Systematic Review and Meta-analysis

Association between the SERPINE1 (PAI-1) 4G/5G insertion/deletion promoter polymorphism (rs1799889) and pre-eclampsia: a systematic review and meta-analysis

Linlu Zhao1,2,*, Michael B. Bracken1,2, Andrew T. DeWan1,2 and Suzan Chen3

1Center for Perinatal, Pediatric and Environmental Epidemiology, Yale Schools of Public Health and Medicine, New Haven, CT 06510, USA 2Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT 06520, USA 3University of Medicine and Health Sciences, New York, NY 10001, USA

*Correspondence address. Linlu Zhao, Yale School of Public Health, Department of Chronic Disease Epidemiology, 60 College Street, New Haven, CT 06520, USA. Tel: +1-331-333-8533; E-mail: linlu.zhao@yale.edu

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ABSTRACT: The SERPINE1—675 4G/5G promoter region insertion/deletion polymorphism (rs1799889) has been implicated in the pathogenesis of pre-eclampsia (PE), but the genetic association has been inconsistently replicated. To derive a more precise estimate of the association, a systematic review and meta-analysis was conducted. This study conformed to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed (MEDLINE), Scopus and HuGE Literature Finder literature databases were systematically searched for relevant studies. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the allelic comparison (4G versus 5G) and genotypic comparisons following the co-dominant (4G/4G versus 5G/5G and 4G/5G versus 5G/5G), dominant (4G/4G+4G/5G versus 5G/5G) and recessive (4G/4G versus 4G/5G+5G/5G) genetic models. Between-study heterogeneity was quantified by $I^2$ statistics and publication bias was appraised with funnel plots. Sensitivity analysis was conducted to evaluate the robustness of meta-analysis findings. Meta-analysis of 11 studies involving 1297 PE cases and 1791 controls found a significant association between the SERPINE1—675 4G/5G polymorphism and PE for the recessive genetic model (OR = 1.36, 95% CI: 1.13–1.64, $P$ = 0.001), a robust finding according to sensitivity analysis. A low level of between-study heterogeneity was detected ($I^2$ = 20%) in this comparison, which may be explained by ethnic differences. Funnel plot inspection did not reveal evidence of publication bias. In conclusion, this study provides a comprehensive examination of the available literature on the association between SERPINE1—675 4G/5G and PE. Meta-analysis results support this polymorphism as a likely susceptibility variant for PE.

Key words: fibrinolysis / genetic association study / pregnancy / plasminogen activator inhibitor 1 / single nucleotide polymorphism

Introduction

Pre-eclampsia (PE) is a multisystem disorder of pregnancy that complicates 2–7% of healthy nulliparous women (Sibai et al., 2005) and causes 16% of pregnancy-related deaths in the USA (Berg et al., 2009). The maternal syndrome of PE is characterized by gestational hypertension and proteinuria and can progress to more severe hypertensive states: eclampsia and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome (Steegers et al., 2010).

Abnormal placentation has long been considered a contributing factor in the unknown etiology of PE. Pregnancy is a thrombophilic state (Kupferminc, 2003; O’Riordan and Higgins, 2003) and enhanced coagulation activation has been proposed as one of the possible pathways associated with abnormal placentation development, which may lead to inadequate maternal–fetal circulation and decreased placental perfusion (Kupferminc, 2003). Placental infarction and necrosis of deciduous vessels are characteristic features of PE (Bonnar et al., 1971; Dekker and Sibai, 1998; Mutze et al., 2008), suggesting that defects in the coagulation and fibrinolysis systems may predispose women to PE. The protein serpin peptidase inhibitor, clade E, member 1 [also known as endothelial plasminogen activator or plasminogen activator inhibitor 1 (PAI-1)] (Gene, 2012), with the gene name...
SERPINE1, is found in increased levels in the pre-eclamptic placenta (Estelles et al., 1994, 1998; Gao et al., 1996; Teng et al., 2009). SERPINE1 is an inhibitor of fibrinolysis (Loskutoff and Curriden, 1990; Collen, 1999) and, as such, genetic mutations of SERPINE1 resulting in alterations in plasma levels or function of the expressed protein may be important determinants for PE. Therefore, gene polymorphisms that modify the transcriptional activity of SERPINE1 have been of particular interest.

