Review

Risk factors for venous thromboembolism in patients with spinal cord injury: A systematic review and meta-analysis

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Context: Patients with spinal cord injury (SCI) are at high risk for venous thromboembolism (VTE). The risk factors for VTE in patients with SCI are complex.
Objective: This meta-analysis was conducted to clarify the risk factors for VTE in patients with SCI.
Methods: The Cochrane Library, PubMed, EBSCO, Web of Science, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), Wanfang Med Data Database, and VIP Database were searched to identify studies reporting on risk factors for VTE in patients with SCI.
Results: The meta-analysis included 25 studies. Findings showed that risk of VTE in patients with SCI was significantly associated with middle- and old-age (OR = 2.08, 95%CI, 1.47, 2.95), male sex (OR = 1.41, 95%CI, 1.26, 1.59), complete paralysis (OR = 3.69, 95%CI, 2.60, 5.24), personal/family history of venous thrombosis (OR = 1.95, 95%CI, 1.35, 2.81), history of smoking (OR = 2.67, 95%CI, 1.79, 3.98), lack of compression therapy (OR = 2.44, 95%CI, 1.59, 3.73), presence of lower limb/pelvic fracture (OR = 3.47, 95%CI, 1.79, 6.75), paraplegia (OR = 1.81, 95%CI, 1.49, 2.19), and diabetes (OR = 4.24, 95%CI, 2.75, 6.52).
Conclusion: The meta-analysis identified 9 risk factors for VTE in patients with SCI. Healthcare providers should be aware of the risk factors for VTE when rehabilitating patients with SCI.

Keywords: Spinal cord injury, Venous thromboembolism, Risk factors, Meta-analysis

Introduction

Spinal cord injury (SCI) is associated with severe neurological and functional morbidity.[1] Patients with SCI experience chronic medical complications, including venous thromboembolism (VTE), which constitutes deep venous thrombosis (DVT) and pulmonary embolism (PE).[2–5] The incidence of DVT and PE in patients with SCI are estimated at 65% and 0%–18%, respectively, with most cases of VTE occurring within the 3 months following SCI.[2,6]

Patients with SCI are at high risk for VTE due to the presence of the three components of Virchow's triad: endothelial dysfunction, altered blood flow (stasis), and hypercoagulability.[7–9] Other factors that are associated with VTE include age, male sex, trauma, paraplegia, severity of injury, previous history of VTE, history of smoking, serum homocysteine (Hcy) level, serum D-dimer level, and factor V Leiden mutation.[3,5,10–13]

Understanding the risk factors for VTE in patients with SCI could lead to prevention; however, the evidence is controversial. One report showed that female sex is an independent risk factor for VTE in patients with SCI,[14] and another indicated that serum D-dimer level is elevated in many conditions and has limited utility for confirming VTE.[15] This meta-analysis was conducted to clarify the risk factors for VTE in patients with SCI. Findings should raise awareness of the risk factors for VTE in

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patients with SCI, and reduce the incidence of VTE in this patient population.

Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16]

Search strategy

Two authors (Bo Wei, Haiqiong Kang) independently searched the Cochrane Library, PubMed, EBSCO, Web of Science, and China National Knowledge Infrastructure (CNKI) databases, the China Biomedical Literature Database (CBM), the Wanfang Med Data Database and the VIP Database from inception to July 2020.

The search strategy for literature published in the English language included the following key words: 'Spinal Cord Injuries', 'Paraplegia', 'Quadriplegia', 'Venous Thromboembolism', 'Venous Thrombosis', 'Pulmonary Embolism' and 'Risk Factors' as the subject words, and 'Spinal Cord Trauma', 'Spinal Cord Injury', 'Paraplegias', 'Tetraplegia', 'Venous Thromboses', 'Deep Vein Thrombosis', 'Pulmonary Embolisms', 'relative risk', 'risks', 'cohort studies' as free words.

The search strategy for literature published in the Chinese language included the following key words: 'spinal cord injury', 'paraplegia', 'limb paralysis', 'venous thromboembolism', 'risk factors', 'case–control study', 'cohort study' as the subject words, and 'Paraplegia', 'spastic paraplegia', 'quadriplegia', 'limb spasm', 'venous thrombosis', 'deep venous thrombosis', 'pulmonary embolism', 'influencing factors', 'etiology', 'related factors' and 'case–control' as free words.

Inclusion and exclusion criteria

Inclusion criteria were: (1) case–control or cohort studies; (2) studies that included patients with confirmed diagnoses of SCI with or without (controls) VTE during the same period; and (3) studies that reported outcomes as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Exclusion criteria were: (1) duplicate studies; (2) studies published in languages other than English or Chinese; (3) studies that lacked a control group; (4) studies with incomplete data; or (5) literature reviews or meta-analyses.

Data extraction

One author examined titles and abstracts and reviewed relevant full text articles to select eligible studies. The author extracted data from the eligible studies including details describing the study population and outcomes.

Assessment of methodological quality

Two authors (Bo Wei, Yuan Yuan) independently assessed the quality of eligible studies using the Newcastle-Ottawa Scale (NOS).[17] The scale assessed quality of sample selection, comparability of cohorts, assessment of outcomes, adequacy of follow up, and drop-out rate. Studies with scores of 0–3, 4–6, and 7–9 were considered low, moderate, and high quality, respectively. Publication bias was explored using funnel plots.[18]

Statistical analysis

Statistical analyses were performed with Review Manager 5.3. A random-effects model was used to pool studies with significant heterogeneity, as determined by the Cochrane Q test ($P \leq 0.10$) and the inconsistency index ($I^2 \geq 50\%$), otherwise a fixed effect model was used. Sensitivity analysis was used to investigate sources of heterogeneity between studies.

Results

The searches identified 1,882 articles. Of these, 1,813 articles were excluded as they were duplicates, reviews, experiments in animals, or irrelevant. The full text of 69 articles was reviewed. Of these, 44 articles were excluded as they were duplicates, irrelevant, reported inappropriate statistical analyses, or were missing outcomes data. Finally, 25 articles were included in the meta-analysis (Fig. 1). The characteristics of the included studies are summarized in Table 1.

