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# Hemicraniectomy for Dominant vs Nondominant Middle Cerebral Artery Infarction: A Systematic Review and Meta-Analysis

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*Objectives:* Decompressive hemicraniectomy decreases mortality and severe disability from space-occupying middle cerebral artery infarction in selected patients. However, attitudes towards hemicraniectomy for dominant-hemispheric stroke have been hesitant. This systematic review and meta-analysis examines the association of stroke laterality with outcome after hemicraniectomy. *Materials and methods:* We performed a systematic literature search up to 6th February 2020 to retrieve original articles about hemicraniectomy for space-occupying middle cerebral artery infarction that reported outcome in relation to laterality. The primary outcome was severe disability (modified Rankin Scale 4–6 or 5–6 or Glasgow Outcome Scale 1–3) or death. A two-stage combined individual patient and aggregate data meta-analysis evaluated the association between dominant-lateralized stroke and (a) short-term ( $\leq 3$  months) and (b) long-term ( $> 3$  months) outcome. We performed sensitivity analyses excluding studies with sheer mortality outcome, second-look strokectomy, low quality, or small sample size, and comparing populations from North America/Europe vs Asia/South America. *Results:* The analysis included 51 studies (46 observational studies, one nonrandomized trial, and four randomized controlled trials) comprising 2361 patients. We found no association between dominant laterality and unfavorable short-term (OR 1.00, 95% CI 0.69–1.45) or long-term (OR 1.01, 95% CI 0.76–1.33) outcome. The results were unchanged in all sensitivity analyses. The grade of evidence was very low for short-term and low for long-term outcome. *Conclusions:* This meta-analysis suggests that patients with dominant-hemispheric stroke have equal outcome after hemicraniectomy compared to patients with nondominant stroke. Despite the shortcomings of the available evidence, our results do not support withholding hemicraniectomy based on stroke laterality.

**Key Words:** Aphasia—Decompressive hemicraniectomy—Dominant hemisphere—Middle cerebral artery infarction—Systematic review

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## Introduction

Space-occupying, ‘malignant middle cerebral artery infarction’ (MMCAI) refers to ischemic stroke caused by occlusion of the middle cerebral artery affecting more than half of the vascular territory and typically resulting in severe neurological defects and poor prognosis. It comprises 2–8% of all hospitalized ischemic strokes<sup>1</sup> with mortality up to 80% with conservative treatment.<sup>2–4</sup> Decompressive hemicraniectomy (DHC) prevents herniation caused by the mass effect and increased intracranial pressure, and reduces mortality and severe morbidity when performed within 48 h after stroke.<sup>5–7</sup>

Despite the benefit of surgery, questions about optimal patient selection remain, one being the effect of stroke laterality on outcome. Some of the early studies on DHC excluded patients with dominant hemisphere stroke due to expected unfavorable outcome.<sup>8–10</sup> Moreover, physicians’, patients’, and relatives’ attitudes towards DHC in dominant hemisphere infarct tend to be more cautious due to a presumed poor quality of life related to aphasia.<sup>11,12</sup> A pooled analysis of three randomized controlled trials (RCT) reported that surgery improved functional outcome in both aphasia and non-aphasia subgroups, although with a smaller absolute risk reduction in the former.<sup>13</sup> A previous systematic review (performed before the RCTs) found no difference in outcome between right- and left-lateralized stroke after DHC.<sup>14</sup> The evidence on the effect of infarct side on outcome after DHC is still inconclusive and debatable.

We conducted a systematic review and meta-analysis to investigate whether patients with dominant hemisphere MMCAI (dMMCAI) undergoing DHC have worse outcome than patients with nondominant MMCAI (nMMCAI). We examined short- and long-term outcomes and conducted sensitivity analyses for subgroups including only functional outcome data, without second-look strokectomy, based on the geographical background of the subject population, and excluding studies with low quality or small sample size.

## Methods

The study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses statement<sup>15</sup> and registered to the PROSPERO registry (ID CRD42020168052).

We performed a literature search in PubMed, Web of Science, Scopus, and Cochrane Library databases on 6th February 2020 with the terms “stroke”, “brain infarction”, “brain ischemia”, “middle cerebral artery” and “hemicraniectomy”, “craniectomy”, “decompression, surgical”, or “surgical decompression”. The search was limited to English language articles, and search restrictions to “Humans” and “Age 18 or above” were applied. The detailed search strategy is presented in Supplementary material.

