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Others

Increased Risk of Venous Thromboembolism in Women with Uterine Leiomyoma: A Nationwide, Population-Based Case-Control Study

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Background: Venous thromboembolism (VTE) is a sex-specific disease that has different presentations between men and women. Women with uterine leiomyoma can present with VTE without exhibiting the traditional risk factors. We investigated the relationship between a history of uterine leiomyoma and the risk of VTE using the National Health Insurance Research Database (NHIRD).

Methods: We conducted a retrospective, nationwide, population-based case-control study using the NHIRD. We identified 2,282 patients with diagnosed VTE and 392,635 subjects without VTE from 2000 to 2013. After development of an age and index diagnosis year frequency-matched model and propensity score-matched model, 2 models with a case-to-control ratio of 1 to 4 were established. Using the diagnosis of uterine leiomyoma as the exposure factor, conditional logistic regression was performed to examine the association between uterine leiomyoma and VTE. Multiple logistic regression analysis was used to investigate the joint effect of uterine leiomyoma and comorbid diseases on the risk of VTE.

Results: A strong association was observed between uterine leiomyoma and VTE in the overall patient model, frequency-matched model and propensity score-matched model [$p < 0.0001$, odds ratio (OR): 1.547; $p = 0.0005$, OR: 1.486; $p = 0.0405$, OR: 1.26, respectively]. In the subgroup analyses, women with uterine leiomyoma who were ≥ 45 years old were less likely to experience VTE, but women with uterine leiomyoma and anemia, cancer, coronary artery disease or heart failure were more likely to experience VTE.

Conclusions: Women with uterine leiomyomas have an increased risk of developing VTE, especially during reproductive periods or in the presence of specific diseases.

Key Words: Uterine leiomyoma • Venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE) presents clinically as deep venous thrombosis (DVT), pulmonary embolism (PE) or both.[1] VTE is associated with significant morbidity and mortality and a large socioeconomic burden. VTE has been shown to exhibit sex-specific differences,[2] and women exposed to reproductive-related risk factors such as oral contraception, postmenopausal hormone therapy, and pregnancy have been reported to be at a higher risk of VTE than men.[1,3] Therefore, women are at a higher risk of developing VTE during their fertile years,[4,5] and men

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are at a higher risk of VTE than women at an older age.

Uterine leiomyomas, monoclonal tumors that arise from uterine smooth muscle tissue, are the most common benign tumors of the genital organs in women of childbearing age. They can cause significant morbidity, including menstrual abnormalities, iron deficiency anemia, and bulk symptoms with increased pelvic pressure.[6] To the best of our knowledge, few case reports have described an association between uterine leiomyomas and VTE.[7-14] In addition, some of these cases of uterine leiomyomas causing VTE have lacked the traditional risk factors for VTE.[13,14]

As no large-scale studies have investigated the association between uterine leiomyoma and VTE, we conducted this study to investigate the relationship between a history of uterine leiomyoma and the risk of VTE in Taiwanese women using data from the National Health Insurance Research Database (NHIRD).

METHODS

Data source and study patients

Data were retrieved from the NHIRD, which includes all claims data from the National Health Insurance program from 1996 to 2012. One million patients were randomly sampled from those enrolled in the Longitudinal Health Insurance Dataset (LHID) 2005, which is a subset of the NHIRD. We identified patients diagnosed with VTE in the LHID2005 dataset from 1996 to 2013. All diseases were identified according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

A flowchart of the subject selection process is shown in Figure 1. Patients diagnosed with VTE, including PE (ICD-9-CM code 415.1) and DVT (ICD-9-CM code 453.8), with at least three records in the claims data from January 1, 2000, to December 31, 2013, were identified and included in this study. The index date was defined as the date when VTE was first diagnosed. Patients < 18 years and > 100 years of age or with incomplete demographic information were excluded. A total of 2,282 female patients diagnosed with VTE and 392,635 subjects without VTE were included. To reduce bias due to confounding variables, two matched study cohorts were established using random frequency-matched (study cohort 1) and propensity score-matched methods (study cohort 2). For each identified VTE patient, four controls were frequency-matched by age and index year. In total, 2,282 patients with VTE and 9,128 age- and index year-matched subjects without VTE were included in study cohort 1. In addition, to balance the measured covariate distribution in the case-control patients, a propensity score for each patient was calculated. The propensity