All articles were published between 2005 and 2020; 14 articles were published in the English language, and 11 articles were published in Chinese. Among the 25 studies, 23 were case–control studies and 2 were cohort studies. The studies involved a total of 2,865 cases of SCI with VTE and 39,488 controls. The methodological quality of the included studies was high (Table 2). There was no evidence of publication bias (for an example, please see Fig. 2).

Risk factors for VTE

Age

Age as a risk factor for VTE in patients with SCI was evaluated in 6 studies.[5,12,19–22] The meta-analysis demonstrated no association between the risk of VTE in patients with SCI and age (OR 1.03, 95% CI 0.99, 1.08; $P = 0.15$; Fig. 3A). There was evidence of

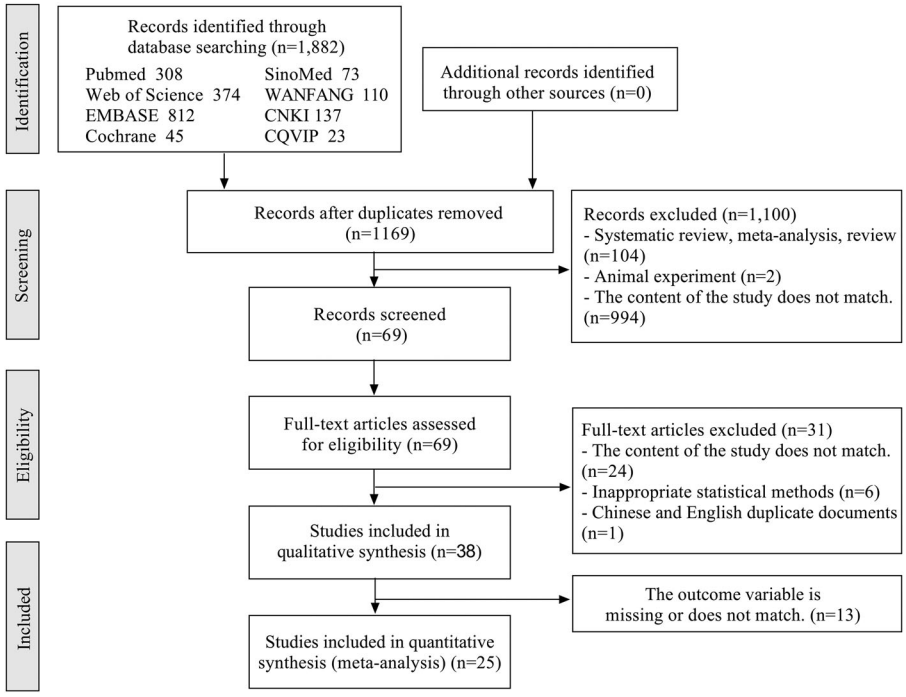

Figure 1 Flow chart of study selection.

significant heterogeneity between studies (I^2 = 80%, P = 0.0002). In a sensitivity analysis that omitted three studies that did not include age as a categorical variable,[5,12,19] the risk of VTE in patients with SCI was significantly associated with age >45 years (OR 2.08, 95% CI 1.47, 2.95; P < 0.0001; Fig. 3B),[20–22] and there was no evidence of heterogeneity between studies (I^2 = 48%, P = 0.14).

Male sex

Male sex as a risk factor for VTE in patients with SCI was evaluated in 5 studies.[5,21,23–25] The meta-analysis demonstrated that the risk of VTE in patients with SCI was significantly associated with male sex (OR = 1.41, 95% CI, 1.26-1.59; P < 0.00001; Fig. 4), and there was no evidence of heterogeneity between studies (I^2 = 11%, P = 0.34).

Complete paralysis

Complete paralysis as a risk factor for VTE in patients with SCI was evaluated in 6 studies.[20,22,24,26–28] The meta-analysis demonstrated that the risk of VTE in patients with SCI was significantly associated with complete paralysis (OR 3.02, 95% CI 1.79, 5.08; P < 0.0001; Fig. 5A). There was evidence of significant heterogeneity between studies (I^2 = 69%, P = 0.006). The source of heterogeneity was thought to arise from differing study populations. Four studies included subjects aged <45 years, and one study included subjects aged >45 years.[32] In a sensitivity analysis, omission of this study confirmed that the risk of VTE in patients with SCI was significantly associated with complete paralysis (OR 3.69, 95% CI 2.60, 5.24; P < 0.00001; Fig. 5B), and there was no evidence of heterogeneity between studies (I^2 = 40%, P = 0.15).[32]

Personal / family history of venous thrombosis

Personal/family history of venous thrombosis as a risk factor for VTE in patients with SCI was evaluated in 5 studies.[12,19,29–31] The meta-analysis demonstrated that the risk of VTE in patients with SCI was significantly associated with personal/family history of venous thrombosis (OR 1.95, 95% CI 1.35, 2.81; P < 0.0003; Fig. 6). There was evidence of significant heterogeneity between studies (I^2 = 67%, P = 0.02). The source of the heterogeneity between studies was not obvious, but a fixed effect model confirmed the findings of the random effects model.

Smoking history

History of smoking as a risk factor for VTE in patients with SCI was evaluated in 4 studies.[13,20,26,32] The meta-analysis demonstrated that the risk of VTE in patients with SCI was significantly associated with history of smoking (OR = 2.67, 95% CI, 1.79, 3.98; P < 0.00001; Fig. 7). There was no evidence of heterogeneity between studies (I^2 = 20%, P = 0.29).

Table 1 Characteristics of the included studies.