The insertion/deletion (I/D) polymorphism at position –675 in the promoter region of the SERPINE1 gene (rs1799889) is a common, well characterized and functionally important single nucleotide polymorphism (SNP); a five guanine (G) nucleotide tract, referred to as the 5G allele, is considered the major allele whereas a deletion of one G nucleotide results in the 4G minor allele, rs1799889(-). While both alleles bind a transcriptional activator, only the 5G allele allows a repressor protein to bind to an overlapping binding site (Eriksson et al., 1995). A functional genetic study found increased transcriptional activity in the absence of bound repressor and a consequent graded increase in plasma SERPINE1 activity with the number of 4G alleles; protein activity was significantly higher in subjects who were homozygous for the 4G allele compared with those homozygous for the 5G allele (Eriksson et al., 1995). Women with the hypofibrinolytic 4G/4G genotype were also more likely to have complicated pregnancies, including PE (Gueck et al., 2000, 2001). Recent reviews on the association between the SERPINE1 –675 4G/5G polymorphism and PE found several studies investigating the association across different populations, but the results have been inconsistent (Mutze et al., 2008; D’Elia et al., 2011). The lack of replication may be explained by inadequate statistical power of individual studies to detect small or moderate effects, population stratification, true variation in the underlying association between populations, misclassification of outcome and other study design issues (Colhoun et al., 2003).

A meta-analysis can be performed to overcome some of the obstacles in individual studies (Salanti et al., 2005). Systematic review and meta-analysis is a methodological paradigm that can increase the statistical power of the analysis to provide a more precise overall effect estimate, assess sources of between-study heterogeneity and identify research needs (Salanti et al., 2005). An earlier meta-analysis estimated a 1.27-fold increased risk for developing PE among carriers of the 4G allele (Wiwanitkit, 2006). However, this meta-analysis contained methodological concerns regarding data abstraction and analysis. Additionally, a number of studies investigating this association have since been published.

Therefore, to provide an updated and more robust overall effect estimate, the present study aimed to evaluate the association between the SERPINE1 –675 4G/5G SNP and PE by performing a systematic review and meta-analysis of the literature. Planned subgroup analysis by ethnicity was conducted to assess the consistency of gene effects across different ethnic populations. Research needs for future studies were also identified.

Materials and Methods

Search strategy

This systematic review and meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). PubMed (MEDLINE) and Scopus literature databases were searched using the following keyword search string: preeclampsia AND (plasminogen activator inhibitor 1 OR PAI-I OR PAI1 OR PLANH1 OR SERPINE1 OR rs1799889) AND (polymorphism OR variant OR mutation OR gene OR allele OR genotype). The HuGE Literature Finder database was consulted for articles listed under the PE phenotype and SERPINE1 gene. Reference lists of studies included in the present review and existing review articles on the association (Wiwanitkit, 2006; Mutze et al., 2009; D’Elia et al., 2011) were examined for additional relevant studies. No search restrictions were applied. The last search was performed on 6 October 2012.

Identification of eligible studies

Abstracts of studies identified from database searches were screened and excluded on the basis of the following criteria: not PE, review article, conference abstract or animal/basic science/clinical research. Studies passing initial screening were scrutinized in their entirety and further excluded based on the previously stated and following criteria: not of case–control study design or having no reported allelic/genotypic frequencies. Among studies with shared subjects, the study with the largest sample size was retained. The study identification and data extraction process was conducted independently by two authors (L.Z. and S.C.) and any discrepancies were resolved by discussion and consensus.

