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Association of *TFPI* polymorphisms rs8176592, rs10931292, and rs10153820 with venous thrombosis

A meta-analysis

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Abstract

Background: *Tissue factor pathway inhibitor* (*TFPI*) polymorphisms are known to be involved in venous thrombosis; however, any correlation between the *TFPI* polymorphisms rs8176592, rs10931292, and rs10153820 and venous thrombosis remains controversial. This meta-analysis aimed to elucidate the relationship between these *TFPI* polymorphisms and the susceptibility to venous thrombosis.

Methods: A literature search for relevant studies was conducted in PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Med Online databases. Odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were calculated using fixed-effect/random-effect models by the STATA 12.0 software. Sources of heterogeneity were analyzed by subgroup analysis.

Results: Eleven case-control studies involving 3740 subjects (1362 venous thrombosis patients and 2378 healthy controls) were included. The *TFPI* rs8176592 polymorphism was associated with increased risk of venous thrombosis in the whole population, while no significant association was found between rs10931292/rs10153820 and venous thrombosis. In subgroup analysis based on ethnicity, an increased risk was observed with rs8176592 polymorphism in Asians (Recessive model, OR = 1.48, 95% CI = 1.06–2.07, $P = .023$). An increased risk associated with rs10931292 was identified in non-Asians (Recessive model, OR = 1.42, 95% CI = 1.03–1.97, $P = .033$). No significant association was found in either Asians or non-Asians with the rs10153820 polymorphism. In subgroup analysis based on source of controls, increased risks were identified in the hospital-based group with rs8176592 polymorphism and in the population-based group with rs10931292 polymorphism, whereas decreased risk was identified in the hospital-based group with the rs10931292 and rs10153820 polymorphisms.

Conclusion: Meta-analysis suggested that different *TFPI* polymorphisms may have different associations with venous thrombosis. *TFPI* rs8176592 polymorphism may increase the risk of venous thrombosis, especially in Asians and hospital-based patients. The *TFPI* rs10931292 polymorphism may increase the venous thrombosis risk for both non-Asians and population-based patients. Moreover, rs10931292 and rs10153820 polymorphisms of *TFPI* may decrease the risk of venous thrombosis for hospital-based patients.

Abbreviations: CIs = confidence intervals, CNKI= China National Knowledge Infrastructure, CVT = cerebral venous thrombosis, DVT = deep vein thrombosis, HWE= Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa quality assessment scale, ORs =

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YZ and AP authors contributed equally for this work.

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Odds ratios, *P* = *P*-value of overall effect, PE = pulmonary embolism, TF = tissue factor, TFPI = tissue factor pathway inhibitor, VTE = venous thromboembolism.

Keywords: meta-analysis, polymorphism, tissue factor pathway inhibitor, venous thrombosis

1. Introduction

Venous thrombosis is a widespread and serious disorder that occurs in the blood coagulation process in the venous system and leads to venous obstruction; deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most commonly encountered manifestations.[1–3] The incidence of venous thrombosis is estimated to vary between 1 and 2 per 1000 annually in the adult population.[4–8] Venous thrombosis is associated with many types of risk factors, such as genetics, weight, age, sex, region, ethnicity, lifestyle, and environmental exposure.[9–12]

Tissue factor pathway inhibitor (TFPI) encodes TFPI, a Kunitz-type serine protease inhibitor.[13] The TFPI downregulates the tissue factor (TF)-dependent pathway by inhibiting both tissue factor-activated factor VII and activation of factor X, thereby limiting clot growth and preventing prothrombin to thrombin conversion.[14–17] Low TFPI plasma level is associated with increases risk of venous thrombosis.[18] The *TFPI* is localized on human chromosome 2q and contains 10 exons and 9 introns.[16,19] The *TFPI* intronic T-33C (rs8176592), promoter T-287C (rs10931292), and promoter C-399T (rs10931292) polymorphisms have been previously investigated.[20,21] This meta-analysis was performed to determine the association between the three *TFPI* polymorphisms and the risk of venous thrombosis.

2. Methods

2.1. Search strategy

Relevant studies were identified in the following databases: PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Med Online databases by searching up to October 23, 2018 without language restrictions. The search terms were as follows: ("tissue factor pathway inhibitor" or "TFPI") and ("polymorphism" or "mutation" or "variant" or "allele" or "genotype" or "SNP") and ("venous thromboembolism" or "VTE" or "deep venous thrombosis" or "deep vein thrombosis" or "DVT" or "venous thrombosis" or "pulmonary thromboembolism" or "PTE" or "pulmonary embolism" or "PE" or "cerebral venous thrombosis" or "CVT"). Moreover, potentially related studies were also collected from the reference lists of the screened full-text articles above.

2.2. Inclusion and exclusion criteria

All studies included in the meta-analysis met the following criteria: First, the design was a cohort or case-control study. Second, evaluated the association between *TFPI* polymorphisms and venous thrombosis. Third, sufficient genotype data for calculating the odds ratios (ORs) with 95% confidence intervals (95% CIs). Exclusion criteria were: First, duplicate publication. Second, animal models. Third, obviously irrelevant studies. Fourth, comment, review, or meta-analysis. Fifth, the genotype frequencies were unavailable.

2.3. Data extraction

The bibliography search and data extraction were conducted independently by 2 investigators. The following information from each study was extracted: the 1st author's name, year of publication, country, ethnicity (Asian or non-Asian), genotyping method, source of controls, venous thrombosis type, numbers of cases and controls with the *TFPI* genotypes, and Hardy–Weinberg equilibrium (HWE) in controls. Source of controls was categorized as hospital-based or population-based population.

2.4. Quality assessment

A quality assessment was independently performed for all of the included studies by 2 authors using the Newcastle–Ottawa quality assessment scale (NOS), and any disagreement was resolved by discussion and consensus.[22] The NOS comprises the following three parameters of quality: selection, comparability, and exposure. The range of the scores is from 0 to 9, and studies with scores of 6 to 9 points are considered to be high quality.