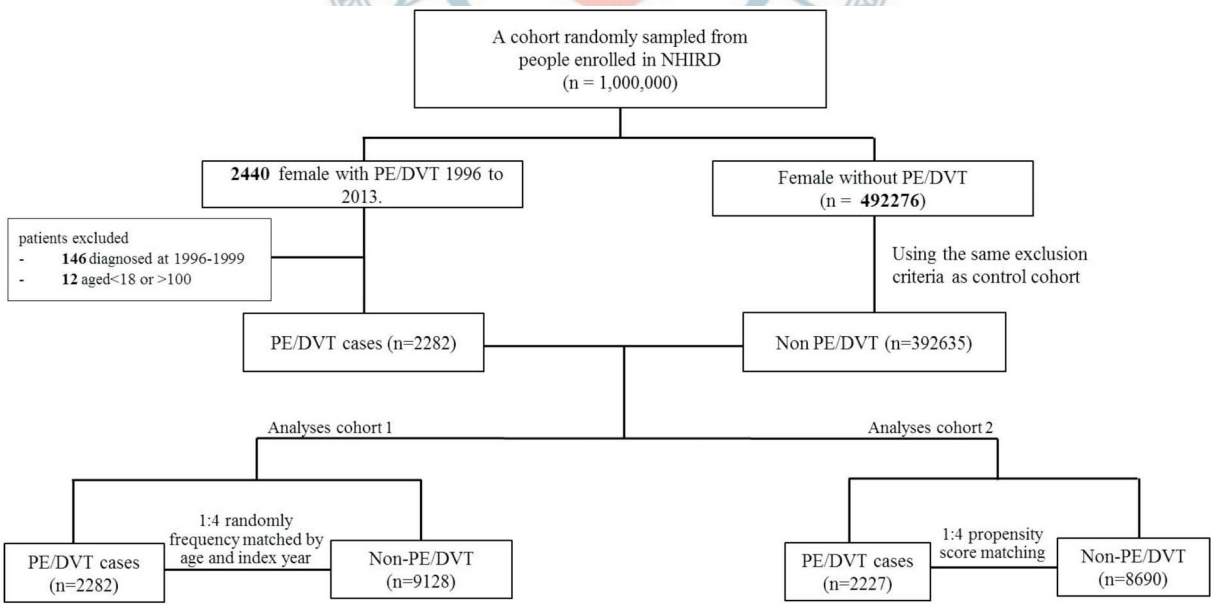

Figure 1. *Flowchart of patients with VTE included from the NHIRD and selection of the control population using age and frequency matching (analysis method 1) or propensity score matching (analysis method 2). DVT, deep venous thrombosis; PE, pulmonary embolism.*

scores were calculated using multivariate logistic regression to predict the probability of the occurrence of VTE. Based on the propensity score, 1:4 propensity score matching was used for study cohort 2. A total of 2,227 patients with VTE and 8,690 propensity score-matched subjects without VTE were included in study cohort 2.

Outcome measures and relevant variables

Uterine leiomyoma exposure

A diagnosis of uterine leiomyoma was identified using ICD-9-CM codes (ICD-9 codes 218.0, 218.1, 218.2 and 218.9) and included submucosal leiomyoma of the uterus (ICD-9 code 218.0), intramural leiomyoma of the uterus (ICD-9 code 218.1), subserosal leiomyoma of the uterus (ICD-9 code 218.2), and unspecified leiomyoma of the uterus (ICD-9 code 218.9). In addition, the diagnosis of uterine leiomyoma was confirmed by the presence of at least three records containing a uterine leiomyoma diagnostic code as indicated by a gynecologist. To increase the reliability of the uterine leiomyoma diagnosis, we identified the patients who also received a gynecologic ultrasound examination (NHI procedure code: 199003 C) during the study period. We also performed sensitivity analysis to test the robustness of the diagnoses of uterine leiomyoma.

Other relevant variables

Major comorbid diseases diagnosed in at least three records in the claims data 1 year before the index date were defined as baseline comorbidities, and included hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), stroke, cardiac dysrhythmia, peripheral artery occlusive disease (PAOD), anemia, all cancers, coronary artery disease, heart failure and lower leg fractures or surgery. The ICD-9 codes are shown in the supplemental file. In addition, the long-term use of medications that were thought to be associated with VTE including anti-diabetic drugs, statins, hormone replacement agents, ferric agents, ferrous agents, and anti-hypertensive drugs, were also assessed.

Statistical methods

The demographic and clinical characteristics of the patients with VTE and the controls without VTE were summarized using numbers and percentages (%) for categorical variables, and means ± standard deviation (SD) for continuous variables. The chi-square test and t test were used to compare the distributions of discrete and continuous variables, respectively. Conditional logistic regression analysis was used to examine the association between uterine leiomyoma and VTE. Confounders including age, monthly income, major comorbidities, and long-term use of medications were adjusted for in the multiple conditional logistic regression analysis to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs). To improve the reliability of the results, we used three study cohorts and two different adjusted models including all of the clinical variables and covariate adjustments using the propensity scores. The joint effects of uterine leiomyoma and comorbid diseases on the risk of VTE between different groups are presented as aORs and 95% CIs, and multiple logistic regression analysis with backward elimination was performed. A two-tailed p value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY).