Statistical analysis

Meta-analysis was performed using Review Manager Version 5.1.6 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Sweden) and Meta-Analyst Version Beta 3.13 (Tufts Medical Center, Boston, MA, USA). Hardy–Weinberg equilibrium (HWE) was checked in study controls using the $\chi^2$ goodness-of-fit test. The pooled frequency of the SERPINE1 –675 4G allele was estimated in various ethnic groups using the fixed-effect inverse variance method (Higgins and Green, 2011). The fixed-effect inverse variance analysis method was also used to estimate the summary odds ratios (ORs) for the allelic comparison (4G versus 5G) and genotypic comparisons of co-dominant (4G/4G versus 5G/5G and 4G/5G versus 5G/5G), dominant (4G/4G+4G/5G versus 5G/5G) and recessive (4G/4G versus 4G/5G+5G/5G) genetic models, with the 4G allele considered the risk allele. The statistical significance of the summary OR was determined by the Z-test with a P-value of <0.05 indicating significance. $I^2$ statistics were calculated for each comparison to quantify the degree of between-study heterogeneity (Higgins et al., 2003). A sensitivity analysis was performed to test the robustness of the meta-analysis findings; the impacts of individual studies and HWE-deviated studies on the summary effect estimates were assessed. Funnel plots were visually inspected to check for evidence of publication bias, which manifests as noticeable asymmetry in the graph. Planned ethnicity-based subgroup analysis was conducted to evaluate the effect of ethnicity on the association as a potential source of between-study heterogeneity.

Results

Study inclusion and characteristics

The study identification and selection process is presented in Fig. 1. Eleven case–control studies examining the SERPINE1 –675 4G/5G polymorphism and PE were included in the meta-analysis (Yamada et al., 2000; Morrison et al., 2002; Fabbro et al., 2003; Hakli et al., 2003; Pegoraro et al., 2003; De Maat et al., 2004; Tempfer et al., 2004; Gerhardt et al., 2005; Dalmaz et al., 2006; Ivanov et al., 2007;
et al. (Kamal and El-Khayat, 2011), black Zulu South African (Pegoraro and genotype frequencies in Table I. of included studies are summarized in Supplementary data, Table SI from HWE was detected in the control subjects of two studies populations, including Brazilian (Dalmaz et al., 2006), Egyptian (Kamal and El-Khayat, 2011), black Zulu South African (Pegoraro et al., 2003) and Japanese (Yamada et al., 2000) populations. Deviation from HWE was detected in the control subjects of two studies (Gerhardt et al., 2005; Kamal and El-Khayat, 2011). Characteristics of included studies are summarized in Supplementary data, Table SI and genotype frequencies in Table I.

Figure 1 Flow diagram of the systematic review and meta-analysis study identification process.

