

Review Article

A meta-analysis: the DVT prevalence and its risk factors among SCI patients

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Abstract: Deep vein thrombosis (DVT), as one of the most common secondary complications of spinal cord injury (SCI), is a potentially catastrophic condition for patients with SCI. We carried out the current meta-analysis to estimate the DVT prevalence and its relationship with the gender and American Spinal Injury Association (ASIA) grades of SCI patients. Relevant studies published before November 3, 2016, were retrieved from PubMed, EMBASE and Web of Science databases. The pooled DVT event rate and 95% confidence interval (CI) among SCI patients was generated, and the odds ratios (ORs) with corresponding 95% CIs of the gender and ASIA grades of SCI patients were also yielded. The overall DVT event rate was 14.8% among SCI patients, 25.9% among those in Asia, 12.1% among those in non-Asia, 19.7% among those from rehabilitation institutes and 9.9% among those from hospitals. With respect to the risk factors of DVT in SCI patients, no significant association between the DVT prevalence and the gender or the ASIA grades of SCI patients was observed. In conclusion, our meta-analysis reveals that the DVT prevalence rate among SCI patients in Asia or rehabilitation institutes is higher than that among those in non-Asia or hospitals, and neither the gender or the ASIA grades of SCI patients was risk factor for DVT prevalence.

Keywords: DVT, SCI patients, prevalence, risk factors, meta-analysis

Introduction

Spinal cord injury (SCI) is a devastating medical emergency that leads to severe physical disabilities for affected individuals [1]. SCI can affect people of all ages, mainly those young, active males at the ages of 16-30 [2]. It has been estimated that approximate 40-80 cases per million persons are living with SCI worldwide, and there are 17,000 cases annually in the US [3, 4]. SCI, damaging axons and disrupting myelination, is physically and psychologically debilitating, which brings out physical, emotional and economic burdens on both the sufferers and the society [5, 6]. When compared with the unaffected individuals, the mortality risk is around 2-5 times higher among those with SCI [7].

Apart from local damage within the spinal cord, several secondary complications such as pulmonary embolism, postural hypotension, gastrointestinal function disorder, neuropathic

pain and spasticity can arise during the SCI process [8]. Deep vein thrombosis (DVT), that is the formation of a blood clot usually occurring in deep veins of the lower leg and thigh, is one of the most common secondary complications [9, 10]. DVT and subsequent pulmonary embolism are reported to be major causes of morbidity, mortality and healthcare burden for individuals with SCI worldwide [11].

A variety of literatures have investigated the incidence and risk factors for DVT in patients with SCI, and the results were inconsistent. Green and colleagues explored the risk factors for DVT in acute SCI patients and found that 21% of SCI patients were diagnosed with DVT, and SCI patients with American Spinal Injury Association (ASIA) C or D grade or male patients were less likely to be diagnosed with DVT, when compared with those with ASIA A or B grade or female patients [12]. However, data from a prospective cohort study, published in 2016, demonstrated that the incidence of DVT in SCI

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patients was 20%, and no significant correlation was detected between the incidence of DVT in SCI patients and the gender or ASIA grades of patients [10]. Thus, we carried out a meta-analysis to comprehensively appraise the prevalence rate of DVT among SCI patients and its relationship with the gender and ASIA grades of SCI patients.

Materials and methods

Literature research

The literature retrieval was performed via a search of PubMed, EMBASE and Web of Science from the inception to November 3, 2016 using the following medical subject heading terms and text words: “Spinal cord injury” OR “spinal injury” OR “spinal fracture” and (“venous thrombosis” OR “thrombophlebitis” OR “thromboembolism” OR “deep vein thrombosis” OR “pulmonary embolism”) AND (risk OR “occurrence rate” OR “incidence rate”). The abstract lists of related national and international meetings and references of included publications were manually reviewed to identify additional articles which might be eligible to our meta-analysis.

Inclusion and exclusion criteria

Retrieved literatures were reviewed by two authors independently, and studies fulfilled the following pre-defined inclusion criteria were included in our analysis: (1) studies investigating the prevalence rate of DVT among SCI patients or its relationship with the gender or ASIA grades of SCI patients; (2) SCI patients over 18 years old; (3) participants were inpatients or from the rehabilitation institute; (4) studies published in English. The major exclusion criteria were as follows: (1) population-based researches; (2) studies in the forms of comments, news, letters or reviews; (3) studies which did not carry sufficient information about the prevalence rate of DVT and its risk factors among SCI patients. When several publications with overlapping cohort were identified, those with a larger sample size were selected. The disagreements were ruled out by discussion and consensus.

Data extraction

The following information was collected and extracted from each study: the first author, year

of publication, country and region, sample source, type of sample and the number and age of participants.