2.5. Statistical analysis

The possible associations between the *TFPI* polymorphisms and venous thrombosis were evaluated by ORs and 95% CIs. Pooled ORs were obtained from combination of individual studies according to the codominant model (T vs C for rs8176592 and rs10931292; C vs T for rs10153820), homozygous model (TT vs CC for rs8176592 and rs10931292; CC vs TT for rs10153820), heterozygous model (TC vs CC for rs8176592 and rs10931292; CT vs TT for rs10153820), dominant model (TT+TC vs CC for rs8176592 and rs10931292; CC+CT vs TT for rs10153820), and recessive model (TT vs TC+CC for rs8176592 and rs10931292; CC vs CT+TT for rs10153820). For each genetic comparison model, subgroup analysis according to ethnicity was investigated to estimate ethnic-specific ORs for Asians and non-Asians. Z-test was used to assess the significance of the pooled OR, with $P < .05$ considered statistically significant. Heterogeneity was assessed by Cochrane's Q test and the I-square statistic.[23] Significant heterogeneity was considered when $P < .05$, or $I^2 > 50\%$. In case of no or moderate heterogeneity ($P > .05$ or $I^2 < 50\%$), the fixed-effect model (Mantel–Haenszel test) was applied; otherwise, the random-effects model (Der Simonian and Laird method) was used.[24] Subgroup analysis based on ethnicity and source of control was carried out to further explore possible explanations for heterogeneity. Sensitivity analysis was performed to confirm whether the results were considerably affected by any single study. Potential publication bias was explored using Begg's test.[25] Associations were considered statistically significant when $P > .05$. Meta-analysis was conducted using STATA version 12.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Search results and study characteristics

The detailed process of study selection is summarized in Figure 1. A total of 234 potentially relevant publications were initially identified; 214 were excluded after the titles and abstracts were screened. The 20 candidate articles were subjected to further evaluation and nine were excluded for the following reasons: 1

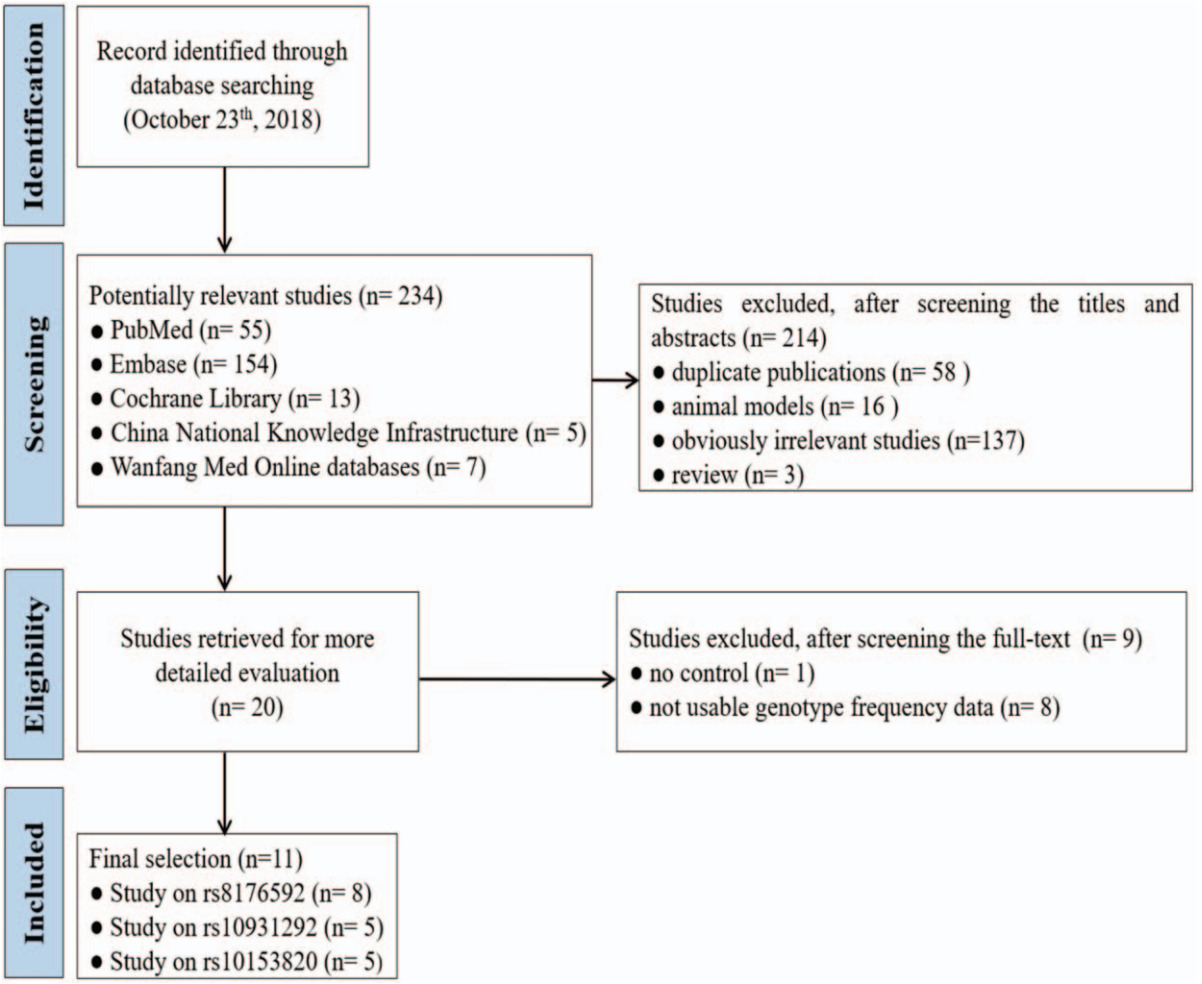

Figure 1. Flow diagram of literature search and study selection.

Table 1

Characteristics of included studies in the meta-analysis.