RESULTS

Characteristics of the study population

The characteristics of the study population are listed and compared in Table 1. When considering the overall patients and the frequency-matched model, consistent differences existed in the baseline characteristics of cases and controls. The patients with VTE were more likely to be older and to have a lower monthly income than those without VTE. In addition, the patients with VTE were also more likely to have hypertension, hyperlipidemia, diabetes mellitus, obesity, CKD, COPD, coronary artery disease (CAD), heart failure, PAOD, cardiac arrhythmia, cancer, anemia, and lower leg fractures or surgery than those without VTE. Medications including anti-diabetic drugs, statins, hormonal replacement therapeutic agents, ferric tablets, ferrous tablets, and antihypertensive drugs were more frequently prescribed to the patients with VTE than those without VTE. In the propensity score-matched model, age and monthly income were similar between the groups. The prevalence

Table 1. Characteristics of cases and controls

	Before matching			Frequency matching by age and index year			Propensity score matching		
	No PE/DVT (n = 392614)	PE/DVT (n = 2282)	p value	No PE/DVT (n = 9128)	PE/DVT (n = 2282)	p value	No PE/DVT (n = 8690)	PE/DVT (n = 2227)	p value
Age	43.15 ± 16.83	64.05 ± 16.11	< 0.001	63.38 ± 16.16	64.05 ± 16.11	0.076	63.6 ± 16.08	64.01 ± 16.05	0.281
Income	15921 ± 13267	12339 ± 11740	< 0.001	130233 ± 12668	12339 ± 11740	0.014	12473.84 ± 12295.71	12415 ± 11794.15	0.839
Comorbidity disease at baseline									
Hypertension	54776 (13.95%)	1318 (57.76%)	< 0.001	3512(38.48%)	1318 (57.76%)	< 0.001	4914 (56.55%)	1266 (56.85%)	0.799
Hyperlipidemia	27001 (6.88%)	581 (25.46%)	< 0.001	1481(16.22%)	581 (25.46%)	< 0.001	2100 (24.17%)	550 (24.7%)	0.602
Diabetes mellitus	24248 (6.18%)	638 (27.96%)	< 0.001	1557(17.06%)	638 (27.96%)	< 0.001	2210 (25.43%)	602 (27.03%)	0.123
Obesity	754 (0.19%)	26 (1.14%)	< 0.001	26(0.28%)	26 (1.14%)	< 0.001	74 (0.85%)	22 (0.99%)	0.539
CKD	7455 (1.9%)	413 (18.1%)	< 0.001	475(5.2%)	413 (18.1%)	< 0.001	1087 (12.51%)	371 (16.66%)	< 0.001
Stroke	11095 (2.83%)	415 (18.19%)	< 0.001	876(9.6%)	415 (18.19%)	< 0.001	1390 (16%)	388 (17.42%)	0.104
COPD	19973 (5.09%)	474 (20.77%)	< 0.001	1029(11.27%)	474 (20.77%)	< 0.001	1572 (18.09%)	451 (20.25%)	0.019
CAD	17199 (4.38%)	612 (26.82%)	< 0.001	1247(13.66%)	612 (26.82%)	< 0.001	2053 (23.62%)	579 (26%)	0.019
CHF	5937 (1.51%)	464 (20.33%)	< 0.001	483(5.29%)	464 (20.33%)	< 0.001	1256 (14.45%)	425 (19.08%)	< 0.001
PAOD	1423 (0.36%)	150 (6.57%)	< 0.001	97(1.06%)	150 (6.57%)	< 0.001	282 (3.25%)	123 (5.52%)	< 0.001
Cardiac dysarrhythmia	8970 (2.28%)	342 (14.99%)	< 0.001	578(6.33%)	342 (14.99%)	< 0.001	1063 (12.23%)	324 (14.55%)	0.003
Cancer	8217 (2.09%)	428 (18.76%)	< 0.001	440(4.82%)	428 (18.76%)	< 0.001	1239 (14.26%)	397 (17.83%)	< 0.001
Anemia	14468 (3.69%)	397 (17.4%)	< 0.001	581(6.37%)	397 (17.4%)	< 0.001	1097 (12.62%)	362 (16.26%)	< 0.001
Lower leg fracture or surgery	8123 (2.07%)	363 (15.91%)	< 0.001	567(6.21%)	363 (15.91%)	< 0.001	1096 (12.61%)	345 (15.49%)	< 0.001
Medication use									
Diabetic drugs	17475 (4.45%)	466 (20.42%)	< 0.002	1143(12.52%)	466 (20.42%)	< 0.001	1624 (18.69%)	437 (19.62%)	0.315
Statin	15102 (3.85%)	449 (19.68%)	< 0.001	943(10.33%)	449 (19.68%)	< 0.001	1543 (17.76%)	419 (18.81%)	0.246
Hormonal replacement therapy	22738 (5.79%)	318 (13.94%)	< 0.001	979(10.73%)	318 (13.94%)	< 0.001	1201 (13.82%)	310 (13.92%)	0.903
Ferric or Ferrous tablet	2223 (0.57%)	81 (3.55%)	< .0001	92(1.01%)	81 (3.55%)	< .0001	187 (2.15%)	72 (3.23%)	0.0028
Antihypertensive drugs	45928 (11.7%)	1207 (52.89%)	< 0.001	2943(32.24%)	1207 (52.89%)	< 0.001	4389 (50.51%)	1156 (51.91%)	0.238
Exposure									
Leiomyoma	16955 (4.32%)	116 (5.08%)	0.073	330(3.62%)	116 (5.08%)	0.001	356 (4.10%)	111 (4.98%)	0.065
Propensity score	0.01 ± 0.02	0.05 ± 0.08	< 0.001	0.01 ± 0.04	0.05 ± 0.08	< 0.001	0.03 ± 0.05	0.04 ± 0.06	< 0.001

CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; PAOD, peripheral arterial occlusive disease; PE, pulmonary embolism.

rates of comorbidities, including hypertension, hyperlipidemia, diabetes mellitus, obesity, and stroke were similar in the patients with and without VTE. Compared to the patients without VTE, the patients with VTE were more likely to have CKD (16.66% vs. 12.51%, p < 0.001), COPD (20.25% vs. 18.09%, p = 0.019), CAD (26% vs. 23.62%, p = 0.019), heart failure (19.08% vs. 14.45%, p < 0.001), PAOD (5.52% vs. 3.25%, p < 0.001), cardiac dysrhythmia (14.55% vs. 12.23%, p = 0.003), cancer (17.83% vs. 14.26%, p < 0.001), anemia (16.26% vs. 12.62%, p < 0.001), lower leg fractures and surgery (15.49% vs. 12.61%, p < 0.001) and a history of long-term ferric or ferrous agent use. The use of anti-diabetic drugs, statins, hormone replacement therapeutic agents, and antihypertensive drugs was similar in both groups. Of the 2,282 patients diagnosed with VTE, 1,612 (70.64%) received anticoagulation therapy. Overall, 17,071 women were diagnosed with uterine leiomyomas, including 16,955 cases in the group without VTE and 116 cases in the group with VTE.

The association between leiomyoma and VTE

Table 2 shows the results of multivariate logistic regression analysis of predictive ability of uterine leiomyoma for VTE. Before matching the data, the multivariate logistic regression analysis showed that the patients with uterine leiomyomas were more likely to suffer from VTE (p < 0.0001, OR: 1.547, 95% CI: 1.27-1.88).

Table 2. Multivariate logistic regression model to assess the associations between uterine leiomyoma and VTE

	VTE case	Control	Adjusted odds ratio$^{Model\ 1}$ (95 % CI)	p value	Adjusted odds ratio$^{Model\ 2}$ (95 % CI)	p value
Before matching data						
Non-leiomyoma	2166 (94.92%)	375659 (95.68%)	1 (reference)		1 (reference)	
Leiomyoma	116 (5.08%)	16955 (4.32%)	1.464 (1.2-1.78)	0.0001	1.547 (1.27-1.88)	< 0.0001
Frequency matching data						
Non-leiomyoma	2166 (94.92%)	8798 (96.38%)	1 (reference)		1 (reference)	
Leiomyoma	116 (5.08%)	330 (3.62%)	1.485 (1.17-1.88)	0.0011	1.486 (1.19-1.86)	0.0005
Propensity score matching data						
Non-leiomyoma	2116 (95.02%)	8334 (95.90%)	1 (reference)		1 (reference)	
Leiomyoma	111 (4.98%)	356 (4.10%)	1.287 (1.03-1.61)	0.025	1.26 (1.01-1.57)	0.0405

Model 1 adjusted for uterine leiomyoma and the significantly different variables in Table 1. Model 2 adjusted for uterine leiomyoma, age and propensity score.
VTE, venous thromboembolism.