Statistical analysis

Studies were combined and analyzed using the STATA 12 software (STATA Corp LP, College Station, Texas, United States). Heterogeneity across studies was estimated by the chi-squared based Q statistic test. An $I^2 > 50\%$ or $P < 0.05$ indicates the presence of statistical heterogeneity between combined studies, and the random-effects model was selected to compute the pooled odds ratio (OR) with corresponding 95% confidence interval (CI). In other hand when the heterogeneity was not statically significant ($I^2 < 50\%$, $P > 0.05$), the fixed-effects model was applied to yield the OR and its 95% CI. We employed the Egger's linear regression test and the visual inspection of funnel plots (Begg's test) to examine potential publication bias. All p values were two sided, and $P < 0.05$ was considered statically significant.

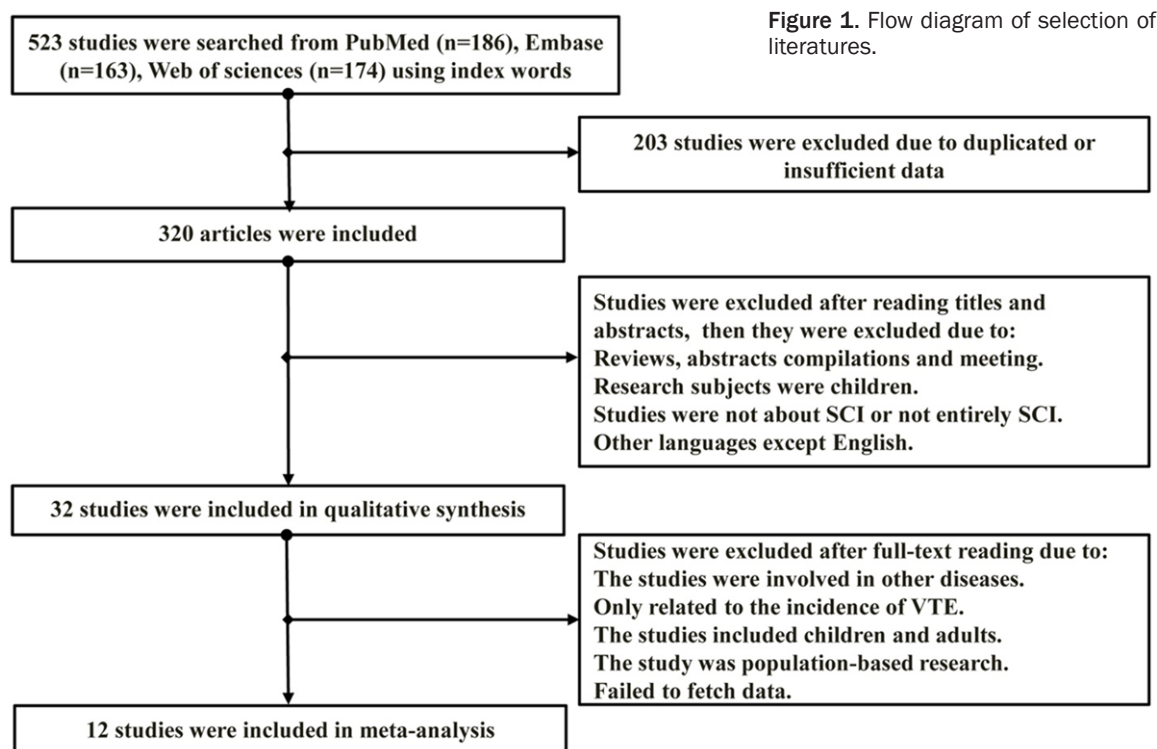
The prevalence rate of DVT in SCI patients expressed as the pooled DVT event rate and 95% CI was regarded as the first outcome of interests, and the association between the prevalence rate of DVT and the gender or ASIA grades of SCI patients which was dichotomous data expressed as OR with 95% CI was considered as secondary outcomes of interests. An $OR > 1$ signifies that the DVT event rate among SCI patients of males or with ASIA A or B grade was higher than that among SCI patients of females or with ASIA C or D grade. A sensitivity analysis was carried out to evaluate the stability of the results.

Results

Study selection and characteristics

Preliminary searches identified 523 literatures for potential inclusion, of which 186 publications were retrieved from PubMed, 163 from EmBase and 174 from web of science. We removed 203 duplications, leaving 320 reports for further estimation. After reading titles and abstracts, 32 publications were left for qualitative synthesis. The remaining 32 literatures were screened by full-text reading, and finally 12 articles [8, 10-20] met our predefined inclusion and exclusion criteria. The process of

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study selection was displayed in **Figure 1**. The publication years of included studies were from 2003 to 2016 and the countries of origin were USA, China, Brazil, Italy, Australia, Canada, Japan and South Africa. The details of each eligible study were presented in **Table 1**.