Gene polymorphisms	Study	Year	Country	Ethnicity	Genotyping methods	Source of controls	Venous thrombosis type	Genotype*		P†	Quality score‡
								Cases	Controls		
rs8176592	Ameziane et al[27]	2002	France	non-Asian	PCR	HB	VTE	167/142/21	384/358/84	.967	8
	Lincz et al[28]	2007	Australia	non-Asian	PCR-RFLP	HB	VTE	7/18/1	29/25/2	.222	7
	Sidelmann et al[29]	2008	Denmark	non-Asian	PCR	HB	DVT	24/28/5	62/33/8	.238	7
	Opstad et al[32]	2010	Norway	non-Asian	Real-time PCR	PB	VT	71/67/0	196/213/0	.000	8
	Prabhakar et al[33]	2012	India	Asian	PCR-RFLP	HB	CVT	32/183/3	20/174/8	.000	7
	Kwon et al[34]	2014	Korean	Asian	Real-time PCR	PB	VTE	33/7/0	34/6/0	.608	8
	Jiang et al[35]	2015	China	Asian	PCR-SSCP, PCR-RFLP	HB	DVT	71/18/4	75/23/2	.879	7
	Kamal et al[36]	2017	India	Asian	PCR-RFLP	HB	DVT	50/45/5	33/57/10	.042	7
rs10931292	Lincz et al[28]	2007	Australia	non-Asian	PCR-RFLP	HB	VTE	20/6/0	39/15/2	.713	7
	Amini et al[30]	2008	England	non-Asian	PCR	HB	DVT	133/23/9	173/52/2	.372	7
	Liu et al[31]	2009	China	Asian	PCR-RFLP	HB	VTE	56/42/12	72/36/8	.246	7
	Opstad et al[32]	2010	Norway	non-Asian	Real-time PCR	PB	VT	110/26/2	296/109/7	.398	8
	Kwon et al[34]	2014	Korean	Asian	Real-time PCR	PB	VTE	15/23/2	11/23/6	.287	8
rs10153820	Miyata et al[26]	1998	Japan	Asian	PCR	PB	DVT	54/46/11	130/96/29	.088	8
	Lincz et al[28]	2007	Australia	non-Asian	PCR-RFLP	HB	VTE	15/10/1	43/13/0	.326	7
	Liu et al[31]	2009	China	Asian	PCR-RFLP	HB	VTE	43/41/26	52/50/14	.712	7
	Opstad et al[32]	2010	Norway	non-Asian	Real-time PCR	PB	VT	106/32/0	324/84/6	.835	8
	Kamal et al[36]	2017	India	Asian	ASP	HB	DVT	65/28/7	88/10/2	.020	7

* Genotype for *TFPI* rs8176592, TT/TC/CC; *TFPI* rs10931292, TT/TC/CC; *TFPI* rs10153820, CC/CT/TT.

† Hardy–Weinberg equilibrium in the control group.

‡ Assessed by the Newcastle–Ottawa Assessment Scale for case-control studies.

ASP= allele specific PCR, *CVT*= cerebral venous thrombosis, *DVT*= deep venous thrombosis, *HB*= hospital-based, *PB*= population-based, *PCR-RFLP*=PCR-restriction fragment length polymorphism, *PCR-SSCP*=PCR-single strand conformation polymorphism, *VT*= venous thrombosis, *VTE*= venous thromboembolism.

