

Association of statin use and the risk of recurrent pulmonary embolism in real-world Chinese population

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Abstract

Background: Previous studies have suggested that statins exert protective effects against venous thromboembolism. However, few randomized studies have explicitly concentrated on patients with pulmonary embolism. Thus far, evidence of the effect of statins on the pulmonary embolism recurrence in China remains lacking.

Methods: A retrospective analysis was conducted utilizing our University database. Patients with an International Coding of Diseases-defined diagnosis of pulmonary embolism from 1 January 2017 to 31 December 2019 were included. The patients were divided into two groups, namely, with statin or without statin treatment. Propensity score matching was applied to balance the covariates between the comparison groups. Univariate analysis and multivariable logistic regression were performed to analyze the association between statin use and pulmonary embolism recurrence.

Results: A total of 365 patients diagnosed with pulmonary embolism were included in the research. Pulmonary embolism recurrence accounted for 15.1% of the patients and was observed during the entire study period. In the initial population, no significant difference in recurrence was observed between the groups with and without statins treatment (statin 15.6% vs. non-statin 14.9%, $p = 0.860$). After propensity score matching, multivariate logistic regression analysis revealed that the odds ratio of pulmonary embolism recurrence in the statin users was 0.489 (95% confidence interval 0.190–1.258, $p = 0.138$).

Conclusions: Our study provides no support for the use of statins as an adjunctive therapy in patients with pulmonary embolism at the initiated time of diagnosis or as a prophylactical plan when anticoagulation is discontinued attempting to reduce the risk of recurrence.

Keywords

pulmonary embolism, recurrence, statin

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Introduction

Pulmonary embolism (PE) is a form of venous thromboembolism (VTE) with high morbidity and mortality. The annual incidence of PE is 60 to 100 cases per 100,000 patients, with a 30-day case fatality rate of 10% to 30%.^{1–3} The cumulative incidence of PE recurrence is high at approximately 53%, with nearly 10 years follow-up.⁴ Clinical studies have shown that PE recurrence not only increases the fatality rate but also prolongs the duration of anticoagulation, reduces the quality of life, and increases the risk of developing chronic thromboembolic pulmonary

hypertension (CTEPH).^{5,6} A reduced dose of apixaban or rivaroxaban for extended anticoagulation should be considered after the first six months of anticoagulant therapy, which increases the risk of bleeding.^{7,8} Importantly, most randomized studies concentrating on anticoagulation for

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VTE have included patients with deep vein thrombosis (DVT) with or without PE; only two randomized studies have specifically focused on patients with PE.^{7,9,10} However, both studies support the idea that prolonged anticoagulant therapy may reduce the risk of recurrent PE but inevitably increases the risk of massive bleeding. This benefit is not maintained after discontinuation of anticoagulation therapy. Therefore, finding an effective and safe drug to reduce the risk of PE recurrence as a complementary treatment is essential.

Statins may represent a relatively safe approach to reduce the incidence of PE; they can be used long term or even lifetime. Thus far, the effect of statins in preventing VTE remains controversial. The trial Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin, which included healthy adults with elevated cholesterol to the borderline range, investigated the effects of oral rosuvastatin (20 mg/day) versus placebo and demonstrated that rosuvastatin (hazard ratio (HR) 0.57; 95% confidence interval (CI) 0.37–0.86; $p=0.007$) reduces the incidence of provoked VTE compared with placebo.¹² Meanwhile, a recent meta-analysis conducted among 29 studies has indicated that statin therapy does not significantly reduce the risk of venous thromboembolic events (odds ratio (OR) 0.89, 95% CI 0.78–1.01; $p=0.080$).¹³ However, inconsistent results have also been reported. A study ($n=432$) proposed that statins are not significantly associated with reducing VTE (OR 1.02, 95% CI 0.36–2.91), whereas another study suggested that statins exert different ages. Specifically, statin use is associated with low risk of recurrent VTE in individuals aged ≤ 80 years (HR 0.70, 95% CI 0.65–0.76) but significantly associated with high risk of recurrent VTE in patients aged >80 years (HR 1.28, 95% CI 1.02–1.60, p for interaction ≤ 0.0001).^{14,15} A recent retrospective study by Stewart et al. has suggested that the recurrence rate of VTE is decreased in patients treated with statins (OR 0.75, 95% CI 0.72–0.79).¹¹

Previous studies have achieved controversial results on the effects of statins on the prevention and treatment of VTE. However, works focusing on recurrent PE in real-world patients are limited. Therefore, this study aims to determine the prevalence of statin use and explore the association of statins on PE recurrence in Chinese patients.