### Table I Genotype frequencies of studies included in the meta-analysis on the SERPINE1 (PAI-1) − 675 4G/5G polymorphism and PE.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cases</th>
<th>Genotypes</th>
<th>Controls</th>
<th>Genotypes</th>
<th>HWE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>MAF (4G)</td>
<td>Genotypes</td>
<td>N</td>
<td>MAF (4G)</td>
<td>Genotypes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4G/4G</td>
<td></td>
<td></td>
<td>4G/5G</td>
</tr>
<tr>
<td>Dalmaz et al. (2006)</td>
<td>Brazil</td>
<td>75</td>
<td>0.493</td>
<td>24</td>
<td>26</td>
<td>25</td>
<td>143</td>
</tr>
<tr>
<td>de Maat et al. (2004)</td>
<td>Netherlands</td>
<td>157</td>
<td>0.592</td>
<td>53</td>
<td>80</td>
<td>24</td>
<td>157</td>
</tr>
<tr>
<td>Fabbro et al. (2003)</td>
<td>Italy</td>
<td>52</td>
<td>0.644</td>
<td>20</td>
<td>27</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>Gerhardt et al. (2005)</td>
<td>Germany</td>
<td>94</td>
<td>0.564</td>
<td>30</td>
<td>46</td>
<td>18</td>
<td>275</td>
</tr>
<tr>
<td>Hakli et al. (2003)</td>
<td>Finland</td>
<td>133</td>
<td>0.504</td>
<td>34</td>
<td>66</td>
<td>33</td>
<td>115</td>
</tr>
<tr>
<td>Ivanov et al. (2007)</td>
<td>Bulgaria</td>
<td>25</td>
<td>0.400</td>
<td>6</td>
<td>8</td>
<td>11</td>
<td>49</td>
</tr>
<tr>
<td>Kamal and El-Khayat (2011)</td>
<td>Egypt</td>
<td>68</td>
<td>0.581</td>
<td>16</td>
<td>47</td>
<td>5</td>
<td>59</td>
</tr>
<tr>
<td>Morrison et al. (2002)</td>
<td>Scotland</td>
<td>403</td>
<td>0.547</td>
<td>123</td>
<td>195</td>
<td>85</td>
<td>164</td>
</tr>
<tr>
<td>Pegoraro et al. (2003)</td>
<td>S. Africa</td>
<td>151</td>
<td>0.152</td>
<td>2</td>
<td>42</td>
<td>107</td>
<td>217</td>
</tr>
<tr>
<td>Tempfer et al. (2004)*</td>
<td>Austria</td>
<td>24</td>
<td>0.167</td>
<td>1</td>
<td>6</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Yamada et al. (2000)</td>
<td>Japan</td>
<td>115</td>
<td>0.761</td>
<td>69</td>
<td>37</td>
<td>9</td>
<td>508</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1297</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; N, genotyped sample size.

*Genotype frequencies were incorrectly reported in the original article. Presented values were derived from reported allele frequencies.

**Pooled SERpine1 − 675 4G allele frequency in controls**

The pooled frequencies of the SERPINE1 − 675 4G allele for European populations were 54.2% [95% confidence interval (CI): 51.9–56.6%] and, excluding the HWE-deviated study (Gerhardt et al., 2005), 51.8% (95% CI: 48.9–54.7%). The 4G allele frequencies were 44.4% (95% CI: 38.7–50.2%), 41.5% (95% CI: 33.0–50.6%), 12.0% (95% CI: 9.2–15.4%) and 67.7% (95% CI: 64.8–70.5%) in Brazilian, Egyptian, black Zulu South African and Japanese populations, respectively.

**Association of SERPINE1 − 675 4G/5G and PE**

Summary ORs and $I^2$ statistics for the allelic and genotypic comparisons are presented in Table II. A significant allelic association between the SERPINE1 − 675 4G/5G polymorphism and PE was observed (4G versus 5G, OR = 1.17, 95% CI: 1.04–1.31, $P = 0.009$, $I^2 = 50%$). Meta-analysis also found a significant association for the recessive genetic model (4G/4G versus 4G/5G+5G/5G, OR = 1.36, 95% CI: 1.13–1.64, $P = 0.001$; Fig. 2) with a low level of between-study heterogeneity ($I^2 = 20%$). Sensitivity analysis demonstrated the robustness of the recessive model finding, where exclusion of individual studies or HWE-deviated studies did not have substantial impact on the summary effect estimate (data not shown). A relatively symmetrical funnel plot indicated a lack of overt publication bias (see Fig. 3 for the recessive model comparison). Genotypic comparisons for the co-dominant and dominant genetic models yielded non-significant summary effect estimates with moderate between-study heterogeneity observed ($I^2 \geq 50%$; see Table II). The funnel plots for these comparisons also showed symmetry (not shown).
Subgroup analysis found a non-significant gene effect (OR = 1.22, 95% CI: 0.97–1.52, P = 0.09) and no between-study heterogeneity (I² = 0%) for the recessive model when studies were subset by European ethnicity (Morrison et al., 2002; Fabbro et al., 2003; Hakli et al., 2003; De Maat et al., 2004; Tempfer et al., 2004; Gerhardt et al., 2005; Ivanov et al., 2007). For non-European studies (Yamada et al., 2000; Pegoraro et al., 2003; Dalmaz et al., 2006; Kamal and El-Khayat, 2011), the summary effect estimate was significant (OR = 1.36, 95% CI: 1.13–1.64, P = 0.001) with moderate between-study heterogeneity (I² = 20%). Non-European studies appeared to account for the heterogeneity observed in the overall comparison (I² = 20%). Publication bias was not detected in the subgroups.