When the frequency-matched and propensity score-matched data were included, the multivariate logistic regression analysis also demonstrated that the women with uterine leiomyomas were more susceptible to the development of VTE (p = 0.0005, OR: 1.486, 95% CI: 1.19-1.86; and p = 0.0405, OR: 1.26, 95% CI: 1.01-1.57, respectively, Table 2). Of the 17,071 subjects diagnosed with uterine leiomyoma, 15,586 (91.3%) received gynecologic ultrasound examinations. To test the robustness of the uterine leiomyoma diagnoses, we also performed sensitivity analysis of uterine leiomyoma and VTE, as identified using stringent criteria (subjects who received gynecologic ultrasound examinations and had at least three records of a uterine leiomyoma diagnostic code indicated by a gynecologist). This analysis showed that the association between uterine leiomyoma and VTE was in agreement with the results in Table 2 (Supplementary Table 2).

Leiomyoma and comorbid disease status and the risk of VTE

The subgroup analyses are shown in Figure 2. We first performed subgroup analysis using the frequency-matched model. In the patients with uterine leiomyoma, no significant differences were noted in any of the data between those with an index age ≥ 45 years and those with an index age < 45 years. In the random frequency-matched model, the patients with an index age ≥ 45 years had a lower risk of VTE than those aged < 45 years (p = 0.009, OR: 0.498, 95% CI: 0.29-0.84). In addition, the patients with anemia and those receiving ferric or ferrous tablets were more likely to have VTE than those without anemia in both the patients overall (p = 0.003, OR: 1.996, 95% CI: 1.27-3.15) and in the random frequency-matched model (p = 0.017, OR: 2.12, 95% CI: 1.14-3.93). The patients with cancer were more likely to suffer from VTE than those without cancer in both the patients overall (p < 0.0001, OR: 6.030, 95% CI: 3.79-9.57) and in the random frequency-matched model (p < 0.0001, OR: 5.071, 95% CI: 2.44-10.54). The patients with CAD had a higher risk of VTE than those without CAD in both the overall patient model (p = 0.0005, OR: 2.853, 95% CI: 1.58-5.14) and the random frequency-matched model (p = 0.0096, OR: 2.791, 95% CI: 1.28-6.07). The patients with congestive heart failure (CHF) had a higher risk of VTE than those without CHF in both the patients overall (p < 0.0001, OR:3.852, 95% CI: 1.79-8.27) and the random frequency-matched model (p = 0.0042, OR: 6.172, 95% CI: 1.78-21.43). The patients with PAOD had a higher risk of VTE than those without PAOD (p = 0.0002, OR: 6.634, 95% CI: 2.45-17.89). However, no significant difference was observed between the patients with PAOD and those without PAOD in the random frequency-matched model (p = 0.2003, OR: 2.862, 95% CI: 0.57-14.3). In the subgroup analysis, no significant difference was observed between the patients with uterine leiomyoma receiving hormone therapy and those not receiving hormone therapy in the overall data analysis and in the random frequency-matched model.

Leiomyoma in different age groups of patients not receiving hormone therapy and the risk of VTE

To clarify the association between uterine leiomyoma

and VTE in different age groups of patients not receiving hormone therapy, we performed subgroup analyses of those aged ≤ 30, 31-40, 41-50, 51-60, and ≥ 61 years, as shown in Table 3. The patients with uterine leiomyoma aged ≤ 30 and 41-50 years had a higher risk of VTE than those without uterine leiomyoma before the data were matched (p = 0.0247, OR: 4.602, CI: 1.21-17.44; p = 0.0129, OR: 1.535, CI: 1.10-2.15). Both the results using the frequency-matched model and the propensity score-matched model were consistent with the results obtained in the overall patient sample.

Leiomyoma in the patients without cancer who did not receive hormone therapy and the risk of developing VTE

Due to concerns about the joint effect of hormone therapy and cancer on VTE, we performed sensitivity analysis by excluding those receiving hormone therapy and cases with a diagnosis of cancer (Table 4), and the results remained consistent with the results in Table 2.

DISCUSSION

In this study, we found that Taiwanese women with uterine leiomyoma were susceptible to venous thromboembolism. Strong correlations were consistently observed in the overall population before matching, and also after age- and index year-matching and propensity score-matching. Although the association between uterine leiomyoma and VTE has not been frequently reported, our findings support several previous case re-