The pooled DVT event rate in SCI patients

All the 12 eligible studies have reported the prevalence rate of DVT among SCI patients ranged from 3% to 43%. Significant heterogeneity ($I^2 = 95.2\%$, $P < 0.001$) was observed when combined all the relevant data together, so the random-effects model was applied for the generation of the pooled overall DVT event rate with its 95% CI. The pooled overall DVT event rate was 14.8% with the corresponding 95% CI ranged from 10.4% to 19.2% (**Figure 2**).

In order to estimate the DVT event rates among SCI patients in Asia and non-Asia, subgroup analysis stratified by nationality was carried out. There were significant heterogeneities (in Asia: $I^2 = 74.0\%$, $P = 0.021$; in non-Asia: $I^2 = 94.7\%$, $P < 0.001$) in the two subgroup analyses, which implied that the different nationalities might be not responsible for the large heterogeneity of the overall analysis. Considering

the large heterogeneities in the subgroup analyses, the random-effects model was chosen to compute the DVT event rates with the corresponding 95% CIs. The results (**Figure 3**) showed that the DVT event rate among SCI patients in Asia (the DVT event rate = 25.9%, 95% CI: 14.5%-37.4%, **Figure 3**) was higher than that among SCI patients in non-Asia (the DVT event rate = 12.1%, 95% CI: 7.8%-16.3%, **Figure 3**).

The subgroup analysis stratified by sample source was also performed to appraise the DVT event rates among SCI patients from hospitals and rehabilitation institutes. Significant heterogeneities (from hospitals: $I^2 = 92.8\%$, $P < 0.001$; from rehabilitation institutes: $I^2 = 70.3\%$, $P = 0.009$) were detected in the two subgroup analyses inferring that the different sample sources might be not responsible for the large heterogeneity of the overall analysis. The random-effects model was used to yield the DVT event rates with the corresponding 95% CIs. The results (**Figure 4**) demonstrated that the DVT event rate among SCI patients from rehabilitation institutes (the DVT event rate = 19.7%, 95% CI: 14.7%-24.7%, **Figure 4**) was higher than that among SCI patients from hospitals

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Table 1. Characteristics of the included studies

Study	Country	Sample source	Type of sample	No. of participants	Age of participants
Adrian A. Maung (2011)	USA	Hospital	Traumatic SCI	18302	42.6±20.3
C Joseph (2016)	South Africa	Hospital	Traumatic SCI	145	>18 years old
Chao-Wei Wang (2016)	China	Hospital	SCI	279	>18 years old
David Green (2003)	USA	Rehabilitation Institute	Acute SCI	143	40.1 ±18.4
JC de Campos Guerra (2014)	Brazil	Physical Medicine and Rehabilitation Institute	SCI	100	>18 years old
John R. Dimar (2009)	USA	Multicenter database for spine trauma patients	SCI	230	41.8±17.8
Jong Geol Do (2013)	USA	Acute rehabilitation unit	SCI	185	49.1 ± 16.5
Matteo Giorgi Pierfranceschi (2013)	Italy	Three neurosurgical units and Rehabilitation Unit	Traumatic SCI	94	40.3±15.9
R Clements (2016)	Australia	Victorian Spinal Cord Service	Acute SCI	222	44 (25-61)
Sang-Bong Chung (2011)	China	Hospital	Acute SCI	37	53±16.6
Siavash Piran (2016)	Canada	Hospital	Acute SCI	151	51 (17-91)
Yoshihisa Sugimoto (2009)	Japan	Kobe Red Cross Hospital or Hyogo Emergency Medical Center	Acute SCI	54	51 (19-94)

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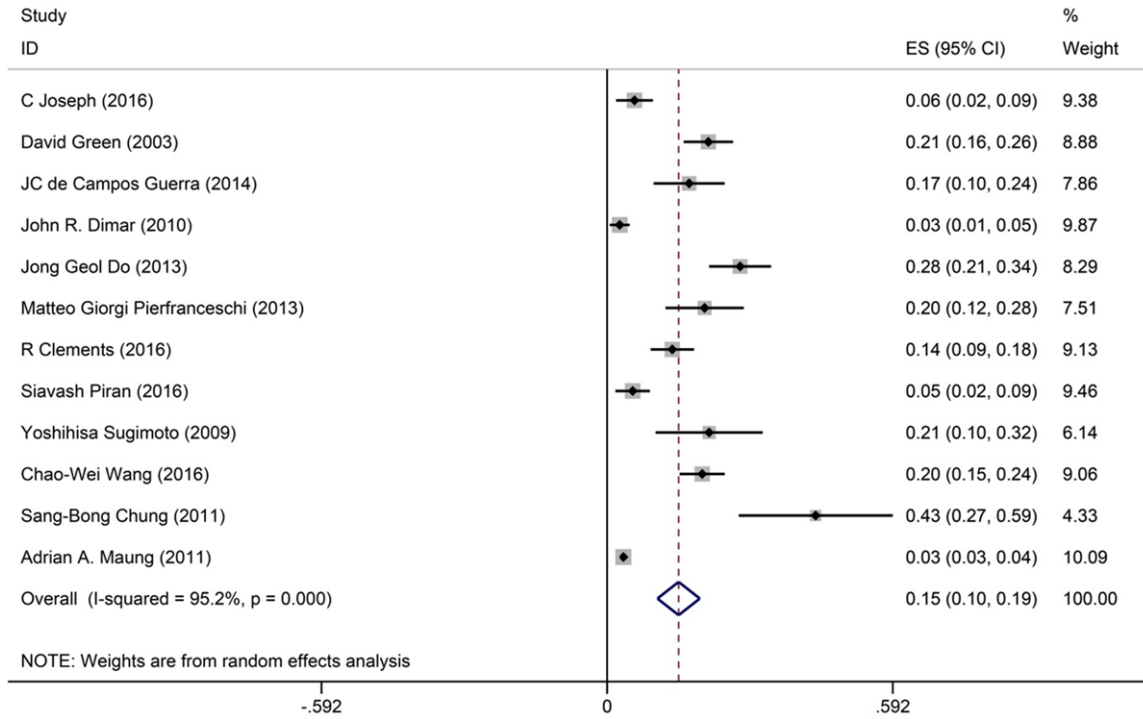