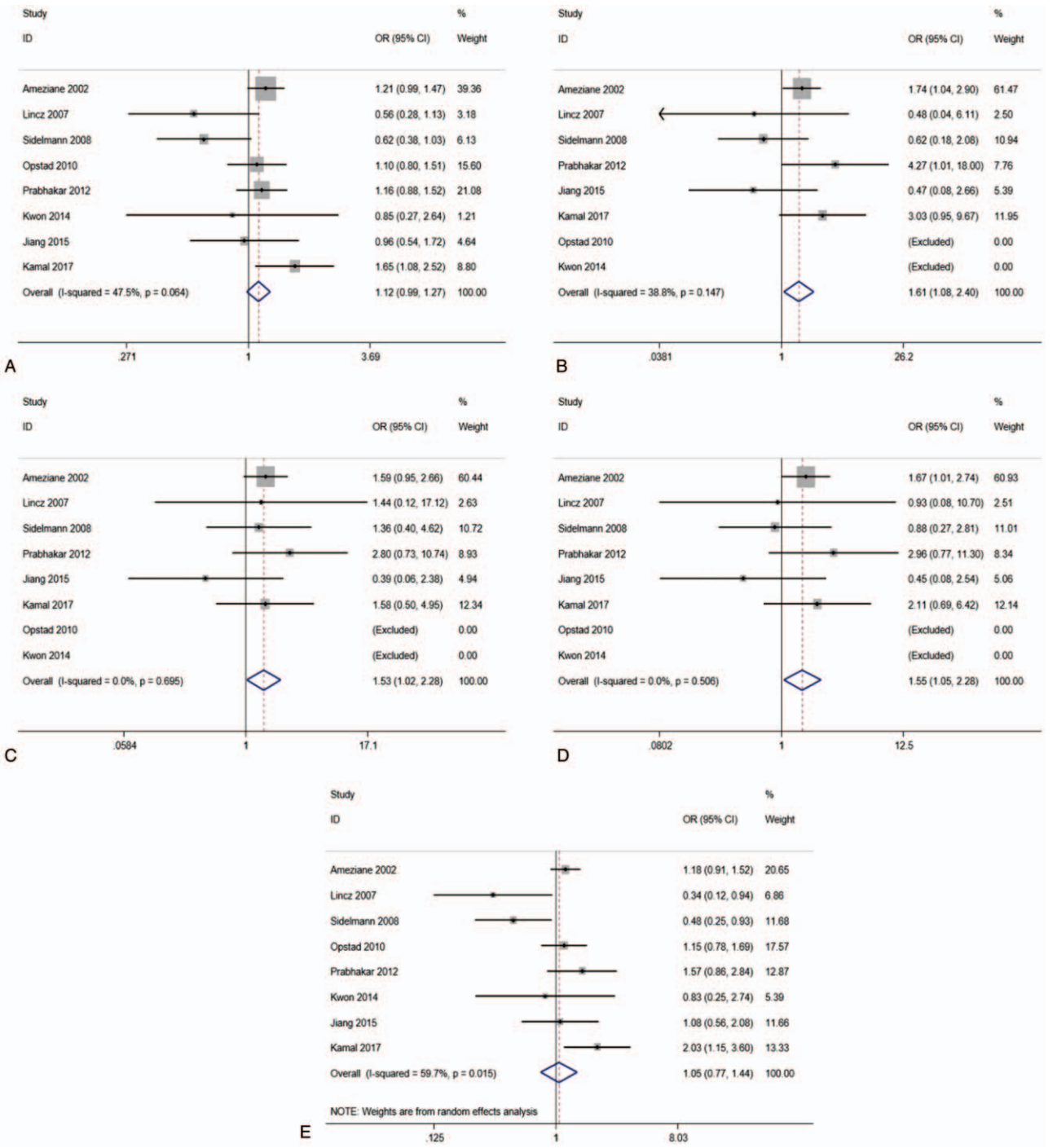

Figure 2. Forest plots for the associations between *TFPI* rs8176592 polymorphism and venous thrombosis. (A) codominant genetic model, (B) homozygous genetic model, (C) heterozygous genetic model, (D) dominant genetic model, (E) recessive genetic model. CI = confidence interval, OR = odds ratio, TFPI = tissue factor pathway inhibitor.

was not control; 8 were not usable genotype frequency data. Finally, 11 articles shown in Table 1 met the inclusion criteria and were included in the final meta-analysis.[26–36] These studies included 3740 subjects (1362 cases and 2378 controls). The *TFPI* genotypic frequencies in all the subjects of control groups were consistent with HWE except three studies for rs8176592, and one study for rs10153820 (Table 1). Study quality was assessed by NOS, and the scores ranged from 7 to 8, so the studies were considered to be high quality.

3.2. Meta-analysis results

The main results of this meta-analysis and heterogeneity assessment are presented in Table 2. The intron 7 rs8176592, promoter rs10931292 and rs10153820 polymorphisms of *TFPI* were studied.[27] There were 8 studies with 976 cases and 1780 controls for *TFPI* rs8176592 polymorphism. All were case-control studies, including 3 venous thromboembolism (VTE) studies,[27,28,34] 3 DVT studies,[29,35,36] 1 venous thrombosis study,[32] and 1 cerebral venous thrombosis (CVT) study.[33]

Table 2

Meta-analysis results for the *TFPI* polymorphisms and venous thrombosis.

Gene polymorphisms	Inherited model	Heterogeneity-test *P* for Q test	I^2 (%)	Analysis model	Pooled OR (95% CI)	*P*
rs8176592	Codominant (T vs C)	.064	47.5	FEM	1.12 (0.99,1.27)	.076
	Homozygous (TT vs CC)	.147	38.8	FEM	1.61 (1.08,2.40)	.020
	Heterozygous (TC vs CC)	.695	0.0	FEM	1.53 (1.02,2.28)	.039
	Dominant (TT+TC vs CC)	.506	0.0	FEM	1.55 (1.05,2.28)	.028
	Recessive (TT vs TC+CC)	.015	59.7	REM	1.05 (0.77,1.44)	.752
rs10931292	Codominant (T vs C)	.080	52.1	REM	1.11 (0.79,1.56)	.558
	Homozygous (TT vs CC)	.071	53.6	REM	0.84 (0.29,2.44)	.754
	Heterozygous (TC vs CC)	.059	55.9	REM	0.73 (0.24,2.22)	.583
	Dominant (TT+TC vs CC)	.085	51.2	REM	0.82 (0.30,2.25)	.697
	Recessive (TT vs TC+CC)	.126	44.4	FEM	1.17 (0.90,1.53)	.240
rs10153820	Codominant (C vs T)	.006	72.6	REM	0.66 (0.44,1.00)	.050
	Homozygous (CC vs TT)	.121	45.2	FEM	0.63 (0.38,1.04)	.070
	Heterozygous (CT vs TT)	.233	28.2	FEM	0.77 (0.47,1.28)	.320
	Dominant (CC+CT vs TT)	.127	44.3	FEM	0.66 (0.41,1.06)	.088
	Recessive (CC vs CT+TT)	.023	64.8	REM	0.64 (0.41,1.00)	.051

CI= confidence interval, *FEM*= fixed-effects model, *OR*=odds ratio, *P*=*P*-value of overall effect, *REM*= random-effects model, TFPI=tissue factor pathway inhibitor.

Subjects were sampled from France, Australia, Denmark, Norway, India, Korean, and China. Significant association between *TFPI* rs8176592 polymorphism and elevated risk of venous thrombosis was found in 3 models (homozygous: OR=1.61, 95% CI=1.08–2.40, *P*=.020; heterozygous model: OR=1.53, 95% CI=1.02–2.28, *P*=.039; dominant model: OR=1.55, 95% CI=1.05–2.28, *P*=.028) (Table 2 and Fig. 2). In the subgroup analysis based on ethnicity, *TFPI* rs8176592 polymorphism significantly increased the risk of venous thrombosis in Asians (recessive model: OR=1.48, 95% CI=1.06–2.07, *P*=.023), but not in non-Asians (recessive: OR=0.81, 95% CI=0.51–1.30, *P*=.387) (Table 3). Moreover, subgroup analysis

Table 3

The results of ethnicity subgroup analysis for *TFPI* polymorphisms and venous thrombosis.