Author	Year	Area	Study design	Admitted time	Onset time	Thrombus type	Case number	Control number	Risk factors*
Adrian A. Maung[5]	2011	USA	Case control study	2007–2008	Not specified	VTE	787	17515	1 2 30 31 32 33 34 35 36
Selassie, A. W.[23]	2011	USA	Case control study	1998.1–2009.12	Acute SCI	VTE	138	3251	2 16 17 18 19 50
Chao-Wei Wang[12]	2016	China	Case control study	2013–2014	<24 h	DVT	55	224	1 3 4 5 6 7 8 9 20
Deborah Rubin-Asher[29]	2010	Israel	Case control study	1996.1–2003.5	Acute SCI	VTE	22	64	4 21
Dong-Mei Wu[19]	2019	China	Case control study	2015.1–2018.9	Acute SCI	DVT	39	168	1 4 5 9 10 11 12 13
JC de Campos Guerra[11]	2014	Brazil	Case control study	2011.1–2012.4	Chronic SCI	DVT	17	83	6 28
Jong Geol Do[74]	2013	Korea	Case control study	2002.1–2011.7	Acute SCI	DVT	51	134	29
Li Chengyan[30]	2018	China	Case control study	2015.12–2016.5	Acute SCI	DVT	14	133	4 27 60
LIU Hong-wei[21]	2018	China	Case control study	2014.6–2017.6	Acute SCI	DVT	62	207	1 2 9 56
Liu, W.[33]	2017	China	Case control study	2015.9–2016.8	Not specified	DVT	68	354	52 53 58 61 62 63
Liu, Y. M.[13]	2018	China	Case control study	2013.5–2014.12	<1w	DVT	56	140	26 56 57
Ma Yujuan[14]	2014	China	Case control study	2012.3–2014.7	≤1w	DVT	9	40	2 58
PAN Hongxia[34]	2018	China	Case control study	2013.12–2015.1	Not specified	VTE	82	83	12 26 52
R Clements[24]	2017	Australia	Case control study	2010–2013	Acute SCI	VTE	47	175	2 23 24 25 26
						DVT	30	192	23 25 26 27
						PE	25	197	2 23 24
Reza Ehsanian[75]	2019	USA	Retrospective cohort study	2009.12–2013.1	Acute SCI	VTE	48	234	54 55
S Aito[36]	2007	Italy	Case control study	1999.7–2004.2	Acute SCI	DVT	43	46	6 22
Seth Ahlquist[76]	2020	USA	Case control study	2013.1–2018.8	Acute SCI	VTE	12	67	53
Tracey Jones[25]	2005	USA	Retrospective cohort study	1991.1–2001.12	Acute SCI	VTE	977	15263	2 26 27 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51
XIAO Long-yi[22]	2018	China	Case control study	2016.1–2017.12	Acute SCI	DVT	31	129	1 9 24 64 56
Xin, K.[26]	2019	China	Case control study	2015.5–2017.5	Acute SCI	DVT	34	131	24 26 56 57 58
Xuan Cheng[31]	2017	China	Case control study	2011.1–2015.12	<24 h	DVT	76	301	4 14 15
Yang, K.[27]	2020	China	Case control study	2015.9–2016.8	Not specified	DVT	68	352	24 27 62 65 63
Yu, X.[20]	2020	China	Case control study	2016.1–2017.12	<48 h	DVT	35	45	1 24 56 57 58
Yu Yingying[32]	2020	China	Case control study	2016.1–2018.12	Not specified	DVT	48	252	26 56 57
Zhu Xiaoguang[28]	2015	China	Case control study	2013.1–2013.12	<48 h	DVT	46	97	24 26 59

*Risk factors:1. Age; 2. Sex; 3. Hypercholesterolemia; 4. History of vein thrombosis; 5. CRP; 6. Homocysteine elevation (HCY elevation); 7. High-density lipoprotein (HDL); 8. Lipoprotein(a) (LP(a)); 9. D-dimer; 10. Macrophage migration inhibitory factor (MIF); 11. Clinical complications; 12. Rehabilitation therapy; 13. IL-6; 14. Chronic kidney disease; 15. Small intestinal bacterial overgrowth (SIBO); 16. Length of stay (LOS); 17. Level I hospital; 18. Level III hospital; 19. Discharge status (Deceased); 20. Fibrinogen; 21. Prothrombin mutation; 22. Inhibitor of plasminogen activator-1 (PAI-1); 23. Weight; 24. Motor paralysis complete or AIS A grade; 25. Time in days between injury and commencement of anticoagulant chemoprophylaxis (per day increase); 26. Associated lower limb or pelvic fracture; 27. Paraplegia; 28. Factor V Leiden; 29. absence of spasticity; 30. Injury Severity Score(ISS); 31. C5-7 vs C1-4; 32. T1-6 vs C1-4; 33. T7-12 vs C1-4; 34. Lumbar vs C1-4; 35. Traumatic brain injury (TBI); 36. Chest trauma; 37. African American; 38. 8–13 yrs; 39. 14–19 yrs; 40. 20–29 yrs; 41. >80 yrs; 42. Insurance status; 43. Elixhauser Comorbidity Index score; 44. Elixhauser Comorbidity Index score (2); 45. Elixhauser Comorbidity Index score (>3); 46. 250–350 beds; 47. <125 beds; 48. Tracheostomy; 49. Unspecified tetraplegia; 50. Incomplete tetraplegia; 51. Unspecified paraplegia; 52. Degree of injury; 53. Early use of low molecular weight heparin or heparin; 54. Low vitamin D without supplementation; 55. vitamin D supplementation; 56. Diabetes; 57. Smoking history; 58. Treatment without limb air pressure and ankle pump; 59. Combined with lumbar nerve injury; 60. Blood type; 61. Degree of education; 62. Abnormal urination; 63. DVT cognitive level; 64. Obesity; 65. No spouse.

Lack of compression therapy

Treatment that did not include compression therapy as a risk factor for VTE in patients with SCI was evaluated in 4 studies.[14,20,26,33] The meta-analysis demonstrated that the risk of VTE in patients with SCI was significantly associated with treatment that did not include compression therapy (OR = 2.44, 95% CI, 1.59, 3.73; P < 0.0001; Fig. 8). There was no evidence of heterogeneity between studies (I^2 = 0%, P = 0.49).

Table 2 Methodological quality of the included studies.

