# Factors related to morbidity and mortality of meningiomas resection-associated venous thromboembolism (Review)

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**Abstract.** Patients undergoing intracranial meningioma removal have been reported to have an increased risk of venous thromboembolism (VTE). The present study aimed to study meningioma operations and ascertain rates of post-operative VTE more closely and to find out the associated parameters with VTE-related morbidity and mortality in meningioma patients following resection. This meta-analysis included articles involving meningiomas surgery and post-operative VTE [thromboembolic complications: deep venous thrombosis (DVT) and pulmonary embolism (PE)] published in full-text form between January 1980 and January 2021). Collected variables included: First author name, study period covered, publication year, total number of patients and age, number of males, surgical duration, body mass index (BMI), tumor location, proliferation marker for human tumor cells Ki-67 and VTE-related morbidity and mortality. After the initial search and applying all exclusion and inclusion criteria, five articles were left in the final article pool. The total number of patients was 6,505 who underwent surgery for meningiomas and 299 (4.5%) revealed postoperative VTE. The final results showed no potentially significant difference between the total sample and the postoperative VTE group in tumor location and proliferation marker Ki-67 for human cells. By contrast, the results of the analysis for surgical duration and BMI showed a statistically significant difference. Patients who had experienced open surgery for meningiomas were associated with postoperative VTE. Furthermore, surgical duration and BMI were statistically significant VTE-related parameters in patients who underwent meningioma surgery, showing an association with VTE-related morbidity and mortality.

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*Key words:* meningioma, thrombosis, risk of thrombosis, postoperative meningiomas complications, meningiomas surgical resection

## Contents



## 1. Introduction

Meningiomas account for the second most frequent primary central nervous system tumor in adults (1). Despite considerable progress in current therapies, microsurgical resection is considered the treatment of choice for a number of patients with meningiomas (2-6).

Patients undergoing intracranial meningioma removal have been reported to have an increased risk of venous thromboembolism (VTE), including pulmonary embolism (PE) and deep venous thrombosis (DVT), when compared with other intracranial tumors (7-9).

The published data on patients with postoperative VTE after meningiomas resection range from 3-72% (7,9,10-12). The precise mechanism for this result is unknown, but some hypotheses have included the following: Brain thromboplastin proliferation during surgical intervention, incited coagulation of the meningeal surface, steroid therapy and a quantity

of tumor-released hormonal and inflammatory factors (1). Consequently, given the clinical effects of postoperative VTE in this patient population, reducing the occurrence of VTE would considerably improve mortality. In addition, new pre- and postoperative management procedures that contain chemical prophylaxis, including low-molecular-weight heparin (LMWH), have poorer effects on VTE compared with patients who do not receive LMWH (13,14).

However, the benefit of anticoagulants is debatable, and they are linked to a higher likelihood of intracranial hemorrhage, making it even more crucial to identify which patients with meningioma have the greatest risk of postoperative VTE in order to improve decision-making concerning the risk-benefit ratio of assertive prophylactic measures (15,16).

The present study performed a meta-analysis for meningioma operations to ascertain rates of postoperative VTE more closely and to ascertain the associated parameters with VTE-related morbidity and mortality in meningioma patients following resection.

## 2. Sources and data extraction

*Search strategy*. The present study searched the comparative articles involving meningiomas surgery and postoperative VTE (thromboembolic complications: DVT and PE) through electronic databases, including the Cochrane Library, Medline (January 1980-January 2021), PubMed (January 1980-January 2021) and EMBASE (January 1980-January 2021). Preferred reporting items for systematic reviews and meta-analyses (PRISMA) were applied for establishing protocol and manuscript design (17). The present study used the keywords 'meningioma', 'thrombosis', and 'risk of thrombosis' in the Medical Subject Headings (MeSH) list.

*Selection of studies*. Two of the reviewers (GF and VEG) independently extracted data from the included articles, following the guidelines of the epidemiology of meta-analysis. The information captured included the following essentials: The main authors, year of publication, total case number in the meningiomas surgery (control) and postoperative VET groups, study type and outcome indicator. The extracted data was entered into a designed, standardized table according to the Cochrane Handbook for Systematic Review of Interventions (v5.1.0) (18). Fig. 1 depicts a flow chart of the study selection process. If there was disagreement, another of the authors had the final say.

*Inclusion and exclusion criteria*. Studies were included in the meta-analysis if the article met the following criteria, as determined by PICOS: i) Population: Limited to patients with intracranial meningiomas and postoperative VTE; ii) intervention: Use of surgical treatment for intracranial meningiomas; iii) comparison: Compared the outcomes and iv) outcome measures: One of the primary outcomes, such as morbidity and mortality, was involved. Tables I and II contain detailed data on these studies. To avoid publication bias, the final aim was to collect a homogenous pool of studies, including articles that compare only two modalities: Intracranial meningioma surgery and postoperative VTE.

The present study included all prospective and retrospective studies that evaluated at least one of the two modalities. Excluded were editorials, reviews, case reports, articles focusing on the pediatric population, unrelated outcomes, co-morbidities, experimental techniques, or one of the two modalities from the article pool. In addition, all that had mixed or unclear results were put into either the meningioma surgery group (the control group) or the VTE group.

