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ORIGINAL ARTICLE

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Risk factors for venous thromboembolism following surgical treatment of fractures: A systematic review and meta-analysis

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Abstract

This study aimed to determine the risk factors for postoperative venous thromboembolism (VTE) in patients treated surgically for fractures using a meta-analytic approach. Electronic searches were performed in PubMed, Embase, and the Cochrane library from inception until February 2022. The odds ratio (OR) and 95% confidence interval (CI) were applied to calculate the pooled effect estimate using the random-effects model. Sensitivity, subgroup, and publication bias tests were also performed. Forty-four studies involving 3 239 291 patients and reporting 11 768 VTE cases were selected for the meta-analysis. We found that elderly (OR: 1.72; 95% CI: 1.38-2.15; $P < .001$), American Society of Anesthesiologists (ASA) ≥ 3 (OR: 1.82; 95% CI: 1.46-2.29; $P < .001$), blood transfusion (OR: 1.82; 95% CI: 1.14-2.92; $P = .013$), cardiovascular disease (CVD) (OR: 1.40; 95% CI: 1.22-1.61; $P < .001$), elevated D-dimer (OR: 4.55; 95% CI: 2.08-9.98; $P < .001$), diabetes mellitus (DM) (OR: 1.36; 95% CI: 1.19-1.54; $P < .001$), hypertension (OR: 1.31; 95% CI: 1.09-1.56; $P = .003$), immobility (OR: 3.45; 95% CI: 2.23-5.32; $P < .001$), lung disease (LD) (OR: 2.40; 95% CI: 1.29-4.47; $P = .006$), obesity (OR: 1.52; 95% CI: 1.27-1.82; $P < .001$), peripheral artery disease (PAD) (OR: 2.13; 95% CI: 1.21-3.73; $P = .008$), prior thromboembolic event (PTE) (OR: 5.17; 95% CI: 3.14-8.50; $P < .001$), and steroid use (OR: 2.37; 95% CI: 1.73-3.24; $P < .001$) were associated with an increased risk of VTE. Additionally, regional anaesthesia (OR: 0.66; 95% CI: 0.45-0.96; $P = .029$) was associated with a reduced risk of VTE following surgical treatment of fractures. However, alcohol intake, cancer, current smoking, deep surgical site infection, fusion surgery, heart failure, hypercholesterolemia, liver and kidney disease, sex, open fracture, operative time, preoperative anticoagulant use, rheumatoid arthritis, and stroke were not associated with the risk of VTE. Post-surgical risk factors for VTE include elderly, ASA ≥ 3, blood transfusion, CVD, elevated D-dimer, DM, hypertension, immobility, LD, obesity, PAD, PTE, and steroid use.

KEYWORDS
fracture, meta-analysis, risk factors, surgical treatments, venous thromboembolism

Key Messages

- the analysis specifically included large number of studies, and the conclusions was robustness than any individual study
- comprehensive risk factors for venous thromboembolism for patients treated surgically for fractures were identified
- stratified analyses were performed according to fracture sites

1 | INTRODUCTION

Venous thromboembolism (VTE) includes deep venous thrombosis and pulmonary embolism as serious complications. The prevalence of VTE during and after hospitalisation can contribute towards the rate of perioperative mortality.[1,2] There are around 300 000 VTE-related deaths annually in the United States, and nearly two-thirds of symptomatic VTE cases were obtained in hospitals. The incidence of VTE after fracture surgery, in China, was reported to range from 15.7% to 58.2%.[3-5] A study reported that the rate of symptomatic VTE in a large number of low-impact community-acquired isolated fractures was 1.47%, while the rate in isolated upper extremity fractures, hip fractures, and pelvis fractures was 1.25%, 2.60%, and 0.70%, respectively.[6] Moreover, the prevalence of VTE in patients following major orthopaedic surgery is significantly higher among all surgical patients.[7] Considering the poor prognosis of VTE, the risk factors for VTE should be identified following the surgical treatment of fractures.

Several systematic reviews and meta-analyses have already been performed to identify risk factors for VTE following surgical treatment of fractures.[8,9] Tan et al[8] included 23 studies and found that age, prior VTE, heart failure (HF), current smoking, hypertension, hyperlipidemia, diabetes mellitus (DM), obesity, multiple fractures, varicose veins, longer operative time, and long bed rest time were risk factors of VTE following surgical treatment of fractures below the hip. Another study performed by Xin et al[9] included 21 studies and found that elderly, longer operative time, thoracolumbar surgery, greater blood loss, hypertension, preoperative walking disability, and DM were closely associated with the risk of VTE after spinal surgery. However, several new studies have recently been published; therefore, the risk factors for postoperative VTE following surgical treatment of fractures should be updated. Therefore, the current study aimed to identify risk factors for postoperative VTE following surgical treatment of fractures using a meta-analytical approach.

