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Decompressive craniectomy for the treatment of malignant infarction of the middle cerebral artery

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Early decompressive craniectomy (DC) has been shown to reduce mortality in malignant middle cerebral artery (MCA) infarction, whereas efficacy of DC on functional outcome is inconclusive. Here, we performed a meta-analysis to estimate the effects of DC on malignant MCA infarction and investigated whether age of patients and timing of surgery influenced the efficacy. We systematically searched PubMed, Medline, Embase, Cochrane library, Web of Science update to June 2014. Finally, A total of 14 studies involved 747 patients were included, of which 8 were RCTs (341 patients). The results demonstrated that early DC (within 48 h after stroke onset) decreased mortality (OR=0.14, 95%CI=0.08, 0.25, p<0.0001) and number of patients with poor functional outcome (modified Rankin scale (mRS)>3) (OR=0.38, 95%CI=0.20, 0.73, p=0.004) for 12 months follow-up. In the subgroup analysis stratified by age, early DC improved outcome both in younger and older patients. However, later DC (after 48h after stroke onset) might not have a benefit effect on lowering mortality or improving outcome in patients with malignant infarction. Together, this study suggested that decompressive surgery undertaken within 48 h reduced mortality and increased the number of patients with a favourable outcome in patients with malignant MCA infarction.

Stroke is the fourth leading cause of death, accounting for 5.2% of all deaths in the United States[1]. Intravenous thrombolysis within 3 to 4.5 hours of onset of stroke improves outcomes in acute ischemic stroke, however, space-occupying, large hemispheric infarction, usually resulting from acute occlusion of the internal carotid artery (ICA) or the middle cerebral artery (MCA), represents a devastating sub-group of severe ischemic stroke[2–4]. Patients with large hemispheric infarction typically present with hemiparalysis, severe sensory deficits, and aphasia when the dominant hemisphere is affected[5,6]. Despite optimal medical treatment such as ICP lowering therapy, controlled hyperventilation, and hypothermia, malignant MCA infarction still leads to death in 70–80% of cases[7,8]. Moreover, survivors were always associated with long-term disability. The poor prognosis is, at least partially, attributed to space-occupying edema, which can induce secondary mechanical and ischemic neuronal injury by compression of normal brain and blood vessels, and lead to herniation and death[9].

Decompressive craniectomy (DC) has been shown to be effective in lowering mortality in patients with malignant MCA infarction. DC is aimed to remove part of the ipsilateral cranium to allow outward herniation of the infarcted brain tissue before compression of formerly healthy brain tissue occurs, decrease the ICP and improve cerebral perfusion pressure, thereby aiding the blood flow to the ischemic penumbra[10–12]. Recently, three randomized controlled trials (RCTs) and their pooled analyses suggested that early DC significantly reduced mortality and improved favorable outcome defined as modified Rankin scale (mRS) ≤ 4[13–16]. However, a more recent meta-analysis following completion of HAMLET demonstrated a non-significant benefit of DC on the favourable outcome defined as mRS ≤ 3[13]. Moreover, there are some important questions unsolved regarding DC for treatment of malignant MCA infarction, such as whether age of patients and timing of surgery influence the effects of surgery. Thus, we present a meta-analysis of the all available studies to with the goal of identifying an optimum time-point and a potential cut-off age for the surgery.