The screening process was performed according to pre-defined criteria in two steps by four independent reviewers (DS, SR, KA, NMM). First, articles on DHC after MMCAI in human adults were identified based on titles and abstracts. Second, the reviewers obtained the selected full articles and made the final selection based on the following criteria: (1) original research article, (2) DHC performed for MMCAI, (3) outcome in relation to laterality reported or retrievable, (4) human studies, and (5) patients’ age 18 years or older. Studies investigating outcome in only dominant- or nondominant-lateralized stroke without a control group were excluded, as were studies with first-line strokectomy. If brain tissue was removed as an emergency procedure in conjunction of DHC or as a second-look surgery, the studies were included but an additional sensitivity analysis excluding patients with strokectomy was performed. In both steps, two reviewers cross-checked the results, and in case of disagreement, the selections were based on consensus. The references of the identified articles were reviewed for additional eligible articles.

The reviewers extracted the following data from the included articles: number of participants, study years, centers, study design, patient demographics, stroke laterality, affected vascular areas besides MCA, recanalization treatment, National Institutes of Health Stroke Scale and Glasgow Coma Scale (GCS) score before DHC, midline shift, time from onset to DHC, functional outcome, quality of life outcomes, mortality, and follow-up time. If the article comprised both surgically and conservatively treated patients, only the former were included. If both the hemispheric dominance/presence of aphasia and lesion side were presented, we used the former for analyses. If only the lesion side was reported, we assumed the left hemisphere to be responsible for language dominance. For clarity, we now use the term ‘dMMCAI’ for either the left or dominant hemisphere and ‘nMMCAI’ for the right and nondominant hemisphere.

Due to variability of outcome measures, our primary outcome was dichotomized severe disability or death (1) up to three months (short-term outcome) or (2) more than three months after stroke (long-term outcome). Severe disability was determined as a modified Rankin Scale (mRS) score 4–6 or 5–6 (depending on the definition of individual studies) or a Glasgow Outcome Scale (GOS) score 1–3. Studies with functional outcome reported only according to the Barthel index were excluded due to lack of general consensus about how to dichotomize the scale for severe disability. However, mortality data from these studies were included.

For analyses, studies were divided into three categories: (1) studies presenting individual patient data (IPD), (2) studies reporting a number of patients with dMMCAI and outcome (aggregate data, AD), and (3) studies reporting summary statistics on the association of laterality with outcome without access to more detailed data. The first

two groups were included in the meta-analysis. The authors of studies in the third group were contacted three times with a request for further data, and if received, or if the study provided odds ratios (OR) for laterality, the study was included in the analyses.

We assessed the quality of the included studies with the Newcastle-Ottawa Scale (NOS) for cohort or case-control studies<sup>16</sup> and with the Risk of bias in randomized trials (RoB 2) tool for RCTs,<sup>17</sup> adapted to evaluate the quality in respect to the current research question. Certainty of the body of evidence was adjudicated with the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) system.<sup>18</sup>

#### *Data synthesis and analysis*

We performed a two-stage combined IPD and AD meta-analysis of the association between dMMCAI and (a) short-term and (b) long-term outcome. From each AD study, we constructed  $2 \times 2$  tables of exposure (dMMCAI versus nMMCAI) and outcome (favorable versus unfavorable) and calculated corresponding ORs and 95% CIs. For studies with available adjusted ORs, we used the adjusted estimates instead of calculated ORs. In each IPD study, we employed logistic regression analysis of identical dichotomous outcomes on stroke laterality, controlled for age and sex. We obtained separate pooled estimates for short-term and long-term prognoses. The mean effect size and CIs of individual studies were illustrated with forest plots. Heterogeneity among IPD studies, AD studies, and between IPD and AD data (overall) was tested with the Cochran's  $Q$  statistic and quantified with the  $I^2$  statistic. After inspecting the forest plots and confirming underlying heterogeneity, we employed random-effects models, irrespectively of dedicated tests. To avoid underestimation of heterogeneity, we utilized the Sidik-Jonkman two-step method, with an initial estimate of tau-squared through the variance component model and the conservative Hartung and Knapp correction on 95% CIs.

We conducted pre-specified sensitivity analyses by excluding studies that (a) included patients with additional strokectomy, (b) reported mortality as sole outcome, (c) included < 25 participants and, (d) were adjudicated as of low quality. We further explored heterogeneity by performing a sub-group analysis comparing the main estimates for the short- and long-term prognosis according to stroke laterality between studies in Europe/North America versus Asia/South America. Inter-subgroup discrepancy in the pooled effect was evaluated with the Cochran's test for heterogeneity between the groups. Random-effects meta-regression was implemented to evaluate the contribution of continuous participant characteristics (mean age, prevalence of women, and GCS at presentation) to the overall heterogeneity of the association between laterality and the outcomes.