*Definition of outcomes*. The primary outcomes involved in the present study included VTE-related mortality and morbidity. In addition, to find out the association between meningioma surgery and VTE, outcome measurements such as surgical duration, body mass index (BMI), location and the proliferation marker for human tumor cells, Ki-67 were collected. The outcomes reported by the included articles were assessed at least 30 days after the surgical treatment of meningiomas.

Patient morbidity was scored Karnofsky Performance Status Scale (KPS) <80 (19); dependent ambulatory (indicating walking with a mobility aid, such as a cane or walking frame), wheel-chair bound, or bedridden. VTE-related mortality was defined as mortality within 30 days following surgery registered with VTE.

The mean surgical duration, defined as the time from anesthesia induction to skin closure, was >310 min. A board-certified neuroradiologist's pre-operative magnetic resonance imaging review described the mean tumor size (mean volume in $cm^3$) and location (supratentorial, infratentorial and skull base). Tumor grade and Ki-67 indices were retrieved from operative pathology reports based on the World Health Organization (WHO) classification (III) assigned by board-certified neuropathologists (20).

Additionally, to decrease the risk of bias in poor articles, a quality assessment tool [the Newcastle Ottawa Scale (NOS)] was used (Table II) (21).

*Evaluation of the risk of bias*. The Cochrane Collaboration's tool to assess the risk of bias (ROB) was used by two reviewers (GF and VEG) for each study (22). The evaluation includes random sequence generation, allocation concealment, blinding of participants and assessors, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The assessment results were classified into three levels: Low risk, high risk and unclear risk. A third reviewer arbitrated any disagreements.

*Data synthesis and assessment of heterogeneity*. All analyses were carried out using Review Manager Software (RevMan), version 5.4 (https://training.cochrane.org/online-learning/core-software/revman). Heterogeneity across trials was identified using $I^2$ statistics; $I^2$>50% was considered as high heterogeneity. A meta-analysis was conducted using a random-effect model according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) (19). When the model parameters were fixed or non-random quantities the fixed-effect model was used. The continuous outcomes were expressed as a weighted mean difference with 95% confidence intervals (CIs). For discontinuous variables, odds ratios (OR) with 95% CIs were applied for the assessment. P<0.05 was considered to indicate a statistically significant difference.