2 | METHODS

2.1 | Data sources, search strategy, and selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement was used to conduct and report this systematic review and meta-analysis.[10] Observational studies reporting risk factors for postoperative VTE following surgical treatment of fractures were eligible for inclusion in this study. The publication language was restricted to English. The electronic databases of PubMed, Embase, and the Cochrane library were systematically searched for eligible studies from inception until February 2022 using the following text word or Medical Subject Heading terms: "fractures, bone," "bone fractures," "thrombosis," "veins," and "risk factors." The reference lists of relevant original or review articles were manually searched to identify new eligible studies that met the inclusion criteria.

Two reviewers independently performed the literature search and study selection following a standardised approach, and any disagreement was resolved by mutual discussion. Details of the inclusion criteria are listed as follows: (a) Participants: patients with fractures that were treated with surgery; (b) Exposure: reported number of risk factors should be ≥3, including age, alcohol, American Society of Anesthesiologists (ASA) ≥ 3, blood transfusion, cancer, current smoking, cardiovascular disease (CVD), preoperative D-dimer, DM, deep surgical site infection (DSSI), fusion surgery, HF, hypercholesterolemia, hypertension, immobility, liver and kidney disease (LKD), lung disease (LD), sex, obesity, open fracture, operative time, peripheral artery disease (PAD), preoperative anticoagulant use (PAU), prior thromboembolic event (PTE), rheumatoid arthritis (RA), regional anaesthesia, stroke, and steroid use; (c) Outcomes: postoperative VTE cases, and the crude data or adjusted effect estimate were reported; and (d) Study design: no restriction were placed on the

study design, prospective and retrospective observational studies were also included.

2.2 | Data collection and quality assessment

The following data were independently abstracted: first author's name, publication year, country, study design, sample size, mean age, male proportion, number of VTE patients, fracture sites, and reported risk factors. The quality of included studies was assessed using the Newcastle-Ottawa Scale, which included eight items in selection (4 items: 4 stars), comparability (1 item: 2 stars), and outcome (3 items: 3 stars) domains.[11] A study with 7-9 stars was considered to be of high quality. Data abstraction and quality assessment were performed by two reviewers, and conflicts between reviewers were adjudicated by an additional reviewer referring to the full text of the original article.

2.3 | Statistical analysis

The effect estimates of the risk factors for postoperative VTE in each study were calculated as odds ratios (ORs) and 95% confidence intervals (CIs) before data pooling. The meta-analysis was then calculated using the random-effects model, which could consider the underlying heterogeneity across the included studies.[12] Heterogeneity, among studies, was assessed using I^2 and the Cochran Q statistic, and significant heterogeneity was defined as $I^2 > 50.0\%$ or $P < .10$.[13,14] Sensitivity analyses were conducted to assess the stability of the pooled conclusion by sequentially removing individual studies.[15] Subgroup analyses were performed according to fracture sites, and the difference between subgroups was calculated using the interaction P test.[16] Publication bias was assessed using both qualitative and quantitative methods, including funnel plots, Egger, and Begg tests.[17,18] The inspection level for a pooled conclusion was two-sided, and $P < .05$ was regarded as statistically significant. All analyses in this