Methods

Overall study design

A population-based, retrospective analysis was performed in collaboration with the Data Process and Application Platform (Yidu-Cloud (Beijing) Technology Co., Ltd., China).^{16,17} De-identified patient information was collected from our University database, a platform of healthcare interoperability resources including data from seven hospitals and approximately more than 3 million patients' records (during 1 January 2017 to 31 December 2019). All

patients diagnosed with PE were screened based on the appropriate codes of International Coding of Diseases (ICD, PE: ICD-10 [I26.x]) over the specified study period of 1 January 2017 to 31 December 2019. The patients' images and reports of computed tomography pulmonary angiography were screened independently by two authors, who discarded studies that were not pertinent to the diagnosis.

Demographic data (including age, sex, smoking, surgery, trauma, and fracture history), clinical data (chief complaint, physical examination, several predefined laboratory markers, and medical therapies), and several predefined comorbidities were collected. These comorbidities included hypertension, atrial fibrillation (AF), heart failure (HF), hyperlipidemia, DVT, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), renal dysfunction, stroke, coronary heart disease (CHD), multiple cancer diagnoses (ovary, bladder, lung, liver, pancreas, laryngeal, and epityphlon), inherited thrombotic disorders, and antiphospholipid antibody syndrome. Laboratory markers included serum cholesterol, low density lipoprotein cholesterol (LDL-C), c-reactive protein (CRP), and d-dimer. The specific ICD codes are presented in Appendix 1 and used in defining each comorbidity. Medical therapies were assessed, including the following medications: warfarin, antiplatelet (aspirin, clopidogrel, and ticagrelor), heparin (low-molecular weight heparin, heparin, and nadroparin), and non-vitamin K antagonist oral anticoagulant (NOACs, rivaroxaban, apixaban, and dabigatran). We collected the medication information from both the electric medical recorders system and the pharmacy system, which enables us to get the complete medication use lists (contained the duration and dose of medication) in the seven medical centers. The exposure to statins was defined as the use of statins for at least 30 consecutive days, including the following medications: atorvastatin (10 mg/day to 20 mg/day), pitavastatin (2 mg/day), pravastatin (20 mg/day), rosuvastatin (10 mg/day), and simvastatin (20 mg/day to 40 mg/day). The recurrent PE was defined as any objectively verified subsequent diagnosis of PE based on the ICD-10 code occurring after the index event. Medical records were reviewed for all patients diagnosed with PE to minimize underestimating the recurrence.

Statistical analysis

We conducted all statistical analyses with Stata/SE 15.1 (StataCorp LLC, College Station, TX). Continuous variables were presented as the mean \pm standard deviation (SD) or median (interquartile range (IQR)), and qualitative variables were expressed as percentage. Normally distributed continuous data were presented as mean \pm SD, whereas data that were not normally distributed were presented as median with IQR. We investigated the utilization status of antithrombotic drugs in patients with PE. We then divided the patients into two groups based on whether they were

treated or not with statins. Subsequently, the demographic data, clinical data, the proportions of baseline comorbidities, and the recurrence of PE between the two groups were compared using one-way analysis of variance or the Kruskal–Wallis test for continuous variables and the Pearson chi-squared test or the Fisher exact test for categorical variables. The normality of both trait distributions was verified using the Shapiro–Wilk test (Shapiro and Wilk 1965). Statistical significance was considered at $p < 0.05$.

A univariate analysis where age, sex, smoking, surgery, trauma and fracture history, hypertension, hyperlipidemia, DVT, DM, AF, COPD, HF, CHD, stroke, renal dysfunction, cancer, as well as statin, antiplatelet and anticoagulants use are the independent variables was conducted to identify the patient characteristics associated with recurrent PE. The multivariable logistic regression model was used to explore the effects of each significant variable to predict the recurrence of PE. OR and 95% CI on predictor variables of interest were calculated for PE recurrence.