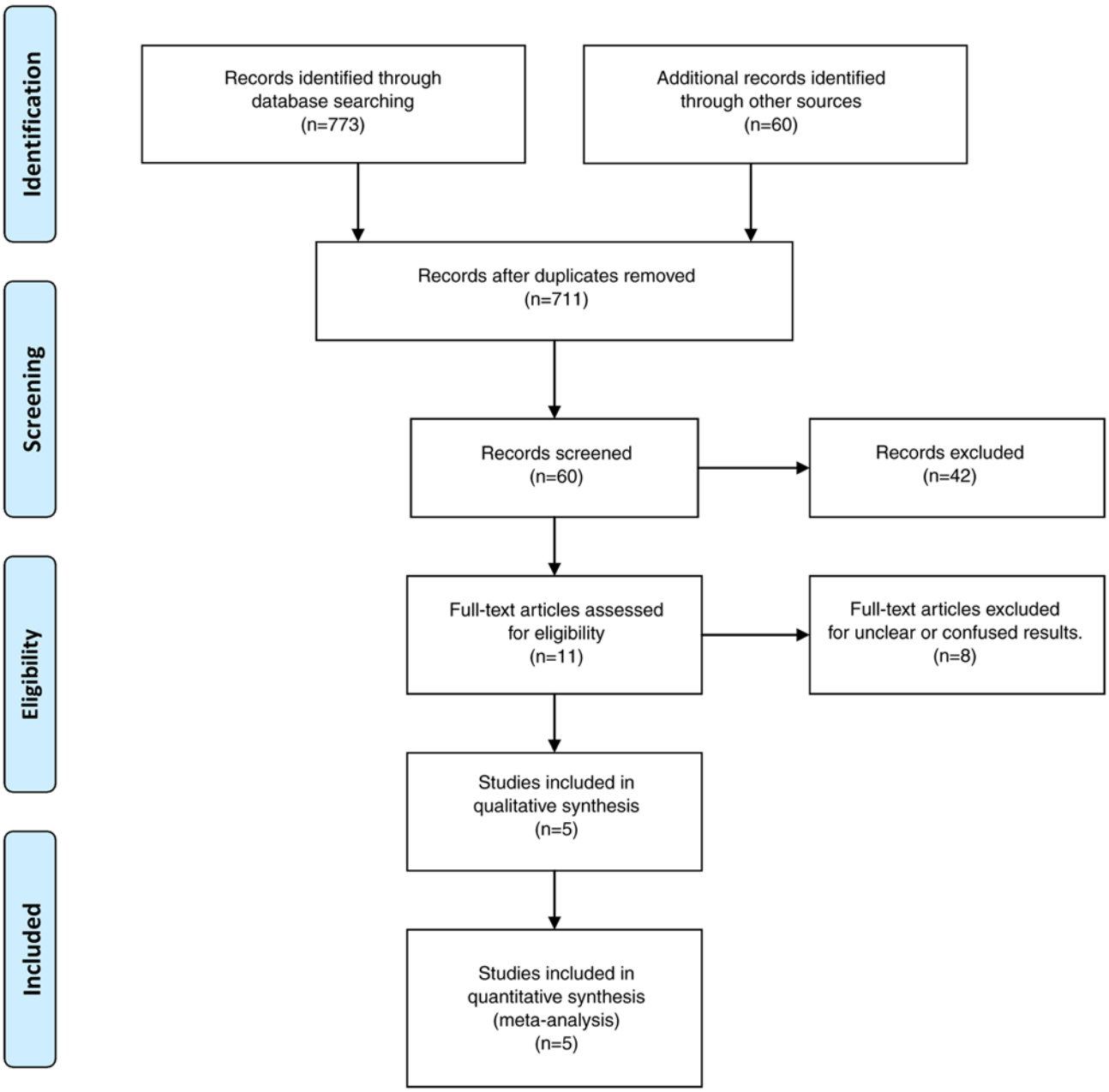


Figure 1. Flow chart of the study selection process.

### 3. Data on parameters associated with VTE-related morbidity and mortality in meningioma patients following resection

Eligibility criteria were met by five articles (1,9,23-25). The total number of patients was 6,505 who underwent surgery for meningiomas and 299 (4.5%) revealed postoperative VTE. The study sample was based on five studies (Table II). All reports were retrospective observational studies.

*Epidemiological and clinical features*. The mean age of patients was 56.9 (60.1 years for the VTE sample) and ranged from 18-77 years. The male-to-female ratio was 1:3.07 (1:1.24 for the VTE group). A total of 1,277 (21.1%) of 6,038/6,505 patients with morbidity data had a KPS of 80 and 191 (63.8%) of 287/299 VTE patients had a poor outcome.

*Surgical duration*. Information on surgical duration was available in four of the five articles (1,9,23,25) with a total of 1,469 patients and 129 with VTE presented with a mean surgical time of 380/429 min for total patients and VTE demonstrated a statistically significant result (OR 0.35, CI 95% 0.14-0.56 and P<0.05) with no heterogeneity (P=0.57 and $I^2$=0%). A very low publication bias was found (Fig. 2).

*BMI*. Information regarding BMI was available in five articles (1,9,23-25) with a total of 6,505 patients and 299 with VTE presented with a mean BMI of 27.9/29.1 (kg/$m^2$) for total patients and VTE demonstrated statistically significant results (OR 2.48, CI 95% 1.58-3.38 and P<0.05) with no heterogeneity (P=0.32 and $I^2$=0%) with no heterogeneity (P=0.32 and $I^2$=0%). A very low publication bias was found (Fig. 3).

Table I. Design of included trials.

| Trial, year | Sample size | | Mean Age (year) | | Number of males | | Surgical duration | | BMI | | Tumor location | | | | | | Ki-67 | | | | | | VTE related Morbidity | | VTE related Mortality | | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Supraten-torial | | Infraten-torial | | Skull base | | Ki-67 <2% | | Ki-67 2-10% | | Ki-67 >10% | | | | | | |
| | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | *VTE* | Control | |
| Gerber DE *et al*, 2007 | 11 | 224 | 68 | 53 | 7 | 57 | 330 | 300 | 25 | 27 | 9 | 130 | 0 | 9 | 0 | 85 | 10 | 204 | 1 | 18 | 0 | 2 | 6 | 34 | 0 | 0 | (1) |
| Hoefnagel D *et al*, 2014 | 89 | 581 | 60.3 | 56.2 | 46 | 180 | 515 | 447 | 28.9 | 26.3 | 58 | 140 | 15 | 115 | 16 | 115 | 71 | 468 | 13 | 88 | 5 | 25 | 69 | 386 | 0 | 0 | (9) |
| Safaee M *et al*, 2014 | 12 | 467 | 56 | 58 | 5 | 136 | 454 | 348 | 32 | 28 | NR | NR | NR | NR | NR | NR | 7 | 376 | 5 | 77 | 0 | 31 | NR | NR | NR | NR | (23) |
| Nunno A *et al*, 2019 | 170 | 5036 | 54.6 | 58 | 66 | 1682 | - | - | 29 | 28 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | 108 | 811 | 10 | 66 | (24) |
| Fluss R *et al*, 2021 | 17 | 197 | 62 | 59.63 | 9 | 62 | 417 | 426 | 31 | 302 | 14 | 120 | 0 | 0 | 2 | 59 | 1 | 5 | 12 | 99 | 4 | 35 | 8 | 46 | 2 | 1 | (25) |

VTE, [Thromboembolic complications: Deep venous thrombosis (DVT), pulmonary embolus (PE)] group; Control, Control group; BMI, body mass index; NR, not reported.

