


ORIGINAL ARTICLE

Paroxysmal supraventricular tachycardia and risk of ischemic stroke: A systematic review and meta-analysis

Pongprueth Rujirachun MD¹ | Phuwadith Wattanachayakul MD¹ |
Arjbordin Winijkul MD² | Patompong Ungprasert MD, MS³ ¹Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand²Division of Cardiology, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand³Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand**Correspondence**Patompong Ungprasert, Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.
Email: p.ungprasert@gmail.com**Abstract****Background:** Paroxysmal supraventricular tachycardia (PSVT) has been traditionally considered as a benign rhythm disorder. However, recent studies have suggested that patients with PSVT may have a higher risk of ischemic stroke although the data are limited and inconclusive. The current systematic review and meta-analysis was conducted with the aims to identify all available studies and summarize their results together to better characterize the risk of ischemic stroke among patients with PSVT.**Methods:** A comprehensive literature review was conducted by searching for published articles indexed in MEDLINE and EMBASE databases from inception through November 11, 2018 to identify all observational studies that compared the risk of ischemic stroke between patients with PSVT and individuals without PSVT. Pooled risk ratio (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method of DerSimonian and Laird.**Results:** A total 5 studies (4 cohort studies and 1 case-control study) with 4 886 977 participants met the eligibility criteria and were included into the meta-analysis. The risk of ischemic stroke among patients with PSVT was significantly higher than individuals without PSVT with the pooled RR of 2.03 (95% CI, 1.22-3.38, $I^2 = 89\%$).**Conclusion:** This study found that PSVT is associated with a higher risk of ischemic stroke. Whether this association is causal and how it should be addressed in clinical practice require further investigations.**KEYWORDS**

meta-analysis, paroxysmal supraventricular tachycardia, risk factor, stroke

1 | INTRODUCTION

Paroxysmal supraventricular tachycardia (PSVT) is a common cardiac arrhythmia characterized by recurrent episodes of narrow QRS complex tachycardia with regular ventricular response initiated by the atria and/or atrioventricular node.¹ The reported incidence rate of PSVT in the United States was approximately 89 000 new cases per year.² Common presentations include recurrent, abrupt onset

and termination of palpitations, diaphoresis, dizziness, and shortness of breath although some patients can be asymptomatic.³ These symptoms can interfere with daily activities and its complication of tachycardia-induced cardiomyopathy has been observed, especially in patients with incessant PSVT.^{4,5}

Stroke is the second leading cause of death and the third leading cause of disability worldwide.^{6,7} Approximately 90% of stroke patients had ischemic stroke. There are several well-recognized risk factors for

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ischemic stroke, such as age, male sex, hypertension, diabetes mellitus, smoking, hypercoagulable state, and atrial fibrillation.^{8,9}

Interestingly, recent literatures have suggested that PSVT may also be a risk factor for ischemic stroke similar to atrial fibrillation (although at a smaller magnitude).^{10–15} Nonetheless, the data were still relatively limited and inconclusive. The current systematic review and meta-analysis was conducted with the aims to comprehensively evaluate the risk of ischemic stroke among patients with PSVT compared to individuals without PSVT by identifying all relevant studies and combining their results together.

2 | METHODS

2.1 | Literature search strategy

Two investigators (P.R. and P.W.) independently searched for published articles indexed in MEDLINE and EMBASE database from inception to November 11, 2018 using the search strategy that included the terms for supraventricular tachycardia and stroke. The search strategy is available as Data S1. References of the included studies were also manually reviewed for additional eligible studies. This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which is available as Data S2.

2.2 | Selection criteria

To be eligible for the meta-analysis, the study could be either cohort study or case-control study that investigated if PSVT is associated with a higher risk of ischemic stroke. Eligible cohort study must start with recruitment of cases with PSVT and comparators without PSVT and, then, follow them until the occurrence of stroke or the end of study. Eligible case-control study must start with cases with stroke and controls without stroke and, then, investigate for their prior history of PSVT. Eligible study must also provide the magnitude of association, which could be either relative risk (RR), hazard ratio (HR), or odds ratio (OR) along with its corresponding confidence interval (CI).

