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ORIGINAL ARTICLE

Incidence and risk factors for venous thromboembolism following surgical treatment of fractures below the hip: a meta-analysis

Lei Tan, Baochang Qi, Tiecheng Yu & Chengxue Wang

Department of Orthopedic Traumatology, The First Hospital of Jilin University, Changchun, China

Key words
Fractures; Low extremity to the hip; Meta-analysis; Risk factors; Venous thromboembolism

Correspondence to
C Wang
Department of Orthopedic Traumatology
The First Hospital of Jilin University
No. 71 Xinmin Street
Changchun, 130021
Jilin, China
E-mail: wangchengxue123@126.com

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Abstract

Venous thromboembolism (VTE) is a common complication after surgical treatment of fractures, which is associated with significant morbidity and mortality. Identifying the risk factors for VTE is important for preventive strategies to reduce the incidence of VTE. Therefore, we conducted a meta-analysis to evaluate the incidence of VTE and the risk factors influencing the development of VTE in patients who underwent surgery for fractures below the hip. PubMed, Embase, Web of Science, SinoMed (Chinese BioMedical Literature Service System, China) and CNKI (National Knowledge Infrastructure, China) databases were systematically searched to identify cohort or case–control studies that investigated the incidence and risk factors for VTE following surgical treatment of fractures below the hip. VTE risk ratios (RRs) were pooled by use of a fixed-effect model or a random-effect model, depending on the heterogeneity among the included studies. Heterogeneity between the studies was assessed by I^2 statistics. Twenty-three studies with a total of 191 294 patients who met the inclusion criteria were included in this meta-analysis. Our results demonstrated that age (≥60 years) (RR = 1·85, 95% confidence interval (CI): 1·34, 2·55; $P = 0·000$), previous VTE(RR = 5·25, 95% CI: 2·77, 9·96; $P = 0·000$), heart failure (RR = 1·74, 95% CI: 1·34, 2·27; $P = 0·000$), current smoking status (RR = 1·23, 95% CI: 1·07, 1·41; $P = 0·004$), hypertension (RR = 1·62, 95% CI: 1·27, 2·06; $P = 0·000$), hyperlipidaemia (RR = 2·16, 95% CI: 1·79, 2·62; $P = 0·000$), diabetes mellitus (RR = 1·46, 95% CI: 1·27, 1·68; $P = 0·000$), obesity (RR = 1·58, 95% CI: 1·35,·1·85; $P = 0·000$), multiple fractures (RR = 2·14, 95% CI: 1·00, 4·60; $P = 0·050$), varicose veins (RR = 3·07, 95% CI: 1·12, 8·47; $P = 0·030$), prolonged operation time (weighted mean differences (WMD) = 1·22, 95% CI: 0·63, 1·81; $P = 0·000$) and prolonged bed rest time (WMD = 3·12, 95% CI: 2·96, 3·29; $P = 0·000$) were associated with an increased risk of developing VTE. The other variables, including age (<60 years), previous smoking, immobility, pregnancy, cancer, open fractures and combination with trauma were not identified as significant risk factors for VTE. Almost all the risk factors mentioned above are in line with the known risk factors for VTE following surgery for fractures below the hip. Thus, surgeons should pay close attention to patients with these medical conditions in order to reduce the incidence of VTE following surgical treatment of fractures below the hip.

Introduction

Venous thromboembolism (VTE), which encompasses asymptomatic and symptomatic deep vein thrombosis (DVT) and pulmonary thromboembolism (PE), is a potentially serious complication of operatively treated fractures in patients undergoing

Key Messages

- this meta-analysis evaluates the incidence of venous thromboembolism (VTE) and risk factors influencing the

development of VTE in patients who underwent surgery for fractures below the hip

- PubMed, Embase, Web of Science, SinoMed and CNKI databases were systematically searched to identify cohort or case–control studies that investigated the incidence and risk factors for VTE following surgical treatment of fractures below the hip
- our results demonstrated that age (≥60 years), previous VTE, heart failure, current smoking, hypertension, hyperlipidaemia, diabetes mellitus, obesity, multiple fractures, varicose veins, prolonged operation time and prolonged bed rest time were associated an increased risk of developing VTE
- the other variables, including age (<60 years), previous smoking, immobility, pregnancy, cancer, open fractures and combination with trauma were not identified as significant risk factors for VTE
- surgeons should pay close attention to patients with these medical conditions in order to reduce the incidence of VTE following surgical treatment of fractures below the hip

major orthopaedic surgery (1). It has been reported that the incidence of VTE in these patients ranges from 8% to 70% for DVT and 1% to 10% for PE (2–4). Moreover, compared with patients without VTE, VTE patients incur ten times the health care costs and more than twice the length of hospital stay (5). The American College of Chest Physicians (ACCP) guidelines recommend that efficient strategies should be implemented in medical and surgical patients to identify the risk factors for VTE and then prevent the occurrence of VTE-related morbidity and mortality (6).

It is a crucial and challenging task to identify risk factors for VTE because there are a large number of potential VTE risk factors that are worthy of attention. Several researches focusing on patient demographic factors, such as increased body mass index and previous history of VTE, have found consistent association between these factors and increased VTE (7–9). However, for other risk factors, including cancer, age and sex, there are controversial results among researches (10–12). These might be attributed to the several design issues including small sample size (7,9), selected patient populations (7), patients recruited from a single institution (10) and insufficient control of confounding factors. Identifying risk factors for VTE is very important for clinical workers to apply efficient strategies to prevent the occurrence of VTE, improve survival and decrease health care costs.

To extend the knowledge of VTE risk, we conducted a meta-analysis based on eligible studies to identify the risk factors for VTE in patients who underwent surgery for fractures below the hip. Based on these identified risk factors, we could provide more information and improved guidance for clinical workers to manage this subgroup of patients and reduce the morbidity, mortality and health care costs.

Materials and methods

Search strategy and review strategy

Two researchers independently conducted a comprehensive literature review. Multiple databases, including PubMed, Embase, Web of Science, SinoMed (Chinese BioMedical Literature Service System, China) and CNKI (National Knowledge Infrastructure, China), were searched for data from 6 May 2015 to 15 July 2015. The structured search strategies used were listed as follows: ('fractures, bone' [MeSH Terms]) OR ('fractures' [All Fields] AND 'bone' [All Fields]) OR ('bone fractures' [All Fields]) OR ('bone' [All Fields] AND 'fracture' [All Fields]) OR ('bone fracture' [All Fields] AND 'veins' [MeSH Terms]) OR ('veins' [All Fields]) OR ('venous' [All Fields] AND 'thrombosis' [MeSH Terms]) OR ('thrombosis' [All Fields]) OR ('thrombus' [All Fields] AND 'risk factors' [MeSH Terms]) OR ('risk' [All Fields] AND 'factors' [All Fields]) OR ('risk factors' [All Fields]). The search was limited to human subjects and no language restriction was imposed. Moreover, we also manually searched the reference lists of the included studies and reviews to identify potential eligible studies until no additional articles could be found.