Table II. Newcastle-Ottawa Scale quality assessment of final article pool.

| Trial, year | Study design | Newcastle-Ottawa Scale | | | | (Refs.) |
|---|---|---|---|---|---|---|
| | | Selection | Comparability | Exposure | Total scores | |
| Gerber *et al*, 2007 | Retrospective | 3 | 3 | 3 | 9 | (1) |
| Hoefnagel *et al*, 2014 | Retrospective | 3 | 3 | 3 | 9 | (9) |
| Safaee *et al*, 2014 | Retrospective | 3 | 3 | 3 | 9 | (23) |
| Nunno *et al*, 2019 | Retrospective | 3 | 2 | 2 | 7 | (24) |
| Fluss *et al*, 2021 | Retrospective | 3 | 2 | 2 | 7 | (25) |

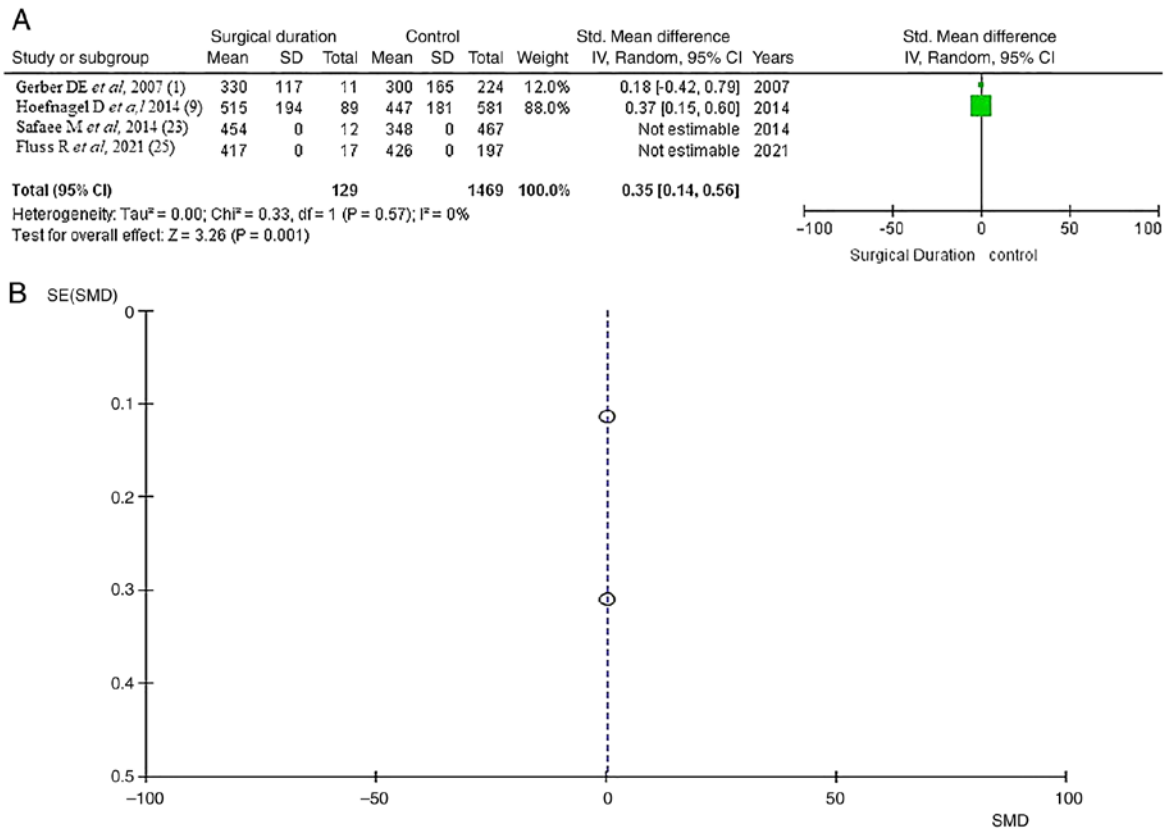


Figure 2. Surgical duration. (A) OR Forest plot surgical duration: Results demonstrated a statistically significant results (OR 0.35, CI 95% 0.14-0.56 and P<0.05). (B) Funnel plot of the Surgical Duration in the group of patients with surgical management of intracranial meningiomas, demonstrated no heterogeneity (P=0.57 and $I^2$=0%). OR, odds ratio; CI, confidence interval; P, P-value; $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance; SE, standard error; SD, standard deviation; SMD, standard mean difference.

*Location*. Information regarding location was available in three of five articles (1,9,25).

*Supratentorial*. Supratentorial location was reported in 390 (38.9%) of the 1,002 patients in the total sample and in 81 (69.2%) of the 117 patients in the VTE group. The results of the analysis demonstrated no statistically significant difference (OR 2.13, CI 95% 0.98-4.63 and P=0.06) with heterogeneity (P=0.02 and $I^2$=75%; (Fig. S1).

*Infratentorial*. As regards the infratentorial location, the total number of patients was 124 (12.3%) from 1,002 in the total sample and 15 (12.8%) from 1,117 in the VTE group. The statistical analysis demonstrated no potentially significant difference [OR 0.83, CI 95% (0.47-1.48), P=0.54], providing no heterogeneity (P=0.91 and $I^2$=0%) (Fig. S2). A very low publication bias was found.

*Skull base*. In total, 259 (24.8%) of 1,002 patients had skull base location and 18 (15.3%) of 117 had VTE. The results of the analysis demonstrated no statistically significant difference (OR 0.58, CI 95% 0.23-1.46 and P=0.25), with low heterogeneity (P=0.23 and $I^2$=33%; Fig. S3).