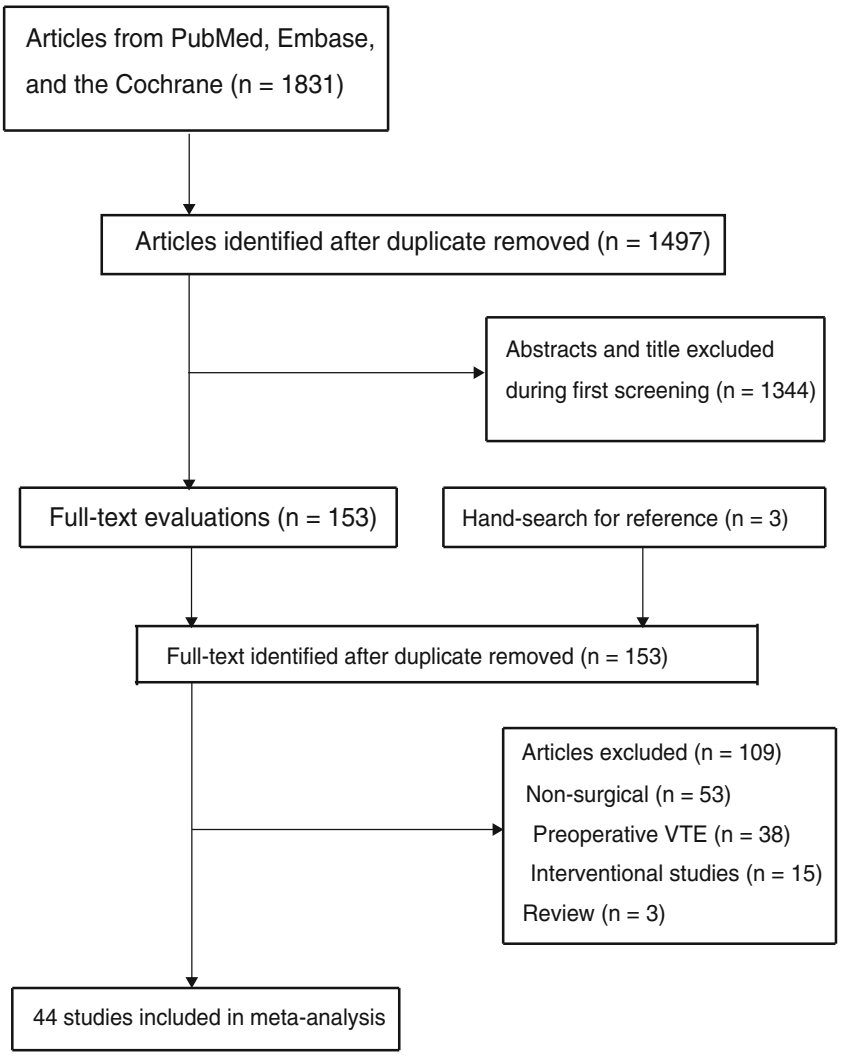

FIGURE 1 The details of literature search and study selection. VTE, venous thromboembolism

TABLE 1 The characteristics of identified studies and involved patients

Study	Country	Study design	Sample size	Mean age (years)	Male (%)	Number of VTE	Fracture sites	Reported factors	Study quality
Ferree 1993[19]	United States	Retro	185	NA	NA	4	Spinal	FS	8
Ferree 1994[20]	United States	Retro	60	44.2	56.7	3	Spinal	Sex	8
Mantilla 2003[21]	United States	Retro	232	69.2	45.0	116	Hip or knee	Sex, age, obesity, PAU, CVD, PTE, DM, smoking, ASA ≥ 3, RAn, BT	7
Browne 2007[22]	United States	Retro	197 461	49.0	45.5	338	Spinal	DM	6
Nicol 2009[23]	United States	Retro	1111	NA	NA	3	Spinal	FS	7
Pedersen 2010[24]	Denmark	Retro	67 469	NA	41.4	1390	Hip	Sex, age, CVD, PTE, DM, RA, LKD, cancer	8
SooHoo 2011[25]	United States	Retro	57 183	51.0	37.0	29	Ankle	Age, DM, PAD, OF	8
Akpinar 2013[26]	Turkey	Retro	1306	66.4	22.8	55	Major orthopaedic	Age, obesity, PTE, cancer, immobility, HF	8
Schoenfeld 2013[27]	United States	Retro	27 730	56.4	51.4	283	Spinal	Age, obesity, DM, ASA ≥ 3, FS	8
Arnold 2014[28]	United States	Pro	278	56.3	59.4	1	Cervical spondylotic myelopathy	DM	7
Golinvaux 2014[29]	United States	Retro	15 480	NA	44.0	209	Spinal	DM	7
Guzman 2014[30]	United States	Retro	2 563 159	NA	47.3	5835	Spinal	DM	8
Wahlsten 2015[31]	Denmark	Retro	57 619	49.2	51.4	594	Knee	Sex, obesity, CVD, PTE, DM, smoking, cancer, PAD, HF, stroke, hypertension, alcohol	8
Tominaga 2015[32]	Japan	Retro	80	75.0	11.3	20	Spinal	Sex, PAU, DM, smoking, immobility, hypertension	7
Park 2015[33]	Korea	Retro	901	57.0	53.7	38	Below the hip	Age, CVD, stroke, LD	7
Wang 2015[34]	United States	Retro	1346	NA	48.6	15	Spinal	Sex, age, FS, obesity, PAU, CVD, PTE, DM, smoking, BT, PAD, HF, hypertension, LD, SU, DSSI, hypercholesterolemia, OT	8
Yang 2015[35]	China	Retro	861	54.0	47.6	147	Spinal	CVD, DM, FS, hypertension, hypercholesterolemia, D-dimer	8
Basques 2015[36]	United States	Retro	4412	50.9	40.4	33	Ankle	Sex, age, obesity, CVD, DM, smoking, ASA ≥ 3, RAn, hypertension, LD, SU	8

TABLE 1 (Continued)

