University City of Texas Stata Company, USA). Cochrane's Q-test and $I^2$ measurements were used to assess the heterogeneity of each study ($I^2$ was defined as the proportion of total variation in the study, which was due to heterogeneity rather than contingency). In case of significant heterogeneity ($P < 0.10$ or $I^2 > 50\%$), a random effects model was adopted [22]. Begg's test was used to test the risk of publication bias, with $P < 0.10$ indicating that there is publishing bias. The validity and reliability of the preliminary meta-analysis were estimated using sensitivity analysis.

## Results

### *Characteristics of studies included in the meta-analysis*

After searching the database, 92 potential eligibility reports were identified (**Figure 1**); 34 records were excluded because of duplicate data, and 27 records were excluded because they were abstracts, editorials, comments, or unrelated to polymorphisms or IS. After carefully reading the full text, 20 articles with duplicate or insufficient data, or those unrelated to *ABCB1* polymorphisms or IS were excluded. Finally, 11 studies, with 2,228 cases and 2,556 controls, were included. The general characteristics of the included studies are shown in **Table 1**.

### *Association between ABCB1 polymorphisms and IS*

Three studies with 1,126 cases and 1,095 controls were included to test the effect of the *ABCB1* rs1045642 polymorphism on IS. **Table 2** shows the overall analysis results of all five genetic models: (A) Allele: OR=1.35, 95% CI (0.98, 1.87), P=0.066; (B) Homozygote: OR=1.67, 95% CI (0.86, 3.25), P=0.129; (C) Heterozygote: OR=1.36, 95% CI (0.91, 2.03), P=0.139; (D) Dominant: OR=1.47, 95% CI (0.94,

**Table 1.** Main characteristics of studies included in this meta-analysis

| Author | Year | Country | Case | Control | Number | | Gene | HWE | NOS Score |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Case | Control | | | |
| Kim YO | 2012 | Korea | IS | Non-IS | 121 | 291 | PCR and sequence | Y | 7 |
| Sharma V | 2012 | India | IS | Non-IS | 560 | 560 | PCR-RFLP | Y | 7 |
| | | | IS (Aspirin resistance) | IS (Aspirin sensitive) | 222 | 338 | PCR-RFLP | Y | 7 |
| Su JF | 2015 | China | IS (clopidogrel resistance) | IS (clopidogrel sensitive) | 51 | 252 | PCR and sequence | Y | 6 |
| Wang ZY | 2016 | China | IS (Aspirin resistance) | IS (Aspirin sensitive) | 75 | 225 | PCR-RFLP | Y | 7 |
| Peng LL | 2016 | China | IS (Aspirin resistance) | IS (Aspirin sensitive) | 33 | 250 | Mass ARRAY | Y | 7 |
| Liu F | 2017 | China | IS | Non-IS | 392 | 429 | SNaPshot | Y | 7 |
| Wang JF | 2017 | China | IS (clopidogrel resistance) | IS (clopidogrel sensitive) | 42 | 58 | PCR and sequence | Y | 8 |
| Hu P | 2017 | China | IS (clopidogrel resistance) | IS (clopidogrel sensitive) | 35 | 75 | PCR-RFLP | Y | 6 |
| Hu P | 2018 | China | IS (clopidogrel resistance) | IS (clopidogrel sensitive) | 62 | 62 | PCR-RFLP | Y | 6 |
| Ikonnikova A | 2022 | Russia | IS (Aspirin resistance) | IS (Aspirin sensitive) | 241 | 220 | PCR and sequence | Y | 8 |
| Yurek E | 2023 | Turkey | IS | Non-IS | 174 | 106 | SNaPshot | Y | 7 |
| | | | IS (Aspirin resistance) | IS (Aspirin sensitive) | 37 | 137 | SNaPshot | Y | 7 |

Abbreviations: IS, ischemic stroke; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Assessment Scale.