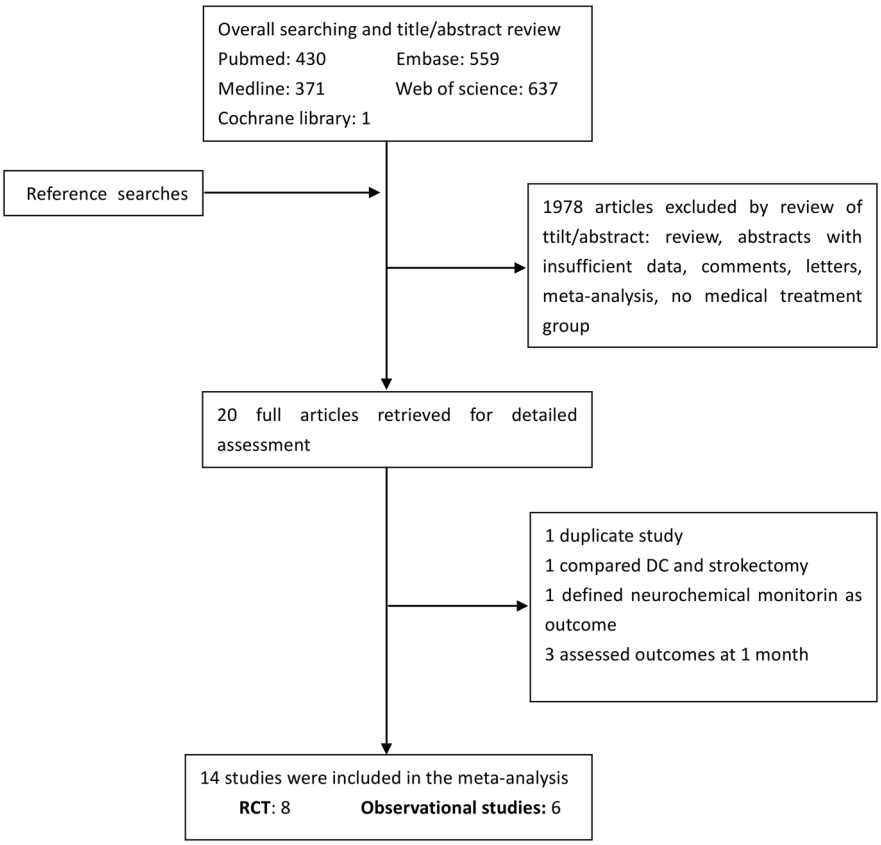

Figure 1 | **Flow chart of the literature search.**

Table 1 | Summary of results included in the meta-analysis

Study, publication year,location	Study type	groups	Age	Male (%)	Stroke onset to treatment (hours)	NIHSS	Hemisphere: Dominant (%)	Mean Follow-up (Months)
DESTINY,2007	RCT	Surgery (17)	43.2 (9.7)	8(47%)	12–36	21 (19–26)	9(53%)	12
Germany		Conservative (15)	46.1 (8.4)	7(47%)	12–36	24 (19–31)	11(73%)	12
DECIMAL, 2007	RCT	Surgery (20)	43.5 (9.7)	9(45%)	<30	22.5 (16–35)	12(60%)	12
France		Conservative (18)	43.3 (7.1)	9(50%)	<30	23.4 (17–38)	11(61%)	12
HAMLET, 2009	RCT	Surgery (32)	50.0 (8.3)	20(63%)	<96	23 (17–34)	12(38%)	12
Netherlands		Conservative (32)	47.4 (9.8)	18(56%)	<96	24 (20–36)	12(38%)	12
Zhao, 2012	RCT	Surgery (24)	63.5 (29–78)	6(25%)	<48	n.r.	9(37.5%)	12
China		Conservative (23)	64 (32–80)	7(30%)	<48	n.r.	9(39.1%)	12
Slezins, 2012	RCT	Surgery (11)	57.2 (49–67)	n.r.	<48	n.r.	n.r.	12
Latvia		Conservative (13)	65 (49–81)	n.r.	<48	n.r.	n.r.	12
DESTINY II, 2014	RCT	Surgery (49)	70 (62–82)	25(51%)	<48	20 (15–40)	16(33%)	12
Germany		Conservative (63)	70 (61–80)	31(49%)	<48	21 (15–38)	25(40%)	12
HeADDFIRST, 2014	RCT	Surgery (14)	52.3(45–59)	9(64%)	<96	21.5 (19–23)	5(36%)	6
America		Conservative (10)	57.9(45–66)	6(60%)	<96	19 (19–21)	5(50%)	6
HAMLET, 2014	RCT	Surgery (32)	50.0 (8.3)	20(63%)	<96	23 (17–34)	12(38%)	36
Netherlands		Conservative (32)	47.4 (9.8)	18(56%)	<96	24 (20–36)	12(38%)	36
Wang, 2006	R	Surgery (11)	61.6(14.5)	6(54.5%)	<24	12.3 (7.9)	2(18.2%)	6
Taiwan		Conservative (41)	66.7(13.2)	27(65.8%)	<24	18.2 (7.6)	23(56.1%)	6
Rahmanian, 2014	P	Surgery (30)	59.0(13.5)	11(36.7%)	<48	n.r.	12(40%)	3
Iran		Conservative (30)	62.1(11.0)	16(53.3%)	<48	n.r.	9(30%)	3
Yang, 2005	R	Surgery (10)	58.7(19.3)	5(50%)	<120	16.1 (1.9)	3(30%)	3
China		Conservative (14)	65.9(16.5)	10(71.4%)	<120	16.5 (2.4)	6(42.9%)	3
Yu, 2012	R	Surgery (58)	62.1 (12.4)	35(60.3%)	<48	16.2	19(32.8%)	6
Korea		Conservative (73)	72.6 (9.35)	36(49.3%)	<48	16.8	27(37%)	6
Rai, 2014	P	Surgery (36)	44.6 (12.2)	27(75%)	<148	19.0 (3.3)	16(44.4%)	12
India		Conservative (24)	57.1 (19.3)	16(66%)	<148	18.4 (3.8)	7(29.2%)	12
Tsai, 2012	P	Surgery (37)	65.5 (15.8)	18(48.6%)	<48	-	13 (35.1%)	6
China		Conservative (42)	75.9 (13.8)	22(52.4%)	<48	-	26 (61.9%)	6