To mitigate potential selection bias when comparing treatment effects on the statin and control groups, we matched patients by using propensity score matching (PSM) with an algorithm of 1:1 matching. A logistic regression model was constructed to assess the propensity scores with caliper 0.05. Statin use was taken as a dependent variable, whereas the confounding differences (age, gender, hypertension, hyperlipidemia, DVT, DM, AF, COPD, HF, stroke, coronary artery disease, renal dysfunction, cancer, history of smoking, surgery, trauma, fracture, the use of antiplatelet and anticoagulant) were used as independent variables. A multivariable logistic regression model was then employed to estimate PE recurrence as a dependent variable from the statin use as one of the independent variables. Variables with $p < 0.2$ in univariate were used as independent variables in multivariate analysis.

Results

A total of 365 patients with PE were included in the study sample. The median follow-up period was 19.2 months (IQR: 10.6–26.2). Approximately 15.1% (55/365) patients developed recurrence during the study period, and the mean time to recurrence was 3.6 months. Of these patients, 96 (26.3%) were taking statin (statin group) and 269 (73.7%) did not take any statins during the study period (no-statin group) as shown in Table 1. The median duration (range) of statin therapy was 104 (5–776) days. Patients in the statin group were significantly older (statin, 75.0 years vs. no-statin, 69.0 years, $p = 0.001$) and more likely tended to have hypertension (52.1% vs. 28.6%, $p < 0.0001$), hyperlipidemia (21.9% vs. 4.5%, $p < 0.0001$), DVT (45.8% vs. 33.5%, $p = 0.031$), HF (24.0% vs. 14.5%, $p = 0.034$), stroke (18.8% vs. 7.4%, $p = 0.002$), and CHD (44.8% vs. 16.4%, $p < 0.0001$) than those in the no-statin group. Meanwhile, more patients in the no-statin group had a smoking history (27.0% vs. 16.1%, $p = 0.011$) and cancer

diagnosis (19.0% vs. 8.3%, $p = 0.015$) than those in the statin group. No significant differences in surgery, trauma, and fracture history were found between the two groups. The baseline serum cholesterol in the statin group was significantly higher than that in the control group (statin vs. no-statin, 4.5, IQR 3.7–5.8 vs. 4.3, IQR 3.4–5.1; $p = 0.045$). However, the difference in LDL-C, d-dimer and CRP between the two groups was not statistically significant. Antiplatelet utilization was higher in the statin group than in the no-statin group (64.4% vs. 14.1%, $p < 0.0001$). Without propensity matching, no statistically significant difference in PE recurrence and anticoagulant utilization was found between the two groups.

Univariable analysis was conducted to identify the patient characteristics associated with recurrent PE. Variables including age, AF, COPD, renal dysfunction, surgery history, and anticoagulation and statin utilization were included in the regression equation as independent predictors. Results of the univariable analysis and multivariable logistic regression analysis are shown in Table 2. Surgery history (OR 2.239, 95% CI 1.111–4.510, $p = 0.024$) and COPD (OR 2.529, 95% CI 1.162–5.507, $p = 0.019$) were the risk factors for PE recurrence, whereas anticoagulant use was the protective factor (OR 0.151, 95% CI 0.042–0.543, $p = 0.004$). No significant difference in the rate of PE-recurrence was found between the statin and no-statin groups.

We applied PSM to control for confounding differences in baseline characteristics to estimate the differences in PE recurrence between the statin and no-statin groups. After PSM, we analyzed the statin group ($n = 88$) and non-statin group ($n = 263$). Table 3 summarized the demographic characteristics and comorbidities of patients in the two matched groups. The remaining baseline characteristics were well balanced between the two groups. Multivariate logistic regression analysis was performed with PE recurrence as the dependent variable in the population after PS matching. The results are shown in Table 4. The PE recurrence comparison of the statin and non-statin groups showed that the OR was 0.489 (95% CI 0.190–1.258, $p = 0.138$).

Discussion

In this population-based study, we enrolled 365 patients with PE and a follow-up median of 1.6 years. The result showed no protective effect of statins on recurrent PE. This insignificant effect persisted after we performed propensity pairing.

To the best of our knowledge, this study is the first to focus on the relationship between recurrent PE and statin use in Chinese patients.⁷ Apparently, PE recurrence implies worse prognosis. Moreover, the research on PE and recurrence is limited. Thus, we conducted the study in an actual Chinese population.