Study	Country	Study design	Sample size	Mean age (years)	Male (%)	Number of VTE	Fracture sites	Reported factors	Study quality
Yoshioka 2015[37]	Japan	Retro	459	61.0	56.9	36	Spinal	Sex, immobility	7
Hohl 2015[38]	United States	Retro	5766	60.3	57.0	89	Spinal	Age, FS	6
Nourian 2016[39]	Canada	Retro	204	58.0	57.4	11	Spinal	Sex, obesity	8
Sebastian 2016[40]	United States	Retro	43 777	57.1	51.4	513	Thoracolumbar	Age, obesity, DM, BT, cancer, immobility, hypertension, SU	8
Wei 2016[41]	China	Retro	2861	61.3	52.8	269	Spinal	Sex, CVD, DM, RA, hypertension, D-dimer	7
Ikeda 2017[42]	Japan	Retro	194	65.7	53.6	57	Spinal	Sex, D-dimer	8
Yamasaki 2017[43]	Japan	Retro	588	70.1	38.1	75	Spinal	CVD, FS, D-dimer	7
Inoue 2018[44]	Japan	Retro	100	68.1	66.0	13	Spinal	Sex, PAU, CVD, PTE, DM, FS, hypertension	8
Cloney 2018[45]	United States	Retro	1269	58.9	50.8	130	Spinal	PTE, FS, OT	7
Su 2018[46]	China	Retro	312	NA	41.0	31	Intertrochanteric	Sex, age, obesity, DM, ASA ≥ 3, RAn, BT, hypertension, OT	8
Lung 2019[47]	United States	Retro	13 299	69.2	43.8	83	Shoulder	Sex, obesity, DM, smoking, ASA ≥ 3, LD	8
Wang 2019[48]	China	Pro	110	44.1	69.1	32	Pelvic and acetabular	Sex, age, obesity, CVD, DM, BT, hypertension, OT, D-dimer	6
Huntley 2019[49]	United States	Retro	23 212	52.7	48.7	142	Foot and ankle	Sex, age, obesity, DM, smoking, ASA ≥ 3, RAn, OF, stroke, LD, DSSI	7
Li 2020[50]	China	Pro	987	45.2	61.1	46	Tibial plateau	Sex, age, obesity, CVD, DM, smoking, ASA ≥ 3, RAn, BT, LKD, OF, stroke, hypertension, alcohol, hypercholesterolemia, D-dimer	8
Cheng 2020[51]	China	Retro	63	46.3	52.4	30	Lower limb	Sex, age, obesity, DM, BT, DSSI, D-dimer	8
Zixuan 2020[52]	China	Retro	1451	43.7	56.9	38	Ankle	Sex, age, obesity, CVD, DM, smoking, ASA ≥ 3, RAn, BT, OF, hypertension, alcohol, hypercholesterolemia, D-dimer	7
Fu 2020[53]	China	Retro	228	71.3	34.2	73	Femoral neck	Sex, CVD, DM, ASA ≥ 3, stroke, hypertension	7

(Continues)

TABLE 1 (Continued)

Study	Country	Study design	Sample size	Mean age (years)	Male (%)	Number of VTE	Fracture sites	Reported factors	Study quality
Stavem 2020[54]	Norway	Retro	300	50.9	49.0	60	Ankle	Sex, age, PAU, PTE, DM, smoking, ASA ≥ 3, cancer, SU	8
Zhao 2021[55]	China	Pro	1672	NA	42.3	123	Intertrochanteric	Sex, age, obesity, CVD, DM, ASA ≥ 3, RA, LKD, cancer, stroke, hypertension, LD, DSSI	7
Ren 2021[56]	China	Retro	308	44.5	68.5	48	Femoral shaft	Sex, age, obesity, DM, smoking, ASA ≥ 3, RAn, BT, LKD, hypertension, alcohol, LD, D-dimer	6
Calotta 2021[57]	United States	Retro	134 938	50.7	42.1	79	Distal radius	Obesity, HF, stroke	7
Ma 2021[58]	China	Retro	2432	49.8	65.7	108	Spinal	Sex, obesity, CVD, DM, smoking, ASA ≥ 3, LKD, hypertension, alcohol, hypercholesterolemia, D-dimer	8
Tan 2021[59]	China	Retro	716	51.3	59.4	29	Isolated patella	Sex, age, obesity, CVD, DM, smoking, ASA ≥ 3, RAn, stroke, hypertension, alcohol, LD, hypercholesterolemia, D-dimer	6
Qu 2021[60]	China	Retro	1454	62.1	45.5	295	Lower extremity	Sex, CVD, DM, ASA ≥ 3, stroke, hypertension	7
Wang 2021[61]	China	Retro	534	45.9	70.1	101	Thoracolumbar	Sex, CVD, DM, BT, hypertension, D-dimer	7
Beauchamp-Chalifour 2022[62]	Canada	Retro	5184	83.0	24.0	144	Hip	Sex, PAU, CVD, PTE, DM, smoking, RAn, LKD, cancer, PAD, HF, stroke, hypertension, LD, hypercholesterolemia	7

Abbreviations: ASA, American Society of Anesthesiologists; BT, blood transfusion; CVD, cardiovascular disease; DM, diabetes mellitus; DSSI, deep surgical site infection; FS, fusion surgery; HF, heart failure; LD, lung disease; LKD, liver and kidney disease; OF, open fractures; OT, operative time; PAD, peripheral artery disease; PAU, preoperative anticoagulant use; PTE, prior thromboembolic event; RA, rheumatoid arthritis; RAn, regional anaesthesia; SU, steroid use; VTE, venous thromboembolism.

study were conducted using STATA (version 10.0; Stata Corporation, College Station, Texas).

3 | RESULTS

3.1 | Literature search

A total of 1831 articles were identified from electronic searches, and 153 studies were retrieved after irrelevant and duplicate topics were excluded. After full-text evaluations, 109 studies were excluded due to the following: contained non-surgical patients (n = 53), reported preoperative VTE (n = 38), interventional studies (n = 15), and reviews (n = 3). The remaining 44 studies were selected for the final analysis.[19-62] Details of study-selection process are presented in Figure 1. No new eligible studies were found by a manual search of the reference lists of the relevant reviews or original articles.