References	Selection	Comparability	Outcome	NOS scores
Adrian A. Maung	★★	★★	★★★	7
Selassie, A. W.	★★	★★	★★★	7
Chao-Wei Wang	★★★	★★	★★★	8
Deborah Rubin-Asher	★★★	★★	★★★	8
Dong-Mei Wu	★★★	★★	★★★	8
JC de Campos Guerra	★★★	★★	★★★	8
Jong Geol Do	★★★	★★	★★★	8
R Clements	★★★	★★	★★★	8
Reza Ehsanian	★★	★★	★★★	7
S Aito	★★★	★★	★★★	8
Seth Ahlquist	★★★	★★	★★★	8
Tracey Jones	★★★	★★	★★★	8
Xuan Cheng	★★★	★★	★★★	8
Yu, X.	★★★	★★	★★★	8
Li Chengyan	★★★	★★	★★★	8
LIU Hong-wei	★★★	★★	★★★	8
Liu, W.	★★★	★★	★★★	8
Liu, Y. M.	★★★	★★	★★★	8
Ma Yujuan	★★	★★	★★★	7
PAN Hongxia	★★★	★★	★★★	8
XIAO Long-yi	★★	★★	★★★	7
Xin, K.	★★	★★	★★★	7
Yang, K.	★★★	★★	★★★	8
Yu Yingying	★★★	★★	★★★	8
Zhu Xiaoguang	★★★	★★	★★★	8

SCI combined with lower limb / pelvic fracture

The presence of a lower limb/pelvic fracture as a risk factor for VTE in patients with SCI was evaluated in 6 studies.[13,25,26,28,32,34] The meta-analysis demonstrated that the risk of VTE in patients with SCI was significantly associated with the presence of a lower limb/pelvic fracture (OR = 2.79, 95% CI, 1.42, 5.50; P = 0.003; Fig. 9). There was evidence of significant heterogeneity between studies (I^2 = 78%, P = 0.0004). One study proposed that trauma to a lower extremity was an independent risk factor for VTE, and did not include lower limb fracture.[25] In a sensitivity analysis, omission of this study[22] confirmed that the risk of VTE in patients with SCI was significantly associated with the presence of a lower limb/pelvic fracture (OR = 3.47, 95% CI, 1.79, 6.75; P = 0.0002). There was evidence of significant heterogeneity between studies (I^2 = 56%, P = 0.06).

Paraplegia

Paraplegia is defined as injury below the cervical spinal cord (T1 and lower), and quadraplegia is defined as injury to the cervical spinal cord (C8 and higher).[35] Paraplegia as a risk factor for VTE in patients with SCI was evaluated in 3 studies.[25,27,30] The meta-analysis demonstrated that the risk of VTE in patients with SCI was significantly associated with paraplegia (OR = 1.81, 95% CI, 1.49, 2.19; P < 0.00001; Fig. 10). There

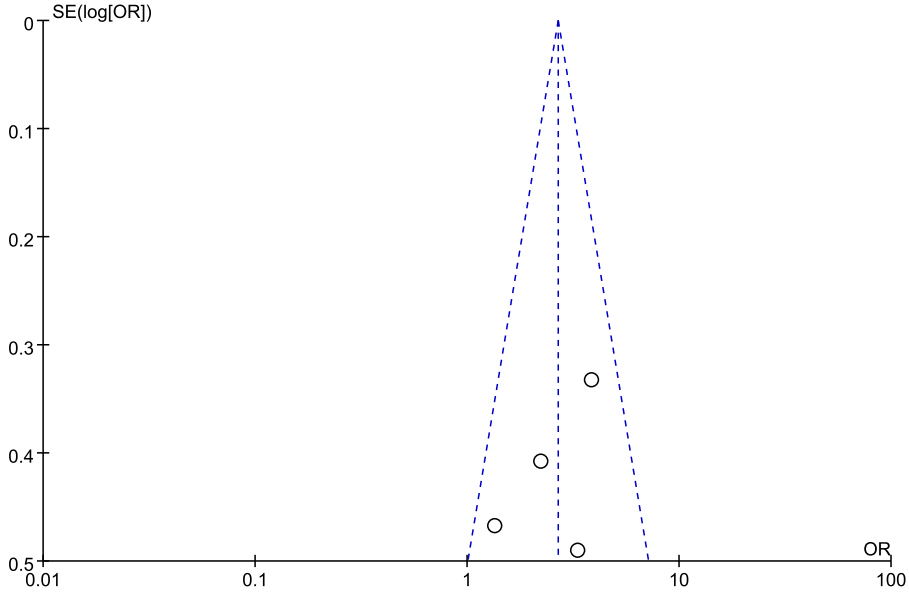

Figure 2 Funnel plot for history of smoking. The symmetrical funnel plot suggested there was no evidence of publication bias.

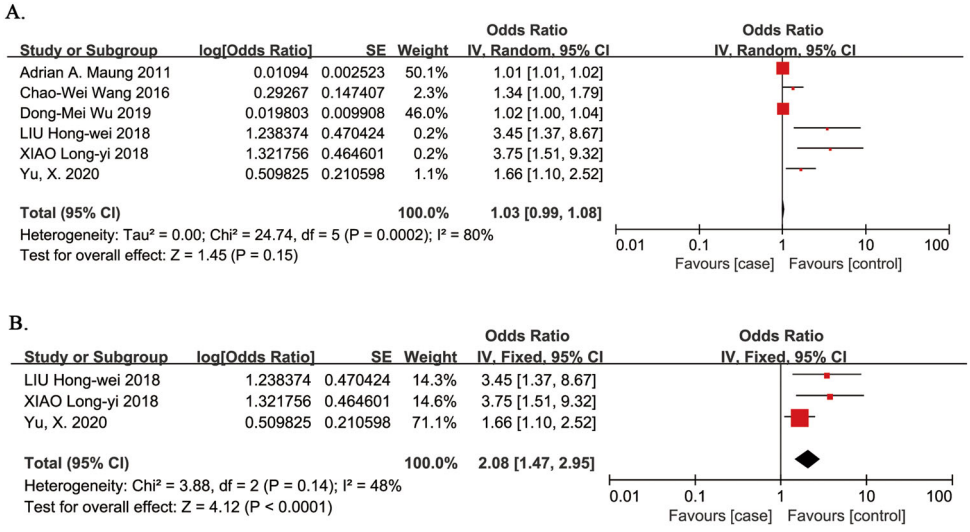

Figure 3 Age as a risk factor for VTE in patients with SCI. A. Primary analysis; there was no association between the risk of VTE in patients with SCI and age. There was evidence of significant heterogeneity between studies (I^2 = 80%, P = 0.0002). B. Sensitivity analysis omitted three studies that did not include age as a categorical variable. The risk of VTE in patients with SCI was significantly associated with age >45 years. There was no evidence of heterogeneity between studies (I^2 = 48%, P = 0.14).

was no evidence of heterogeneity between studies (I^2 = 46%, P = 0.16).