**Table 2.** Result of pooled ratios (ORS) in this meta-analysis to investigate the association between ABCB1 gene polymorphisms and IS

| SNP | Included studies | Genetic model | Heterogeneity-test | $I^2$ (%) | Analysis model | Pooled OR (95% CI) | P |
|---|---|---|---|---|---|---|---|
| rs1045642 | 3 | Allele (T vs C) | 0.004 | 82.0% | Random model | 1.35 (0.98, 1.87) | 0.066 |
| | | Homozygous (TT vs CC) | 0.015 | 76.3% | Random model | 1.67 (0.86, 3.25) | 0.129 |
| | | Heterozygous (CT vs CC) | 0.023 | 73.6% | Random model | 1.36 (0.91, 2.03) | 0.139 |
| | | Dominant (TT+CT vs CC) | 0.005 | 81.0% | Random model | 1.47 (0.94, 2.31) | 0.094 |
| | | Recessive (TT vs CC+CT) | 0.137 | 49.7% | Fixed model | 1.50 (1.22, 1.84) | 0.000 |
| rs1128503 | 2 | Allele (C vs T) | 0.756 | 0.0% | Fixed model | 0.92 (0.77, 1.09) | 0.315 |
| | | Homozygous (CC vs TT) | 0.784 | 0.0% | Fixed model | 0.77 (0.53, 1.13) | 0.182 |
| | | Heterozygous (CT vs TT) | 0.892 | 0.0% | Fixed model | 1.01 (0.79, 1.29) | 0.951 |
| | | Dominant (CC+CT vs TT) | 0.821 | 0.0% | Fixed model | 0.95 (0.75, 1.21) | 0.690 |
| | | Recessive (CC vs CT+TT) | 0.808 | 0.0% | Fixed model | 0.77 (0.54, 1.10) | 0.147 |

Abbreviations: OR, odds ratio; CI, confidence interval; F, fixed-effects model; IS, ischemic stroke.

2.31), P=0.094; (E) Recessive: OR=1.50, 95% CI (1.22, 1.84), P=0.000. Two studies with 512 cases and 720 controls were conducted to examine the impact of *ABCB1* rs1128503 polymorphism on IS. **Table 2** shows the overall analysis results of all five genetic models: (A) Allele: OR=0.92, 95% CI (0.77, 1.09), P=0.315; (B) Homozygote: OR=0.77, 95% CI (0.53, 1.13), P=0.182; (C) Heterozygote: OR=1.01, 95% CI (0.79, 1.29), P=0.951; (D) Dominant: OR=0.95, 95% CI (0.75, 1.21), P=0.690; (E) Recessive: OR=0.77, 95% CI (0.54, 1.10), P=0.147. The results showed that IS incidence was not significantly correlated with *ABCB1* rs1045642 or rs1128503 polymorphisms.

*Association between ABCB1 rs1045642 polymorphisms and aspirin resistance in IS*

We analyzed the relationship between *ABCB1* rs1045642 polymorphisms and aspirin resistance in 5 articles containing 1,081 cases and 803 controls. The following results of overall analysis in all five genetic models were observed: (A) Allele model: OR=1.5, 95% CI (1.10, 2.05), P=0.010; (B) Homozygote model: OR=2.02, 95% CI (1.01, 4.05), P=0.047; (C) Heterozygote model: OR=1.37, 95% CI (0.91, 2.08), P=0.132; (D) Dominant model: OR=1.75, 95% CI (1.09, 2.81), P=0.021; (E) Recessive model: OR=1.61, 95% CI (1.01, 2.57), P=0.045 (**Figure 2**). The results showed that the aspirin resistance in the IS group was significantly correlated with the *ABCB1* rs1045642 polymorphism (**Figure 2**).