3.2 | Study characteristics

The baseline characteristics of the included studies and involved participants are shown in Table 1. Of the 44 included studies, a total of 3 239 291 patients and 11 768 VTE cases were included. Four studies were prospective in design, while 40 studies were retrospective. Twenty-one studies included patients with fractures above the hip, while the remaining 23 studies included patients with fractures occurring below the hip. Overall, 39 studies were of high quality, while the remaining five studies were of moderate quality.

3.3 | Meta-analysis

The pooled results of the risk factors for postoperative VTE following surgical treatment of fractures are shown in Figure 2 and Supplementary file 1. The risk factors for postoperative VTE following surgical treatment of

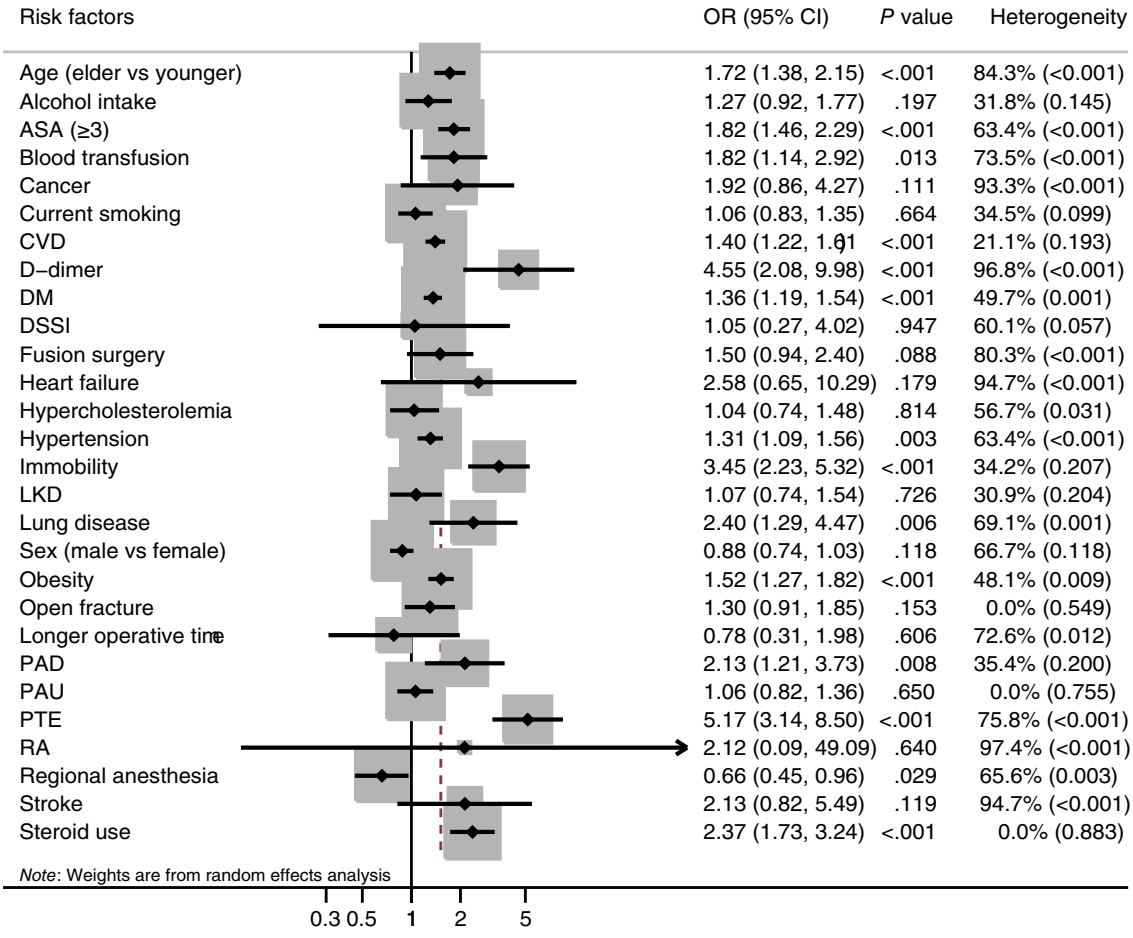

FIGURE 2 The summary risk factors for venous thromboembolism following surgical treatment of fractures. ASA, American Society of Anesthesiologists; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; DSSI, deep surgical site infection; LKD, liver and kidney disease; OR, odds ratio; PAD, peripheral artery disease; PAU, preoperative anticoagulant use; PTE, prior thromboembolic event; RA, rheumatoid arthritis