Endnote (version X, Thomson Reuters, Inc., Philadelphia, PA) bibliographic software was used to establish an electronic library of citations identified in the database searches. Two reviewers independently performed the title/abstract screening and then the full-text screening. Disagreements between the two reviewers were resolved by consulting with a third reviewer.

Study inclusion and exclusion criteria

All studies investigating the incidence and risk factors for VTE in a series of patients with fractures below the hip were considered eligible for analysis. To be included, publications had to meet the following inclusion criteria: (i) the study population was composed of adult patients who underwent an operative procedure for a fracture below the hip; (ii) the study was performed with a case–control or cohort design and (iii) results reported data on the incidence and risk factors for VTE. Reports were excluded from the final analysis if the participants were younger than 18 years or underwent non-operative treatment. Reviews, editorials, comments and letters were excluded from this analysis.

Data extraction and quality assessment

We estimated a data extraction sheet based on the Cochrane Consumers and Communication Review Group data extraction template. Two independent investigators extracted the following information: author, age, patients in each group, sex, number of DVT/PE, sociodemographic risk factors for VTE after the surgical treatment of fractures and study design. For the studies without directly available data in the paper, we contacted the corresponding author for this information.

The modified Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality of the studies included in this meta-analysis (13). The scale consists of three items: patient selection, comparability of intervention/control group and outcome assessment (13). The total score of NOS is 9

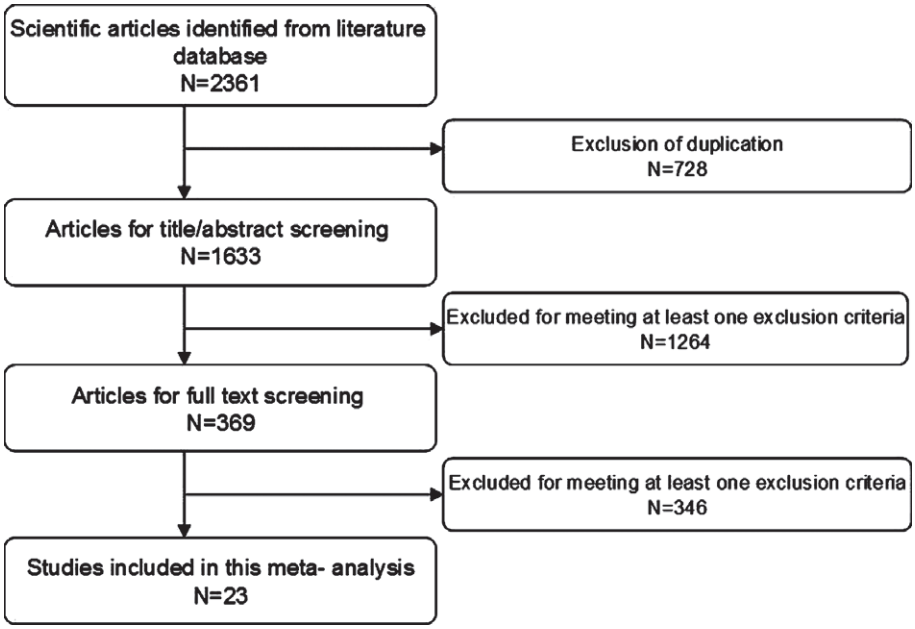

Figure 1 Eligibility of studies for inclusion in meta-analysis.

points, and articles with a total score of more than 5 points are considered as high quality (13).

Statistical analysis

We investigated the incidence and risk factors for VTE following surgical treatment of fractures based on the data from the studies included in this meta-analysis. For dichotomous variables (i.e., incidence and risk factors for VTE), the number of case events and control number of patients were extracted from the included studies. Afterwards, the risk ratio (RR) with 95% confidence intervals (95% CIs) was calculated. For continuous outcomes (i.e., duration of operation and bed rest), the number of total patients, mean time and standard error were extracted, and they were expressed as weighted mean differences (WMD) with 95% CIs.

Pooled estimates of RR or WMD were calculated using a fixed-effects model (Mantel-Haenszel method) (14).When substantial heterogeneity existed, a random-effects model (DerSimonian-Laird method) (15) was used to pool the data.

I^2 statistics, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance, was used to test for heterogeneity. Studies with an I^2 value of <25%, ~50%, ~75% and ~100% were considered to have no, low, moderate and high heterogeneity, respectively (16).

The presence of publication bias was evaluated using the Begg's and Egger's tests (17,18). A P value <0·05 was judged as statistically significant. All statistical analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX).

Results

Identification of eligible studies

The initial search yielded a total of 2361 articles. After screening title/abstract and full-text information, 728 were excluded because of duplicated publications, and 1610 were excluded because the data they provided was not available or unrelated to our topic. Finally, 23 articles that met the inclusion criteria were included in this meta-analysis (19–41). The flow chart of the search strategy is shown in Figure 1.

Characteristics of eligible studies

The 23 studies provided a total of 191 294 patients, 3459 of whom developed VTE after surgical treatment. Of the 23 studies, 15 were carried out in China, two in Denmark, one in USA, one in Korea and one in Turkey. The mean age at the time of surgery was 47·0 years (range 18–96 years), and 103 681(54·2%) patients were male. Of the 191 294 patients, 1046 (0·5%) were treated prior to the initiation of chemoprophylaxis. The modified NOS scale for these studies ranged from 7 to 8 (median scale 8), indicating high quality. The baseline characteristics of the included studies are presented in Table 1.

Incidence of VTE

All studies reported data on the incidence of VTE (19–41). The pooled estimates, using a random-effect model, indicated that the incidence of VTE in patients who underwent surgery for fractures below the hip was 21% (95%CI: 17%, 24%; $P = 0{\cdot}000$) (Figure 2).

Egger's test ($P = 0{\cdot}438$) and Begg's test ($P = 0{\cdot}553$) revealed publication bias.

Demographic factors of DVT

Age

Table 2 illustrates the aggregated RRs for the most important risk factors for VTE. Ten studies (20–23,25,32,37–40) examined age as a risk factor for VTE. Pooled estimates using a random-effects model ($P = 0{\cdot}000$) showed that patients younger

Table 1 Characteristics of included studies to assess risk factors for surgical site infection following spinal surgery