Figure 2. Forest plot of study estimating the overall DVT event rate among SCI patients.

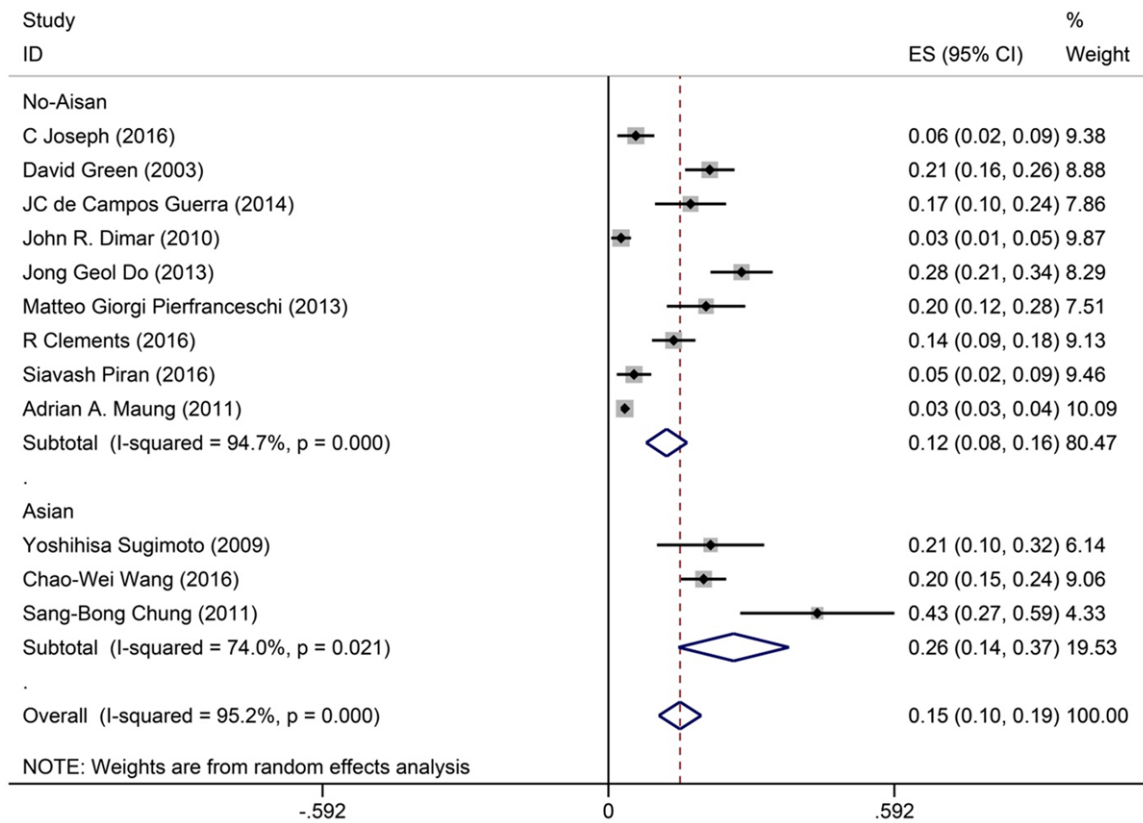


Figure 3. Forest plot of study assessing the DVT event rates among SCI patients in Asia and in non-Asia.