Data are number (%), mean (SD) or median (range); R, retrospective; P, prospective; RCT, randomised controlled trials; n.r., not reported; NIHSS, National Institutes of Health stroke scale.

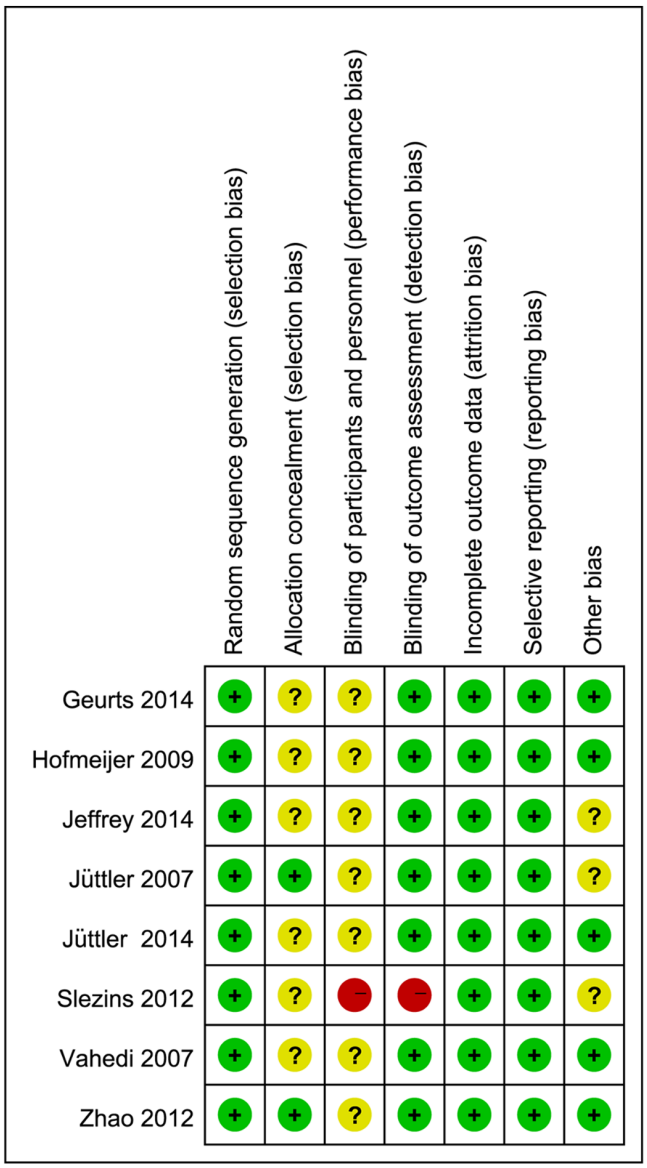

Figure 2 | Risk of bias assessment for randomized controlled trials. '+': low risk of bias, '−': high risk of bias, and '?': Indicates unclear risk of bias.

Results

Search Results and Study Characteristics. A diagram summarizing the process of study selection is shown in Figure 1. The combined search yielded 1998 citations, of which 1978 were excluded by review of titles and abstracts, because they were reviews, case reports, letters to editor, comments, and duplicate studies. Further, full texts of the remaining 20 articles were reviewed and analyzed in detail. Eventually, 14 studies met our inclusion criteria, comprising of 349 patients in the surgical treatment group and 398 patients in the conservative group. Of which, eight studies (341 patients) were RCTs[13,14,16–21], 4 (286 patients) were retrospective studies and 2 (120 patients) were prospective studies[22–27], The main characteristics of the studies included in this meta-analysis are summarized in Table 1.