Study	Year	Country	Study design	Sample size	Case	control	Risk factors	NOS scale
Wahlsten *et al.* (19)	2015	Denmark	Cohort	57619	594	57025	Heart failure/previous DVT/previous PE/cancer/hypertension/diabetes/obesity/ current smoking	8
Akpinar *et al.* (20)	2013	Turkey	Case–control	1306	55	1251	Age/obesity/immobility/cancer/previous VTE/heart failure	8
Park *et al.* (21)	2015	Korea	Cohort	901	38	863	Age/lung disease/neurologic disease/cardiovascular disease/open fractures/isolated fractures/multiple fractures	7
SooHoo *et al.* (22)	2013	USA	Case–control	57183	29	57154	Age/lateral fractures/open fractures/diabetes	8
Pedersen *et al.* (23)	2010	Denmark	Case–control	67469	1390	66079	Age/diabetes/cancer/previous VTE/cardiovascular disease	8
Sen *et al.* (24)	2011	India	Case–control	56	24	32	Previous VTE/proximal thrombi/immobility	7
Riou *et al.* (25)	2007		Case–control	2761	178	2582	Age/previous VTE/diabetes/current smoking/severe injury/moderate injury/immobilisation	8
Xu and Xu (26)	2008	China	Case–control	136	24	112	Age/previous VTE/diabetes/cardiovascular disease	7
Mantilla *et al.* (27)	2003	USA	Case–control	232	116	116	Previous VTE/cardiovascular disease/diabetes/current smoking	7
Wang (28)	2013	China	Case–control	103	52	51	Diabetes/hypertension/hyperlipidaemia/isolated fractures/multiple fractures	7
Long (29)	2013	China	Case–control	145	73	72	Isolated fractures/multiple fractures/hypertension/hyperlipidaemia/diabetes	8
Li and Xu (30)	2013	China	Case–control	100	58	42	Hyerlipidaemia/hypertension/diabetes/current smoking	7
Guo (31)	2013	China	Case–control	180	98	82	Hyerlipidaemia/hypertension/diabetes/current smoking	8
Huang (32)	2014	China	Case–control	160	80	80	Hyerlipidaemia/hypertension/diabetes/isolated fractures/multiple fractures/age	8
Yao (33)	2012	China	Case–control	459	64	395	Hyerlipidaemia/hypertension/diabetes	8
Yang *et al.* (34)	2010	China	Case–control	515	58	457	Current smoking/obesity/	7
Wang *et al.* (35)	2015	China	Case–control	336	58	278	Age/hypertension/open fractures/multiple fractures	8
Hou *et al.* (36)	2014	China	Case–control	329	98	231	Hypertension/diabetes/failure disease/cancer/ pregnancy/hyperlipidaemia/varicose veins	8
Zhang *et al.* (37)	2012	China	Case–control	319	161	158	Age/previous VTE/cancer/pregnancy	7
Zhu *et al.* (38)	2012	China	Case–control	448	79	369	Age/current smoking/combination with trauma	8
Gu *et al.* (39)	2007	China	Case–control	102	18	84	Age/obesity/current smoking/alcohol consumption/varicose veins/diabetes	8
Li *et al.* (40)	2014	China	Case–control	287	37	250	Age/current smoking/combination with trauma	8
Yi (41)	2011	China	Case–control	148	77	71	Failure disease/diabetes/hypertension/ hyperlipidaemia/cancer	7

DVT, deep venous thrombosis; NOS, Newcastle–Ottawa Scale; PE, pulmonary embolism; VTE, venous thromboembolism.

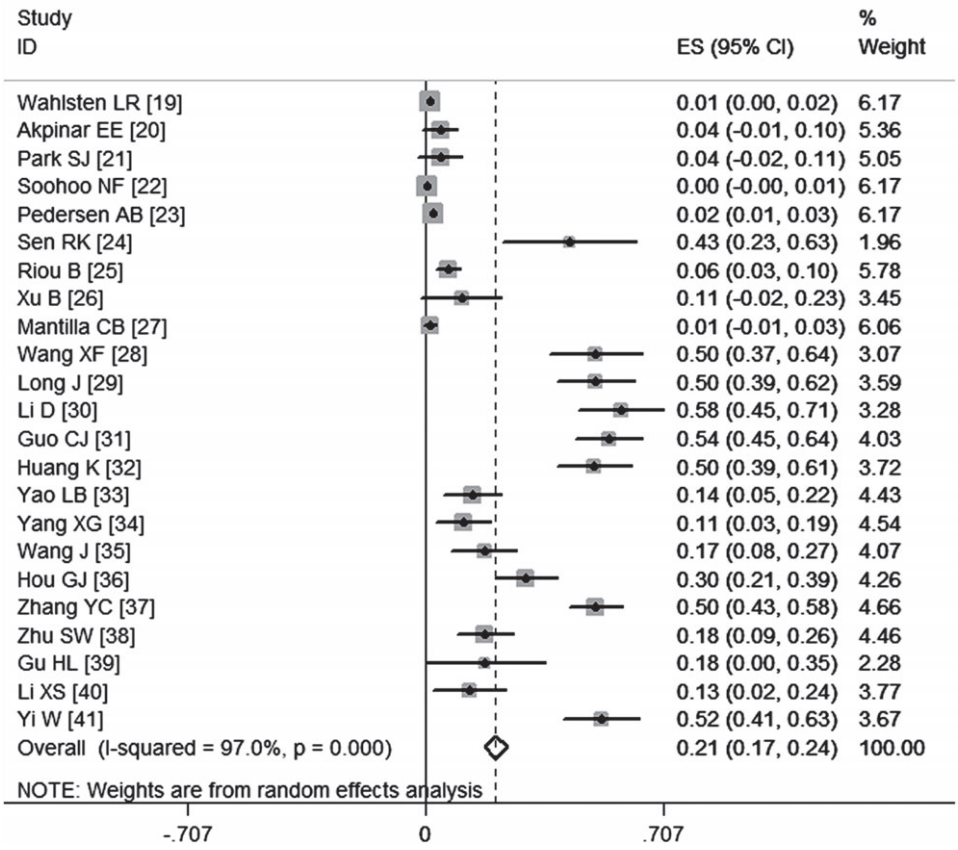

Figure 2 Meta-analysis of the incidence of venous thromboembolism.

than 60 years had a decreased risk of VTE (RR = 0·53, 95% CI: 0·40, 0·71; $P = 0·000$) (Figure 3), whereas patients older than 60 years of age had almost twice the higher risk of developing VTE (RR = 1·85, 95% CI: 1·34, 2·55; $P = 0·000$) (Figure 4). Egger's test ($P = 0·19$) and Begg's test ($P = 1·00$) revealed no publication bias.

Smoking

Nine studies (19,25,27,30,31,34,38–40) have assessed the association between smoking and VTE. Pooled results using a fixed-effects model ($P = 0·094$) suggest that patients who had a previous history of smoking were not at a significant risk of VTE (RR = 1·35, 95%CI: 0·99, 1·86; $P = 0·059$) (Figure 3), whereas patients who were currently smoking were at a significant risk of developing VTE (RR = 1·23, 95%CI: 1·07, 1·41; $P = 0·004$) (Figure 3).Egger's test ($P = 0·566$) and Begg's test ($P = 0·754$) revealed no publication bias.

Immobility

Four studies (20,25,38,40) have evaluated the association between immobility and the development of VTE. The aggregated results obtained using a random-effects model ($P = 0·000$) show that immobility was not a significant risk factor of VTE (RR = 1·38, 95%CI: 0·97, 1·95; $P = 0·069$) (Figure 5). As the number of included studies was less than five, the assessment of publication bias was not performed.