Diabetes

Diabetes as a risk factor for VTE in patients with SCI was evaluated in in 6 studies.[13,20–22,26,32] The meta-analysis demonstrated that the risk of VTE in patients with SCI was significantly associated with diabetes (OR = 3.22, 95% CI, 1.62, 6.41; P = 0.0009; Fig. 11A). One study did not specify that patients had acute SCI.[32] In a sensitivity analysis, omission of this study confirmed that the risk of VTE in patients with SCI was significantly associated with diabetes (OR = 4.24, 95% CI, 2.75, 6.52; P < 0.00001; Fig. 11B), and there was no evidence of heterogeneity between studies (I^2 = 23%, P = 0.27).[32]

Elevated serum Hcy

Elevated serum Hcy level as a risk factor for VTE in patients with SCI was evaluated in 3 studies.[11,12,36] The meta-analysis demonstrated no association between the risk of VTE in patients with SCI and elevated serum Hcy level (OR = 3.90, 95% CI, 0.82, 18.54; P = 0.09; Fig. 12).

Elevated serum D-dimer

Elevated serum D-dimer level as a risk factor for VTE in patients with SCI was evaluated in 4 studies.[12,19,21,22] The meta-analysis demonstrated no association between the risk of VTE in patients with SCI and elevated serum D-dimer level (OR = 1.06, 95% CI, 1.00, 1.12; P = 0.05; Fig. 13).

Overall, the meta-analysis identified 9 risk factors for VTE in patients with SCI, which are summarized in Table 3.

Discussion

This meta-analysis identified age, male sex, complete paralysis, personal/family history of VTE, history of smoking, lack of compression therapy, presence of a

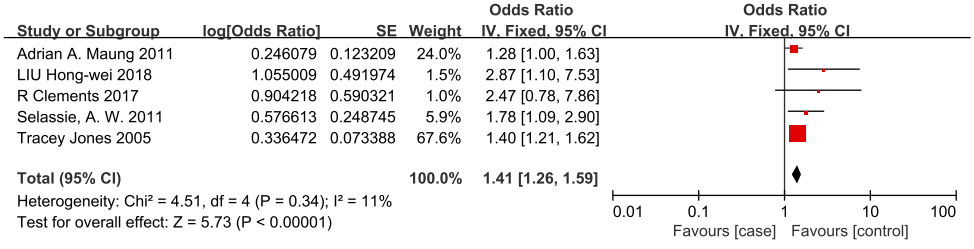

Figure 4 Male sex as a risk factor for VTE in patients with SCI. The risk of VTE in patients with SCI was significantly associated with male sex. There was no evidence of heterogeneity between studies (I^2 = 11%, P = 0.34).

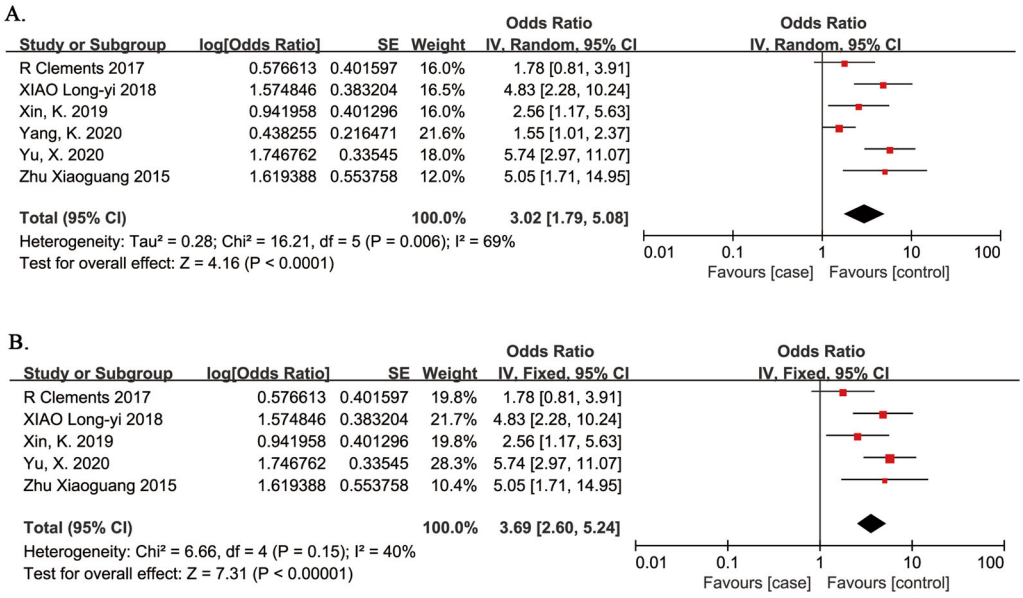

Figure 5 Complete paralysis as a risk factor for VTE in patients with SCI. A. Primary analysis; the risk of VTE in patients with SCI was significantly associated with complete paralysis. There was evidence of significant heterogeneity between studies ($I^2 = 69\%$, P = 0.006). B. Sensitivity analysis omitted a study in subjects aged >45 years. The risk of VTE in patients with SCI was significantly associated with complete paralysis. There was no evidence of heterogeneity between studies ($I^2 = 40\%$, P = 0.15).

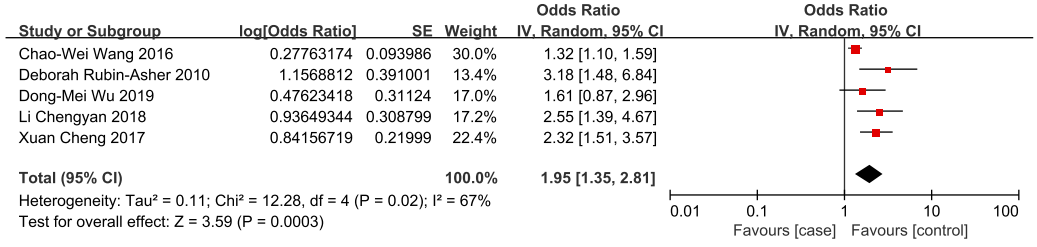

Figure 6 Personal/family history of venous thrombosis as a risk factor for VTE in patients with SCI. The risk of VTE in patients with SCI was significantly associated with personal/family history of venous thrombosis. There was evidence of significant heterogeneity between studies ($I^2 = 67\%$, P = 0.02).

lower limb/pelvic fracture, paraplegia, and diabetes as risk factors for VTE in patients with SCI.