*Ki-67 is a proliferation marker for human tumor cells*

*Ki-67 <2%*. Information regarding Ki-67 <2% was available in four of five articles (1,9,23,25) and demonstrated no statistical significance (OR 0.98, CI 95% 0.72-1.31 and P=0.87)

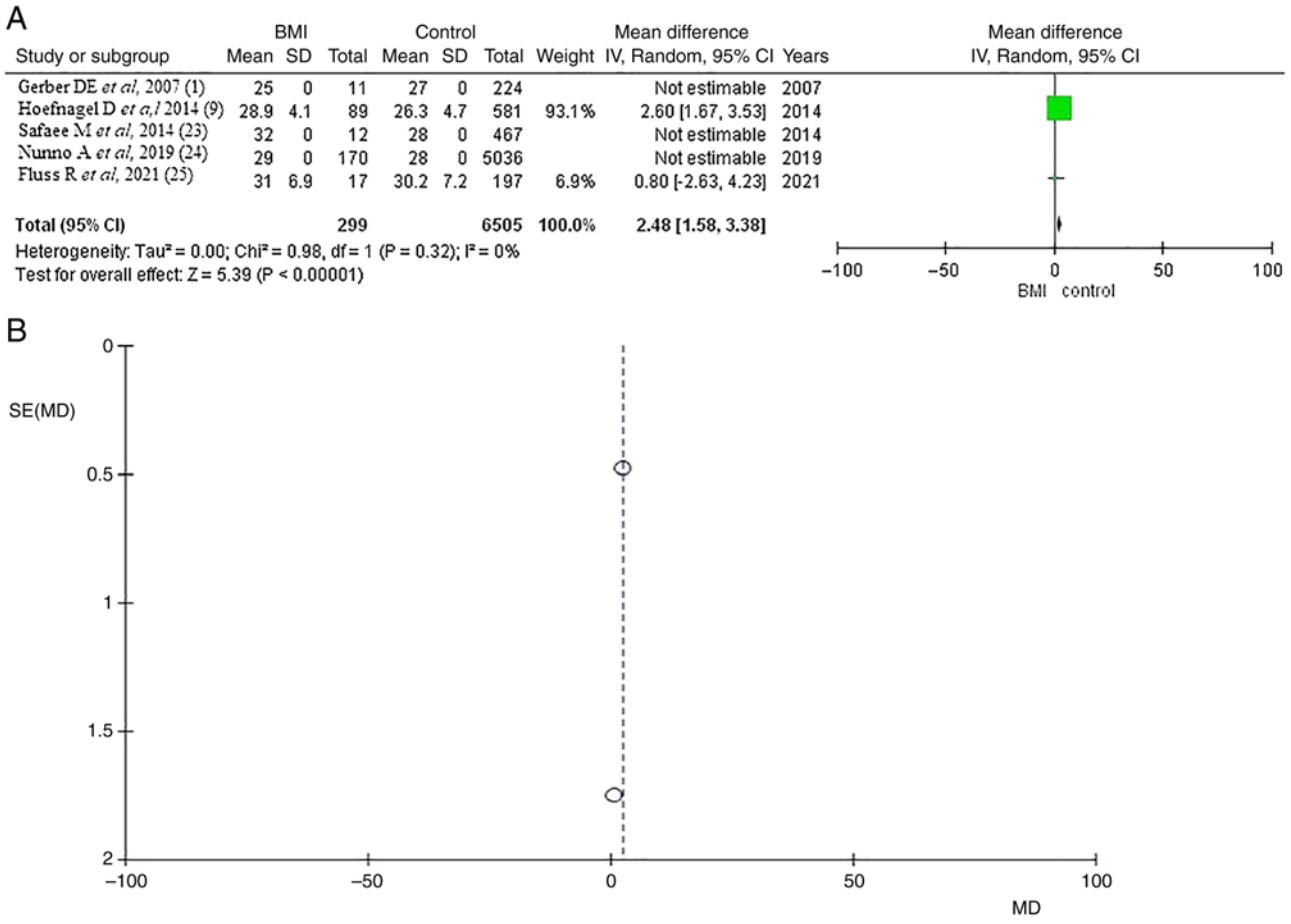


Figure 3. BMI significance. (A) Forest plot body mass index (BMI): Results demonstrated a statistically significant result (OR 2.48, CI 95% 1.58-3.38 and P<0.05). (B) Funnel Plot, testing the sensitivity with funnel plot for BMI, there was no heterogeneity and thus low publication bias (P=0.32 and $I^2$=0%). BMI, body mass index; OR, odds ratio; CI, confidence interval; P, P-value; $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance; SE, standard error; SD, standard deviation; MD, mean difference.

with no heterogeneity (P=0.76 and I2=0%;Fig. S4). Ki-67 <2% was found in 1,053 of 1,469 (71.6%) patients in the total group, compared with the VTE group, where Ki-67 <2% was diagnosed in 89 of 129 (68.9%) patients.

*Ki-67 2-10%*. There were 282 (19.1%) of the 1,469 patients with Ki-67 (2-10%) and 31 (24.0%) of the 129 patients with VTE in the total group of patients. The results of the analysis demonstrated no statistically significant difference (OR 1.30, CI 95% 0.84-2.01 and P=0.24), with no heterogeneity (P=0.45 and $I^2$=0%; Fig. S5).