Table 2 Pooled estimates of risk ratios obtained from meta-analysis of risk factors for venous thromboembolism following surgical treatment of fracture below the hip

Risk factors	RR	95% Confidence interval (CI)	*P* value
Age (≥60 years)	1·85	1·34–2·55	0·000
Age (<60 years)	0·53	0·40–0·71	0·000
Previous smoking	1·35	0·99–1·86	0·059
Current smoking	1·23	1·07–1·41	0·004
Immobility	1·38	0·97–1·95	0·069
Pregnancy	1·09	0·42–2·80	0·864
Previous VTE	5·25	2·77–9·96	0·000
Heart failure	1·74	1·34–2·27	0·000
Hypertension	1·62	1·27–2·06	0·000
Hyperlipidaemia	2·16	1·79–2·62	0·000
Cancer	1·69	0·99–2·87	0·054
Diabetes mellitus	1·46	1·27–1·68	0·000
Obesity	1·58	1·35–1·85	0·000
Open fractures	0·97	0·74–1·27	0·0848
Isolated fractures	0·50	0·30–0·85	0·010
Multiple fractures	2·14	1·00–4·60	0·050
Varicose veins	3·07	1·12–8·47	0·030
Combination with trauma	1·22	1·05–1·41	0·628

Pregnancy

Two studies (36,37) report pregnancy as a risk factor for VTE. The aggregated results obtained using a fixed-effects

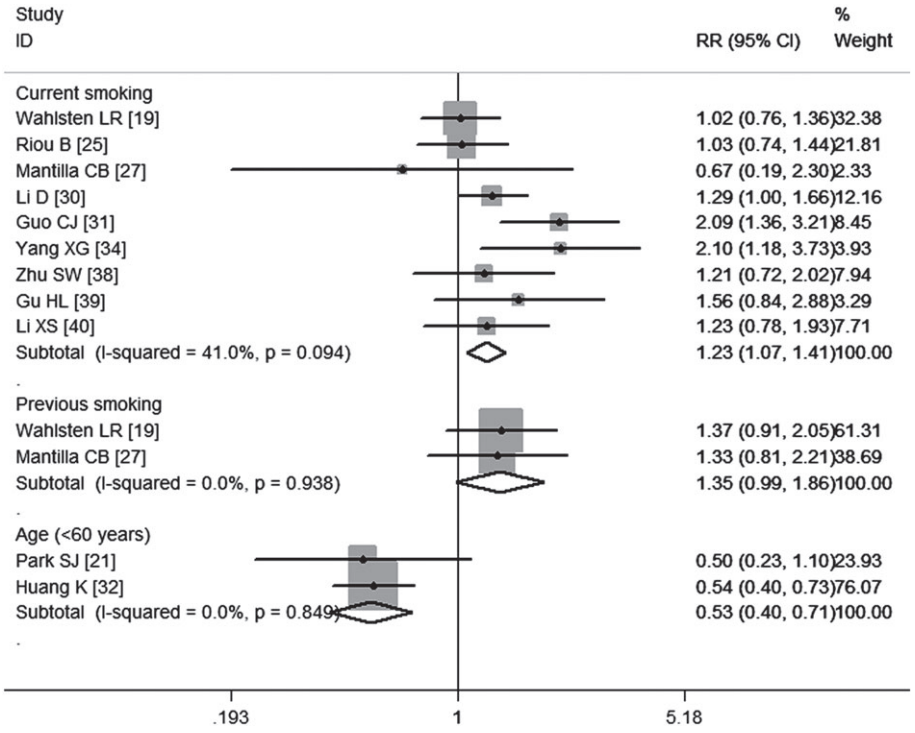

Figure 3 Meta-analysis of the association between current smoking, previous smoking, age (<60 years) and venous thromboembolism.

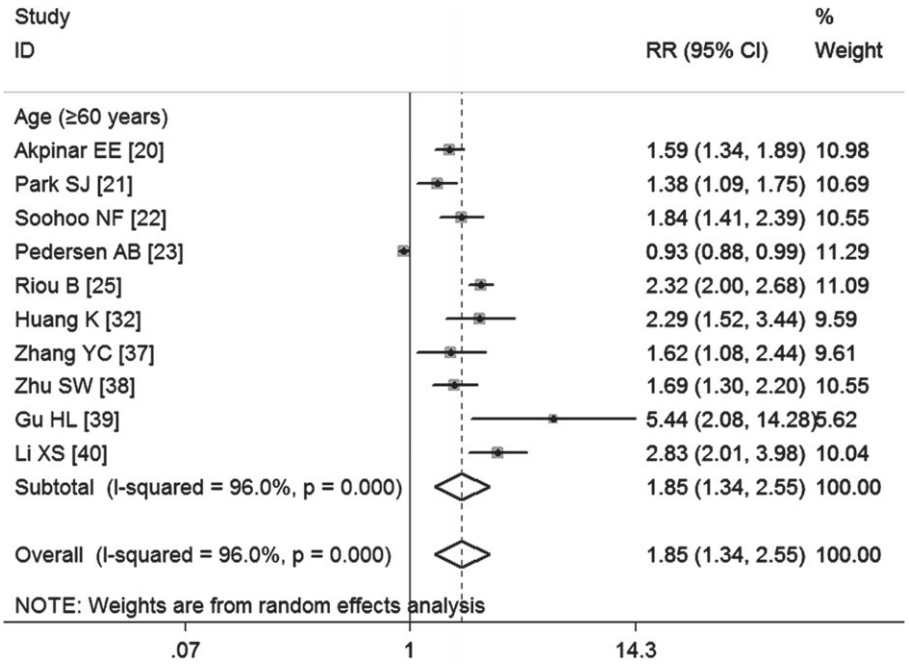

Figure 4 Meta-analysis of the association between age (≥60 years) and venous thromboembolism.

model ($P = 0{\cdot}832$) suggest that pregnancy was not a risk factor for VTE (RR = 1·09, 95% CI: 0·42, 2·80; $P = 0{\cdot}864$) (Figure 5).

Clinical factors of VTE

Previous VTE

Six studies (19,20,23,25,27,37) have evaluated the association between previous history of VTE and the postoperative VTE. The pooled estimates obtained using a random-effects model ($P = 0{\cdot}000$) demonstrate that a previous history of VTE was a high risk factor for the development of postoperative VTE (RR = 5·25, 95% CI: 2·77, 9·96; $P = 0{\cdot}000$) (Figure 6). Egger's test ($P = 0{\cdot}439$) and Begg's test ($P = 1{\cdot}000$) revealed no publication bias.