*Association between ABCB1 rs1045642 polymorphisms and clopidogrel resistance in IS*

We analyzed 4 studies, including 190 patients and 447 controls that assessed the association between *ABCB1* rs1045642 polymorphism and clopidogrel resistance in IS. *ABCB1* rs1045642 polymorphism was potentially associated with clopidogrel resistance in IS: (A) Homozygote model: OR=3.35, 95% CI (1.99, 5.63), P=0.000; (B) Heterozygote model: OR= 0.81, 95% CI (0.54, 1.21), P=0.895; (C) Dominant model: OR=1.41, 95% CI (0.59, 3.36), P=0.435; (D) Recessive model: OR= 3.43, 95% CI (2.14, 5.51), P=0.000 (**Figure 3**). The findings indicated a significant correlation between clopidogrel resistance in IS and the *ABCB1* rs1045642 polymorphism (**Figure 3**).

*Sensitivity analysis and publication bias*

In the sensitivity analysis of the association between *ABCB1* rs1045642 polymorphism and aspirin resistance (clopidogrel resistance) in IS, the elimination of each study in a sequential manner made no qualitative difference in the analyses of the remaining studies. Publication biases in the included studies were assessed using Begg's test. Begg's test for the *ABCB1* rs1045642 polymorphism and aspirin resistance (clopidogrel resistance) revealed no significant publication bias (**Figures 4** and **5**).

## Discussion

Many patients use antiplatelet medications such as aspirin and clopidogrel to prevent major vascular incidents such as myocardial infarction and stroke [23]. Despite the development of new antiplatelet medications, aspirin, and clopidogrel remain the most commonly used antiplatelet drugs. Although many studies have confirmed the clinical efficacy of aspirin and clopidogrel as antithrombotic drugs, their effects in preventing platelet aggregation are not consistent in all patients [10-21]. Studies have shown that approximately 4-44% of patients have no response to clopidogrel [12] and approximately 5-65% of patients have no response to aspirin [10]. Although the exact cause of aspirin or clopidogrel resistance remains unclear, the response to these drugs is influenced by genetic factors (including *ABCB1* gene polymorphisms), clinical factors (age, drug interactions, chronic kidney disease, diabetes, body mass index, and intestinal absorption), and pathophysiological factors (platelet turnover rate and regulation of the P2Y12 receptor) [24, 25]. The environmental risk factors include aging, smoking, and hypercholesterolemia [26].

In this meta-analysis, we summarized the available data on the association of the *ABCB1* rs1045642 polymorphism with the response to aspirin or clopidogrel. These results suggest that the rs1045642 polymorphism might be related to an increased risk of clopidogrel or aspirin resistance in IS. Therefore, when prescribing clopidogrel or aspirin to patients with ischemic stroke, the *ABCB1* rs1045642 polymorphism, known for its significant role in