*Ki-67 >10%*. As regards the Ki-67 >10%, the total number of patients was 93 (6.3%) from 1,469 patients and 9 (6.9%) from 129 in the VTE group. The statistical analysis demonstrated no potentially significant difference (OR 1.37, CI 95% (0.43-2.80), P=0.38), providing no heterogeneity (P=0.86 and $I^2$=0%; Fig. S6). A very low publication bias was found.

*Morbidity*. Morbidity data were available in four of the five articles (1,23-25) with a total of 1,277 (21.1%) patients; poor KPS in 191 (66.5%) of 287 VTE patients, a statistically significant difference (OR 2.58, CI 95% 1.11-5.99 and P=0.03) and heterogeneity (P=0.05 and $I^2$=92%; Fig. 4). Testing the sensitivity, the present study used the 'leave out one' model and removed one study at a time (Table III). After removing the article by Safaee *et al* (23), a statistically significant difference result was found (OR 4.19, CI 95% 3.30-5.31 and P<0.05), with no heterogeneity (P=0.37 and $I^2$=0%; Fig. 4B). It was found that the study results without the Safaee *et al* (23) displayed superior dispersion, with very low publication bias.

*Mortality*. As regards the mortality rate, information was available in four of the five articles (1,9,23,25). In the total group of patients, there were 129 (8.7%) from 1,469 patients diagnosed and 12 (17.9%) from 67 in the VTE group. The pooled results demonstrated a statistically significant result (OR 29.12, CI 95% 7.89-107.38 and P<0.05) with no heterogeneity (P=0.92 and $I^2$=0%; Fig. 5).

## 4. Discussion

The present study suggested that open surgery for meningiomas was associated with postoperative VTE in 4.5% of patients. More precisely, a mean surgical duration time >380 min and a mean BMI >27.9 kg/$m^2$ were statistically significant VTE-related parameters in patients who underwent meningiomas surgery, showing an association with VTE-related morbidity and mortality. The findings of the present meta-analysis study suggested that surgical duration and BMI