Heart failure

Seven studies (19–21,23,27,36,41) report heart failure as a risk factor for VTE. The aggregate results obtained using a random-effects model ($P = 0{\cdot}031$) show that patients with heart failure had almost twice the risk of developing postoperative

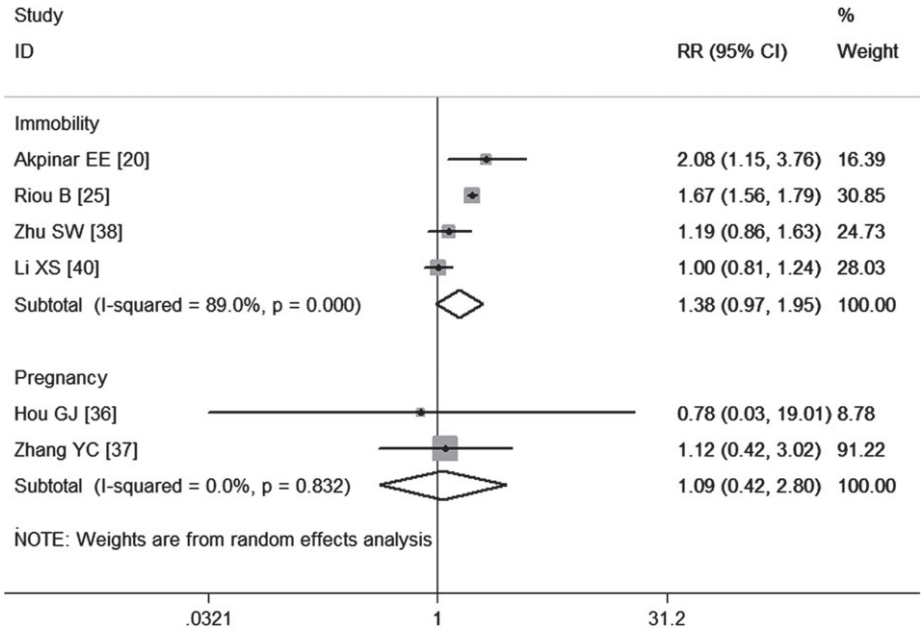

Figure 5 Meta-analysis of the association between immobility, pregnancy and venous thromboembolism.

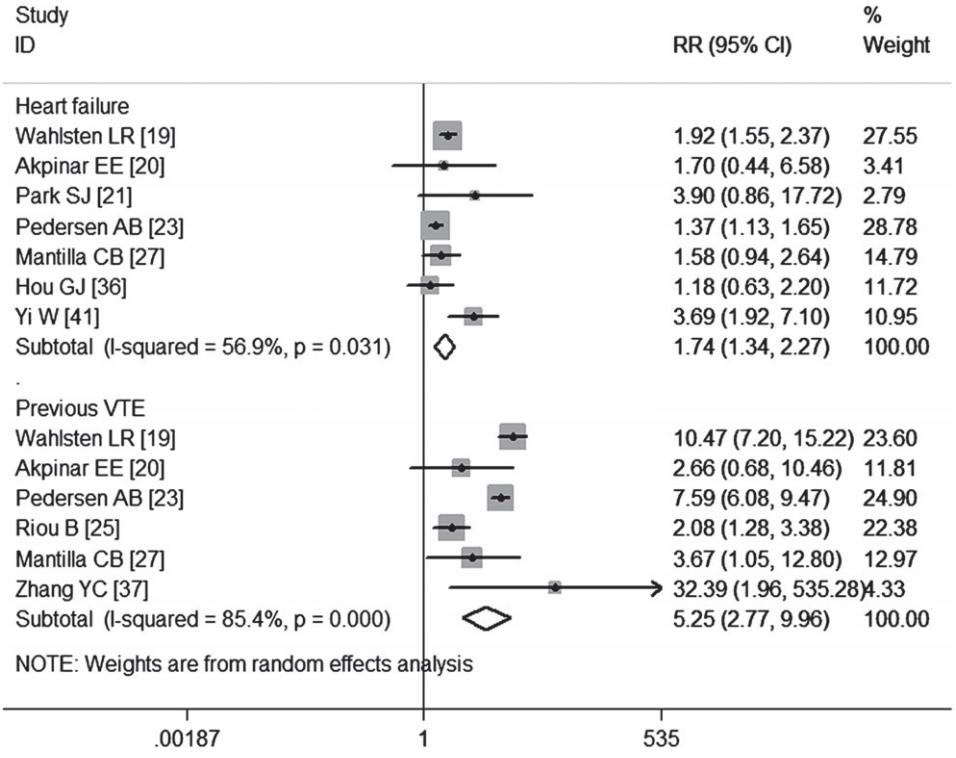

Figure 6 Meta-analysis of the association between heart failure, previous venous thromboembolism (VTE) and VTE.

VTE (RR = 1·74, 95% CI: 1·34, 2·27; $P = 0·000$) (Figure 6). Egger's test ($P = 0·406$) and Begg's test ($P = 0·368$) revealed no publication bias.

Hypertension

Nine studies (19,28–33,35,41) have evaluated the association between hypertension and VTE. The pooled estimates obtained using a fixed-effects model ($P = 0·024$) demonstrate that hypertension was significantly associated with a higher risk of developing VTE (RR = 1·62, 95% CI: 1·27, 2·06; $P = 0·000$) (Figure 7). Egger's test ($P = 0·353$) and Begg's test ($P = 0·348$) revealed no publication bias.

Cancer

Six studies (19,20,23,36,37,41) report cancer as a risk factor of VTE. The aggregate results obtained using a random-effects

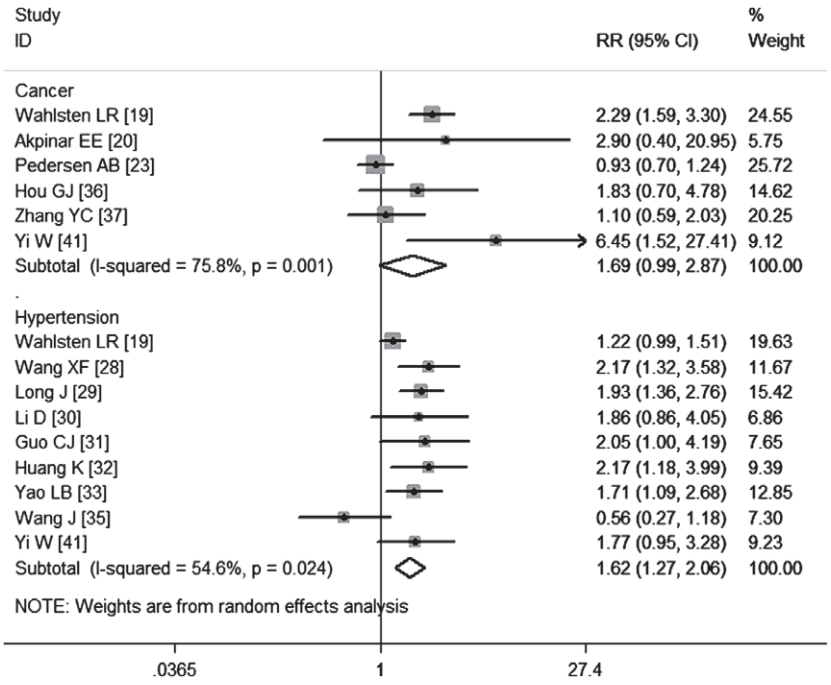

Figure 7 Meta-analysis of the association between cancer, hypertension and venous thromboembolism.

model ($P = 0{\cdot}001$) show that cancer was not a significant risk factor of VTE (RR = 1·69, 95%CI: 0·99, 2·87; $P = 0{\cdot}054$) (Figure 7). Egger's test ($P = 0{\cdot}311$) and Begg's test ($P = 0{\cdot}452$) revealed no publication bias.