Several previous studies on the recurrence of VTE obtained mixed results. A population-based study from

Table 1. Clinical characteristics of patients stratified by statin use vs. no statin use.

	No Statin (N = 269)	Statin (N = 96)	p
Demographics			
Age, y	69.0 (62.0, 78.0)	75.0 (66.0, 81.5)	0.001*
Male gender (%)	61.0	57.3	0.529
Medical history			
Hypertension (%)	28.6	52.1	<0.0001
Hyperlipidemia (%)	4.5	21.9	<0.0001
Deep vein thrombosis (%)	33.5	45.8	0.031
Diabetes mellitus (%)	12.6	15.6	0.463
Atrial fibrillation (%)	6.0	7.3	0.643
Chronic obstructive pulmonary disease (%)	26.4	29.2	0.350
Heart failure (%)	14.5	24.0	0.034
Stroke (%)	7.4	18.8	0.002
Coronary heart disease (%)	16.4	44.8	<0.0001
Renal dysfunction (%)	4.8	9.4	0.109
Cancer (%)	19.0	8.3	0.015
Smoking history (%)	27.0	16.1	0.011
Surgery history (%)	29.2	21.1	0.127
Trauma or/and fracture (%)	9.7	7.3	0.488
Antiphospholipid-syndrome	0.4	0	0.551
Chronic thromboembolic pulmonary hypertension	0.7	2.1	0.280
Laboratory values			
Serum cholesterol (mmol/L)	4.3 (3.4, 5.1)	4.5 (3.7, 5.8)	0.045*
Low density lipoprotein cholesterol (mmol/L)	2.5 (1.9, 3.0)	2.5 (2.0, 3.4)	0.228*
D-dimer (ng/mL)	3790 (1000, 10350)	2764 (1150, 6900)	0.337*
C-reactive protein (mg/L)	22.2 (6.7, 75.0)	15.1 (5.0, 51.8)	0.200*
Medical therapies			
Antiplatelet (%)	14.1	64.6	<0.0001
Anticoagulants (%)	95.5	97.9	0.299
Recurrence (%)	14.9	15.6	0.860

Data are shown as mean \pm SD or median (interquartile range) for continuous outcomes and n (%) for categorical outcomes. *p* values were based on one-way analysis of variance or the Kruskal–Wallis test for continuous outcomes and the Pearson chi-squared test or the Fisher exact test for categorical outcomes. The test utilization in continuous variables was presented with * for the Kruskal–Wallis test.

Table 2. The univariable analysis and multivariate logistic regression analysis with associated odds ratios for pulmonary embolism recurrence.

Variable	Pulmonary embolism recurrence			
	Univariable		Multivariable	
	Odds ratios (95% CI)	<i>p</i>	Odds ratios (95% CI)	<i>p</i>
Age	.	0.093	1.008 (0.981–1.035)	0.569
Male gender	0.838 (0.452–1.570)	0.550	0.558 (0.264–1.178)	0.126
Hypertension	1.302 (0.685–2.432)	0.379	1.091 (0.536–2.220)	0.811
Hyperlipidemia	0.538 (0.102–1.835)	0.314	0.591 (0.155–2.260)	0.443
Deep vein thrombosis	1.179 (0.622–2.199)	0.583	0.978 (0.506–1.892)	0.948
Diabetes mellitus	1.321 (0.527–3.004)	0.488	1.195 (0.495–2.883)	0.692
Atrial fibrillation	2.110 (0.647–5.949)	0.127	1.671 (0.500–5.593)	0.405
Chronic obstructive pulmonary disease	1.837 (1.095–3.477)	0.045	2.529 (1.162–5.507)	0.019
Heart failure	1.103 (0.465–2.402)	0.798	0.909 (0.366–2.258)	0.837
Stroke	1.589 (0.592–3.822)	0.276	1.345 (0.475–3.801)	0.576
Coronary heart disease	1.109 (0.528–2.217)	0.760	0.866 (0.373–2.012)	0.738
Renal dysfunction	2.868 (1.935–7.923)	0.024	2.513 (0.844–7.487)	0.098
Cancer	1.562 (0.696–3.292)	0.217	2.039 (0.910–4.570)	0.084
Smoking history	0.856 (0.390–1.762)	0.659	1.026 (0.438–2.399)	0.954

(continued)

Table 2. Continued.