We investigated the presence of publication bias by funnel plots of precision and by the Begg & Mazumdar regression tests for asymmetry. The analyses were performed with STATA package, version 12.1 (StataCorp, College Station, Texas, USA) and the module "ipdmetan". We deemed statistical significance at  $P < 0.05$ .

## **Results**

### *Literature search*

Fig. 1 summarizes the results of our systematic search. From a total of 3196 screened articles, we identified 51 studies (2361 patients), published between 1995 and 2019, with functional outcome or mortality data for the quantitative analysis: 4 RCTs,<sup>5-7,19</sup> 1 nonrandomized trial,<sup>20</sup> and 46 observational studies<sup>21-66</sup> (Supplementary Table I). Of the included studies, 30 reported AD and 21 IPD, but 10 of the latter were analyzed collectively with AD studies, either because of a low number of patients or events or missing data on confounding factors. Five additional articles were excluded for not returning our request for further data.<sup>67-71</sup> Ten studies reported mortality as the only outcome variable and 24 provided short-term outcome and 35 long-term outcomes (Supplementary Table I). The number of patients per study ranged from 5 to 355, and altogether 896 (38.0%) participants had dMMCAI. Most studies were conducted in Europe and Asia, and five studies included patients with additional emergency strokectomy. Four AD studies used adjusted estimates and 11 IPD studies provided data on age and sex for adjusted analyses (Supplementary Table II).

The quality assessment according to NOS alluded that 7 of the observational studies had high quality, 7 had medium quality, and 33 had poor quality. The evaluation of RCTs according to RoB 2 indicated some concerns of risk of bias for all four RCTs (Supplementary Table III).

### *Short-term outcomes*

After synthesizing available IPD and AD, dMMCAI was not associated with increased odds for adverse short-term outcomes (pooled OR 1.00, 95% CI 0.69-1.45,  $P = 0.99$ ) (Fig. 2). No heterogeneity was found within AD studies or between IPD and AD studies. There was no association of stroke laterality with outcome in either AD (pooled OR 0.98, 95% CI 0.64-1.49) or IPD studies (pooled OR 1.46, 95% CI 0.29-7.35).

When studies reporting on only mortality after the index stroke were excluded, no association of dMMCAI with unfavorable short-term prognosis was observed (pooled OR 1.15, 95% CI 0.66-2.01,  $P = 0.60$ ,  $I^2 = 0\%$ ). Sensitivity analyses including only (a) patients without strokectomy (pooled OR 1.13, 95% CI 0.75-1.71,  $P = 0.54$ , overall  $I^2 = 0\%$ ), (b) studies with > 25 participants (pooled OR 1.02, 95% CI 0.62-1.68,  $P = 0.93$ ,  $I^2 = 23.2\%$ ), or (c) studies of at least moderate quality (pooled OR 0.96, 95%