TABLE 2 Risk factors for venous thromboembolism stratified by fracture sites

Risk factors	Subgroup	Number of studies	OR and 95% CI	*P* value	I^2 (%)	*P* for *Q* test	Interaction test
Age	Below the hip	17	1.68 (1.33-2.12)	<.001	83.7	<.001	0.005
	Upper the hip	3	1.82 (0.80-4.14)	.157	86.2	.001	
Alcohol	Below the hip	5	1.34 (1.00-1.80)	.051	19.2	.292	0.123
	Upper the hip	1	0.60 (0.24-1.49)	.271	—	—	
American Society of Anesthesiologists ≥ 3	Below the hip	13	1.59 (1.33-1.91)	<.001	22.7	.214	<0.001
	Upper the hip	3	2.68 (1.83-3.94)	<.001	56.3	.102	
Blood transfusion	Below the hip	9	1.82 (1.09-3.03)	.022	76.5	<.001	0.965
	Upper the hip	1	1.85 (0.64-5.36)	.257	—	—	
Cancer	Below the hip	7	1.92 (0.86-4.27)	.111	93.3	<.001	—
	Upper the hip	0	—	—	—	—	
Current smoking	Below the hip	10	0.98 (0.75-1.27)	.856	32.7	.147	0.061
	Upper the hip	4	1.50 (0.98-2.29)	.059	0.0	.398	
Cardiovascular disease	Below the hip	14	1.52 (1.32-1.75)	<.001	10.8	.335	0.005
	Upper the hip	6	1.04 (0.84-1.30)	.700	0.0	.912	
D-dimer	Below the hip	7	3.28 (1.65-6.50)	.001	86.2	<.001	<0.001
	Upper the hip	5	5.98 (1.71-20.89)	.005	97.2	<.001	
Diabetes mellitus	Below the hip	20	1.45 (1.16-1.82)	.001	58.3	.001	0.431
	Upper the hip	12	1.33 (1.16-1.53)	<.001	28.8	.163	
Deep surgical site infection	Below the hip	3	0.67 (0.28-1.61)	.367	0.0	.503	0.013
	Upper the hip	1	6.19 (1.35-28.42)	.019	—	—	
Fusion surgery	Below the hip	0	—	—	—	—	—
	Upper the hip	9	1.50 (0.94-2.40)	.088	80.3	<.001	
Heart failure	Below the hip	4	2.67 (0.58-12.41)	.209	96.0	<.001	0.505
	Upper the hip	1	2.10 (0.27-16.29)	.478	—	—	
Hypercholesterolemia	Below the hip	4	1.26 (0.69-2.30)	.447	59.5	.060	0.389
	Upper the hip	3	0.77 (0.38-1.55)	.461	64.9	.058	
Hypertension	Below the hip	14	1.37 (1.16-1.63)	<.001	45.9	.031	0.003
	Upper the hip	6	1.16 (0.74-1.83)	.513	74.0	.002	
Immobility	Below the hip	2	3.02 (1.61-5.67)	.001	71.8	.059	0.360
	Upper the hip	2	5.50 (2.08-14.52)	.001	0.0	.677	
Liver and kidney disease	Below the hip	5	0.99 (0.64-1.53)	.957	38.9	.162	0.408
	Upper the hip	1	1.53 (0.69-3.38)	.293	—	—	
Lung disease	Below the hip	7	2.77 (1.39-5.54)	.004	72.8	.001	0.146
	Upper the hip	2	1.20 (0.26-5.53)	.818	42.9	.186	
Sex (male vs female)	Below the hip	18	0.89 (0.76-1.03)	.115	51.3	.006	0.743
	Upper the hip	10	0.82 (0.48-1.41)	.481	80.5	<.001	
Obesity	Below the hip	15	1.52 (1.28-1.82)	<.001	40.0	.055	0.826
	Upper the hip	5	1.36 (0.70-2.67)	.368	69.8	.010	
Open fracture	Below the hip	4	1.30 (0.91-1.85)	.153	0.0	.549	—
	Upper the hip	0	—	—	—	—	
Operative time	Below the hip	2	1.26 (0.39-4.04)	.701	71.6	.061	0.014
	Upper the hip	2	0.44 (0.18-1.10)	.078	29.1	.235	

TABLE 2 (Continued)

Risk factors	Subgroup	Number of studies	OR and 95% CI	*P* value	I^2 (%)	*P* for *Q* test	Interaction test
Peripheral artery disease	Below the hip	3	2.25 (1.15-4.41)	.018	56.0	.103	0.756
	Upper the hip	1	1.45 (0.19-11.06)	.720	—	—	
Preoperative anticoagulant use	Below the hip	3	1.01 (0.77-1.31)	.963	0.0	.916	0.244
	Upper the hip	3	1.63 (0.76-3.51)	.212	0.0	.573	
Prior thromboembolic event	Below the hip	6	5.06 (2.86-8.98)	<.001	79.7	<.001	0.152
	Upper the hip	3	5.78 (1.45-22.97)	.013	68.7	.041	
Rheumatoid arthritis	Below the hip	2	0.48 (0.26-0.89)	.019	0.0	.788	<0.001
	Upper the hip	1	28.04 (14.21-55.32)	<.001	—	—	
Regional anaesthesia	Below the hip	9	0.66 (0.45-0.96)	.029	65.6	.003	—
	Upper the hip	0	—	—	—	—	
Stroke	Below the hip	10	2.13 (0.82-5.49)	.119	94.7	<.001	—
	Upper the hip	0	—	—	—	—	
Steroid use	Below the hip	3	2.43 (1.76-3.34)	<.001	0.0	.919	0.485
	Upper the hip	1	1.41 (0.32-6.26)	.651	—	—	