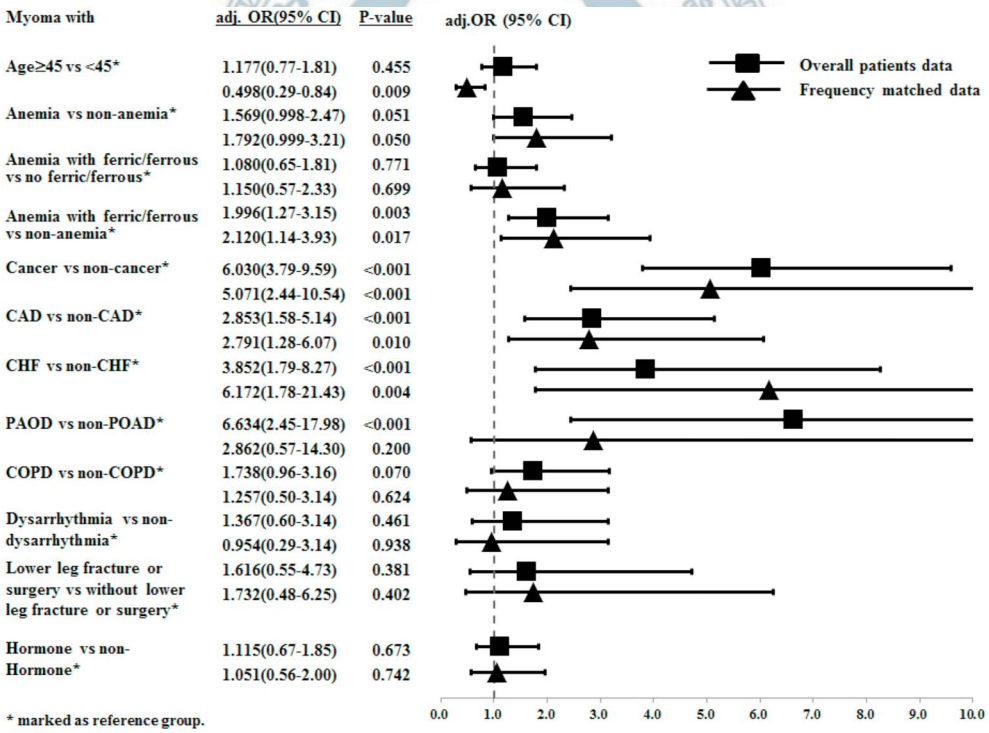

Figure 2. *The subgroup analysis is shown in the forest plot. Abbreviations are in Table 1.*

Table 3. The risk of VTE in patients with uterine leiomyomas in different age group after excluding those receiving hormone therapy

Subgroup	Before matching data		Frequency matched data		Propensity score matched data	
	Adjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
≤ 30	4.602 (1.21-17.44)	0.0247	6.407 (1.57-26.2)	0.0097	5.927 (1.45-24.24)	0.0133
31-40	1.212 (0.55-2.69)	0.6360	1.361 (0.61-3.05)	0.4534	0.951 (0.42-2.16)	0.9049
41-50	1.535 (1.10-2.15)	0.0129	1.607 (1.04-2.47)	0.0310	1.468 (1.05-2.05)	0.0231
51-60	1.203 (0.83-1.74)	0.3268	1.213 (0.84-1.75)	0.3034	1.183 (0.82-1.70)	0.3626
≥ 61	1.076 (0.60-1.93)	0.8053	1.056 (0.47- 2.37)	0.8943	0.956 (0.53-1.74)	0.956

Table 4. Multivariate logistic regression model to assess the associations between uterine leiomyoma and VTE after excluding the patients with hormone therapy and cancer diagnosis in uterine leiomyoma comparison

	VTE case[#]	Control	Adjusted odds ratio[Model 1] (95 % CI)	p value	Adjusted odds ratio[Model 2] (95 % CI)	p value
Before matching data						
Non-leiomyoma	1539 (95.47%)	348283 (95.97%)	1 (reference)		1 (reference)	
Leiomyoma*	73 (4.53%)	14623 (4.03%)	1.632 (1.283-2.076)	< 0.0001	1.579 (1.245-2.003)	0.0002
Frequency matching data						
Non-leiomyoma	1539 (95.47%)	7523 (96.61%)	1 (reference)		1 (reference)	
Leiomyoma*	73 (4.53%)	264 (3.39%)	1.615 (1.220-2.137)	0.0008	1.650 (1.256-2.168)	0.0003
Propensity score matching data						
Non-leiomyoma	1518 (95.47%)	6249 (96.35%)	1 (reference)		1 (reference)	
Leiomyoma*	72 (4.53%)	237 (3.65%)	1.387 (1.056-1.823)	0.0188	1.341 (1.023-1.758)	0.0334

Model 1 adjusted for uterine leiomyoma and the significantly different variables in Table 1. Model 2 adjusted for uterine leiomyoma, age and propensity score.
VTE, venous thromboembolism.