All retrieved articles were reviewed independently by the first 2 investigators (P.R. and P.W.) for their eligibility. The last 2 investigators (A.W. and P.U.) reviewed all the included studies again to ensure that the inclusion criteria were met and also served as the deciding votes when different determinations of study eligibility were made by the first 2 investigators. Newcastle-Ottawa quality assessment scale was used to assess the quality of the included cohort and case-control studies.¹⁶ This scale evaluates the quality of the included studies in 3 areas including recruitment of participants, comparability between the groups and ascertainment of the outcome of interest for cohort study or ascertainment of the exposure of interest for case-control study.

2.3 | Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, study design, year(s)

of study, country of origin, year of publication, sample size, baseline characteristics of participants, methods used to identify, and verify the diagnosis of paroxysmal supraventricular tachycardia and stroke, confounders that were adjusted and adjusted effect estimates with 95% CI. This data extraction was independently performed by the same 2 investigators (P.R. and P.W.) to minimize error. Any discrepancies found in the case record forms were resolved by referring back to the original articles.

2.4 | Statistical analysis

Review Manager 5.3 software from the Cochrane Collaboration was used for data analysis. Point estimates and standard errors were extracted from individual study and were combined together using the generic inverse variance method as described by DerSimonian and Laird.¹⁷ Random-effect model, rather than a fixed-effect model, was used because the included studies were of different methodologies and background populations. OR of case-control study was used as an estimate for RR to calculate the pooled RR along with RRs of cohort studies. Statistical heterogeneity was assessed using

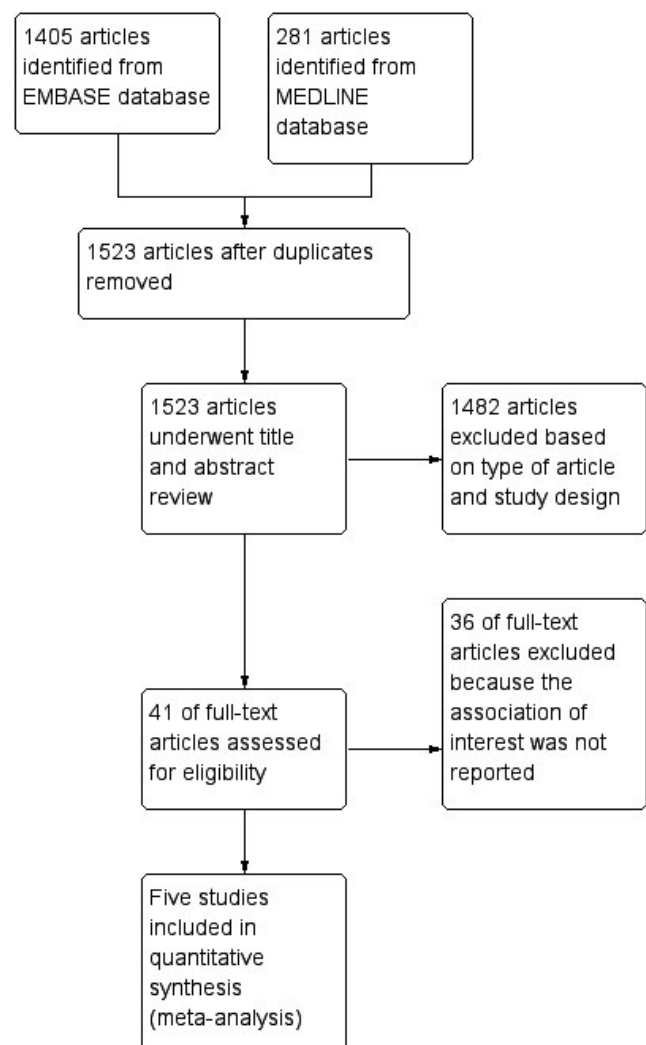


FIGURE 1 Flow-chart of literature review process

the Cochran's Q test. This statistic is complemented with the I^2 statistic which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0%-25% represents insignificant heterogeneity, 26%-50% low heterogeneity, 51%-75% moderate heterogeneity and >75% high heterogeneity.¹⁸ Presence of publication bias would be assessed by visualization of funnel plot and Egger regression test if enough studies were eligible for the meta-analysis. Egger regression test would be conducted using Comprehensive Meta-Analysis program, version 2.2 (Biostat, Englewood, NJ).