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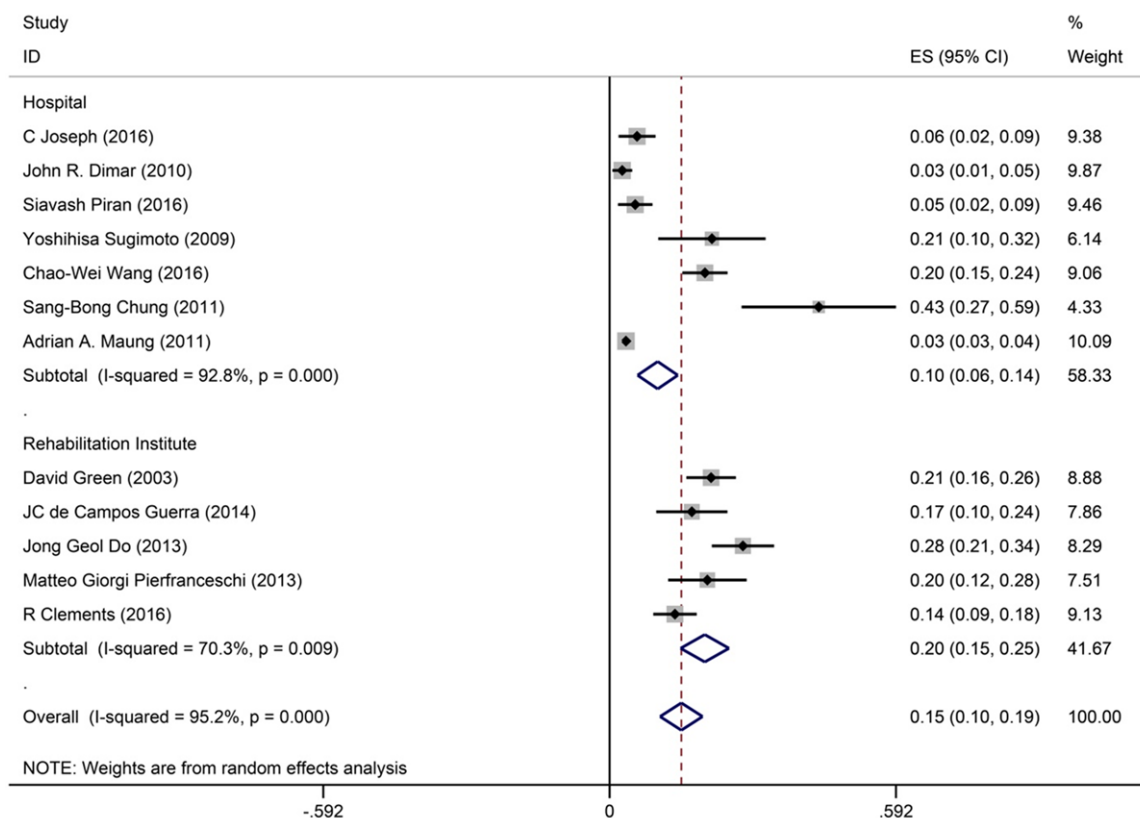


Figure 4. Forest plot of study appraising the DVT event rates among SCI patients from hospitals and rehabilitation institutes.

(the DVT event rate = 9.9%, 95% CI: 5.8%-14.4%, **Figure 4**).

The association between the gender of SCI patients and the DVT prevalence

Data from 7 eligible studies were combined to assess the relationship between the gender of SCI patients and the DVT prevalence, and the results were illustrated in **Figure 5**. The fixed-effects model was chosen for the generation of OR and its 95% CI due to the relatively small heterogeneity across studies ($I^2 = 33.1%$, $P = 0.175$). The value of OR was 0.985 (95% CI: 0.710 - 1.368), and the value of P was higher than 0.05, which signified that no significant association between the gender of SCI patients and the DVT prevalence was observed, and the gender of individuals was not a risk factor for the DVT prevalence among SCI patients.

The association between the ASIA grades of SCI patients and the HIV prevalence

A total of 8 studies were included to evaluate the relationship between the ASIA grades of

SCI patients and the DVT prevalence, and the results were exhibited in **Figure 6**. There was relatively large heterogeneity ($I^2 = 50.3%$, $P = 0.050$) between the eligible studies, so the random-effects model was introduced to yield OR and its corresponding 95% CI. The value of OR was 0.909 (95% CI: 0.678-1.219), and the value of P was higher than 0.05, which implied that the DVT event rate among SCI patients with ASIA C or D grade was similar to that among those with ASIA A or B grade, and the ASIA grades of sufferers was not a risk factor for the DVT prevalence among SCI patients.

Publication bias

The funnel plots of the analyses estimating the relationships between the DVT prevalence and the gender and ASIA grades of SCI patients were listed in **Figure 7A** and **7B**, and the shape of the funnel plots was symmetry indicating no evident publication bias. It was further validated by the Egger's linear regression test (the gender: $P = 0.234$; the ASIA grades: $P = 0.500$).