Diabetes mellitus

Fourteen studies (19,22,23,25,27–33,36,39,41) have assessed the association between diabetes mellitus and VTE. Pooled results obtained using a fixed-effects model ($P = 0{\cdot}472$) suggest that diabetes mellitus increased the risk of developing VTE (RR = 1·46, 95%CI: 1·27, 1·68; $P = 0{\cdot}000$) (Figure 8). Egger's test ($P = 0{\cdot}171$) and Begg's test ($P = 0{\cdot}324$) revealed no publication bias.

Hyperlipidaemia

Eight studies (28–33,36,41) have assessed the association between hyperlipidaemia and VTE. Pooled results obtained using a fixed-effects model ($P = 0{\cdot}582$) suggest that hyperlipidaemia increased the risk of developing VTE (RR = 2·16, 95% CI: 1·79, 2·62; $P = 0{\cdot}000$) (Figure 9). Egger's test ($P = 0{\cdot}205$) and Begg's test ($P = 0{\cdot}108$) revealed no publication bias.

Obesity

Three studies (19,20,39) have assessed the association between obesity and VTE. Pooled results obtained using a fixed-effects model ($P = 0{\cdot}458$) suggest that obesity increased the risk of developing VTE (RR = 1·58, 95% CI: 1·35, 1·85; $P = 0{\cdot}000$) (Figure 9).

Open fractures

Three studies (21,22,35) report open fractures as a risk factor of VTE. The aggregate results obtained using a fixed-effects model ($P = 0{\cdot}817$) show that patients with open fractures were not at a significant risk of developing VTE (RR = 0·97, 95% CI: 0·74, 1·27; $P = 0{\cdot}0848$) (Figure 10).

Isolated fractures

Four studies (21,28,29,32) have assessed the association between isolated fractures and VTE. Pooled results obtained using a random-effects model ($P = 0{\cdot}000$) suggest that isolated fractures decreased the risk of developing VTE (RR = 0·50, 95%CI: 0·30, 0·85; $P = 0{\cdot}010$) (Figure 11).

Multiple fractures

Five studies (21,28,29,32,35) report multiple fractures as a risk factor of VTE. The aggregate results obtained using a random-effects model ($P = 0{\cdot}000$) show that patients with multiple fractures were at a higher risk of developing VTE (RR = 2·14, 95%CI: 1·00, 4·60; $P = 0{\cdot}050$) (Figure 11). Egger's test ($P = 0{\cdot}10$) and Begg's test ($P = 0{\cdot}462$) revealed no publication bias.

Varicose veins

Two studies (36,39) have assessed the association between varicose veins and VTE. Pooled results obtained using a fixed-effects model ($P = 0{\cdot}110$) suggest that varicose veins increased the risk of developing VTE (RR = 3·07, 95% CI: 1·12, 8·47; $P = 0{\cdot}030$) (Figure 10).

Combination with trauma

Two studies (38,40) report the combination with trauma as a risk factor of VTE. The aggregate results obtained using a random-effects model ($P = 0{\cdot}015$) show that patients who had combined with trauma were not at a significantly higher risk

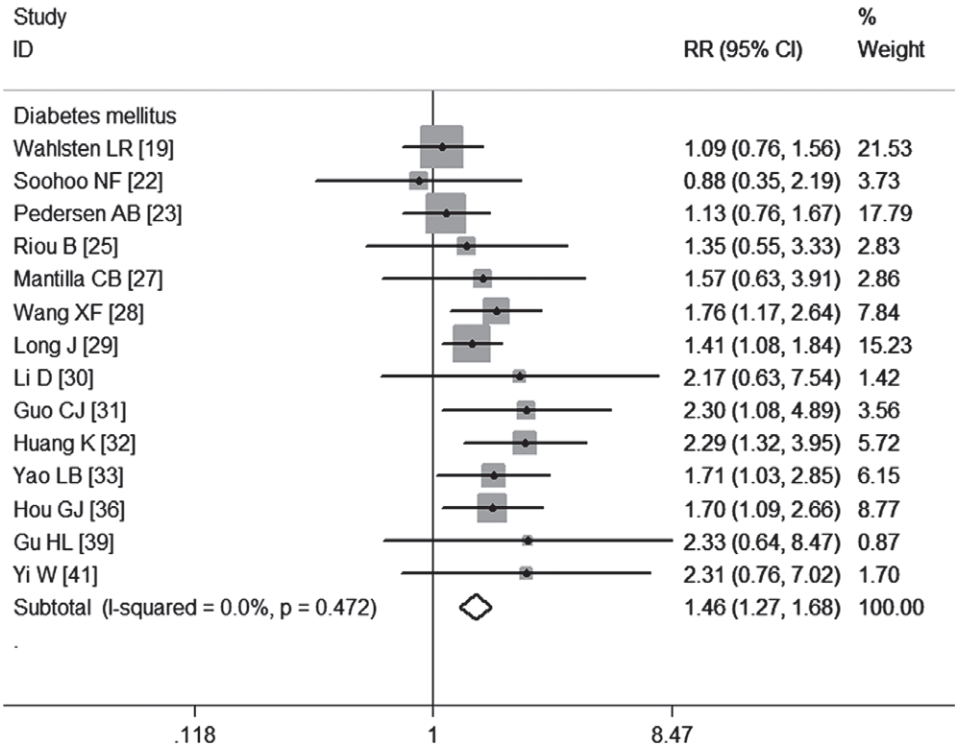

Figure 8 Meta-analysis of the association between diabetes mellitus and venous thromboembolism.

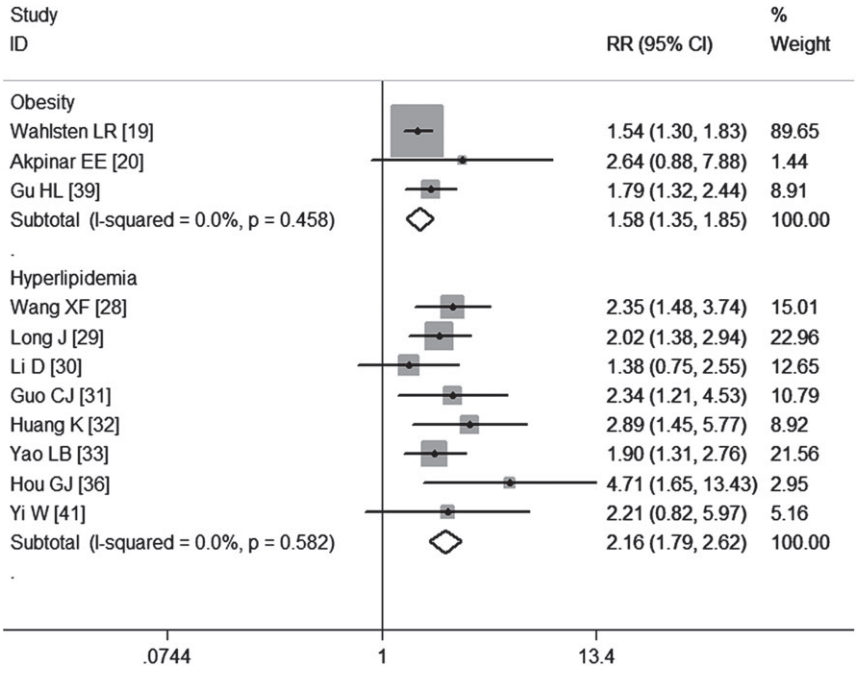

Figure 9 Meta-analysis of the association between obesity, hyperlipidaemia and venous thromboembolism.

of developing VTE (RR = 0·81, 95% CI: 0·35, 1·88; $P = 0·628$) (Figure 11).