Quality assessments for RCTs and cohort studies were summarized in the Supplementary Table S1–S2 and Figure 2. Briefly, for RCTs, randomization methods were described in 3 studies[13,17,19] and allocation concealments were adequate in 2 studies[14,21]. For blinding, 6 studies used blind observers to assess outcome, while blinded for carers or patients were unlikely in all RCTs. In addition, 2 studies reported the follow-up rates as 100[13,21]%, which were not mentioned in other studies. Finally, none study had selective outcome reporting. (Figure 2) For cohort studies, the results of quality assessment showed that all six studies had a moderate risk of bias and reached 6–7 out of 9 points. (Supplementary Table S1 and 2)

Early Decompressive Craniectomy. *Effect on Neurological outcome.* The proportion of patients with poor neurological outcome (defined as mRS>3) was reported for 3-month follow-up in 3 studies, 6 months follow-up in 8 studies, 12 months follow-up in 6 studies, and 36 months follow up in 1 study. The results indicated decompressive surgery significantly decreased number of patients with a poor outcome for 3 months follow up (OR=0.1, 95%CI=0.02, 0.48, p=0.004), 6 months follow-up (OR=0.34, 95%CI=0.20, 0.59, p=0.0001), and 12 months follow-up (OR=0.38, 95%CI=0.20, 0.73, p=0.004), but not for 36 months follow-up (OR=0.91, 95%CI=0.20, 4.09). (Figure 3 and Table 2)

In the subgroup analysis stratified by age of patients, the number of patients with poor functional outcome was significantly decreased in early DC group for 6 months follow-up (OR=0.28, 95%CI=0.10, 0.80, p=0.02 in younger patients and OR=0.28, 95%CI=0.10, 0.78, p=0.02 in older patients). (Figure 4A and Table 2) Moreover, no significant between-study heterogeneity was detected in either subgroup or overall analysis (p_h>0.2 for all comparisons).

Effect on Mortality. The results of pooled analysis demonstrated that early DC significantly reduced mortality (OR=0.14, 95%CI= 0.08, 0.25, p<0.0001). (Supplementary Figure S1) Similar results were observed in younger patients (OR=0.14, 95%CI=0.06, 0.35, p<0.0001) and in older patients (OR=0.20, 95%CI=0.11, 0.33, p<0.0001). (Supplementary Figure S2) Heterogeneity was not observed in all comparisons except for in one comparison (p_h=0.07), in which a random-effects model was used.

Survivors with moderately severe or severe disability. Meta-analysis of all 13 studies suggested there was no significant difference between early DC and best medical treatment in terms of proportion of survivors with moderately severe or severe disability for 3 months (OR=0.20, 95%CI=0.04, 1.03, p=0.05), 6 months (OR=0.65, 95%CI=0.34, 1.24, p=0.19), and 12 months (OR=1.67, 95%CI=0.74, 3.79, p=0.22) follow-up. (Figure 5 and Table 2) Similarly, in the subgroup analysis, early DC did not increase survivors with moderately severe or severe disability in younger patients (OR=0.68, 95%CI=0.21, 2.23, p=0.53) or in older patients (OR=0.53, 95%CI=0.17, 1.65). (Figure 4B and Table 2)

Later Decompressive Craniectomy. A total of 4 studies involved 97 patients were eligible for the analysis of the efficacy of later DC on functional outcome in patients with malignant MCA infarction, which indicated DC performed after 48 h of stroke onset was not associated with the improvement of functional outcome or reduction of mortality ((OR=0.16, 95%CI=0.02, 1.11, p=0.06 and OR=0.43, 95%CI=0.09, 1.94, p=0.27, respectively).

Assessment of Publication Bias. Publication bias was assessed by funnel plots and Egger's test. The shape of funnel plot did not reveal evidence of obvious asymmetry. (Figure 6) Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry, which did not show any evidence of publication bias (p>0.12 for all comparisons), indicating that our results are statistically robust.