Variable	Pulmonary embolism recurrence			
	Univariable		Multivariable	
	Odds ratios (95% CI)	<i>p</i>	Odds ratios (95% CI)	<i>p</i>
Surgery history	1.529 (0.779–2.921)	0.172	2.239 (1.111–4.510)	0.024
Trauma or/and fracture	0.760 (0.186–2.301)	0.620	0.753 (0.234–2.427)	0.635
Statin use	1.060 (0.515–2.087)	0.859	1.026 (0.436–2.417)	0.952
Antiplatelet	1.353 (0.684–2.594)	0.336	1.470 (0.642–3.368)	0.362
Anticoagulant	0.216 (0.063–0.796)	0.003	0.151 (0.042–0.543)	0.004

CI: confidence interval.

Table 3. Clinical characteristics of patients stratified by statin use vs. no statin use following propensity matching.

	No Statin (N = 263)	Statin (N = 88)	<i>p</i>
Age, y	75.8	73.0	0.105
Male gender (%)	55.7	55.7	1
Hypertension (%)	51.1	51.1	1
Hyperlipidemia (%)	17.0	18.2	0.844
Deep vein thrombosis (%)	39.8	43.2	0.648
Diabetes mellitus (%)	8.0	13.6	0.227
Atrial fibrillation (%)	5.7	8.0	0.552
Chronic obstructive pulmonary disease (%)	40.9	29.5	0.116
Heart failure (%)	23.9	23.9	1
Stroke (%)	21.6	18.2	0.574
Coronary heart disease (%)	39.8	43.2	0.648
Renal dysfunction (%)	12.5	9.1	0.469
Cancer (%)	4.5	9.1	0.234
Smoking history (%)	14.8	17.0	0.682
Surgery history (%)	20.5	19.3	0.851
Trauma or/and fracture (%)	11.4	8.0	0.447
Antiplatelet (%)	61.4	63.6	0.319
Anticoagulant (%)	100.0	98.9	0.228

Table 4. Multivariate logistic regression analysis with associated odds ratios for pulmonary embolism recurrence in propensity score matched samples.

Variable	Pulmonary embolism recurrence	
	<i>p</i>	Odds ratios (95% CI)
Age	0.331	0.981 (0.942–1.020)
Atrial fibrillation	0.024	6.499 (1.273–33.179)
Chronic obstructive pulmonary disease	0.006	4.373 (1.537–12.440)
Renal dysfunction	0.095	2.891 (0.832–10.044)
Surgery history	0.753	1.233 (0.334–4.547)
Anticoagulant	Omitted ^a	Omitted ^a
Statin	0.138	0.489 (0.190–1.258)

^aOmitted, all patients with no anticoagulant were recurrent PE.

CI: confidence interval.

Stewart et al. reported that statin use is associated with a reduced risk of recurrent VTE.¹¹ In addition, some registration studies from the Dutch and Danish populations are in favor of this view.^{15,18,19} Unfortunately, these studies did

not focus on whether or not persistence is only in patients with PE recurrence. Delluc et al. found no trend of association between statin use and recurrent VTE. Similarly, this study did not focus on patients with PE.¹⁴

Thus far, the mechanism of statin on VTE is unknown. Some studies, which are in favor of the positive effect of statins on VTE, suggested that the cause may be the combination of anti-thrombotic properties and anti-inflammatory effect by the downstream effects of reduced cholesterol synthesis and increased liver uptake.²⁰ In addition, statins reduce thrombin generation and attenuate fibrinogen cleavage by inhibiting tissue factor expression and platelet activation.^{21–23} However, statins also cause proteinuria through tubular inhibition of active transport of small-molecular-weight proteins.^{24,25} A number of reports to the US Food and Drug Administration (FDA) indicate proteinuria with statins, particularly in patients receiving rosuvastatin or simvastatin.²⁶ Previous studies have demonstrated that urinary protein is associated with VTE prognosis.^{27,28} Therefore, we speculate that the benefit of statins may be offset by proteinuria. However, we have not been able to collect data on

urinary protein. Thus, this conjecture needs to be confirmed by future studies.