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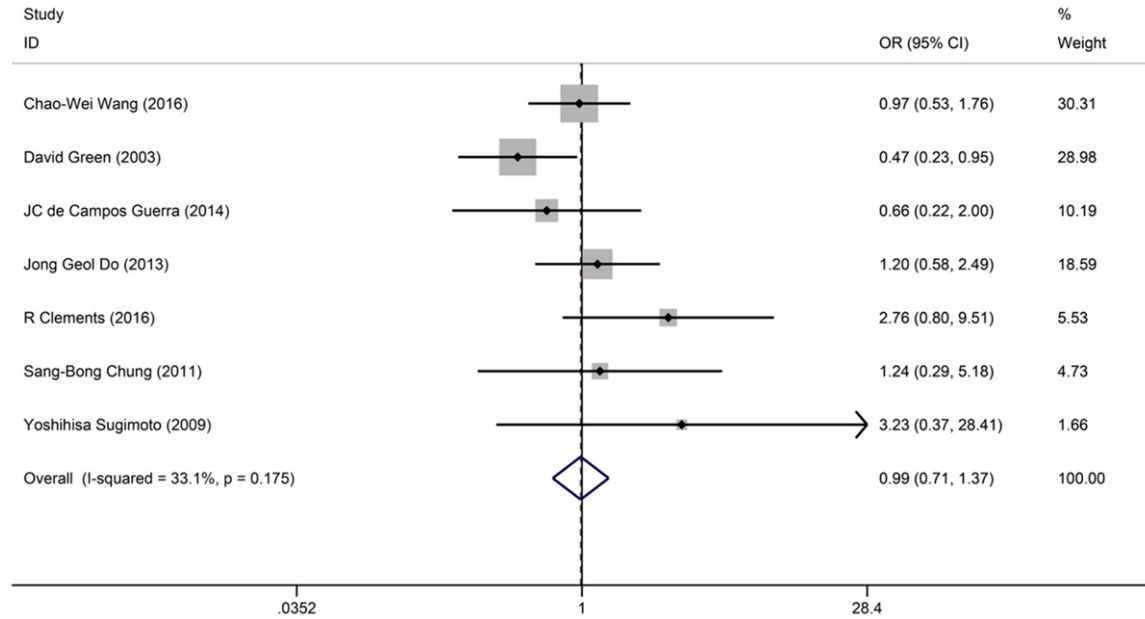


Figure 5. Forest plot of study evaluating the relationship between the gender of SCI patients and the DVT prevalence.

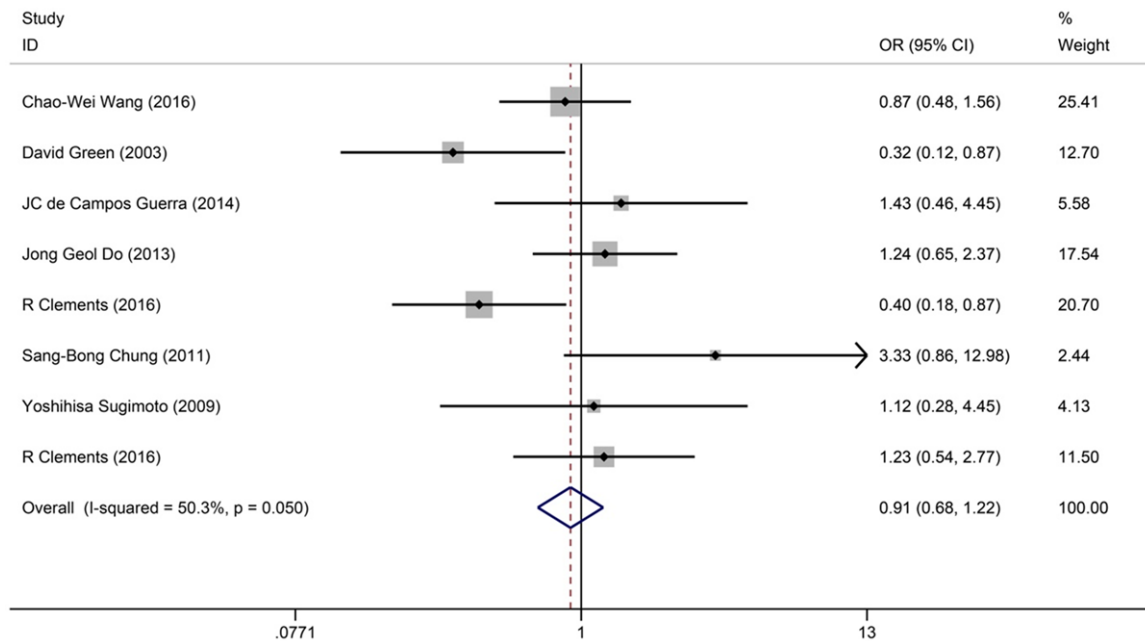


Figure 6. Forest plot of study estimating the relationship between the ASIA grades of SCI patients and the DVT prevalence.