Discussion

The present meta-analysis demonstrated that early decompressive surgery (within 48 hours after the onset of stroke) significantly increased the chance of a favorable functional outcome in patients with malignant MCA infarction, whereas later decompressive surgery might not reduce mortality or poor functional outcome.

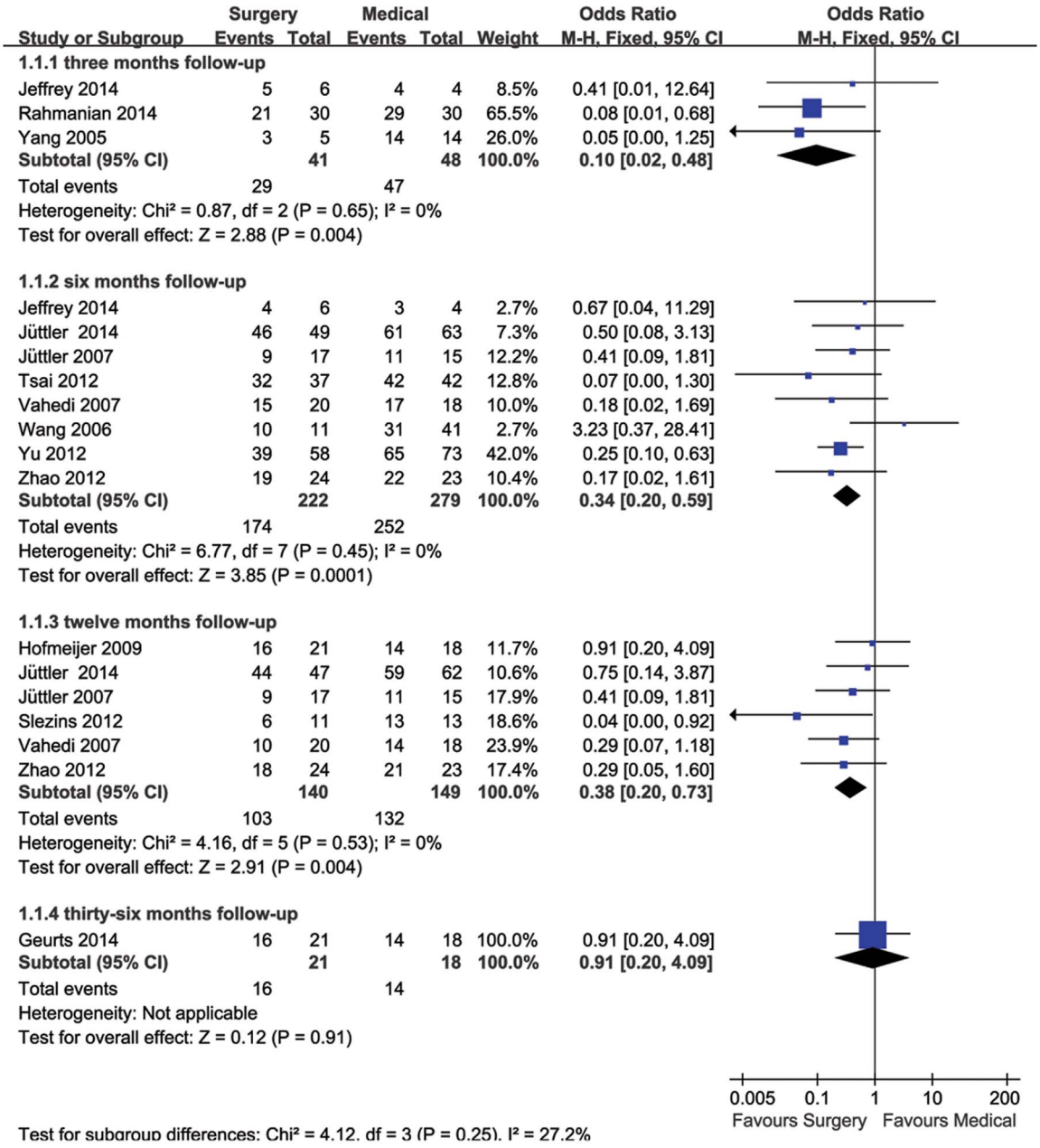

Figure 3 | **Forest plot with OR estimating with the corresponding 95% CI for unfavourable outcome (defined as mRS>3) associated with early DC versus medical treatment for individual trials and the pooled population at 3 months, 6 months, 12 months and 36 months follow-up (patients in all ages) CI, confidence interval; DC: decompressive craniectomy; OR, odds ratio; mRS: modified Rankin scale.**

Moreover, early DC did not increase the rate of patient survival with moderately severe or severe disability.