Table II Summary ORs and 95% CIs of the association between the SERPINE1 (PAI-1) −675 4G/5G polymorphism and PE.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Subgroup</th>
<th>Number of studies</th>
<th>OR (95% CI)</th>
<th>P-valuea</th>
<th>I² (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allelic</td>
<td>Overall</td>
<td>11</td>
<td>1.17 (1.04–1.31)</td>
<td>0.009</td>
<td>50</td>
</tr>
<tr>
<td>Co-dominant model</td>
<td>Overall</td>
<td>11</td>
<td>1.22 (0.95–1.58)</td>
<td>0.13</td>
<td>58</td>
</tr>
<tr>
<td>Dominant model</td>
<td>Overall</td>
<td>11</td>
<td>0.95 (0.77–1.17)</td>
<td>0.65</td>
<td>57</td>
</tr>
<tr>
<td>Recessive model</td>
<td>Overall</td>
<td>11</td>
<td>1.04 (0.86–1.27)</td>
<td>0.68</td>
<td>61</td>
</tr>
<tr>
<td>European</td>
<td>Overall</td>
<td>7</td>
<td>1.36 (1.13–1.64)</td>
<td>0.001</td>
<td>20</td>
</tr>
<tr>
<td>Non-European</td>
<td>Overall</td>
<td>4</td>
<td>1.75 (1.26–2.45)</td>
<td>0.001</td>
<td>41</td>
</tr>
</tbody>
</table>

Cl, confidence interval; OR, odds ratio.
aP-value corresponding to the Z-test for the summary effect estimate (P < 0.05 considered statistically significant).
bGuideline for interpretation of the I² statistic: I² = 0% no heterogeneity, I² = 25% low heterogeneity, I² = 50% moderate heterogeneity and I² = 75% high heterogeneity (Higgins et al., 2003).

Discussion

The present meta-analysis of 11 studies, involving 1297 cases and 1791 controls, found a significant association between the SERPINE1 −675 4G/5G polymorphism and PE for the recessive model (4G/4G versus 4G/5G + 5G/5G) for all studies. Meta-analysis was performed using an inverse variance (IV) fixed-effect model. The OR for each study is represented in the plot as a black square with the area corresponding to study weight. The 95% CI is represented as a horizontal line. The summary effect estimate is symbolized as a diamond in the forest plot.

Figure 2 Forest plot of the association between the SERPINE1 (PAI-1) −675 4G/5G polymorphism and PE for the recessive model (4G/4G versus 4G/5G + 5G/5G) for all studies. Meta-analysis was performed using an inverse variance (IV) fixed-effect model. The OR for each study is represented in the plot as a black square with the area corresponding to study weight. The 95% CI is represented as a horizontal line. The summary effect estimate is symbolized as a diamond in the forest plot.
level of between-study heterogeneity in the recessive genetic model comparison based on all studies ($I^2 = 20\%$). However, the heterogeneity was removed or increased in subgroup analysis by ethnicity ($I^2$ = 0% in Europeans and 41% in non-Europeans), indicating the observed between-study heterogeneity could be explained by ethnic differences. Publication bias was not evident for this comparison.