Previous reports indicate that age is an independent risk factor for VTE in patients with SCI.[3,6,37,38] Age less than 14 years was predictive of not developing VTE in patients with complete or incomplete SCI (OR = 0.2), [25] but the risk of developing VTE increased with age.[4,5,10,39] In one study, the mean age of patients with SCI and VTE was 40 years, while the mean age of patients with SCI and no VTE was 32 years.[6] In another study, age >45 years was a risk factor for VTE in patients with acute SCI

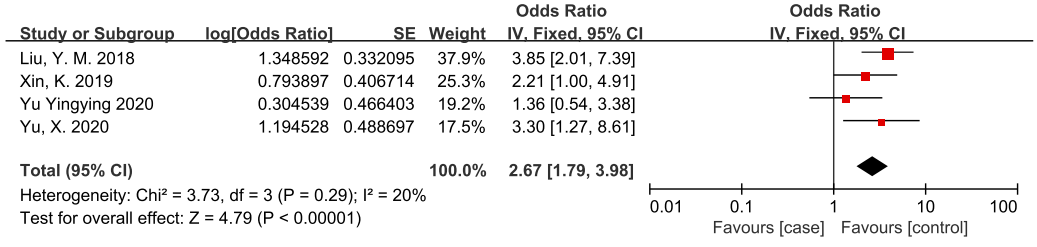

Figure 7 History of smoking as a risk factor for VTE in patients with SCI. The risk of VTE in patients with SCI was significantly associated with history of smoking. There was no evidence of heterogeneity between studies ($I^2 = 20\%$, P = 0.29).

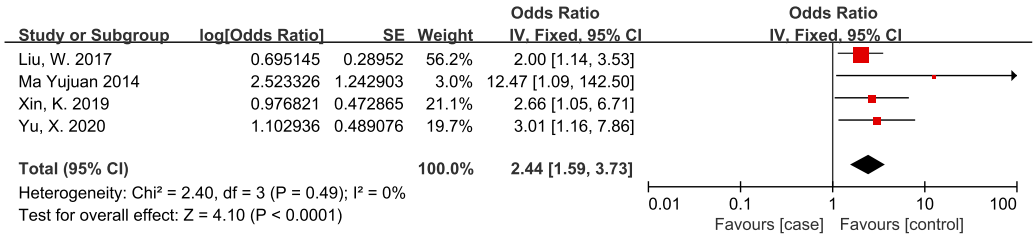

Figure 8 Lack of compression therapy as a risk factor for VTE in patients with SCI. The risk of VTE in patients with SCI was significantly associated with treatment that did not include compression therapy. There was no evidence of heterogeneity between studies.

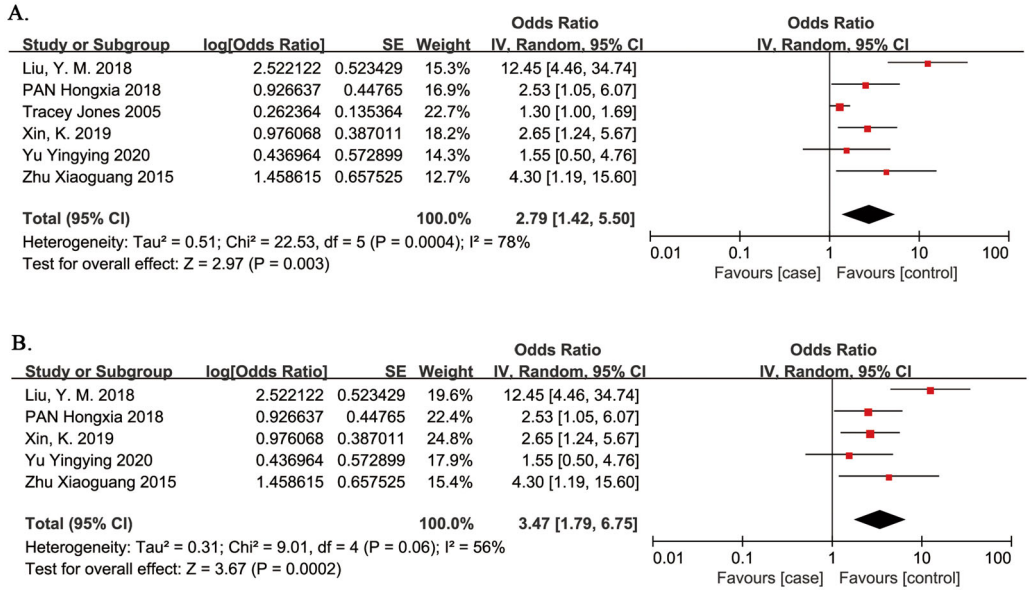

Figure 9 Presence of a lower limb/pelvic fracture a risk factor for VTE in patients with SCI. A. Primary analysis; the risk of VTE in patients with SCI was significantly associated with the presence of a lower limb/pelvic fracture. There was evidence of significant heterogeneity between studies ($I^2 = 78\%$, $P = 0.0004$). B. Sensitivity analysis omitted one study that proposed trauma to a lower extremity was an independent risk factor for VTE, and did not include lower limb fracture. The risk of VTE in patients with SCI was significantly associated with the presence of a lower limb/pelvic fracture. There was evidence of significant heterogeneity between studies ($I^2 = 56\%$, $P = 0.06$).

(hazard ratio = 8.4).[40] Accordingly, the results of our pooled analyses revealed that the risk of VTE in patients with SCI was significantly associated with age >45 years (OR = 2.08).