3 | RESULTS

The systematic search identified 1686 potentially relevant articles (1405 articles from EMBASE and 281 articles from MEDLINE). After the exclusion of 163 duplicated articles, 1523 articles underwent title and abstract review. A total of 1482 articles were excluded at this stage as they clearly did not fulfill the eligibility criteria based on the type of article, study design, participants, and outcome of interest. A total of 41 articles were retrieved for full-length article review and 36 articles were excluded at this

stage as they did not report the association of interest. Finally, 5 observational studies¹¹⁻¹⁵ (4 cohort studies and one case-control study) with 4 886 977 participants (17 033 patients had PSVT) were eligible for the meta-analysis. The literature retrieval, review, and selection process are shown in Figure 1. The characteristics of the included studies and their quality assessment are described in Table 1. It should be noted that even 2 studies^{12,14} were conducted by the same group of investigators, the databases used in each study were different (California State Inpatient Database and State Emergency Department Database in one study¹² and national Medicare beneficiaries' database in another¹⁴). Therefore, there was no patient duplication between the 2 studies.

3.1 | Risk of ischemic stroke among patients with paroxysmal supraventricular tachycardia

The pooled analysis found a significantly increased risk of ischemic stroke among patients with PSVT compared to individuals with PSVT without the pooled RR of 2.03 (95% CI, 1.22-3.38). The between-study heterogeneity was high with an I^2 of 89%. Figure 2 demonstrates the forest plot of this meta-analysis.

TABLE 1 Baseline characteristics of studies included in the meta-analysis

	Aronow et al ¹¹	Kamel et al ¹²	Kamel et al ¹⁴	Chiang et al ¹³	Johnson et al ¹⁵
Year of publication	1996	2013	2016	2017	2018
Country of origin	United states	United states	United states	Taiwan	Sweden
Study design	Prospective cohort study	Retrospective cohort study	Retrospective cohort study	Case-control study	Prospective cohort study
Study subjects	Cases: Cases were patients with PSVT who were diagnosed based on 24-hour ambulatory ECG. Cases were residences of a long-term healthcare facility. Comparators: Comparators were individuals who underwent 24-hour ambulatory ECG and were found to have sinus rhythm. Patients with AF were excluded from the analysis. Mean follow-up time was 43 ± 27 months (range 2-117 mo).	Cases: Cases were patients with PSVT who were identified from the 2009 California State Inpatient Database and State Emergency Department Database which collected data of all ED visits and hospital stays at non-federal acute care hospitals across the state of California from January 1, 2009 to December 31, 2009. Comparators: Comparators were the rest of patients in the database who did not carried a diagnosis of PSVT. Patients with AF were excluded from the analysis.	Cases: Cases were patients with PSVT who were identified from the 2010 to 2011 database of 5% sample of Medicare beneficiaries Comparators: Comparators were the rest of patients in the database who did not carried a diagnosis of PSVT. Patients with AF were excluded from the analysis. Median follow-up time was 1.8 years.	Cases: Cases were adult patients aged > 20 years with ischemic stroke who were identified from the database of the Taiwan Longitudinal Health Insurance Database in the year 2000 (LHID2000) which randomly collected health data of approximately one million patients through the records of the National Health Insurance program. Controls: Controls were individuals aged > 20 y without a history of stroke who were recruited from the same database.	Cases: Cases were patients with PSVT who were diagnosed based on 24-hour ambulatory ECG. The ECG was done as a part of a population-based study named Malmö Diet and Cancer study (MDCS) that recruited participants between 1991 and 1996. Comparators: Comparators were individuals who underwent 24-hour ECG screening and were not found to have PSVT. Patients with AF were excluded from the analysis. Mean follow-up time was 13.2 y

(Continues)

TABLE 1 (Continued)