Findings of this study are consistent with the previous meta-analysis by Wiwanitkit (2006); carriers of the 4G allele have increased risk of developing PE. The Wiwanitkit meta-analysis contained two concerns. First, genotype frequencies were incorrectly abstracted for the studies by Yamada et al. (2000) and Pegoraro et al. (2003) and reversed for cases and controls for the study by Tempfer et al. (2004). Secondly, only basic statistical analysis was performed. Between-study heterogeneity, publication bias and study influence were not assessed. Although the present study attempted to improve upon the previous meta-analysis, several weaknesses inherent to the systematic review and meta-analysis process for complex diseases remain caveats in the interpretation of the conclusions.

Meta-analyzed studies differed in PE diagnostic criteria (see Supplementary data, Table SI for a comparison), which is of concern as inconsistent phenotype definitions may weaken the validity of meta-analysis. Control groups were also not uniformly defined. Furthermore, few reviewed studies differentiated PE by severity (mild versus severe) and time of onset, both of which are factors that may modify the genetic association with PE. For example, a study found a significantly earlier onset of severe PE in women with the 5G/5G genotype (Gerhardt et al., 2005). More precisely defined case–control phenotypes may not only improve efficiency and validity in individual studies, but also for the overarching meta-analysis (Zhao and Bracken, 2011), and should be a consideration in study design.

The frequency of the 4G allele ranged from 12.0 to 67.7%. The pooled allele frequency was 54.2% for European populations and individual study frequencies of 44.4, 41.5, 12.0 and 67.7% for Brazilian, Egyptian, black Zulu South African and Japanese populations, respectively. Reference populations showed similar genetic diversity (45.7 and 61.8% in two European populations and 25.0% in an African-American population; Database of Single Nucleotide Polymorphisms (dbSNP), 2012). Ethnic differences in PE rates also exist: African-American women were found to have higher risk of PE compared with whites (OR = 1.41, 95% CI: 1.25–1.62), while Asian (OR = 0.79, 95% CI: 0.72–0.88) and Hispanic (OR = 0.90, 95% CI: 0.84–0.97) women have lower risk (Caughrey et al., 2005). Given the ethnic differences of this SNP, there is a need for further examination of the relationship between the SERPINE1 – 675 polymorphism and PE in non-European populations, as the association was largely investigated in European populations.

Population stratification may have confounded reported associations, by creating spurious associations or masking true associations (Sham and McGuffin, 2004), in studies with non-homogeneous ethnic composition [e.g. Dalmaz et al. (2006) reported 68.0% Caucasian in cases and 74.5% Caucasian in controls] and even in studies with apparently homogeneous ethnic groups (Thomas and Witte, 2002). Assessment for population stratification was not reported by any of the studies included in the meta-analysis. However, population stratification may be indicated by deviation from HWE (Wigginton et al., 2005), which was observed in studies by Gerhardt et al. (2005) and Kamal and El-Khayat (2011). Population stratification effects are generally considered small, but may still be influential in genetic association studies, where small-to-moderate effects are typically addressed (Little et al., 2009), and deserves attention in future studies.

Although overt publication bias was not evident in funnel plots and multiple sources of literature were consulted, the completeness of evidence may still be impeded by several issues, namely file drawer effect, language bias and inadequate reporting. The file drawer effect is the tendency for positive rather than negative findings to be published, while the latter findings are 'tucked away in file drawers' (Rosenthal, 1979). Even a small number of such 'tucked away' studies can produce a significant bias (Scargle, 2000). Similar to the file drawer effect is language bias, where positive findings from studies conducted in non-English speaking countries tend to be published in international journals and negative findings in local journals (Juni et al., 2002). Many local and non-English language journals are not indexed in major international bibliographic databases, such as the ones searched in this study. Unintentional exclusion of non-English studies may introduce bias and conceal the genetic association in these ethnic groups. Finally, inadequate reporting of findings by studies also limits the ability to synthesize all available evidence (Little et al., 2009). For example, a study identified by the systematic review process examined the association between SERPINE1 – 675 4G/5G and adverse pregnancy outcomes, but did not report separate genotypes for the individual outcomes, including PE, despite identifying the case frequency of each complication (Glueck et al., 2001). Another instance is a study that would have otherwise been included in the meta-analysis, but was omitted due to a missing table in the published article reporting the relevant genotypes (Mozgovaia et al., 2002). The corresponding authors of these studies were contacted for additional information, but unfortunately did not respond by the time of analysis and writing and the papers were thus excluded. It is understood by the authors that not all studies were conducted with the intention for eventual integration into systematic reviews and meta-analyses. However, to
enhance the ability of the scientific community to assess the quality of evidence and to synthesize this evidence, adherence to reporting guidelines [e.g. STREGA (Little et al., 2009)] is highly recommended for future studies.