Abbreviations: CI, confidence interval; OR, odds ratio.

fractures included elderly (OR: 1.72; 95% CI: 1.38-2.15; $P < .001$), ASA ≥ 3 (OR: 1.82; 95% CI: 1.46-2.29; $P < .001$), blood transfusion (OR: 1.82; 95% CI: 1.14-2.92; $P = .013$), CVD (OR: 1.40; 95% CI: 1.22-1.61; $P < .001$), elevated D-dimer (OR: 4.55; 95% CI: 2.08-9.98; $P < .001$), DM (OR: 1.36; 95% CI: 1.19-1.54; $P < .001$), hypertension (OR: 1.31; 95% CI: 1.09-1.56; $P = .003$), immobility (OR: 3.45; 95% CI: 2.23-5.32; $P < .001$), LD (OR: 2.40; 95% CI: 1.29-4.47; $P = .006$), obesity (OR: 1.52; 95% CI: 1.27-1.82; $P < .001$), PAD (OR: 2.13; 95% CI: 1.21-3.73; $P = .008$), PTE (OR: 5.17; 95% CI: 3.14-8.50; $P < .001$), and steroid use (OR: 2.37; 95% CI: 1.73-3.24; $P < .001$). However, we noted that regional anaesthesia was associated with a reduced risk of VTE following surgical treatment of fractures (OR: 0.66; 95% CI: 0.45-0.96; $P = .029$). Moreover, alcohol intake (OR: 1.27; 95% CI: 0.92-1.77; $P = .197$), cancer (OR: 1.92; 95% CI: 0.86-4.27; $P = .111$), current smoking (OR: 1.06; 95% CI: 0.83-1.35; $P = .664$), DSSI (OR: 1.05; 95% CI: 0.27-4.02; $P = .947$), fusion surgery (OR: 1.50; 95% CI: 0.94-2.40; $P = .088$), HF (OR: 2.58; 95% CI: 0.65-10.29; $P = .179$), hypercholesterolemia (OR: 1.04; 95% CI: 0.74-1.48; $P = .814$), LKD (OR: 1.07; 95% CI: 0.74-1.54; $P = .726$), sex (OR: 0.88; 95% CI: 0.74-1.03; $P = .118$), open fracture (OR: 1.30; 95% CI: 0.91-1.85; $P = .153$), operative time (OR: 0.78; 95% CI: 0.31-1.98; $P = .606$), PAU (OR: 1.06; 95% CI: 0.82-1.36; $P = .650$), RA (OR: 2.12; 95% CI: 0.09-49.09; $P = .640$), and stroke (OR: 2.13; 95% CI: 0.82-5.49; $P = .119$) were not associated with the risk of VTE following surgical treatment of fractures.

There was potentially significant heterogeneity for age ($I^2 = 84.3\%$; $P < .001$), ASA ≥ 3 ($I^2 = 63.4\%$; $P < .001$), blood transfusion ($I^2 = 73.5\%$; $P < .001$), cancer ($I^2 = 93.3\%$; $P < .001$), current smoking ($I^2 = 34.5\%$; $P = .099$), D-dimer ($I^2 = 96.8\%$; $P < .001$), DM ($I^2 = 49.7\%$; $P = .001$), DSSI ($I^2 = 60.1\%$; $P = .057$), fusion surgery ($I^2 = 80.3\%$; $P < .001$), HF ($I^2 = 94.7\%$; $P < .001$), hypercholesterolemia ($I^2 = 56.7\%$; $P = .031$), hypertension ($I^2 = 63.4\%$; $P < .001$), LD ($I^2 = 69.1\%$; $P = .001$), obesity ($I^2 = 48.1\%$; $P = .009$), operative time ($I^2 = 72.6\%$; $P = .012$), PTE ($I^2 = 75.8\%$; $P < .001$), RA ($I^2 = 97.4\%$; $P < .001$), regional anaesthesia ($I^2 = 65.6\%$; $P = .003$), and stroke ($I^2 = 94.7\%$; $P < .001$).

3.4 | Sensitivity analysis

The results of sensitivity analysis for each risk factor of postoperative VTE following surgical treatment of fractures are shown in Supplementary file 2. We noted the pooled conclusions for age, alcohol, ASA ≥ 3, blood transfusion, cancer, current smoking, CVD, D-dimer, DM, DSSI, fusion surgery, HF, hypercholesterolemia, hypertension, immobility, LKD, LD, obesity, open fracture, PAU, PTE, RA, stroke, and steroid use were stable. However, sensitivity analyses found the pooled conclusions for sex, operative time, PAD, and regional anaesthesia were variable after sequentially removing single studies.