	Aronow et al ¹¹	Kamel et al ¹²	Kamel et al ¹⁴	Chiang et al ¹³	Johnson et al ¹⁵
Number of subjects	Cases: 493 Comparators: 782	Cases: 14 121 Comparators: 4 792 709	Cases: 2245 Comparators: 39 907	Cases: 5633 Controls: 30 895	Cases: 24 Comparators: 168
Baseline characteristics of subjects	Mean age: Cases: 82 ± 8 y Comparators: 80 ± 8 y Percentage of female: Case: 70% Comparators: 71% Use of warfarin at enrollment: Cases: 1% Comparators: 1% Use of aspirin at enrollment: Cases: 25% Comparators: 24%	Median (IQR) age: Cases: 69 (55-81) y Comparators: 46 (30-62) y Percentage of female: Cases: 60% Comparators: 59% Race/ethnicity: Cases: 66.3% White 9.1% Black 14.4% Hispanic 8.0% Asian or Pacific Islander 0.1% Native American 2.2% Other Comparators: 53.8% White 9.7% Black 26.5% Hispanic 6.9% Asian or Pacific Islander 0.1% Native American 3.0% Other Payment source: Cases: 56.7% Medicare 7.4% Medicaid 29.8% Private insurance 3.8% Self-pay 2.3% Other Comparators: 23.7% Medicare 14.8% Medicaid 41.5% Private insurance 13.8% Self-pay 6.2% Other Vascular risk factors: Cases: 51.5% HT 22.6% DM 22.3% CHD 13.5% COPD 15.5% CHF 11.3% RI 5.3% PAD Comparators: 22.8% HT 11.1% DM 6.2% CHD 4.1% COPD 3.1% CHF 3.0% RI 1.4% PAD	Mean age: Cases: NA Comparators: NA Percentage of female: Cases: NA Comparators: NA	Mean age: Cases: 69 ± 12 y Controls: 49 ± 13 y Percentage of female: Case: 42% Controls: 53% Prevalent HT at enrollment: Cases: 84.4% Controls: 20.1% Prevalent DM at enrollment: Cases: 44.8% Controls: 9.7% Prevalent CKD at enrollment: Cases: 11.8% Controls: 2.2% HBV infection at enrollment: Cases: 5.8% Controls: 8.0% HCV infection at enrollment: Cases: 3.8% Controls: 2.2% Use of aspirin at enrollment: Cases: 1.3% Controls: 11.5%	Mean age: Cases: 67 ± 5 y Comparators: 63 ± 6 y Percentage of female: Case: 58% Comparators: 56% Mean CHA ₂ DS ₂ -VASc Score at enrollment: Cases: 2.1 Comparators: 1.8 History of CHF at enrollment: Cases: 0% Comparators: 0% History of coronary event, PCI, CABG, or PAD at enrollment: Cases: 6.7% Comparators: 3.6% Prevalent HT at enrollment: Cases: 75.0% Comparators: 64.3% Prevalent DM at enrollment: Cases: 8.3% Comparators: 7.1%

(Continues)

3.2 | Sensitivity analysis

To further explore the high between-study heterogeneity, a jack-knife sensitivity analysis was conducted by excluding 1 study at a time from

the complete analysis to investigate if a particular study has an especially high influence on the between-study variation. The complete results of the sensitivity analysis are provided as Data S3. In brief, the pooled results continued to show a significantly increased risk

TABLE 1 (Continued)

	Aronow et al ¹¹	Kamel et al ¹²	Kamel et al ¹⁴	Chiang et al ¹³	Johnson et al ¹⁵
Diagnosis of PSVT	PSVT was detected by 24-hour ambulatory ECG	Presence of ICD-9-CM for PSVT in the database	Presence of ICD-9-CM for PSVT in the database	Presence of ICD-9-CM for PSVT in the database	PSVT was detected by 24-hour ambulatory ECG showing episode(s) of regular supraventricular tachycardia without p-waves
Diagnosis of stroke	Cases and comparators were routinely seen by physicians as a part of care provided by the long-term healthcare facility. Stroke was diagnosed by a neurologist if a focal neurologic event occurred suddenly but without prolonged unconsciousness, nuchal rigidity, fever, pronounced leukocytosis or bloody spinal fluid and also confirmed by computerized axial tomography in 97% patients.	Presence of ICD-9 -CM for ischemic stroke in the database after the index date without accompanying codes for rehabilitation, trauma, ICH or SAH	Presence of ICD-9 -CM for ischemic stroke in the database after the index date	Presence of ICD-9 -CM for ischemic stroke in the database after the index date without accompanying codes for rehabilitation, trauma, ICH or SAH	Presence of ICD-9 -CM for ischemic stroke in the database after the index date
Confounder adjusted in the multivariate analysis	None	Age, sex, race, payment source and vascular risk factors (HT, DM, CHD, COPD, CHF, RI and PAD)	Demographic characteristics and vascular risk factors	Age, sex, HT, DM, CKD, HBV infection, HCV infection and aspirin use	Age and sex
Newcastle-Ottawa score	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars	Selection: 3 stars Comparability: 2 stars Exposure: 3 stars	Selection: 4 stars Comparability: 1 star Outcome: 3 stars