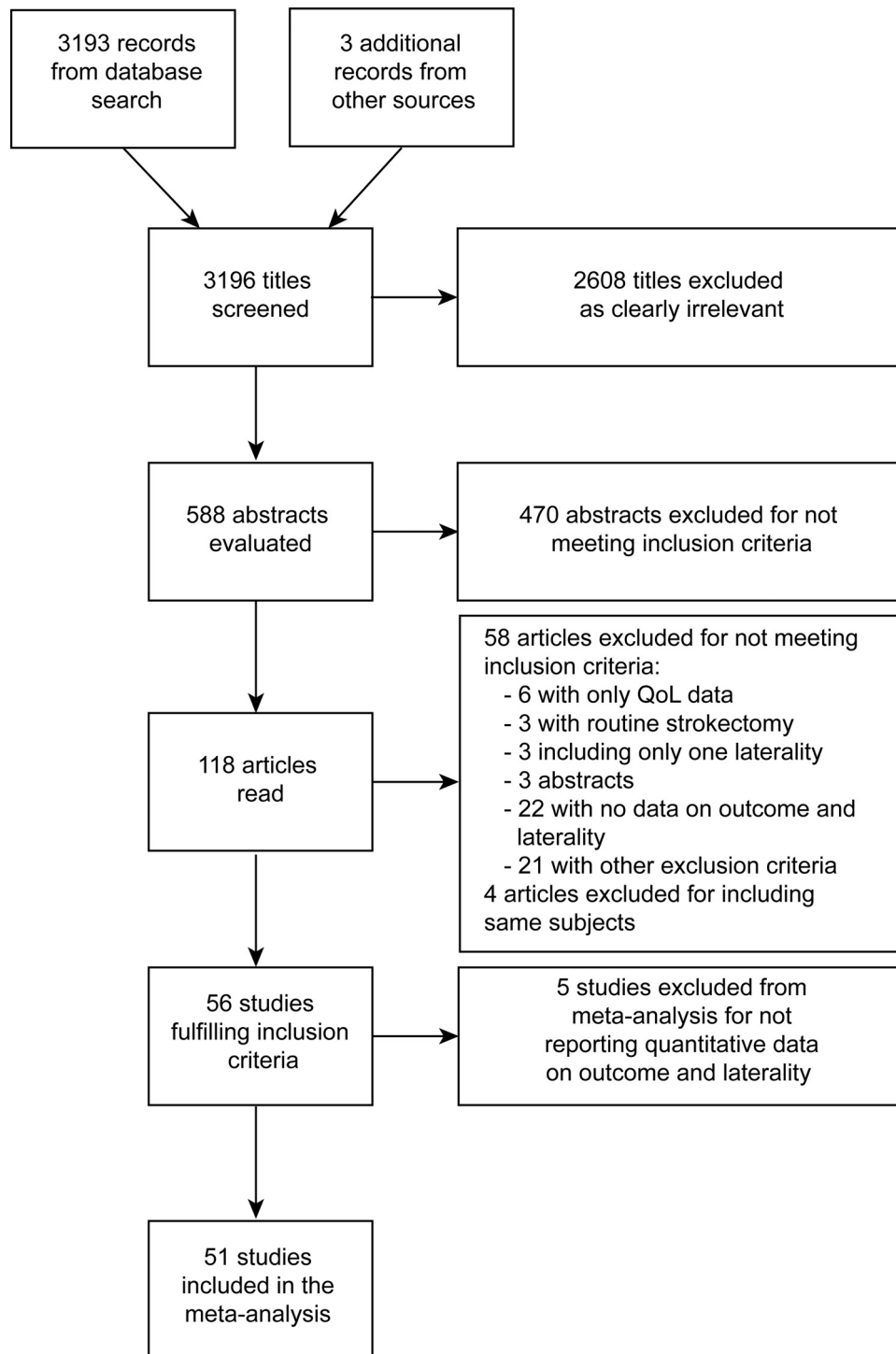


Fig. 1. Flowchart of the meta-analysis. QoL, quality of life.