Duration of operation and duration of bed rest

Four studies (30,31,33,36) report data on the duration of operation. Pooled estimates obtained using a random-effects model revealed that patients who had postoperative DVT had 1·22 hours of operative duration more than those who had no postoperative DVT (WMD = 1·22, 95%CI: 0·63, 1·81; $P = 0·000$) (Figure 12), which indicated that prolonged operation time increased the risk of developing VTE.

Three studies (30,31,33) provide data on the duration of bed rest. Pooled results obtained using a random-effects model suggest that patients who had postoperative DVT had 3·12 hours of bed rest more than those who had no postoperative DVT

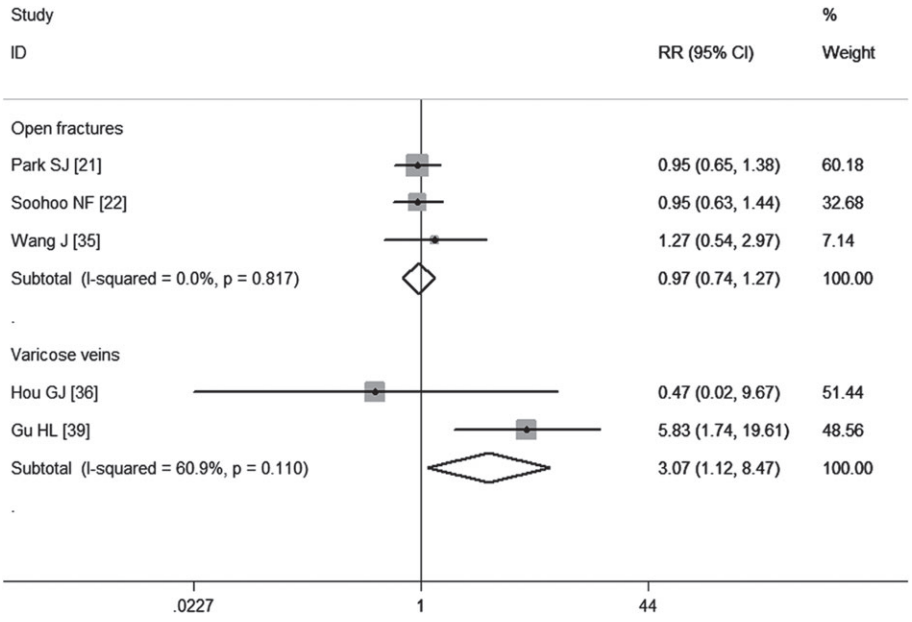

Figure 10 Meta-analysis of the association between open fractures, varicose veins and venous thromboembolism.

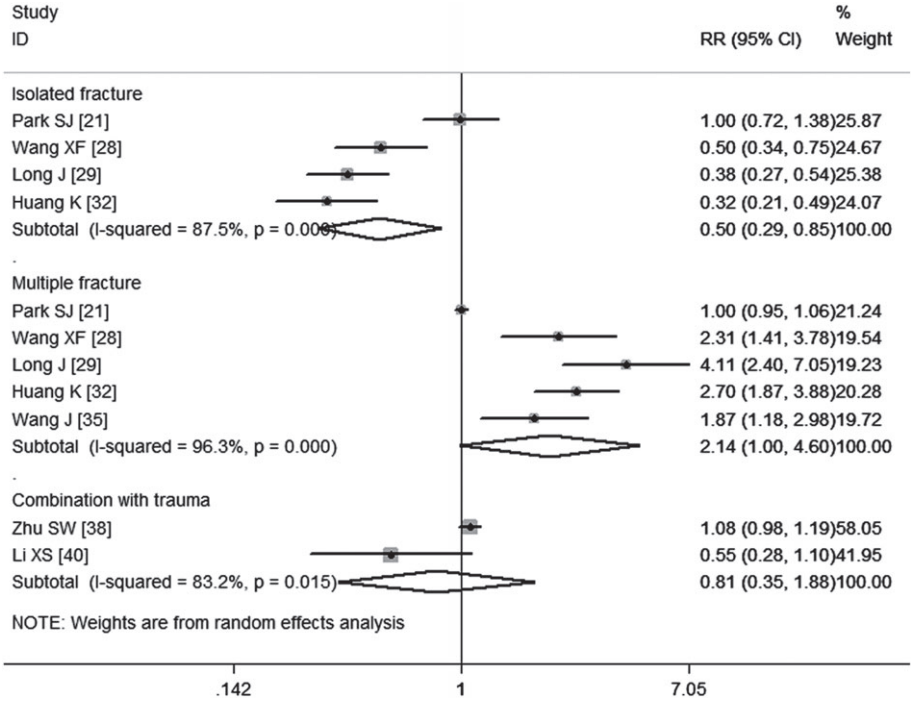

Figure 11 Meta-analysis of the association between isolated fracture, multiple fractures, combination with trauma and venous thromboembolism.

(WMD = 3·12, 95%CI: 2·96, 3·29; $P = 0·000$) (Figure 12), indicating that prolonged bed rest time increased the risk of developing VTE.

Discussion

In this meta-analysis, we identified independent risk factors for patients who develop VTE following surgical treatment of fractures below the hip. In our analysis of clinically significant postoperative VTEs, about 20 risk factors that might have a potential impact on the development of VTE have been identified. Using the meta-analysis method of aggregating the data, we were able to identify 12 independent risk factors that were associated with an increased risk of developing VTE. Previous history of VTE was the strongest independent risk factor followed by varicose veins, hyperlipidaemia, multiple fractures, age (≥60 years), heart failure, obesity, hypertension, diabetes mellitus, current smoking, prolonged operation time and prolonged bed rest time.