Some evidence suggests that male sex is an independent risk factor for VTE in patients with SCI.[5,24,38,41–44] Consistent with this, findings from the present study confirmed that the risk of VTE in patients with

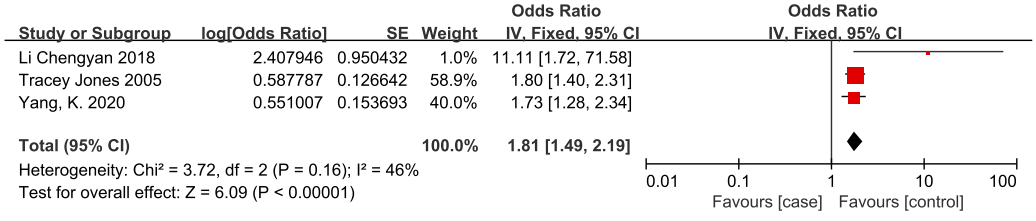

Figure 10 Paraplegia as a risk factor for VTE in patients with SCI. The risk of VTE in patients with SCI was significantly associated with paraplegia. There was no evidence of heterogeneity between studies ($I^2 = 46\%$, $P = 0.16$).

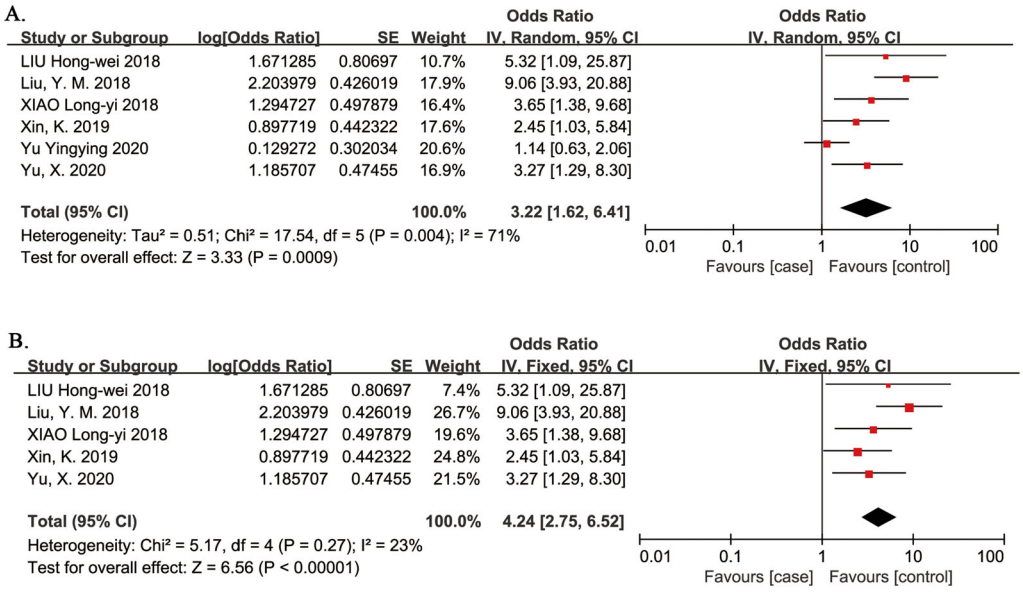

Figure 11 Diabetes as a risk factor for VTE in patients with SCI. A. Primary analysis; the risk of VTE in patients with SCI was significantly associated with diabetes. There was evidence of significant heterogeneity between studies ($I^2 = 71\%$, P = 0.004). B. Sensitivity analysis omitted one study that did not specify that patients had acute SCI. The risk of VTE in patients with SCI was significantly associated with diabetes. There was no evidence of heterogeneity between studies ($I^2 = 23\%$, P = 0.27).

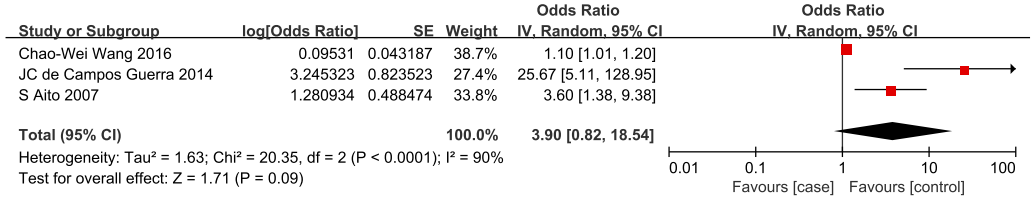

Figure 12 Elevated serum Hcy level as a risk factor for VTE in patients with SCI. There was no association between the risk of VTE in patients with SCI and elevated serum Hcy level.

SCI was significantly associated with male sex (OR = 1.41). The role of sex as an influencing factor in VTE is not clear. The increased incidence of VTE in men may be related to height, as individuals with longer limbs have a greater risk of developing DVT, [45,46] or hormonal factors.

Several studies show that severity of injury and loss of motor function are risk factors for VTE in patients with SCI, [4,5,10,25,47–49] while other reports suggest there is no difference in the incidence of DVT between patients with complete paralysis or incomplete paralysis.[50] In one study, the risk of DVT was greater in patients with Frankel A SCI compared to patients with Frankel B, C or D SCI.[38] Other studies showed that the risk of thrombosis was increased in patients with AIS Grade A injuries, where complete loss of motor or sensory function in the sacral segments S4–S5 means that the skeletal-muscle pump cannot aid in

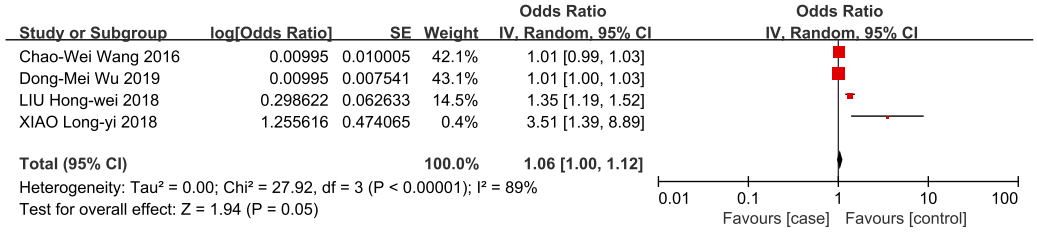

Figure 13 Elevated serum D-dimer level as a risk factor for VTE in patients with SCI. There was no association between the risk of VTE in patients with SCI and elevated serum D-dimer level.

Table 3 Risk factors for VTE in patients with SCI.