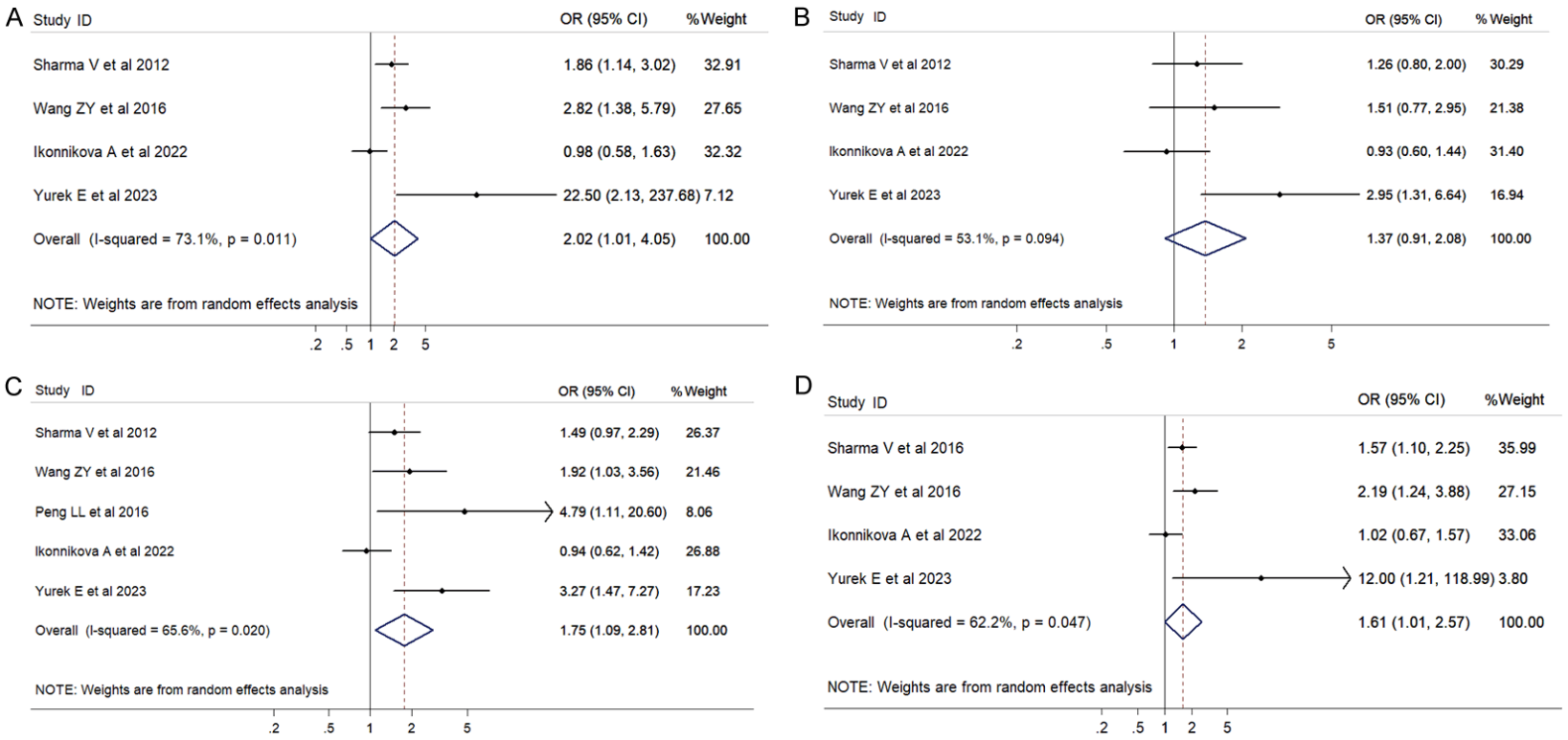


**Figure 2.** Forest plots for association between ABCB1 rs1045642 polymorphisms and aspirin resistance in IS. A. Homozygote model; B. Heterozygous model; C. Dominant model; D. Recessive model.