Gene polymorphisms	Inherited model	Subgroup	Heterogeneity-test *P* for Q test	I^2 (%)	Analysis model	Pooled OR (95% CI)	*P*
rs8176592	Codominant (T vs C)	Non-Asian	.027	67.2	REM	0.92 (0.66,1.28)	.605
	Codominant (T vs C)	Asian	.368	5.1	REM	1.22 (0.98,1.52)	.074
	Homozygous (TT vs CC)	Non-Asian	.213	35.4	REM	1.15 (0.52,2.57)	.729
	Homozygous (TT vs CC)	Asian	.126	51.7	REM	2.05 (0.63,6.69)	.235
	Heterozygous (TC vs CC)	Non-Asian	.972	0.0	FEM	1.55 (0.97,2.47)	.068
	Heterozygous (TC vs CC)	Asian	.227	32.6	FEM	1.48 (0.67,3.23)	.330
	Dominant (TT+TC vs CC)	Non-Asian	.567	0.0	FEM	1.49 (0.95,2.33)	.084
	Dominant (TT+TC vs CC)	Asian	.217	34.5	FEM	1.74 (0.81,3.74)	.158
	Recessive (TT vs TC+CC)	Non-Asian	.011	72.9	REM	0.81 (0.51,1.30)	.387
	Recessive (TT vs TC+CC)	Asian	.391	0.2	REM	1.48 (1.06,2.07)	.023
rs10931292	Codominant (T vs C)	Non-Asian	.424	0.0	REM	1.23 (0.92,1.64)	.168
	Codominant (T vs C)	Asian	.037	77.1	REM	0.98 (0.44,2.17)	.956
	Homozygous (TT vs CC)	Non-Asian	.117	53.4	REM	0.65 (0.13,3.35)	.610
	Homozygous (TT vs CC)	Asian	.045	75.1	REM	1.26 (0.17,9.39)	.819
	Heterozygous (TC vs CC)	Non-Asian	.095	57.5	REM	0.43 (0.07,2.53)	.349
	Heterozygous (TC vs CC)	Asian	.180	44.4	REM	1.27 (0.36,4.55)	.711
	Dominant (TT+TC vs CC)	Non-Asian	.113	54.2	REM	0.60 (0.11,3.09)	.538
	Dominant (TT+TC vs CC)	Asian	.079	67.6	REM	1.23 (0.24,6.45)	.804
	Recessive (TT vs TC+CC)	Non-Asian	.884	0.0	REM	1.42 (1.03,1.97)	.033
	Recessive (TT vs TC+CC)	Asian	.098	63.5	REM	0.92 (0.38,2.21)	.849
rs10153820	Codominant (C vs T)	Non-Asian	.093	64.5	REM	0.72 (0.33,1.60)	.423
	Codominant (C vs T)	Asian	.004	82.3	REM	0.61 (0.34,1.11)	.107
	Homozygous (CC vs TT)	Non-Asian	.106	61.6	REM	0.77 (0.02,25.74)	.885
	Homozygous (CC vs TT)	Asian	.101	56.4	REM	0.56 (0.24,1.29)	.172
	Heterozygous (CT vs TT)	Non-Asian	.187	42.5	FEM	1.37 (0.16,12.16)	.775
	Heterozygous (CT vs TT)	Asian	.169	43.7	FEM	0.75 (0.44,1.26)	.275
	Dominant (CC+CT vs TT)	Non-Asian	.127	57.2	REM	0.88 (0.03,24.13)	.942
	Dominant (CC+CT vs TT)	Asian	.095	57.5	REM	0.60 (0.27,1.36)	.219
	Recessive (CC vs CT+TT)	Non-Asian	.151	51.5	REM	0.70 (0.33,1.47)	.347
	Recessive (CC vs CT+TT)	Asian	.011	77.7	REM	0.60 (0.30,1.18)	.140

CI=confidence interval, *FEM*=fixed-effects model, *OR*=odds ratio, *P*=*P*-value of overall effect, *REM*=random-effects model, TFPI=tissue factor pathway inhibitor.

Table 4

The results of source of controls subgroup analysis for *TFPI* polymorphisms and venous thrombosis.

Gene polymorphisms	Inherited model	Subgroup	Heterogeneity-test *P* for Q test	I^2 (%)	Analysis model	Pooled OR (95% CI)	*P*
rs8176592	Codominant (T vs C)	HB	.023	61.8	REM	1.04 (0.81,1.35)	.757
	Codominant (T vs C)	PB	.664	0.0	REM	1.08 (0.79,1.46)	.630
	Homozygous (TT vs CC)	HB	.147	38.8	FEM	1.61 (1.08,2.40)	.020
	Homozygous (TT vs CC)	PB	–	–	FEM	–	–
	Heterozygous (TC vs CC)	HB	.695	0.0	FEM	1.53 (1.02,2.28)	.039
	Heterozygous (TC vs CC)	PB	–	–	FEM	–	–
	Dominant (TT+TC vs CC)	HB	.506	0.0	FEM	1.55 (1.05,2.28)	.028
	Dominant (TT+TC vs CC)	PB	–	–	FEM	–	–
	Recessive (TT vs TC+CC)	HB	.004	70.8	REM	1.02 (0.67,1.57)	.919
	Recessive (TT vs TC+CC)	PB	.611	0.0	REM	1.12 (0.77,1.61)	.556
rs10931292	Codominant (T vs C)	HB	.209	36.0	FEM	0.86 (0.65,1.15)	.311
	Codominant (T vs C)	PB	.880	0.0	FEM	1.47 (1.03,2.09)	.034
	Homozygous (TT vs CC)	HB	.245	29.0	FEM	0.43 (0.20,0.95)	.037
	Homozygous (TT vs CC)	PB	.346	0.0	FEM	2.16 (0.66,7.06)	.202
	Heterozygous (TC vs CC)	HB	.065	63.4	REM	0.44 (0.09,2.28)	.329
	Heterozygous (TC vs CC)	PB	.287	11.7	REM	1.54 (0.44,5.40)	.497
	Dominant (TT+TC vs CC)	HB	.185	40.8	FEM	0.47 (0.22,1.02)	.055
	Dominant (TT+TC vs CC)	PB	.371	0.0	FEM	1.93 (0.61,6.09)	.260
	Recessive (TT vs TC+CC)	HB	.113	54.2	REM	1.00 (0.58,1.72)	.990
	Recessive (TT vs TC+CC)	PB	.960	0.0	REM	1.55 (1.02,2.35)	.041
rs10153820	Codominant (C vs T)	HB	.057	65.1	REM	0.46 (0.25,0.84)	.011
	Codominant (C vs T)	PB	.941	0.0	REM	0.99 (0.76,1.29)	.927
	Homozygous (CC vs TT)	HB	.559	0.0	FEM	0.37 (0.19,0.72)	.004
	Homozygous (CC vs TT)	PB	.372	0.0	FEM	1.20 (0.57,2.50)	.633
	Heterozygous (CT vs TT)	HB	.774	0.0	FEM	0.47 (0.24,0.94)	.033
	Heterozygous (CT vs TT)	PB	.370	0.0	FEM	1.39 (0.65,2.94)	.396
	Dominant (CC+CT vs TT)	HB	.720	0.0	FEM	0.39 (0.21,0.74)	.004
	Dominant (CC+CT vs TT)	PB	.381	0.0	FEM	1.26 (0.62,2.57)	.517
	Recessive (CC vs. CT+TT)	HB	.042	68.4	REM	0.45 (0.21,0.96)	.039
	Recessive (CC vs CT+TT)	PB	.975	0.0	REM	0.92 (0.66,1.26)	.588