ports and case series studies. Previous studies have also reported that uterine leiomyomas, especially those with a large size, may cause DVT because of venous stasis due to mechanical compression of the iliac veins or inferior vena cava. The most frequent site of venous compression is the common iliac vein, regardless of whether on the left, right or both.[14] Once DVT occurs in the large veins of the lower extremities, the thrombus is likely to detach and embolize, resulting in a PE sequence.[1] Furthermore, in a case series study, Barsam et al. found that the site of the uterine leiomyoma was not always correlated to the site of DVT.[13] It is possible that direct compression of the uterine leiomyoma is not the only cause of DVT. As pregnancy causes physical enlargement of the uterus but does not usually cause DVT, and as many women apparently have uterine leiomyomas without DVT, it seems that the size of the uterus may not be the only factor predisposing women to DVT. However, the presence of uterine leiomyomas may cause non-uniform enlargement of the uterus accompanied by shape changes, and this could easily predispose the uterus by impinging on the veins.[15] The reason for the higher risk of VTE in the patients with uterine leiomyomas could also be explained by a hormone-related trend toward VTE in patients with uterine leiomyomas.[13] Wolanska et al. found that an increased expression of type 1 basic fibroblast growth factor receptors, which act as a heparin-binding growth factor, in the endometrium of uterine leiomyoma may interfere with normal coagulation.[16] An elevated expression of thrombospondin 1, a glycoprotein involved in the platelet adhesion response, has also been observed in uterine leiomyoma compared to normal endometria.[17] Gokdeniz et al. identified a marked expression of endothelial nitrogen oxide synthase in uterine leiomyoma tissue compared with normal myometrium.[18] They also found that nitrogen oxide could contribute to VTE by either mediating the growth-promoting effects of estrogen on uterine leiomyoma or by enhancing alterations in pelvic blood flow.[18]

The findings of the current study revealed that the patients with uterine leiomyomas who were older than 45 years of age had a lower risk of VTE than those with uterine leiomyomas who were younger than 45 years of age. Based on observational studies, the incidence of uterine leiomyomas initially increases during puberty, is most frequent during perimenopause, and then decreases rapidly after menopause.[6] The incidence of uterine leiomyoma peaks at 40-44 years of age because of the natural regression in uterine leiomyomas after menopause.[19,20] The decreasing incidence and impact of uterine leiomyomas in women older than 45 years of age may then contribute to the lower susceptibility to VTE. In our study, we found that in the women aged ≤ 30 and 40-50 years who did not receive hormone therapy, uterine leiomyomas were significantly associated with the risk of VTE. The possible explanations are as follows. The mean age of menopause in Taiwan is 49 years, but in some women, menopause can start from 40 years of age.[21] Gurka et al. showed that women had a

rapid increase in the risk of cardiovascular atherosclerosis during the menopausal transition, and this increased cardiovascular risk during this transitional period led to a greater susceptibility to arterial or venous thrombosis.[22] In contrast, women aged ≤ 30 years with uterine leiomyomas in the current study had the highest risk of developing VTE (aOR: 5.927-6.407). The underlying mechanism of this finding is unknown, however it raised concerns about anticoagulation therapy in young subjects with uterine leiomyomas.

In subgroup analysis, the patients with uterine leiomyoma and comorbid diseases including anemia, cancer, CAD and CHF had an increased risk of VTE. We also found that the patients with uterine leiomyoma and anemia were more susceptible to VTE, regardless of whether anemia was managed with ferric or ferrous tablets. In patients with anemia, low blood viscosity may cause decreased secretion of antithrombotic mediators resulting in increased blood clotting.[23] In addition, the severity of anemia has been shown to be correlated to the diameter of uterine leiomyomas and the menorrhagic period.[24] Anemia may be related to occult cancer, and patients with cancer also exhibit a higher risk of developing VTE. We also demonstrated that the patients with both uterine leiomyoma and cancer had a greater risk of developing VTE. Cancer is well known to increase the risk of VTE, and approximately 15-18% of all cases of VTE are associated with cancer.[25,26] VTE is also a preclinical marker of cancer, especially in the first year after the diagnosis of VTE.[27] Anemia has been shown to increase the risk of VTE after a cancer diagnosis, further supporting this connection.[28]

The association between venous thromboembolism and atherosclerosis has been clarified in recent studies, and these two diseases are no longer considered to be separate clinical entities.[29-31] Atherosclerosis is believed to be associated with the activation of platelets and blood coagulation and an increase in fibrin turnover to induce a pro-thrombotic state in the slow-flowing venous system.[32] This study supported the strong correlation between CAD and VTE.

CHF is well known to be associated with the risk of VTE, and also to be an independent risk factor for VTE.[33,34] Women with severe heart failure, as assessed from either the lower left ventricular ejection fraction or a higher serum N-terminal pro-brain natriuretic peptide level, appear to have a higher risk of VTE than those with less severe or no heart failure.[35,36] Among patients with heart failure, both decreased cardiac output and patient immobility produce the negative effects in Virchow's classic triad, namely, blood flow stasis, endothelial dysfunction, and abnormalities in blood constituents.[33] Patients with heart failure are predisposed to thrombus formation because of their chronic inflammatory state.[37] Consistent with previous studies, we demonstrated that the women with uterine leiomyoma and HF had a higher risk of VTE.