Sensitivity analysis

The sensitivity analysis was conducted to explore the impact of each included study on the global results for the associations between the DVT prevalence and the gender and ASIA

grades of SCI patients. The results were displayed in [Supplementary Figure 1A](#) and [1B](#), demonstrating that none of the incorporated studies had a greater weight on the overall results, and the results of our meta-analysis were relatively stable.

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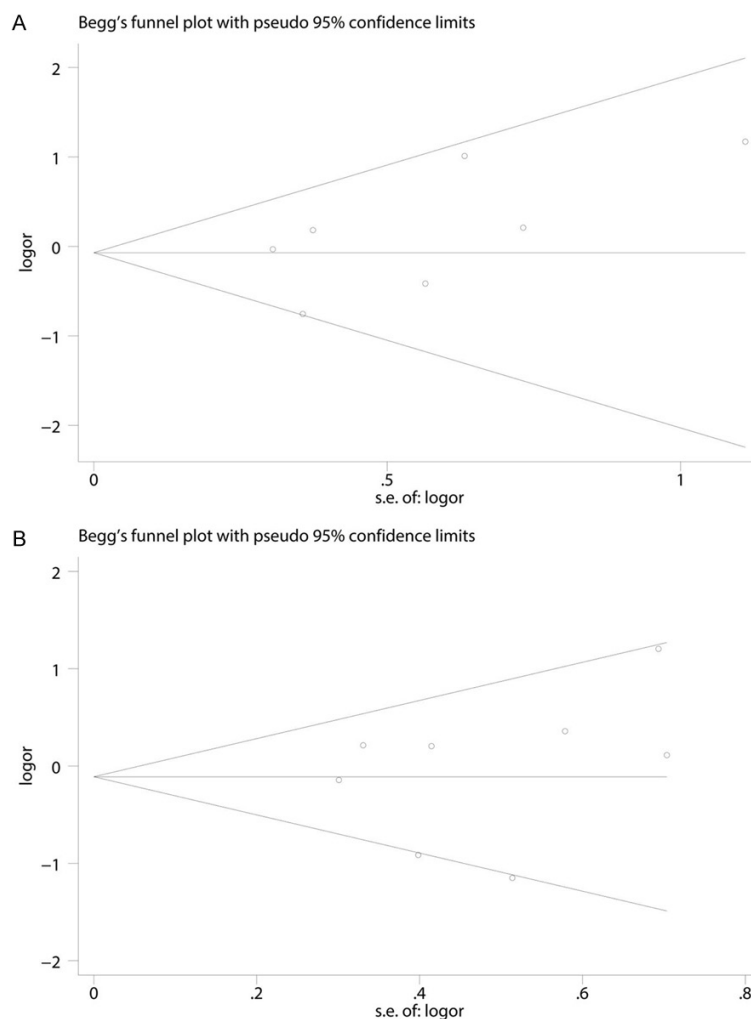


Figure 7. Funnel plots of the Begg's test for the analyses of the associations between the DVT prevalence and the gender (A) and ASIA grades (B) of SCI patients.

Discussion

Several studies reporting the prevalence of DVT among SCI patients and its relationship with the gender and ASIA grades of SCI patients have been carried out, and the results were controversial. The present meta-analysis, with strict inclusion and exclusion criteria, was aimed to evaluate the DVT event rates and its risk factors among SCI patients. The results showed that the overall DVT event rate was 14.8% among SCI patients, 25.9% among those in Asia, 12.1% among those in non-Asia, 19.7% among those from rehabilitation institutes and 9.9% among those from hospitals, and neither the gender or the ASIA grades of SCI patients was risk factor for DVT prevalence.

SCI is a traumatic and life-disrupting condition that affects millions of persons in the world with considerable socioeconomic burden on not only patients and their families but also the healthcare system [21, 22]. Its incidence among males is at least twice higher than that among females and its mortality among the in-hospital patients is ranged from 3% to 13% [3, 23]. SCI, resulting from serious physical trauma to the spine, can be caused by sports injuries, vehicle accidents, acts of violence, gunshots and other reasons [3, 24]. Damage to the spinal cord often leads to a variety of secondary complications characterized by a broad spectrum of autonomic abnormalities including cardiovascular, respiratory, urinary, gastrointestinal and so on, which frequently evokes increase morbidity and mortality and decreased employability and quality of life [25, 26].

DVT, as one of the major complications after SCI, is a potentially catastrophic condition with its incidence varies from population-to-population and from country-to-country [11, 27]. Some clinical manifestations including redness of the skin, pain, warmth and swelling commonly occur at the site of the blood clot of the body, usually of the lower extremities, but sometimes the DVT is asymptomatic [28]. Many factors have been documented to increase the risk of DVT such as cancer, older age, injury, surgery, certain long-term medical conditions, obese, some inherited blood dysfunction and so on [9]. And patients with SCI are more vulnerable to DVT than those with other diseases [29]. The current meta-analysis detected that the overall DVT prevalence rate was 14.8% among SCI patients, and SCI patients in Asia or rehabilitation institutes seemed to be have higher DVT prevalence rate than those in non-Asia or hospitals.