CI=confidence interval, *FEM*=fixed-effects model, *HB*=hospital-based, *OR*=odds ratio, *P*=*P*-value of overall effect, *PB*=population-based, *REM*=random-effects model, TFPI=tissue factor pathway inhibitor.

based on source of controls demonstrated that *TFPI* rs8176592 polymorphism was related to increased venous thrombosis risk in the hospital-based group (homozygous: OR=1.61, 95% CI=1.08–2.40, *P*=.020; heterozygous: OR=1.53, 95% CI=1.02–2.28, *P*=.039; dominant: OR=1.55, 95% CI=1.05–2.28, *P*=.028) (Table 4), while no statistical correlation was found in the population-based group.

There were 5 studies with 453 cases and 795 controls for *TFPI* rs10931292 polymorphism. All were case-control studies, including three VTE studies,[28,31,34] 1 DVT study,[30] and 1 venous thrombosis study.[32] Subjects were sampled from Australia, England, China, Norway, and Korea. No obvious associations between *TFPI* rs10931292 polymorphism and the risk of venous thrombosis were found in any of the 5 genetic models (Table 2). In the ethnicity subgroup analysis, *TFPI* rs10931292 polymorphism significantly increased the risk of venous thrombosis in non-Asians (recessive: OR=1.42, 95% CI=1.03–1.97, *P*=.033), but not in Asians (recessive: OR=0.92, 95% CI=0.38–2.21, *P*=.849) (Table 3). Subgroup analysis based on source of controls showed that *TFPI* rs10931292 polymorphism significantly increased the risk of venous thrombosis in the population-based group (codominant: OR=1.47, 95% CI=1.03–2.09, *P*=.034; recessive: OR=1.55, 95% CI=1.02–2.35, *P*=.041), but significantly decreased that in the hospital-based group (homozygous: OR=0.43, 95% CI=0.20–0.95, *P*=.037) (Table 4).

For *TFPI* rs10153820 polymorphism, 5 studies with 459 cases and 883 controls were included to assess the association. All were case-control studies, including 2 VTE studies,[28,31] 2 DVT studies,[26,36] and 1 venous thrombosis study.[32] Subjects were sampled from Japan, Australia, China, Norway, and India. No obvious associations were found in any of the genetic models (Table 2). In the ethnicity subgroup analysis, the *TFPI* rs10153820 polymorphism had no significant association with the risk of venous thrombosis in Asians or non-Asians (Table 3). However, subgroup analysis based on source of controls demonstrated that *TFPI* rs10153820 polymorphism was related to decreased venous thrombosis risk in hospital-based group (codominant: OR=0.46, 95% CI=0.25–0.84, *P*=.011; homozygous: OR=0.37, 95% CI=0.19–0.72, *P*=.004; heterozygous: OR=0.47, 95% CI=0.24–0.94, *P*=.033; dominant: OR=0.39, 95% CI=0.21–0.74, *P*=.004; recessive: OR=0.45, 95% CI=0.21–0.96, *P*=.039) (Table 4).

3.3. Publication bias

The publication bias of the selected articles was detected by Begg's test. No publication bias was detected for rs8176592 polymorphism in any of the genetic comparison models (codominant: $t=-1.60$, $P=.160$; homozygous: $t=-0.71$, $P=.519$; heterozygous: $t=-0.63$, $P=.563$; dominant: $t=-0.84$, $P=.448$; recessive: $t=-1.02$, $P=.349$) (Fig. 3). In addition, no publication