As is commonly acknowledged, previous VTE was confirmed as a risk factor in patients who underwent surgical treatment of fractures below the hip. This conclusion was also identified in this meta-analysis in which patients with previous history of VTE had five times higher risk of developing VTE (RR = 5·25, 95% CI: 2·77, 10·0; $P = 0·000$). However, among the studies included in this meta-analysis, Akpinar *et al.* (20)

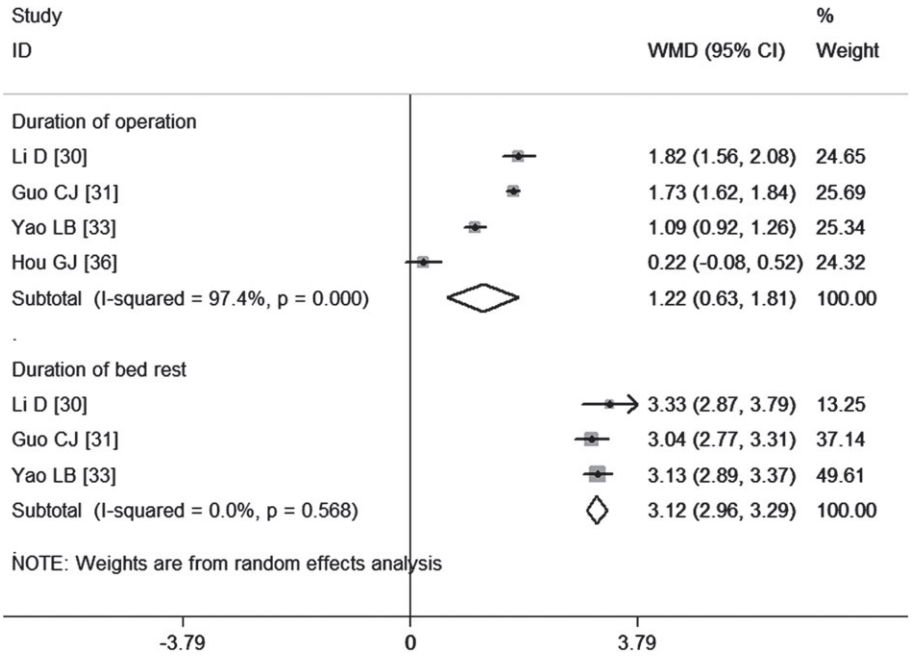

Figure 12 Meta-analysis of the association between duration of operation, duration of bed rest and venous thromboembolism.

found that previous VTE was not a risk factor of VTE, and the authors attributed this negative result to the inadequate medical records of patients with previous VTE.

Of the included studies, several have reported that patients with diabetes mellitus were at a significantly higher risk of developing postoperative VTE. Our result is consistent with that of these studies. However, some studies came to the reverse conclusion that diabetes mellitus was not a risk factor of VTE (19,22,23,25). In a meta-analysis conducted by Zhang *et al.* (42), the authors pooled 14 studies to identify the risk factors for VTE after total hip arthroplasty (THA) or total knee arthroplasty (TKA), and they found no correlation between diabetes mellitus and postoperative VTE (odd ratio (OR) = 1·02, 95%CI: 0·80·1.31; $P = 0·88$). However, these estimates were calculated based on five studies, while our result was based on 14 studies, and no heterogeneity was identified between them. Additionally, according to the previous research, diabetes mellitus is often associated with increased levels of procoagulant factors and the inhibition of endogenous fibrinolysis (43,44).

Varicose veins have been confirmed as a risk factor of VTE in our meta-analysis. However, this conclusion was calculated based on only two studies as others did not provide the available data for analysis. In a retrospective case–control study that was conducted by Gu *et al.* (39), 27·8% (5/18) of the patients in the VTE group had varicose veins compared to 4·8% (4/84) in the non-VTE group. This result suggests that varicose veins were significantly higher in the VTE group. However, in another study that investigated varicose veins as a risk factor of VTE (36), the prevalence of varicose veins in the two groups (1·0% versus 0·87%) appeared to be lower than that in Gu's study; there was no significant difference between them ($P = 0·492$).

Several studies have found that obesity (body mass index (BMI) ≥ 30) was a significant risk factor for VTE, which was also observed in this meta-analysis. However, it was not described as a significant risk factor of VTE in the study conducted by Akpinar *et al.* (20). In that study, obesity was not found to be an independent risk factor for VTE, but the authors did not give any explanation for this negative result. According to the previous studies, obesity was considered a higher risk factor for VTE because it could reduce antithrombin levels and fibrinolytic activity, and it was also associated with higher levels of prothrombotic factors, including fibrinogen, plasminogen activator inhibitor and factor (45,46). Additionally, obese patients have metabolic disturbances, are less active and more likely to be hospitalised with immobilisation, which might lead to the development of VTE (45–47).

Contrary to some reports (19,41), cancer was not identified as an independent risk factor for VTE in this meta-analysis (RR = 1·69, 95% CI: 0·99, 2·88; $P = 0·054$). Akpinar *et al.* (20) reported that 4·7% (28/594) of patients in the VTE group had cancer compared with 2·1% (1174/57 025) in the non-VTE group (hazard ratio = 1·65, 95% CI: 1·12, 2·42), indicating that cancer was a significant risk factor for VTE. Conversely, in another study conducted by Pedersen *et al.* (23), 3·9% (46/1185) of the patients who developed VTE had cancer compared with 1·1% (2768/66 284) in those without VTE (RR = 0·93, 95% CI: 0·68, 1·28), which suggested that cancer was not a significant risk factor for VTE. In a recently published meta-analysis, Zhang *et al.* (42) found that 'active' cancer was a marginally significant risk factor for the development of VTE after THA or TKA (OR = 1·28, 95% CI: 1·01, 1·62; $P = 0·04$). Considering the inconsistent results of these studies (20,23,42), more research is necessary before definite conclusions can be drawn.

Both heart failure and hypertension were found to be significantly associated with an increased risk of developing VTE in this meta-analysis. These might be explained by the blood's hypercoagulable state (48–50). Patients with heart failure were always less active, and they had haemostatic abnormalities that might predispose them to the occurrence of VTE (50).

One of the main limitations of this meta-analysis is the heterogeneity among the included studies, which might influence

the finally pooled estimates of all the meta-analyses. This could be explained by the following factors: the characteristics of patients, study design (cohort study or case–control study), the diagnostic criteria, the duration of follow-up, type of fracture and time of surgery. Because all of the included studies were of observational design, the study was performed based on hospital diagnoses. Therefore, patients with asymptomatic VTE were not registered even as an outcome, which would lead to an underestimated incidence of VTE. For some risk factors, the predictive variables may not have sufficient statistical power because of the limited number of included studies (<5). In some studies, chemoprophylaxis was administered to the patients, which confounded or strengthened the risk factors. However, a major strength of this study is the large number of patients and the high quality of the included studies, which greatly enhances the statistical power of pooled results.

In conclusion, we found that age (older than 60 years), current smoking, previous history of VTE, heart failure, hypertension, hyperlipidaemia, diabetes mellitus, obesity, multiple fractures, varicose veins, prolonged operation time and prolonged bed rest time are associated with an increased risk of developing VTE. By identifying these factors, patients with a relatively higher risk of developing VTE could be treated more intensively and, therefore, the incidence of VTE would be reduced.

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All the authors declare that they have no conflict of interest.

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