Risk factors	Number of documents	OR	95%CI	Heterogeneity test			Test for overall effect	
				Q	P	I^2(%)	*Z*	P
>45 years old	3	2.08	1.47–2.95	3.88	0.14	48	4.12	<0.0001
Male sex	5	1.41	1.26–1.59	4.51	0.34	11	5.73	<0.00001
Complete paralysis	5	3.69	2.60–5.24	6.66	0.15	40	7.31	<0.00001
Personal / family history of VTE	5	1.95	1.35–2.81	12.28	0.02	67	3.59	0.0003
History of smoking	4	2.67	1.79–3.98	3.73	0.29	20	4.79	<0.00001
Lack of compression therapy	4	2.44	1.59–3.73	2.40	0.49	0	4.10	<0.0001
Presence of a lower limb /pelvic fracture	5	3.47	1.79–6.75	9.01	0.06	56	3.67	0.0002
Paraplegia	3	1.81	1.49–2.19	3.72	0.16	46	6.09	<0.00001
Diabetes	5	4.24	2.75–6.52	5.17	0.27	23	6.56	<0.00001

venous return.[33,39] Our search identified no studies reporting on the incidence of DVT in lower AIS grades. The results of our pooled analyses revealed that the risk of VTE in patients with SCI was significantly associated with complete paralysis (OR = 3.69).

One study indicates that lack of compression therapy is a risk factor for VTE in patients with SCI.[26] Skeletal muscles in the lower extremities become atrophied and fatigued and cannot maintain venous return following SCI, which can lead to VTE.[33] Compression therapy can limit stasis in the paralyzed lower extremities and reduce the risk of VTE in patients with SCI.[20,26,32,33] Consistent with this, findings from the present study confirmed that the risk of VTE in patients with SCI was significantly associated with lack of compression therapy (OR = 2.44).

Some evidence suggests that personal/family history of venous thrombosis is a risk factor for VTE, although the pathogenesis is unclear.[12,31,40,51,52] Environmental and genetic factors may increase the risk of developing VTE in patients with acute SCI.[12,53] One study proposed that 50% of patients with a personal or family history of VTE have a weak plasma anticoagulant response to activated protein C (APC), which is a serine protease with strong anticoagulant activity.[54] Other studies showed that a point mutation at nucleotide 1691 of the Factor V gene leads to the formation of factor V Leiden (FVL), APC resistance, and thrombosis,[55] and identified FVL and prothrombin 20210A (PT-20210A) variants as risk factors for VTE.[56] The results of our pooled analyses confirmed that the risk of VTE in patients with SCI was significantly associated with personal/family history of venous thrombosis (OR = 1.95).

Several studies show that history of smoking is associated with VTE in the general population and in patients with various diseases.[53,57–59] Nicotine and benzopyrene in tobacco may increase platelet activation, platelet aggregation and blood viscosity, induce vascular endothelial injury, and promote a hypercoagulable state. Oxidative stress and inflammation induced by smoking can directly act on the vascular endothelium and cause endothelial dysfunction. Together, these factors may increase the risk of VTE.[13,20,26,32] Consistent with this, findings from the present study confirmed that the risk of VTE in patients with SCI was significantly associated with history of smoking (OR = 2.67).

Previous reports indicate that presence of a limb/ pelvic fracture is an independent risk factor for VTE in patients with SCI.[10,25,28,60,61] Lower limb/ pelvic fracture can destroy the integrity of blood vessels and damage vascular endothelial cells. Subsequent bed rest and surgical stress can reduce blood flow, trigger an inflammatory reaction, and increase blood viscosity, thus increasing the risk of DVT.[13,26,32,34,62] Accordingly, the results of our pooled analyses revealed that the risk of VTE in patients with SCI was significantly associated with the presence of a lower limb/ pelvic fracture (OR = 3.47).

Compared with quadraplegia, paraplegia may be a risk factor for VTE.[5,6,10,25,40] This may be because mortality is higher in patients with quadraplegia compared to paraplegia; however, the influence of other factors, such as the degree of spasticity, presence of long bone and pelvic fractures and studies with small sample sizes, should also be considered.[5,25,40] One report showed no difference in the incidence of VTE in patients with paraplegia or tetraplegia.[63] Findings from the present study suggested that the risk of VTE in patients with SCI was significantly associated with paraplegia (OR = 1.81). Despite this, the findings should be interpreted with caution as the pooled analysis only included 3 studies.

There is growing evidence that diabetes is associated with an increased risk of VTE, although some meta-

analyses show no significant association between diabetes and VTE in the general population.[64–67] Hyperglycemia, hyperinsulinemia, and insulin resistance in patients with diabetes may damage endothelial cells and endothelial function, cause chronic inflammation, and promote hypercoagulability. Alternatively, the increased risk of VTE in individuals with diabetes may be due to confounding factors such as age, BMI, race, hypertension, dyslipidemia, or smoking rather than an inherent effect of diabetes.[66,67] The results of our pooled analyses revealed that the risk of VTE in patients with SCI was significantly associated with diabetes (OR = 4.24).

Previous reports indicate that elevated serum Hcy levels are associated with an increased risk of VTE.[12,68–70] However, findings from the present study suggested that the risk of VTE in patients with SCI was not associated with elevated serum Hcy. These disparate findings may be explained by our small sample size and the design of the included studies. One study analyzed elevated Hcy as a categorical rather than a continuous variable, and reported that serum Hcy levels of 15–30 μmol/L were associated with the risk of DVT.[11]

Our pooled analyses also revealed that the risk of VTE in patients with SCI was not associated with elevated serum D-dimer level. This is consistent with findings from other studies, which report that normal or low serum D-dimer levels are useful for excluding VTE.[4,6,15,47,71,72]

This meta-analysis had several limitations. First, several studies reported on the association of other factors with VTE, which were not included in our review due to a lack of data. Second, our pooled analyses for some factors included a small number of studies. Third, many older articles that do not report ORs were not included in the meta-analysis; therefore, potentially relevant risk factors for VTE may have been missed. In future, these articles may be included in a narrative review. Last, we did not differentiate between chronic and acute SCI, even though this may have clinical implications.[73]

In conclusion, this meta-analysis identified 9 risk factors for VTE in patients with SCI, including middle and old age, male sex, complete paralysis, personal/family history of venous thrombosis, history of smoking, lack of compression therapy, presence of a lower limb/pelvic fracture, paraplegia, and diabetes. Healthcare providers should be aware of the risk factors for VTE when rehabilitating patients with SCI.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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