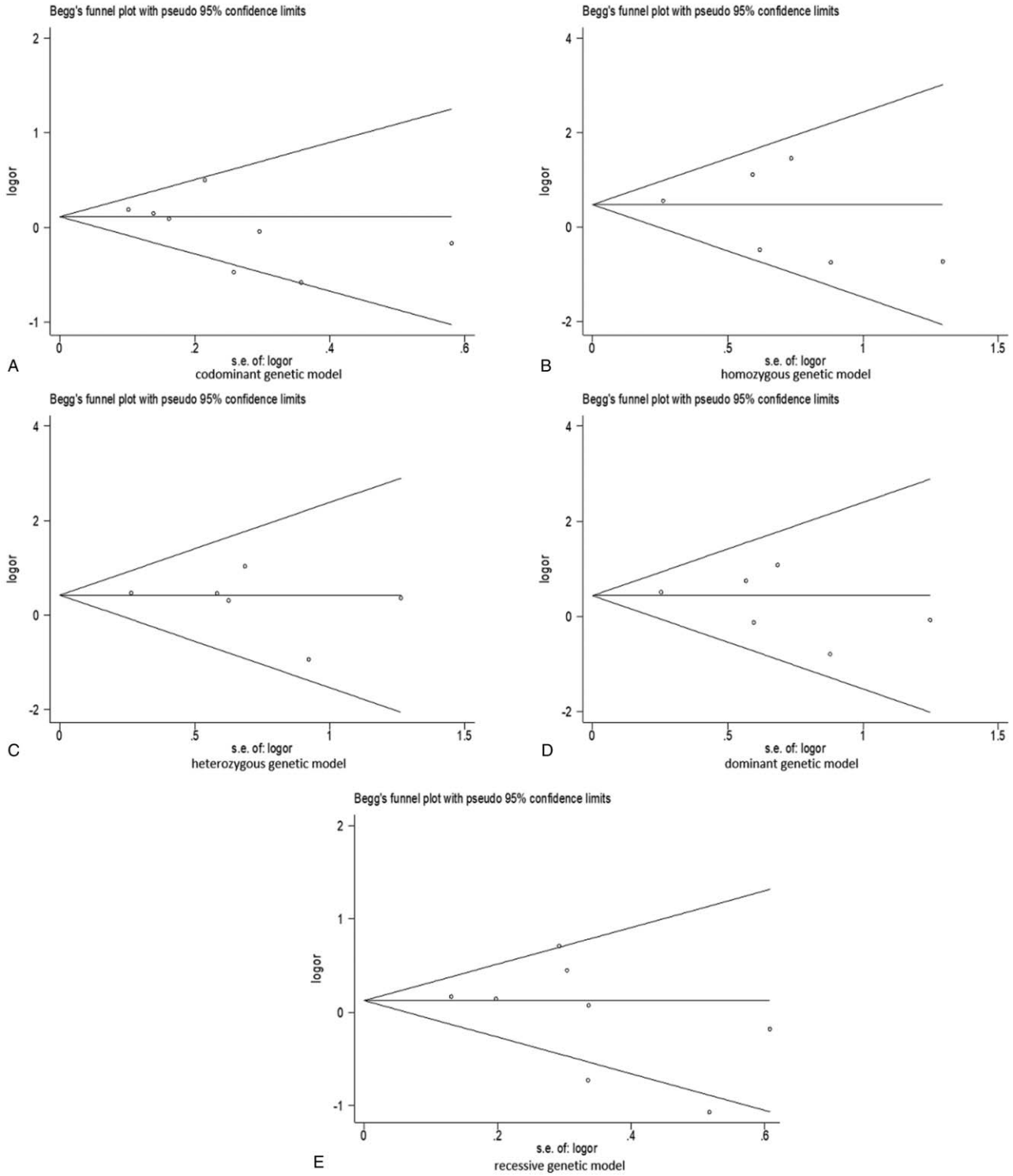

Figure 3. Funnel plots for the association between *TFPI* rs8176592 polymorphism and venous thrombosis. (A) codominant genetic model, (B) homozygous genetic model, (C) heterozygous genetic model, (D) dominant genetic model, (E) recessive genetic model. OR = odds ratio, TFPI = tissue factor pathway inhibitor.

bias was detected for rs10931292 and rs10153820 polymorphisms in any of the genetic comparison models (all results: $P > .05$).

3.4. Sensitivity analysis

Sensitivity analysis was conducted to detect the influence of each individual study on the pooled ORs by sequentially removing one study each time. The data demonstrated that the pooled ORs were stable with the removal of any study in any of the models (Fig. 4).

4. Discussion

Venous thrombosis is the 3rd most common cardiovascular disease that seriously endangers human health.[7] While its