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; CABG, coronary artery bypass graft; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECG, electrocardiogram; ED, emergency department; HBV, hepatitis B virus; HCV, hepatitis C virus; HT, hypertension; ICD-9-CM, international classification of diseases, ninth revision, clinical modification; ICH, intracerebral hemorrhage; IQR, interquartile range; LHID2000, 2000 longitudinal health insurance database; NA, not available; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PSVT, paroxysmal supraventricular tachycardia; RI, renal insufficiency; SAH, subarachnoid hemorrhage.

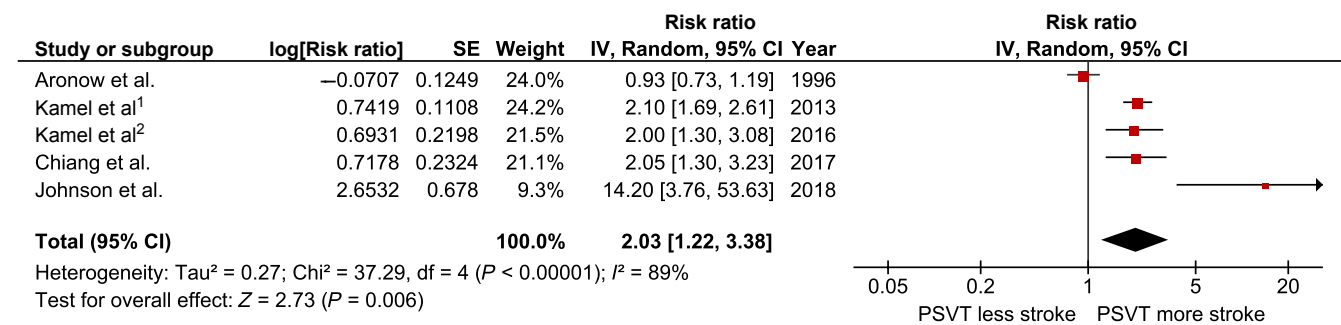


FIGURE 2 Forest plot of the meta-analysis

of ischemic stroke among patients with PSVT compared to individuals with PSVT with exclusion of any individual study. Exclusion of the study by Aronow et al.¹¹, the only study that did not adjust its effect

estimate for any potential confounders, had the highest impact on between study heterogeneity that the I² decreased to moderate level (62%).