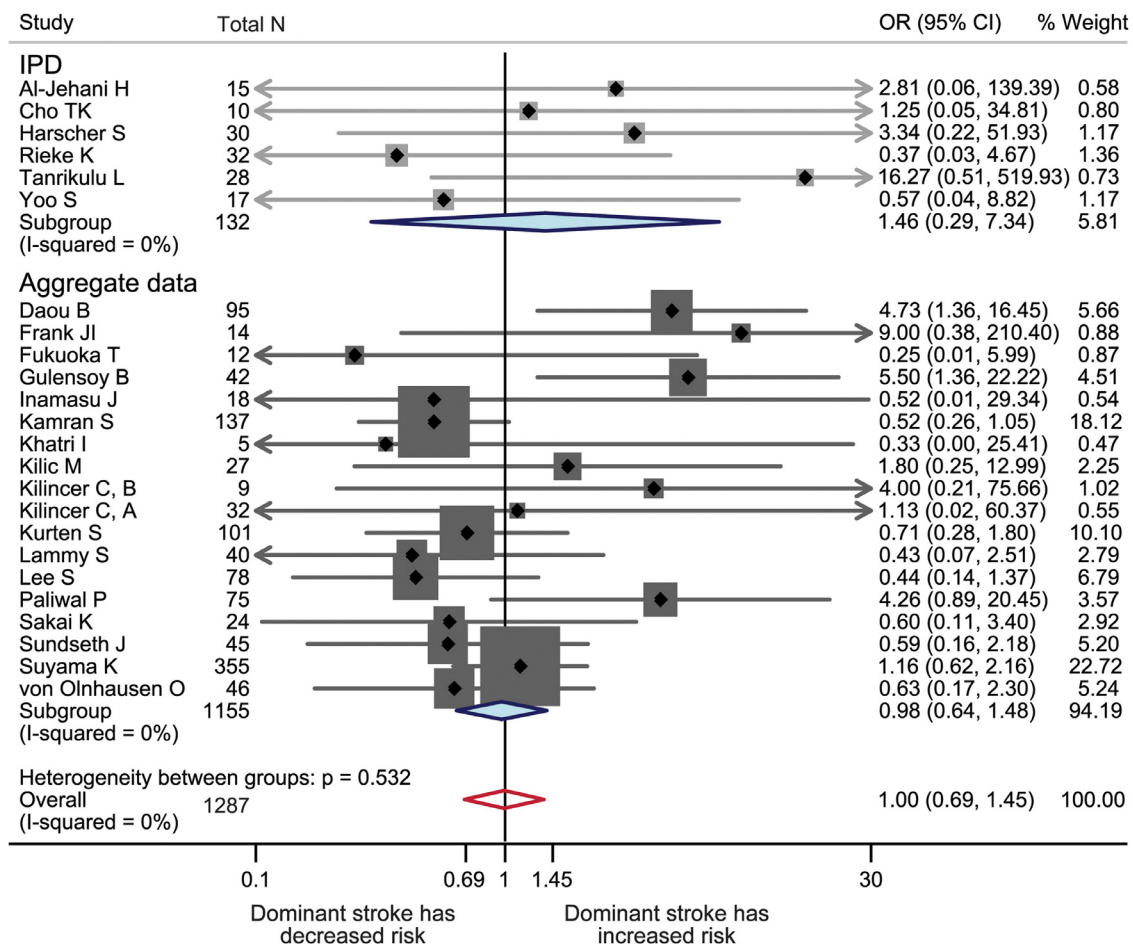
CI 0.48–1.93,  $P = 0.90$ ,  $I^2 = 53.8\%$ ) further showed lack of association between laterality and short-term prognosis.

#### Long-term outcomes

Dominant-hemispheric stroke was not related to unfavorable long-term outcome (pooled OR 1.01, 95% CI 0.76–1.33,  $P = 0.97$ ) (Fig. 3). Moderate heterogeneity was

observed within AD studies ( $I^2 = 20.4\%$ ) and small heterogeneity was seen overall ( $I^2 = 3.1\%$ ). No association of dMMCAI with unfavorable prognosis was seen in AD (pooled OR 1.07, 95% CI 0.74–1.56) or IPD (pooled OR 0.82, 95% CI 0.42–1.60) studies.

The result did not change when all-cause mortality was not included among assessed outcomes (pooled OR 1.03, 95% CI 0.70–1.53,  $P = 0.87$ ,  $I^2 = 26.3\%$ ) or when patients



**Fig. 2.** ORs and 95% CIs for dominant as compared to nondominant stroke for short-term prognosis (severe disability or death  $\leq 3$  months). Boxes represent the ORs and lines the 95% CIs for individual studies. The diamonds and their width represent the pooled ORs and the 95% CIs, respectively. Pooled estimates are derived from a random-effects model with the Sidik-Jonkman two-step estimator and the Hartung and Knapp correction. IPD, individual patient data; OR, odds ratio; CI, confidence interval.

with strokectomy were excluded (pooled OR 0.99, 95% CI 0.72–1.34,  $P = 0.92$ ,  $I^2 = 5.4\%$ ). Further sensitivity analyses demonstrated no association of stroke laterality with adverse prognosis after excluding small (pooled OR 0.90, 95% CI 0.63–1.29,  $P = 0.52$ ,  $I^2 = 0\%$ ) or low-quality studies (OR 0.97, 95% CI 0.67–1.40,  $P = 0.88$ ,  $I^2 = 0\%$ ).