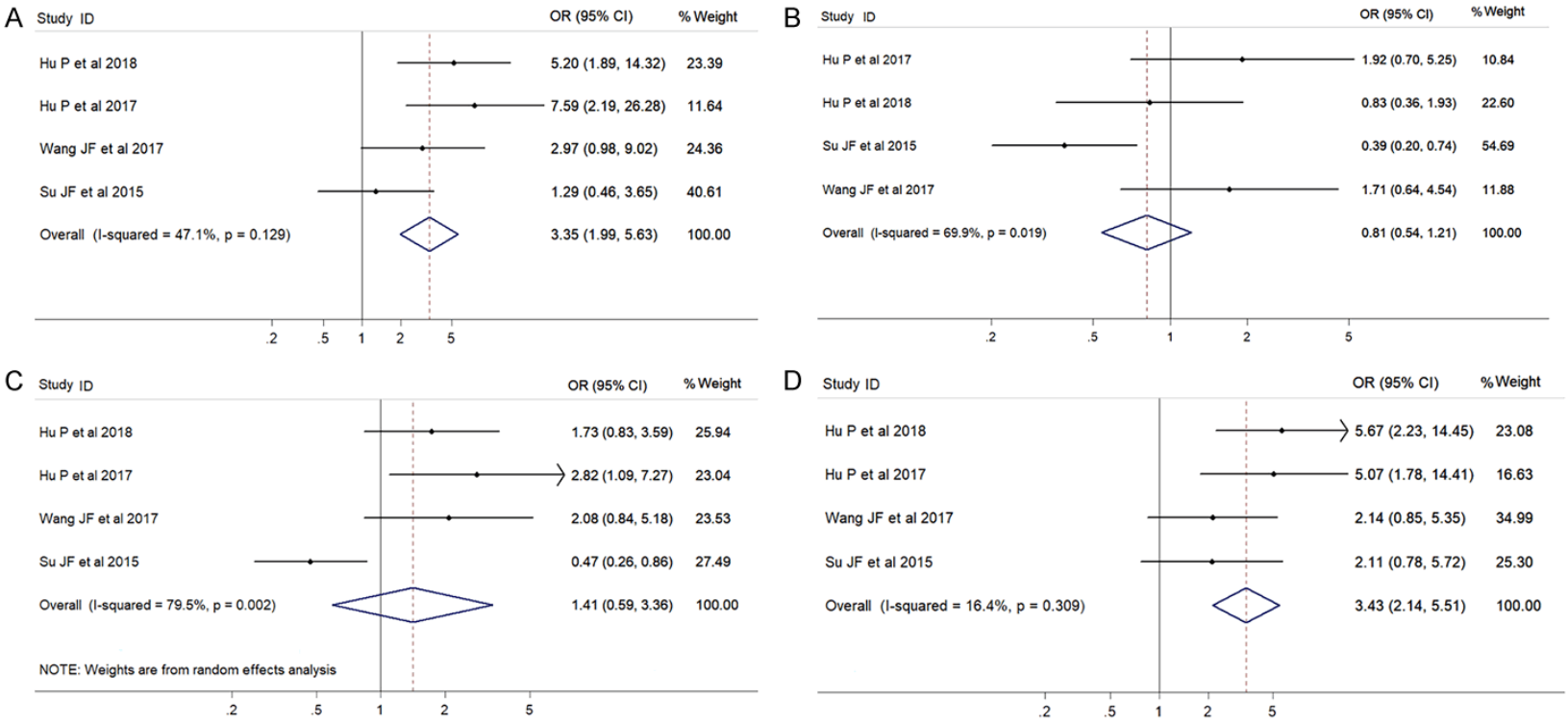


**Figure 3.** Forest plots for association between ABCB1 rs1045642 polymorphisms and clopidogrel resistance in IS. A. Homozygote model; B. Heterozygous model; C. Dominant model; D. Recessive model.