This study included a larger number of RCTs than two previous meta-analyses, which indicated early DC saved lives and increased good functional outcome (defined as mRS $\leq$ 4) in patients with malignant MCA infarction, but had a non-significant improvement in the percentage of survivors with good outcomes defined as mRS $\leq$ 3[13,15]. A mRS of 4 implied that the patient was unable to walk or attend to their own body need without assistance, thus, which was usually identified as an unfavourable outcome[13,14,28]. Moreover, in a recent study, a mRS of 4 was considered acceptable by less than half of the physicians (38.0%), whereas a mRS of 3 was considered acceptable by the majority (79.3%)[29]. Thus, we defined poor neurological outcome as mRS>3 and favourable outcome as mRS $\leq$ 3, and the results showed that DC performed within 48 h after stroke onset significantly reduced mortality and poor neurological outcome at 3 months, 6 months and 12 months follow-up.

We further investigated the association between age and functional outcome in patients underwent decompressive surgery, which was inconclusive in previous studies[30–32]. In the subgroup analysis stratified by age, the results showed reduced mortality with early DC compared with medical management (OR=0.20, 95%CI=0.11, 0.33, p<0.0001) in patients >60 years of age. Moreover, there was a significant reduction of unfavorable clinical outcome (mRS>3) in older patients (OR=0.20, 95%CI=0.10, 0.78, p=0.02), suggesting early DC had a benefit effect on functional outcome in older patients with malignant infarction.

Recent observational studies have strongly suggested that age is a main predictor of poor functional outcome after decompressive surgery[33]. In our meta-analysis, the proportion of older patients who had

Table 2 | ARR and OR estimates with the corresponding 95% CI for unfavourable outcome in early and later DC

Variables	Follow-up	Outcome	Number of patients	ARR (95%CI)	P	OR (95%CI)	P	P_h
Early DC (<48 h)	3 months follow-up	mRS>3	89	28% (12%, 44%)	0.0006	0.10 (0.02, 0.48)	0.004	0.65
Patients in all ages		Death	89	46% (28%, 65%)	<0.0001	0.14 (0.05, 0.36)	<0.0001	0.51
		mRS=4 or 5	50	30% (6%, 54%)	0.01	0.20 (0.04, 1.03)	0.05	0.87
	6 months follow-up	mRS>3	501	12% (6%, 18%)	<0.0001	0.34 (0.20, 0.59)	0.0001	0.45
		Death	501	35% (27%, 43%)	<0.0001	0.23 (0.15, 0.34)	<0.0001	0.07
		mRS=4 or 5	261	8% (−3%, 18%)	0.14	0.65 (0.34, 1.24)	0.19	0.72
	12 months follow-up	mRS>3	289	13% (5%, 22%)	0.002	0.38 (0.20, 0.73)	0.004	0.53
		Death	289	43% (33%, 53%)	<0.0001	0.14 (0.08, 0.25)	<0.0001	0.65
		mRS=4 or 5	136	12% (−28%, 4%)	0.13	1.67 (0.74, 3.79)	0.22	0.22
	36 months follow-up	mRS>3	39	2% (−25%, 28%)	0.91	0.91 (0.20, 4.09)	0.91	-
		Death	39	54% (27%, 80%)	<0.0001	0.09 (0.02, 0.40)	0.002	-
		mRS=4 or 5	20	−69% (−103%, −34%)	<0.001	18.82 (0.85, 414.97)	0.06	-
Patients below 60 years	6 months follow-up	mRS>3	105	22% (6%, 37%)	0.007	0.28 (0.10, 0.80)	0.02	0.91
		Death	105	43% (26%, 60%)	<0.0001	0.14 (0.06, 0.35)	<0.0001	0.83
		mRS=4 or 5	63	10% (−16%, 37%)	0.45	0.68 (0.21, 2.23)	0.53	0.95
Patients over 60 years	*6 months* follow-up	mRS>3	274	8% (1%, 14%)	0.02	0.28 (0.10, 0.78)	0.02	0.86
		Death	274	39% (30%, 49%)	<0.0001	0.20 (0.11, 0.33)	<0.0001	0.11
		mRS=4 or 5	122	9% (−4%, 21%)	0.18	0.53 (0.17, 1.65)	0.27	0.78
Later DC (>48 h)	3 months follow-up	mRS>3	33	31% (−2%, 63%)	0.06	0.16 (0.02, 1.11)	0.06	0.36
		Death	33	21% (−12%, 54%)	0.21	0.43 (0.09, 1.94)	0.27	0.20
		mRS>4	33	16% (−19%, 50%)	0.37	0.55 (0.13, 2.32)	0.41	0.08
	6 months follow-up	mRS>3	14	−8% (−57%, 40%)	0.73	1.5 (0.15, 15.46)	0.73	-
		Death	14	−4% (−55%, 46%)	0.87	1.20 (0.13, 11.05)	0.87	-
		mRS>4	14	13% (−40%, 65%)	0.64	0.60 (0.07, 5.14)	0.64	
	12 months follow-up	mRS>3	25	1% (−37%, 34%)	0.94	1.07 (0.18, 6.21)	0.94	-
		Death	25	8% (−28%, 45%)	0.65	0.68 (0.12, 3.77)	0.65	-
		mRS>4	64	13% (−9%, 36%)	0.24	0.51 (0.16, 1.58)	0.24	0.65
	36 months follow-up	mRS>3	24	1% (−36%, 38%)	0.94	0.93 (0.16, 5.54)	0.94	-
		Death	24	13% (−26%, 51%)	0.51	0.57 (0.10, 3.18)	0.52	-
		mRS>4	24	13% (−26%, 51%)	0.51	0.57 (0.10, 3.18)	0.52	-