The management of uterine leiomyomas is well described in clinical practice guidelines and should be individualized depending on the patient's symptomatology, size and location of the uterine leiomyoma, patient's age, and concern for the preservation of fertility.[38] The present study specifically addressed the risk of VTE in women with uterine leiomyomas and may provide therapeutic references for those women. In clinical application, if women are diagnosed with VTE during reproductive age and lack the traditional risk factors, a gynecological work-up should be performed to determine the presence of uterine leiomyoma.

Study limitations

There are several limitations to this study. The first limitation pertains to the use of an administrative database and the case control study. This limitation has been well described in other population-based studies using the NHIRD.[39] Further prospective studies are needed to confirm our observations. Second, the accuracy and validity of diagnoses based on ICD-9 codes may be an issue that needs to be addressed. To achieve quality and accuracy in the diagnosis of a disease, the diagnoses of uterine leiomyoma and VTE in this study were determined according to the presence of at least three records of the appropriate diagnostic code as coded by specialists. Finally, the prevalence of uterine leiomyoma may be underestimated. Without menstrual abnormalities or bulk symptoms, women with uterine leiomyomas will not seek medical aid and will therefore not have a diagnosis of uterine leiomyoma recorded in NHIRD. In addition, women of reproductive age are more likely to seek medical aid because of menstrual abnormalities and pain symptoms related to uterine leiomyomas than older women.

CONCLUSIONS

Taiwanese women with uterine leiomyomas are susceptible to VTE. Women with specific comorbid diseases including anemia, cancer, coronary artery disease or heart failure and a younger age have a greater risk of developing VTE.

CONFLICTS OF INTEREST

None.

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SUPPLEMENT

Supplementary Table 1. ICD-9-CM codes used to identify uterine leiomyoma, venous thromboembolism, and comorbid conditions

Diseases	Corresponding ICD-9-CM codes
Uterine leiomyoma	218.0, 218.1, 218.2 and 218.9
Venous thromboembolism	
Pulmonary artery embolism	415.1
Deep vein thrombosis	453.8
Co-morbid diseases	
Hypertension	401.x–405.x
Diabetes mellitus	250.x
Hyperlipidemia	272.x
Chronic kidney disease	580.x-589.x
Coronary artery disease	410.x–414.x
Congestive heart failure	428.x
Cardiac dysarrhythmia	427.x
Peripheral artery occlusive disease	443.x–444.x
COPD	416.x, 490.x -505.x, 506.4, 508.x
Anemia	280.0, 280.9, 285.x
All cancer	140.x -208.x
Stroke	430.x–438.x
Lower leg fracture or surgery	820.x, 821.x
	OP icd-9: 81.51, 81.52, 81.53, 81.54

COPD, chronic obstructive pulmonary disease; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification.

Supplementary Table 2. Multivariate logistic regression model to assess the associations between uterine leiomyoma and VTE
We carried out a sensitivity analysis in diagnosis of uterine leiomyoma and VTE identified using a stringent criterion. The analysis showed that the association between uterine leiomyoma and VTE was in agreement with the results in Table 2.
Sensitivity table:

	VTE case#	Control	Adjusted odds ratio Model 1 (95 % CI)	p-value	Adjusted odds ratio Model 2 (95 % CI)	p-value
Before matching data						
Non-leiomyoma	1550 (96.15%)	377760 (96.05%)	1 (reference)		1 (reference)	
Leiomyoma*	62 (3.85%)	15524 (3.95%)	1.417 (1.087-1.846)	0.0100	1.444 (1.107-1.883)	0.0067
Frequency matching data						
Non-leiomyoma	1550 (96.15%)	6243 (96.82%)	1 (reference)		1 (reference)	
Leiomyoma*	62 (3.85%)	205 (3.18%)	1.645 (1.190-2.274)	0.0026	1.371 (1.015-1.851)	0.0397
Propensity score matching data						
Non-leiomyoma	1536 (96.3%)	6158 (97.13%)	1 (reference)		1 (reference)	
Leiomyoma*	59 (3.7%)	182 (2.87%)	1.456 (1.071-1.979)	0.0164	1.464 (1.081-1.982)	0.0137

Model 1 adjusted for uterine leiomyoma and the significantly different variables in Table 1. Model 2 adjusted for uterine leiomyoma, age and propensity score.
* The diagnosis of leiomyoma was confirmed by gynecologic ultrasound. # The diagnosis of VTE was confirmed using patients received anticoagulation therapy.
VTE, venous thromboembolism.