Our findings indicate that we could not endorse the use of statins not only as an adjunctive therapy in patients with PE at the initiated time of diagnosis but also as a prophylactical plan when anticoagulation is discontinued in an attempt to reduce the risk of recurrence. Although statins may be an alternative with relatively few side effects, our study suggests that statin is not useful to reduce the recurrence of PE. Therefore, we believe that appropriate prolongation of the use of oral anticoagulants is still the most effective method to reduce the recurrence of PE. However, this approach also causes inevitable bleeding risk. Safe substitutable method to anticoagulant therapy should be especially noteworthy.

The present study has some limitations. First, given the methodology framework of our study, the initial screening relied on ICD codes. The recurrence of VTE may be underestimated. Second, we found a higher proportion of patients using statin on multiple comorbidities in the initial study population, for which we obtained a more balanced group by propensity matching. While propensity matching produced a more balanced population, subtle differences remained. Moreover, propensity matching could not replace the role of randomized controlled trials. In addition, due to potential geographical limitations, some patients outside the province may have been ignored for treatment. It is possible that a portion of patients in the “non-statin” group actually received a statin prescription that was not captured in this analysis.

Conclusion

In conclusion, statin does not decrease the risk of PE recurrence. Oral anticoagulant remains the most effective method at present, although it also carries an inevitable risk of bleeding. In addition, finding an effective and safe drug to reduce the risk of PE recurrence as a complementary treatment requires urgent attention.

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Ethics approval and consent to participate

The Human Research Committee of our University approved this study and waived the need for informed consent.

Availability of data and materials

The data that support the findings of this study are available from the Yiducoud (Chongqing) Technology Co., Ltd. and the cooperative Medical Data Science Academy of Chongqing Medical University. These data, which were used under license for the current study, are restricted and not publicly available. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

L.W., W.W., T.S. and H.C. were responsible for the data screening, data extraction and analysis. L.W. and T.S. were responsible for writing the manuscript. P.F., R.X., and W.H. were responsible for reviewing the final manuscript. All authors have read and approved the manuscript.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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Appendix I

Variable name	Variable description/Coded values
Age	Age of patient at the time of the pulmonary embolism.
Gender	0 = Female 1 = Male Null = Unknown
Pulmonary embolism	ICD codes that were used to define pulmonary embolism included ICD-10 codes I26; 1 = Positive 0 = Negative
Hypertension	ICD codes that were used to define hypertension included ICD-10 codes I10-I11; 1 = Positive 0 = Negative
Hyperlipidemia	ICD codes that were used to define hyperlipidemia included ICD-10 codes R77 and E78; 1 = Positive 0 = Negative
Deep vein thrombosis	ICD codes that were used to define deep vein thrombosis included ICD-10 codes I80 and I82; 1 = Positive 0 = Negative
Diabetes mellitus	ICD codes that were used to define diabetes mellitus included ICD-10 codes E10, E11, E13 and E14; 1 = Positive 0 = Negative
Atrial fibrillation	ICD codes that were used to define atrial fibrillation included ICD-10 codes I48; 1 = Positive 0 = Negative
Chronic obstructive pulmonary disease	ICD codes that were used to define chronic obstructive pulmonary disease included ICD-10 codes J44; 1 = Positive 0 = Negative
Heart failure	ICD codes that were used to define heart failure included ICD-10 codes I50; 1 = Positive 0 = Negative

(continued)

Continued.

Variable name	Variable description/Coded values
Stroke	ICD codes that were used to define stroke included ICD-10 codes I60-64, and I69; 1 = Positive 0 = Negative
Coronary artery disease	ICD codes that were used to define CAD included ICD-10 codes I20-25; 1 = Positive 0 = Negative
Renal dysfunction	ICD codes that were used to define renal dysfunction included ICD-10 codes N17-19 and R94.4; 1 = Positive 0 = Negative
Cancer	ICD codes that were used to define cancer included ICD-10 codes C22.000, C22.900, C25.100, C26.901, C34.900, C78.201 and Z51.100; 1 = Positive 0 = Negative
Smoking history	1 = Positive 0 = Negative
Surgery history	1 = Positive 0 = Negative
Trauma and/or fracture	ICD codes include I79., I76., X59.952, Z87.8, Z54.4, T91-93, T02, S82, S72, S62, S52, S42, S32, S22, S12; 1 = positive 0 = negative
Antiphospholipid syndrome	ICD codes include R79.801; 1 = positive 0 = negative