With regard to the DVT prevalence among SCI patients of different genders, data from a retrospective study [17] manifested that no significant difference in the DVT event rate was found between patients of females and those of males, which was inconsistent with that of another related study covering 143 participants [12]. The present meta-analysis, with a larger sample size, demonstrated that the gender of SCI patients had a null effect on the DVT event rate.

ASIA, first published in 1982, is a useful scoring system for the evaluation of neurological damage for SCI patients [7]. ASIA A infers complete motor and sensory damage below the level of the injury, while ASIA E indicates normal motor and sensory function, and patients with ASIA A or B grade have more severe motor and sensory injury than those with ASIA C or D grade [30, 31]. As for the DVT prevalence among SCI patients, our study showed that there was no significant difference in the DVT event rate between patients with ASIA A or B grade and those with ASIA C or D grade.

With the purpose of having more reliable and accurate estimation, we excluded researches conducted among SCI patients younger than 18. However, there are still some limitations in the current meta-analysis. Firstly, when we evaluated the prevalence of DVT among SCI patients, the number of samples from the eligible study performed by Maung and colleagues [13] was relatively large, which might be resulted in some bias for our meta-analysis. Additionally, all the incorporated data were from publications in English.

Conclusively, the present meta-analysis reveals that the DVT prevalence rate is 14.8% among SCI patients; the DVT prevalence rate among SCI patients in Asia (25.9%) or rehabilitation institutes (19.7%) is higher than that among those in non-Asia (12.1%) or hospitals (9.9%); the gender or the ASIA grades of SCI patients has null impact on the DVT prevalence.

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Disclosure of conflict of interest

None.

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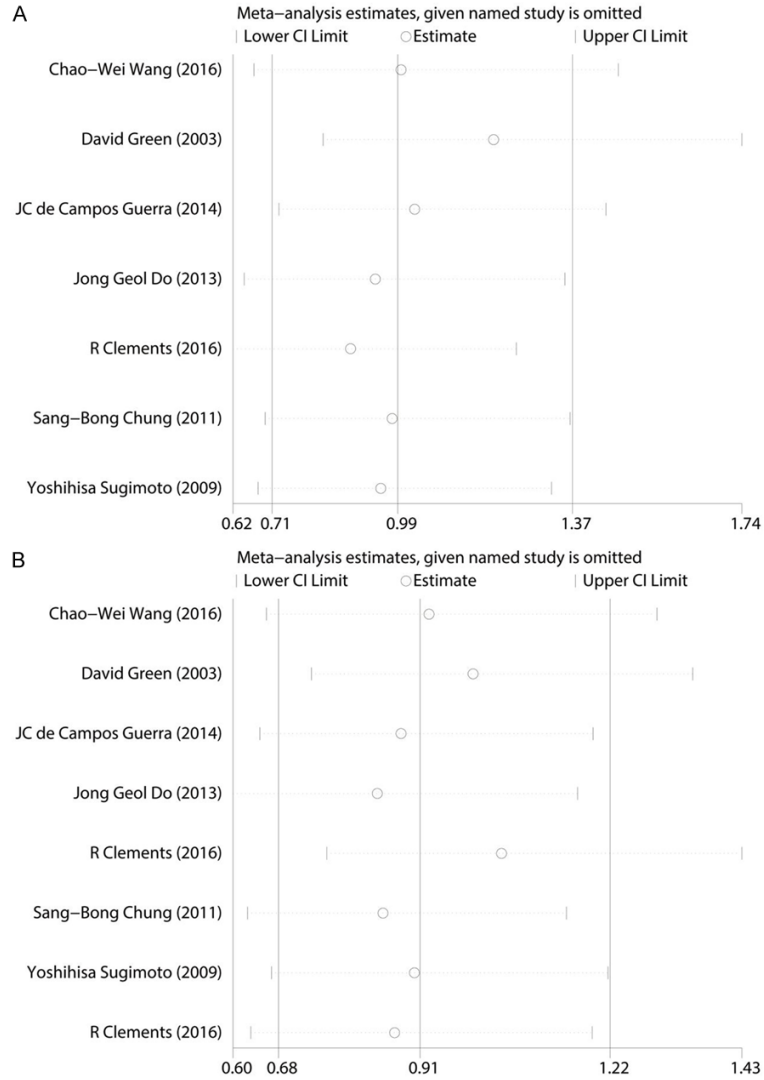
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Supplementary Figure 1. Sensitivity analyses of the associations between the DVT prevalence and the gender (A) and ASIA grades (B) of SCI patients.