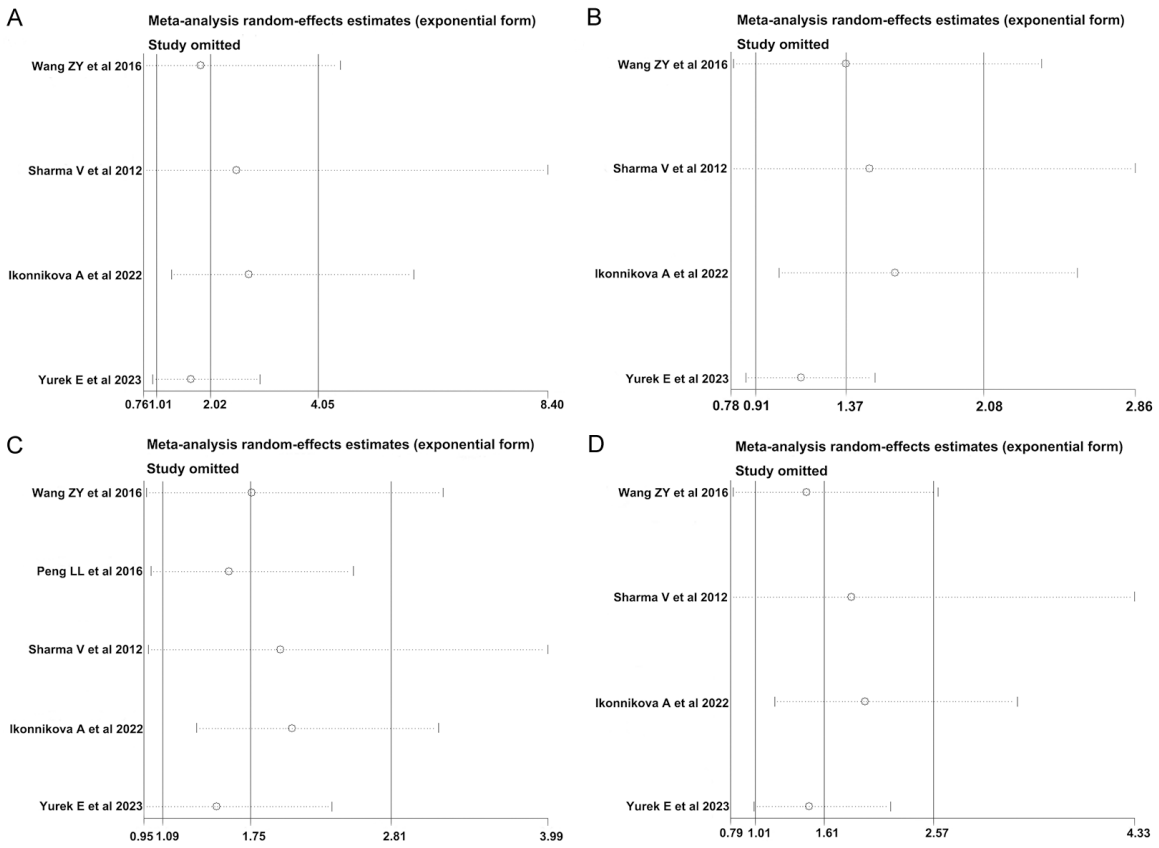


**Figure 4.** Sensitivity analysis for meta-analysis of association between ABCB1 rs1045642 polymorphisms and aspirin resistance in IS under the allelic model. A. Homozygote model; B. Heterozygous model; C. Dominant model; D. Recessive model.

the intestinal absorption of these medications, should be considered. Clinicians can tailor treatment strategies and seek more personalized and effective therapies according to the patients' genetic makeup [24]. For example, ticagrelor can be used as a superior alternative for clopidogrel resistance [25]. To improve the efficacy of antiplatelet monotherapy, aspirin-ticagrelor combination is recommended for acute short-term treatment in patients resistant to clopidogrel [27].

Genetic testing can be used to individualize anticoagulant therapy; however, pharmacogenetic testing has not been widely applied in clinical practice. There are conflicting findings among pharmacogenetic studies [28]. Therefore, randomized controlled trials targeting stroke are needed to verify the effectiveness of genetically guided therapies in the future.

There are some restrictions inherent to this study. First, the meta-analysis contained relatively small sample sizes and insufficient patient information for more in-depth subgroup studies, such as race, age, sex, lifestyle, and drug interactions. Second, the detection methods for *ABCB1* polymorphisms in different studies were inconsistent, which may have affected the accuracy of the results. To better elucidate the relationship between *ABCB1* polymorphisms and aspirin or clopidogrel resistance in ischemic stroke, additional evidence needs to be collected through carefully designed large sample studies to confirm our results.

## Conclusion

In summary, our results suggest that the *ABCB1* rs1045642 polymorphism may be associated with aspirin or clopidogrel resistance in patients with ischemic stroke. However, cohort expansion and further studies on the mechanisms underlying this genetic factor in aspirin and clopidogrel resistance are necessary.