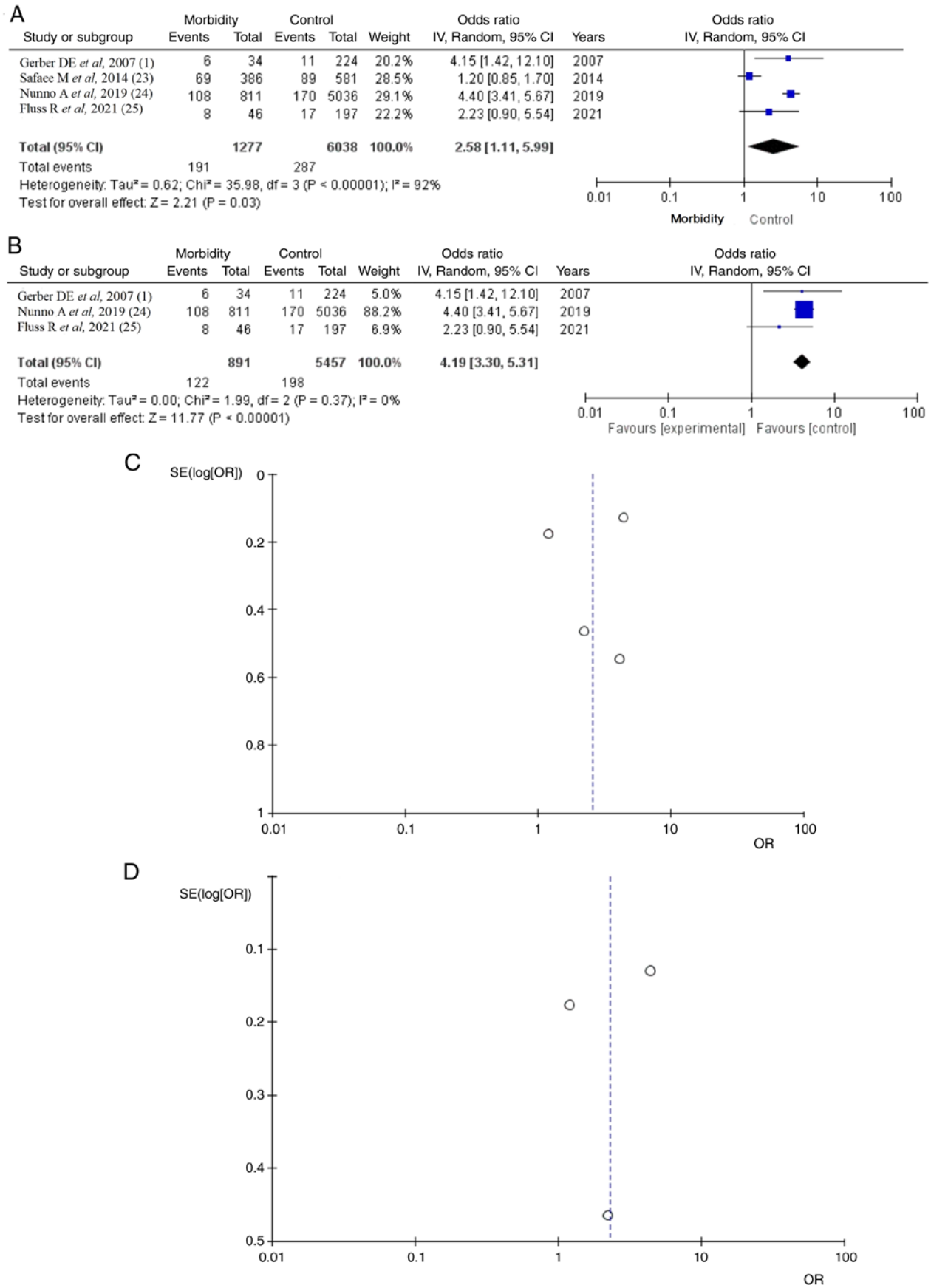


Figure 4. Morbidity. (A) Forest plot morbidity: Results demonstrated a statistically significant difference between total surgical meningiomas and VTE groups (OR 0.63, CI 95%-0.06-1.32 and P=0.05). (B) OR forest plot morbidity without Safaee *et al* (23): Results demonstrate again a statistically significant difference result, (OR 4.19, CI 95% 3.30-5.31 and P<0.05). (C and D) Funnel plots of the mortality in the total surgical meningiomas and VTE groups, with (left) or without (right) Safaee *et al* (23) and with (left) heterogeneity (P<0.05 and $I^2$=92%) or without (right) heterogeneity (P=0.37 and $I^2$=0%). VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval; P, P-value; $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance; SE, standard error.

Table III. Meta-analysis results.

| Outcome | Trial n=5 | Group | | Overall effect | | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|
| | | VET | Control | Effect estimate | CI 95% | P-value | $I^2$ (%) | P-value |
| Surgical duration (mean) | 4 | 429 | 380 | 0.35 | (0.14-0.56) | <0.05 | 0 | 0.57 |
| BMI (mean) | 5 | 29.1 | 27.9 | 2.48 | (1.58-3.38) | <0.05 | 0 | 0.32 |
| Tumor location | | | | | | | | |
| Supratentorial | 3 | 81 | 390 | 2.13 | (0.98-4.63 | 0.06 | 75 | 0.02 |
| Infratentorial | 3 | 15 | 124 | 0.83 | (0.47-1.48) | 0.54 | 0 | 0.91 |
| Skull base | 3 | 18 | 259 | 0.58 | (0.23-1.46) | 0.25 | 33 | 0.23 |
| Ki-67 | | | | | | | | |
| <2% | 4 | 89 | 1,053 | 0.98 | (0.72-1.31) | 0.87 | 0 | 0.76 |
| 2-10% | 4 | 31 | 282 | 1.30 | (0.84-2.01) | 0.24 | 0 | 0.45 |
| >10% | 4 | 9 | 93 | 1.37 | (0.67-2.80) | 0.38 | 0 | 0.86 |
| Morbidity | 4 | 191 | 1,277 | 2.58 | (1.11-5.99) | 0.03 | 92 | <0.001 |
| | 3 | 185 | 1,243 | 2.29 | (0.85-6.16) | 0.10 | 94 | <0.001 |
| | 3 | 122 | 891 | 4.19 | (3.30-5.31) | <0.05 | 0 | 0.37 |
| | 3 | 83 | 466 | 1.95 | (0.94-4.07) | 0.07 | 65 | 0.06 |
| | 3 | 183 | 1,231 | 2.71 | (0.97-7.52) | 0.06 | 94 | <0.001 |
| Mortality | 4 | 12 | 67 | 29.12 | (7.89-107.38) | <0.05 | 0 | 0.92 |

P-values in bold indicate a statistically significant difference. VTE, [Thromboembolic complications: Deep venous thrombosis (DVT), pulmonary embolus (PE)] group; Control, Control group; BMI,body mass index; CI, confidence interval; P, P-value; $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance.