#### Sub-group and meta-regression analyses

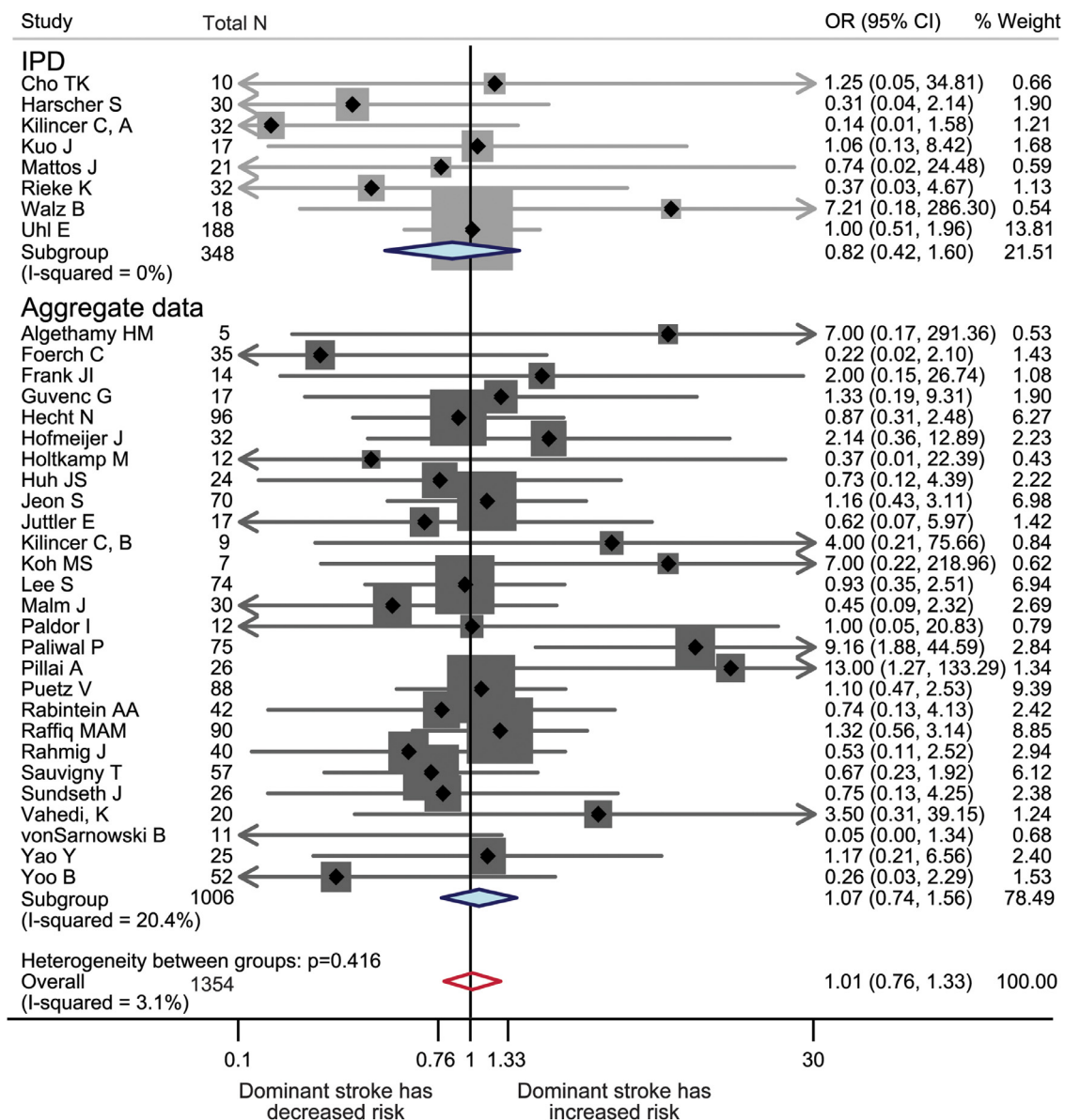
A stratified analysis according to studies' continent did not reveal a differential effect of stroke lateralization for short- (pooled OR 0.96, 95% CI 0.61–1.53,  $I^2 = 31.2\%$  versus OR 1.17, 95% CI 0.52–2.64,  $I^2 = 0\%$ , for European/North American and Asian/South American populations, respectively,  $P$  for interaction = 0.74) and long-term outcomes (pooled OR 0.94, 95% CI 0.45–1.98,  $I^2 = 47.8\%$  versus OR 0.93, 95% CI 0.60–1.45,  $I^2 = 0\%$ ,  $P$  for interaction = 0.97). Among continuous predictors, mean age, mean percentage of female patients, and mean GCS did not modify the association of dMMCAI and the outcomes ( $P$  for all meta-regression analyses  $> 0.1$ )

#### Publication bias

Funnel plots for the association of dMMCAI with unfavorable short- and long-term outcomes were asymmetrical at the left lower part, especially for the long-term prognosis (Fig. 4a and b). However, regression tests for asymmetry did not confirm a possible small-studies effect ( $P > 0.1$  for both outcomes), favoring rather the absence of small studies with a significant protective effect of dMMCAI than a true publication bias.