3.5 | Subgroup analysis

The results of the subgroup analysis for each risk factor of postoperative VTE following surgical treatment of fractures are shown in Table 2. We noted the fracture site could affect the postoperative VTE related to age ($P = .005$), ASA ≥ 3 ($P < .001$), CVD ($P = .005$), D-dimer ($P < .001$), DSSI ($P = .013$), hypertension ($P = .003$), operative time ($P = .014$), and RA ($P < .001$).

3.6 | Publication bias

Publication biases for each risk factor of postoperative VTE following surgical treatment of fractures are shown in Supplementary file 3. We noted potential significant publication biases for age (*P* value for Egger: .011; *P* value for Begg: .417), while no significant publication biases were observed for other risk factors.

4 | DISCUSSION

This systematic review and meta-analysis explored all potential risk factors for postoperative VTE following surgical treatment of fractures. A total of 3 239 291 patients and 11 768 VTE cases from 44 studies were included, with a broad range of study and patient characteristics. This study found the following risk factors for postoperative VTE following surgical treatment of fractures: elderly, ASA ≥ 3, blood transfusion, CVD, elevated D-dimer, DM, hypertension, immobility, LD, obesity, PAD, PTE, and steroid use. Moreover, for fractures that occurred below the hip and the risk factors for postoperative VTE included age, ASA ≥ 3, blood transfusion, CVD, D-dimer, DM, hypertension, immobility, LD, obesity, PAD, PTE, and steroid use. However, the risk factors for postoperative VTE for fractures occurring above the hip included ASA ≥3, D-dimer, DM, DSSI, immobility, PTE, and RA.

Although prior systematic reviews have already identified risk factors for VTE for patients with fractures that were treated with surgery,[8,9] two limitations of these prior studies should be addressed: (a) several included studies did not mention if patients received surgical treatment; and (b) the VTE cases occurred preoperatively and postoperatively across the included studies. These two limitations restricted the reliability of the reported risk factors for patients with VTE, highlighting potential bias. Therefore, the current study was performed to identify risk factors for postoperative VTE following surgical treatment of fractures. Moreover, subgroup analyses were also performed according to fracture sites.

As compared with a prior meta-analysis,[8] our study identified several new risk factors, including ASA ≥3, blood transfusion, CVD, D-dimer, LD, PAD, and steroid use for fractures that occurred below the hip. There are several explanations for these results: (a) an ASA score of 3 indicated severe systemic disturbance, and ASA ≥3 suggests very advanced disease status[63]; (b) increased blood viscosity could be induced by blood transfusion[64]; (c) patients with CVD have impaired endothelial function, which plays an important role in the risk of VTE[65]; (d) D-dimer could reflect disease severity, and indicate a hypercoagulable state in vascular endothelial damage, which is significantly related to the risk of VTE[66]; (e) hypercoagulability, inflammation, immobilisation, and pulmonary hypertension caused by LD could impair lung function and hypoxia, which could affect the risk of VTE[67]; (f) the characteristics of PAD are atherosclerotic occlusion of vessels in the lower limbs, which significantly increases the risk of major atherothrombotic vascular events[68]; and (g) the use of steroids is significantly related to disease status, and the risk of VTE is mainly attributed to the disease status.

Similarly, our study identified several new risk factors of postoperative VTE for fractures occurring above the hip, including ASA ≥3, D-dimer, DSSI, PTE, and RA. The potential reason for ASA and D-dimer have already been addressed above. An explanation for the role of DSSI, PTE, and RA can be explained as follows: (a) DSSI results in the release of cytokines and causes an inflammatory state, which results in an elevated risk of VTE[69]; (b) the incidence of recurrent VTE in patients with PTE was higher than the first occurrence of VTE; and (c) RA may activate inflammatory pathways, which may cause systemic effects, including impaired endothelial function, hypercoagulability, and stasis.[70]

Several shortcomings of this study should be highlighted. (a) The analysis contained both prospective and retrospective studies, and the results could be affected by selection and recall biases. (b) Most studies did not report the adjusted effect estimates, and the results could be affected by potential confounders. (c) Heterogeneity, for most risk factors, was substantial and was not fully explained by fracture sites. (d) The analysis was based on published articles; therefore, publication bias was inevitable. (e) The analysis used pooled data, and so a detailed analysis was restricted.

5 | CONCLUSIONS

This study reports the risk factors for postoperative VTE following surgical treatment of fractures, which included elderly, ASA ≥3, blood transfusion, CVD,

elevated D-dimer, DM, hypertension, immobility, LD, obesity, PAD, PTE, and steroid use. Moreover, fracture sites could affect the risk of postoperative VTE, which was related to age, ASA ≥3, CVD, D-dimer, DSSI, hypertension, operative time, and RA. A further prospective study should be performed to verify the results of this study and identify risk factors in patients with specific characteristics.

AUTHOR CONTRIBUTIONS

Qun Wang: Data curation; formal analysis; methodology; writing—original draft. **Zhen-Hua Xia**: Conceptualization; resources; investigation; writing—review and editing. **Wei-Hua Chen**: Conceptualization; resources; investigation; writing—review and editing. Zhen-Hua Xia and Wei-Hua Chen contributed equally, and all authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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