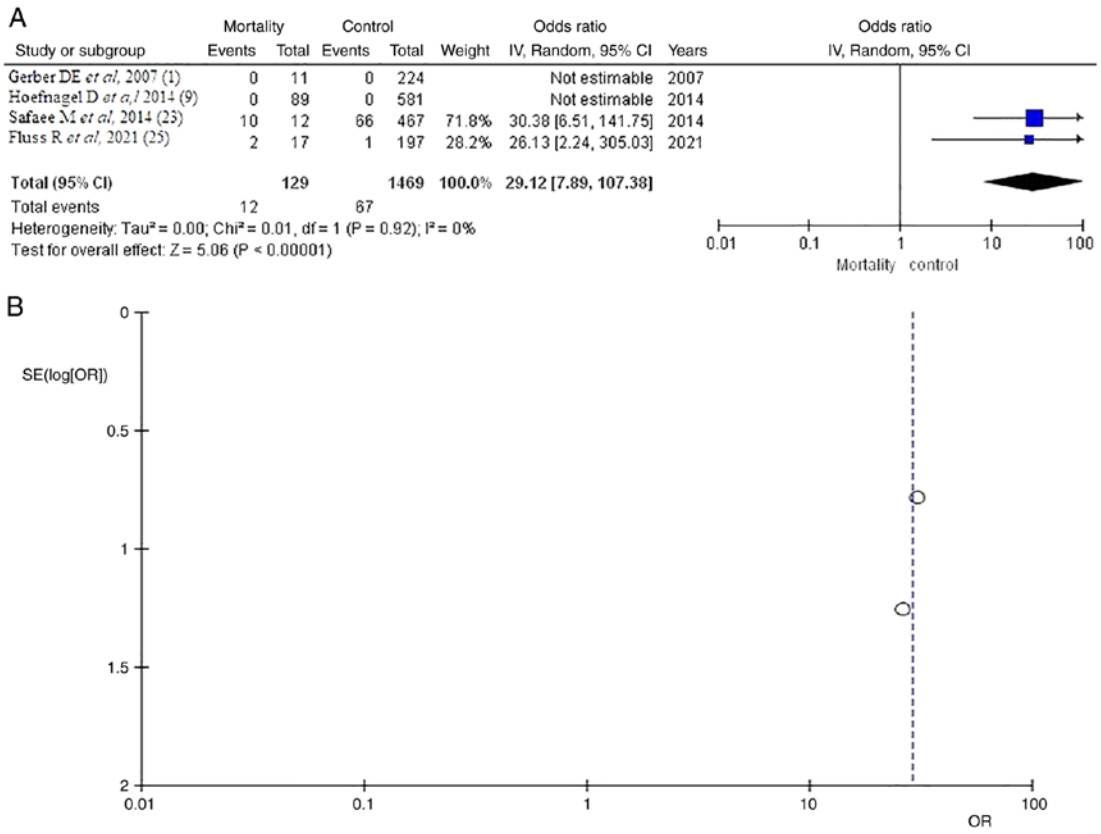


Figure 5. Mortality. (A) Forest plot mortality: Results demonstrated a statistically significant result (OR 29.12, CI 95% 7.89-107.38 and P<0.05). (B) Funnel Plot, testing the sensitivity with funnel plot for mortality; there was no heterogeneity and thus low publication bias (P=0.92 and $I^2$=0%). OR, odds ratio; CI, confidence interval; P, P-value; $I^2$, the percentage of total variation across studies that is due to heterogeneity rather than chance; SE, standard error.

are related to a high risk of VTE and, thus, an increased risk of postoperative morbidity (KPS <80) and mortality.

The 4.5% postoperative VTE rate taken out of these data is certainly lower than rates accounted for in other studies, which have reported up to 72% of patients with meningiomas developing VTE (26). However, this approximation relies on how VTE is defined. Thus, the literature on symptomatic postoperative VTE mentions a much lower percentage, with rates between 3.09 and 7.2% (9,11), which fits the results of the present study.

A number of the risk factors identified in the present study have been previously reported (24). A mean surgical duration has not been correlated with patients with meningioma but is a known risk factor for VTE (27,28). A mean surgical duration of more than 310 min, defined as the time from anesthesia induction to skin closure, appears to be associated with poor outcome and a high risk of mortality and morbidity in patients with postoperative VTE after meningiomas resection in the present study.

In addition, obesity, defined by BMI, has not been correlated with patients with meningioma but is known as another risk factor for VTE (10). The present study included BMI as one of the main parameters associated with postoperative meningiomas and VTE-related morbidity and mortality.

Although a number of risk factors have been found significant for the development of VTE, such as larger tumor size and skull base location (8,29), the present study found no statistically significant results. Additionally, the Ki-67 proliferation marker for human tumor cells does not relate to VTE-related mortality and morbidity in patients who underwent surgical resection for meningiomas.

In the present study, the mortality rate of patients with postoperative VTE was found to be 17.9%, which is almost double the 5.88% derived from the literature (9,24). This inconsistency may be due to measuring the mortality rate in the different postoperative periods.

*Study limitations*. There are several limitations to the present study. First, all eligible reports that were included were retrospective. These retrospective studies, by definition, rely on imprecision and can suffer from data loss. Additionally, the methods of the included studies differed significantly. Among these differences were the operative technique (e.g., anterior/lateral approach) and length of follow-up (e.g., 30-90 days). Finally, limitations of the other studies were the small sample size and that there was not among the included studies in the current paper a clearly separated information about receiving LMWH. Thus the identification of VTE risk in patients receiving LMWH compared with those not receiving LMWH or other VTE prophylaxis measures could be indicate the aim of a possible future study.

## 5. Conclusions

The present study investigated the clinical outcomes of patients who had postoperative VTE following intracranial meningioma resection. The findings demonstrated that open surgery for meningiomas was associated with postoperative VTE. Furthermore, surgical duration and BMI were statistically significant VTE-related parameters in patients who underwent meningioma surgery, showing an association with VTE-related morbidity and mortality. The findings of the present meta-analysis study highlighted that surgical duration and BMI are related to a high risk of VTE and, thus, an increased risk of postoperative morbidity and mortality.

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## Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

## Authors' contributions

GF and VEG conceived the study. VEG, AAF, KT, PS, DAS, GF and NT analyzed the data and wrote and prepared the draft of the manuscript. VEG and GF provided critical revisions. All authors contributed to manuscript revision and have read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors have no competing interests.

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