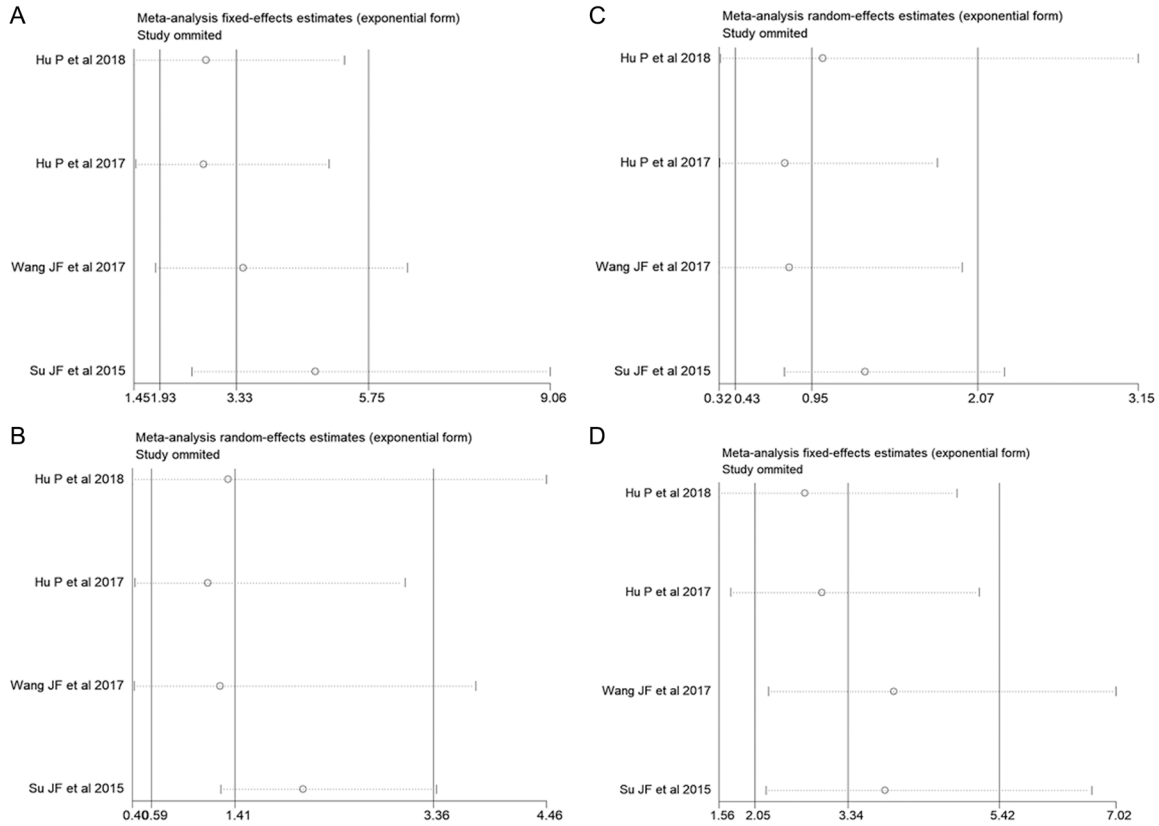


**Figure 5.** Sensitivity analysis for meta-analysis of association between ABCB1 rs1045642 polymorphisms and clopidogrel resistance in IS under the allelic model. A. Homozygote model; B. Heterozygous model; C. Dominant model; D. Recessive model.

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## Disclosure of conflict of interest

None.

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**Supplementary Table 1.** PRISMA Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review. | Title |
| ABSTRACT | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Abstract |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Introduction |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Introduction |
| METHODS | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for syntheses. | Methods |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Methods |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Methods |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Methods |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Methods |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Methods |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Methods |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Methods |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Methods |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Methods |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Methods |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Methods |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Methods |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Methods |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Methods |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Methods |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Methods |

| | | | |
|---|---|---|---|
| RESULTS | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Results, **Figure 1** |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Results, **Figure 1** |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Results, **Table 1** |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Results, **Table 1** |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Results |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Results, **Figures 2-5** **Table 2** |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Results, **Figures 2-5** **Table 2** |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Results |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Results, **Figures 4**, **5** |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Results |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Results |
| DISCUSSION | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Discussion |
| | 23b | Discuss any limitations of the evidence included in the review. | Discussion |
| | 23c | Discuss any limitations of the review processes used. | Discussion |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Discussion |
| OTHER INFORMATION | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | -- |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | -- |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | -- |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Acknowledgements |
| Competing interests | 26 | Declare any competing interests of review authors. | Title page |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | References, Results, **Table 1** |

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.