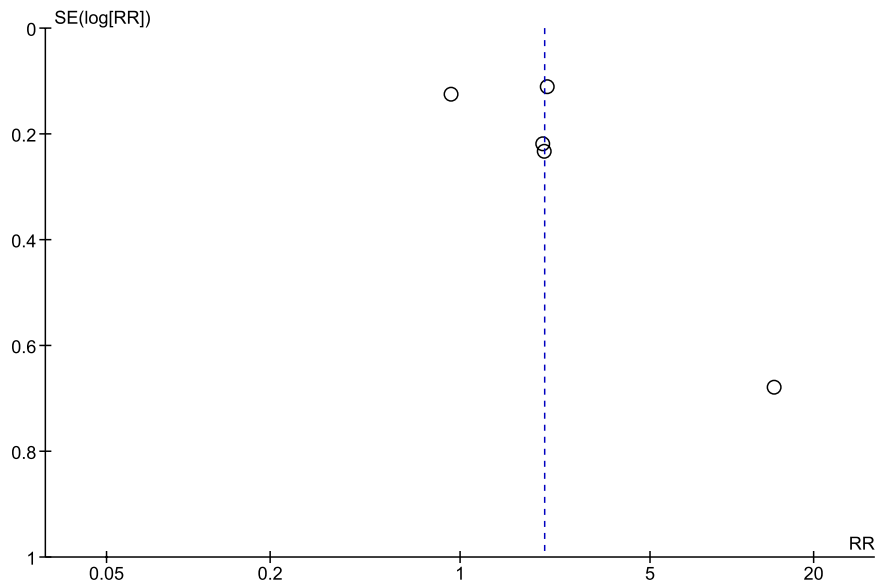


FIGURE 3 Funnel plot of the meta-analysis

3.3 | Evaluation for publication bias

Funnel plot was created for evaluation for publication bias. The plot was relatively symmetric which was not suggestive of publication bias in favor of studies with positive results (Figure 3). Publication was also not detected by Egger regression test with *P*-value of 0.36.

4 | DISCUSSION

This study is the first systematic review and meta-analysis that summarized data from all available studies on the risk of ischemic stroke among patients with PSVT and found 2-times higher risk of stroke compared to individuals without PSVT. There are few possible mechanisms to explain this observed increased risk.

The first possible explanation is related to the development of atrial cardiomyopathy.^{10,12,15} Elevated heart rate from PSVT can lead to overwork of myocardium which would subsequently lead to depletion of myocardial energy storage, abnormal calcium handling and accumulation of reactive oxygen species.^{19,20} In the event of persistent or frequent recurrent PSVT, this process can eventually lead to apoptosis of myocardial cells and fibrosis, resulting in permanent structural changes of the atria.²¹ One of the frequent structural changes seen in patients with atrial cardiomyopathy is left atrial enlargement,^{22,23} which is known to provoke stasis of blood flow and increase the risk of thrombus formation.²⁴ In addition, atrial fibrosis is associated with poor atrial contractility,^{25–27} which would further promote stagnation of the flow.

The second explanation is the increased risk of subsequent atrial fibrillation, the prime predisposing factor for thromboembolic events.^{12,15,28} As mentioned above, frequent PSVT may lead to the development of atrial fibrosis and left atrial enlargement.

The combination of these 2 pathologies can serve as a fertile ground for the development of atrial fibrillation as fibrosis has been shown to play a major role in the creation of reentrant circuits that are vital in the pathogenesis of initiation and maintenance of atrial fibrillation.²⁹

Nonetheless, the apparent association between PSVT and ischemic stroke may not be causal. PSVT has been historically viewed as an isolated conduction defect of otherwise young and healthy individuals.^{1,11,12} However, more recent data have suggested that PSVT is indeed more common in older individuals with higher burden of atherosclerotic diseases,^{12,30} suggesting that PSVT could be a consequence of conductive tissue injury from associated cardiovascular diseases. Thus, it is also possible that the presence of PSVT is just a marker of higher burden of cardiovascular disease and the increased risk of ischemic stroke is a function of the higher overall burden with no direct causal pathway to PSVT itself.

Although the included studies were of high quality and the literature review process was thorough, we acknowledge that the study had some limitations and the results should be interpreted with caution.

First, the meta-analysis had high between-study heterogeneity. The difference in adjustment for potential confounders for the effect estimates was the most likely explanation for the heterogeneity as demonstrated by the sensitivity analysis. Second, most of the included studies were medical registry-based studies that relied on diagnostic codes to identify and diagnose PSVT and ischemic stroke. Therefore, the accuracy of the diagnoses from those studies was relatively limited. Third, the reliability of evaluation for publication was limited by the small number of included studies. Thus, it is still possible that publication bias in favor of studies that report positive results may have been present, despite the relatively symmetric funnel plot.

5 | CONCLUSION

This study found that PSVT is associated with a higher risk of ischemic stroke. Whether this association is causal and how it should be addressed in clinical practice require further investigations.

CONFLICT OF INTEREST

All authors declare no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

All authors designed the study. P.R. and P.W. collected the data and drafted the manuscript. P.U. performed statistical analysis. A.W. and P.U. made critical revisions. P.R. and P.W. revised the final manuscript. All authors read and approved the final manuscript.

ORCID

Patompong Ungprasert  <https://orcid.org/0000-0002-4817-9404>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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