The SERPINE1 – 675 4G/5G polymorphism may be utilized clinically by its inclusion in genetic risk models to predict patient PE risk. Although the individual impact of this polymorphism is modest, screening patients at high risk of developing PE for several common risk-associated alleles could lead to stronger predictive power (Drenos et al., 2007). Numerous meta-analysis of other candidate genes and PE have been performed: angiotensin AGT M235T (Lin et al., 2012; Ni et al., 2012), endothelial nitric oxide synthase eNOS 4b/a (Chen et al., 2012) and methyleneetahydrofolate reductase MTHFR C677T (Xia et al., 2012) showed significant association, angiotensin II receptor type 1-1166AA>C (Zhao et al., 2012) eNOS –788TT>C (Chen et al., 2012), Interleukin 6–174G>C, Interleukin 10–1082G>A, tumor necrosis factor α–308G>A (Xie et al., 2011), AGT T174M (Lin et al., 2012), Factor V Leiden and prothrombin gene mutations (Rodger et al., 2010) showed no association, while angiotensin converting enzyme ACE I/D (Shaik et al., 2011; Zhong et al., 2012) and eNOS G894T (Chen et al., 2012) showed conflicting findings. As meta-analysis provides the possibility of deriving more robust ORs, summary effect estimates from the aforementioned and present meta-analyses have value in disease risk prediction. However, risk prediction for PE is still premature at this time.

The functional significance of the SERPINE1 – 675 4G/5G polymorphism suggests that it may be a potential therapeutic target not only for PE but also other diseases with similar pathogenesis due to misregulation of the fibrinolytic system. A survey of recent systematic reviews and meta-analyses found this polymorphism to be significantly associated with coronary artery disease (Li, 2012), myocardial infarction (Gong et al., 2012), venous thromboembolism (Gohil et al., 2009), hemorrhagic stroke (Peck et al., 2008), polycystic ovary syndrome (Bagos, 2009), asthma (Nie et al., 2012) and meningococcal disease (Brouwer et al., 2010), but not with cerebral venous thrombosis (Marjot et al., 2011), recurrent miscarriage (Sotiriadis et al., 2007) and ischemic stroke (Attia et al., 2007; Tsantes et al., 2007), though the latter was significantly associated with the I/D polymorphism in a meta-analysis limited to studies in the Han Chinese population (Xu et al., 2008). Further study is necessary to fully characterize and validate the clinical impact of the SERPINE1 – 675 4G/5G polymorphism on PE and other diseases.

Conclusions
Based on available literature evidence, the present study found a significant association between the SERPINE1 – 675 4G/5G SNP and PE. Meta-analysis results revealed that women with the 4G/4G genotype have an increased risk of developing PE compared with women carrying the 5G allele, suggesting the SERPINE1 – 675 4G/5G polymorphism likely plays a role in the pathogenesis of PE.

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Authors’ roles
S.C. and L.Z. designed the study, searched the literature, performed the statistical analysis and drafted the manuscript. M.B.B. and A.T.D. advised on the statistical analysis. All authors interpreted the results, revised for important intellectual content, and read and approved the final manuscript.

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Conflict of interest
The authors declare no conflicts of interest, financial or otherwise.

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