#### Certainty/grading of evidence

According to the GRADE system, the certainty of evidence on the association between laterality and outcome based on the selected studies is very low for the short-term outcome and low for the long-term outcome. This mainly stems from the methodological limitations of small observational studies, as well as from the risk of bias due to insufficient adjusting for confounding factors, imbalance of patients with dMMCAI and nMMCAI, implying different criteria for inclusion, and imprecision (Table 1).



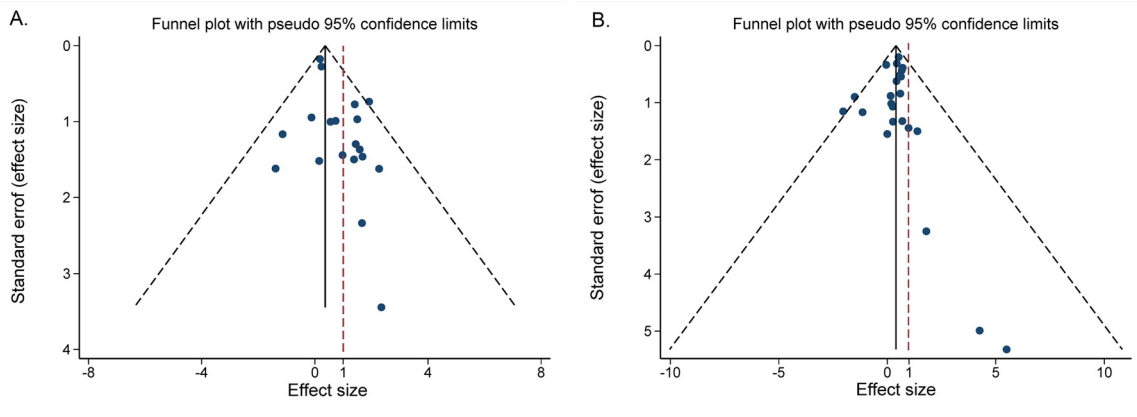
**Fig. 3.** ORs and 95% CIs for dominant as compared to nondominant stroke for long-term prognosis (severe disability or death > 3 months). Boxes represent the ORs and lines the 95% CIs for individual studies. The diamonds and their width represent the pooled ORs and the 95% CIs, respectively. Pooled estimates are derived from a random-effects model with the Sidik-Jonkman two-step estimator and the Hartung and Knapp correction. IDP, individual patient data; OR, odds ratio; CI, confidence interval.

However, no signs of publication bias were detected, and the results were consistent in all sensitivity analyses.

## Discussion

We found no difference in outcome after DHC between patients with dMMCAI and nMMCAI. The results were similar for short- and long-term follow-up, for both the combined outcome and functional outcome, and remained in all sensitivity analyses. The grade of evidence was very low for short-term outcome and low for long-term outcome, because the data come mostly from observational studies.

In a previous systematic review on the topic from 2004, the authors found no difference in functional outcome between the affected hemispheres.<sup>14</sup> Another study reviewed the effect of stroke laterality on mortality and morbidity in MMCAI patients treated either surgically or conservatively and discovered no significant difference between the sides.<sup>72</sup> Additionally, a recent meta-analysis of seven trials on endovascular thrombectomy for large vessel occlusion found no difference in outcome between patients with right or left hemisphere stroke.<sup>73</sup> Neither has there been outcome disadvantage for patients with left hemisphere strokes after intravenous thrombolysis;<sup>74</sup> in fact, one study reported that they have better functional



**Fig. 4.** Publication bias for (a) short- and (b) long-term outcomes and dominant hemisphere stroke. Circles represent individual studies and the vertical line the pooled estimate of the logarithmic odds ratio (OR) for each outcome.

outcome.<sup>75</sup> Moreover, another study on MCA strokes discovered that injury to the right hemisphere leads to less favorable long-term outcome and increased mortality compared to left hemisphere strokes.<sup>76</sup>