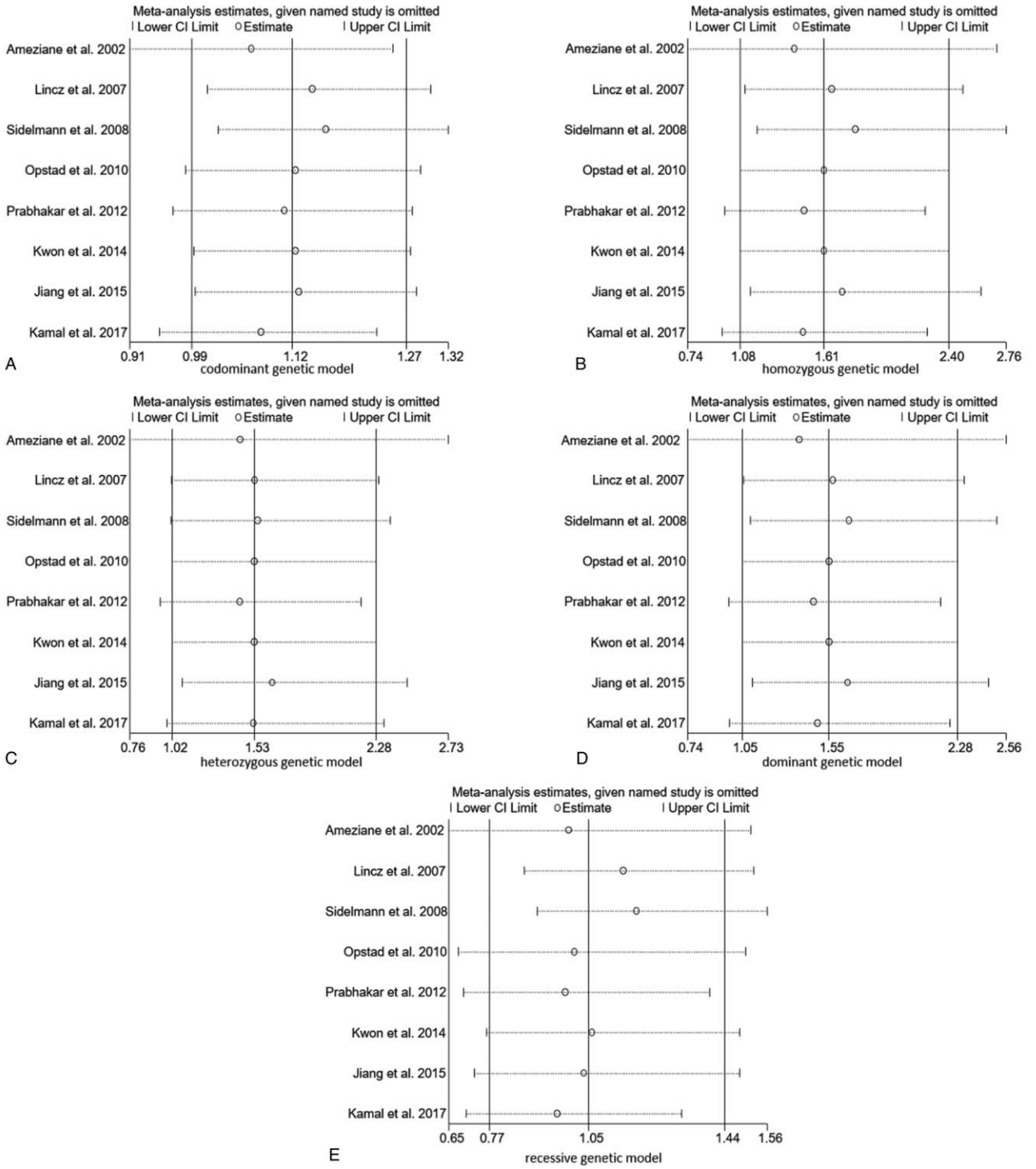

Figure 4. Sensitivity analysis for the associations between the *TFPI* rs8176592 polymorphism and venous thrombosis. (A) codominant genetic model, (B) homozygous genetic model, (C) heterozygous genetic model, (D) dominant genetic model, (E) recessive genetic model. CI = confidence interval, TFPI = tissue factor pathway inhibitor.

pathogenesis is still unclear, accumulating evidence has demonstrated that gene polymorphisms are involved.[37] The TFPI is an important natural anticoagulant between the blood and the vascular cells which inhibits the earliest steps in activation of the extrinsic coagulation pathway.[38–41] Any changes that occur in *TFPI* have the potential to impact the ability of the coagulation pathway, which may affect the occurrence and the development of venous thrombosis.[42]

Despite recent attention paid to the association between the polymorphisms of *TFPI* (rs8176592, rs10931292, and rs10153820) and the risk of venous thrombosis in recent years, the opinions are still controversial. For example, 5 studies report

that *TFPI* rs8176592 polymorphism was related to the risk of venous thrombosis, [27,28,32,33,36] while 3 studies report it was not.[29,34,35] Amini reported that the *TFPI* rs10931292 polymorphism was related with venous thrombosis risk.[30] while 4 other studies reported that it was not related to the risk of venous thrombosis.[28,31,32,34] In addition, 4 studies reported that the *TFPI* rs10153820 polymorphism was related to the risk of venous thrombosis,[28,31,32,36] while Miyata reported that it was not.[26] Therefore, we conducted the present meta-analysis to comprehensively evaluate the available data on the association between *TFPI* rs8176592, rs10931292, and rs10153820 polymorphisms and venous thrombosis risk. According to the standards of NOS, all 11 studies were considered to be high quality research.

In this study, pooled analysis demonstrated that *TFPI* rs8176592 polymorphism was significantly associated with increased risk of venous thrombosis, especially in Asians and hospital-based patients. A possible reason for the increased association among Asians is the linkage disequilibrium patterns in alleles in different ethnicities. The *TFPI* rs8176592 polymorphism may play a more important role in the risk of venous thrombosis in Asians. No significant association was found in the population-based group, which may be due to the limited sample size of the available studies. However, no significant association was found between rs10931292/rs10153820 and venous thrombosis in any of the 5 models. Subgroup analysis based on ethnicity showed that *TFPI* rs10931292 polymorphism was associated with increased risk of venous thrombosis in non-Asians, whereas no significant association was found in Asians, indicating that *TFPI* rs10931292 polymorphism may be a potential biomarker of venous thrombosis for non-Asians. Interestingly, subgroup analysis based on source of controls demonstrated that *TFPI* rs10931292 polymorphism might increase the risk of venous thrombosis in the population-based group while decrease the risk of venous thrombosis in the hospital-based group. The possible reason may be attributed to the differences in the patient selection criteria, as well as the number of subjects. Moreover, in subgroup analysis based on source of controls, it was found that *TFPI* rs10153820 polymorphism might decrease the risk of venous thrombosis in the hospital-based group in all genetic models but not in the population-based group, suggesting a higher importance of *TFPI* rs10153820 polymorphism for hospital-based patients.

In addition to ethnicity and source of controls, subgroup analysis was also considered from venous thrombosis type and genotyping methods, but the genetic frequency was not available and the subgroup analysis could not be carried out. Furthermore, even though the region was divided according to ethnicity, the ethnic origin of venous thrombosis patients and healthy controls could not be obtained because of the limited information in the included studies. Still, the sensitivity analysis showed that no individual study had a significant effect on the pooled results, and Begg's test provided no evidence for funnel-plot asymmetry, indicating that there was no obvious publication bias in the present study.

To our knowledge, this is the meta-analysis that reveals the association between *TFPI* polymorphism and the risk of venous thrombosis. Our findings contribute to the better understanding of genetic polymorphisms of *TFPI* in venous thrombosis and pinpoint a novel biomarker and potential therapeutic target for venous thrombosis patients. Meanwhile, we are aware of several limitations in this study. Firstly, the sample size of the individual studies included in the current meta-analysis were relatively small and the information concerning the patients was not adequate to perform more thorough subgroup studies such as age, weight, sex, lifestyle, environmental exposures, and subtype of venous thrombosis to evaluate the heterogeneity among the included studies. Secondly, the polymorphisms of *TFPI* rs8176592, rs10931292, and rs10153820 were detected by different methods, which might influence the accuracy of the results. Moreover, even though the geographical information could be obtained from the included studies, the information of the ethnic origin of patients was unavailable from the enrolled studies. Further evidence gathered through well-designed and well-conducted trials to better elucidate the relation between *TFPI* polymorphism and venous thrombosis is needed to confirm our results.

5. Conclusion

Meta-analysis of the available data suggested that different *TFPI* polymorphisms may have different associations with venous thrombosis risk. *TFPI* rs8176592 associated with increased risk of venous thrombosis, especially in Asians and hospital-based patients. The *TFPI* rs10931292 may increase the risk of venous thrombosis in non-Asians and population-based patients, while decrease that in hospital-based patients. *TFPI* rs10153820 polymorphism may decrease the risk of venous thrombosis in hospital-based patients. These findings highlight the role of *TFPI* polymorphism in venous thrombosis and offer potential biomarkers for the risk evaluation, diagnosis, and therapeutic strategy for the clinic.

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