Most of the studies included in the present meta-analysis were observational cohort studies or case series. However, there were also four RCTs providing data on aphasia and outcome, whose surgery groups were included in our analysis. The data of the first three RCTs on DHC for MMCAI<sup>5-7</sup> were analyzed for crude ORs either as retrieved from the original study<sup>5</sup> or from the meta-analysis including patients treated within 48 h of the

stroke onset.<sup>13</sup> In addition to the data used in our analysis, the RCTs provided information on the benefit of DHC versus conservative treatment in an aphasia subgroup. In both DECIMAL and DESTINY<sup>6,7</sup> DHC produced a significant absolute risk reduction of poor functional outcome for patients with aphasia, whereas in HAMLET<sup>5</sup> the results of functional outcome at 12 months were neutral, seconding the main results of the study. However, in the meta-analysis on patients treated within 48 h, the absolute risk reduction for unfavorable functional outcome (mRS 5-6) with surgery was 44.2%.<sup>13</sup> Finally, a recent meta-analysis combining data from seven RCTs showed that

**Table 1.** Grading of evidence for the association of stroke laterality and unfavorable outcome.

Number of studies	Study design	Risk of bias	Certainty assessment				Publication bias	Certainty
			Inconsistency	Indirectness	Imprecision			
<b>Short-term combined outcome</b>								
24 (1287 patients)	22 observational studies, 1 non-randomized open trial, 1 randomized controlled trial	Very serious (7 studies with very serious, 17 studies with serious risk of bias)	No serious (no important or moderate $I^2$ in main analyses, overlap of point estimates, consistent subgroup analyses)	No serious	Serious (wide CIs)	Undetected	⊕⊕⊕⊕ Very low	
<b>Long-term combined outcome</b>								
35 (1354 patients)	31 observational studies, 4 randomized controlled trials	Serious (7 studies with very serious, 22 studies with serious and 6 studies with not serious risk of bias)	No serious (no important or moderate $I^2$ in main analyses, overlap of point estimates, consistent subgroup analyses)	No serious	Serious (wide CIs)	Undetected	⊕⊕⊕⊕ Low	



patients with aphasia have higher odds for achieving mRS  $\leq 3$  after DHC compared to conservative treatment.<sup>4</sup>

The ominous attitude towards dMMCAI seems to arise from the disposition to value verbal communication as a defining attribute for an acceptable quality of life and, on the other hand, underestimate the effect of nondominant hemisphere injury on cognition, independence, and mental health. However, the studies on quality of life do not to verify this assumption.<sup>56,63,77–81</sup> Moreover, patients with aphasia may recover some of their language function with intensive rehabilitation, especially in younger age groups.<sup>82</sup> Additionally, the right insular cortex seems to dominate in the neural regulation of autonomic functions,<sup>83</sup> supporting the hypothesis that right hemisphere stroke patients are more susceptible to cardiovascular complications.<sup>76</sup>

The relatively low number of patients with dMMCAI in our study implies a predisposition to withhold surgery in this patient group and imposes one of the greatest risks of bias to our results. First, the presence of aphasia may have affected the families' decision to consent to DHC.<sup>12</sup> Second, in many studies, the decision to operate was based on the treating physicians' individual evaluation, previously shown to gravitate towards conservative treatment for patients with dMMCAI.<sup>11</sup> Indeed, two nonrandomized studies stated the dominant location of stroke as a reason (family- or protocol-driven) to not perform surgery for some patients.<sup>20,58</sup> Thus, we cannot exclude the effect of an unprejudiced allocation on our results.

We acknowledge the following limitations when interpreting our results. First, only a subset of the included studies focused primarily on the association of laterality and outcome in patients undergoing DHC. Accordingly, most studies did not perform adjusted analyses, which weakens the grade of evidence. IPD, enabling adjustment for some confounding factors, were retrievable for approximately one fourth of the patients. Second, the definition of unfavorable functional outcome differed between the studies. Thus, there remains uncertainty about the effect of stroke lateralization on achieving moderately severe disability (mRS 4). Furthermore, as mRS emphasizes mobility over social or cognitive function,<sup>84</sup> it may not be an optimal tool to assess differences in functional outcome of patients with aphasia versus neglect. Finally, only some of the studies defined dominance of stroke, whereas most reported the side of the infarct. We assumed that the left side would represent the dominant hemisphere for the majority of the patients, which might have led to some flawed categorizations.

As a consequence of the limitations of the available data, our results are indicative at best. However, in shortage of larger, high-quality studies, we believe that the present meta-analysis can shed some light on the topic that prevails in the daily clinical decision making of stroke physicians and neurosurgeons and can guide better-

informed decisions for patients and their families facing this catastrophe.

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## Registration-URL

<https://www.crd.york.ac.uk/prospero/>; Unique identifier: CRD42020168052.

## Declaration of Competing Interest

None declared.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.jstrokecerebrovasdis.2021.106102](https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.106102).

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