ARR: absolute risk reductions; CI: confidence interval; DC: decompressive craniectomy; mRS: modified Rankin scale; OR: odds ratios; P_h: P value for heterogeneity test; PS: prospective study; RCTs: randomised controlled trials; RS: retrospective study, mRS=4 or 5: survivors with mRS=4 or 5.

poor functional outcome (88.3% ± 6.1%) was significant higher than that of younger patients (66.8% ± 11.3%, p=0.016). These results were consistent with a recent review, in which just 6 (8%) of 72 older patients (>60 years of age) had a favorable outcome after surgery[34]. Together, these results suggested that early DC saved lives and improved neurological outcome in patients >60 years of age. In addition, higher age was a powerful predictor of poor outcome in patients with DC.

The time-point for decompressive surgery is another clinical factor that is associated with the efficacy of decompressive surgery on patients with malignant MCA infarction[5,29,35]. The present pooled-analysis, including 97 patients who underwent DC after 48 h of stroke onset, showed that later DC did not decrease unfavourable outcome and mortality in patients with malignant infarction. (OR=0.16, 95%CI=0.22, 1.11, p=0.06 and OR=0.43, 95%CI=0.09, 1.94, p=0.27, respectively) Generally, patients with malignant infarction deteriorate after 48 h from edema formation, and death usually occurs in most patients within 72 h to 96 h[36]. By that time, cerebral edema would be getting close to its normal peak, thus, DC seems to lose its superiority over medical treatment. However, the lack of perceived benefit in the later DC group might not be very conclusive owning to relatively small number of patients in previous studies.

In addition, recent studies indicated DC for malignant MCA infarction thus resulted in a significant reduction in mortality, but nearly all survivors suffer moderately severe or severe disability (defined as mRS=4 or 5). Whether there was a trend towards an increase in the number of patients with moderately severe or severe disability undergoing DC is unclear[15,18]. Our meta-analysis indicated that, the proportion of patients surviving with moderately severe or severe disability was not increased in DC group compared with conservative treatment group (OR=0.68, 95%CI=0.21, 2.23, p=0.53 in younger patients, and OR=0.53, 95%CI=0.17, 1.65, p=0.17 in older patients).

Several limitations of our study should be considered. First, the mRS score mainly reflects motor abilities and dependency, and may have a neglect for neuropsychological functions and quality of life. Second, for the analysis in older patients, 2 RCTs and 1 retrospective study including patients >60 years, and the other retrospective study used ≥70 years as their age. Thus, this might introduce some bias due to the possibility that some of patients between 60 and 70 years were not included in this meta-analysis. Third, in the subgroup analysis by age, 40% percents older patients were from non-RCTs, which might have a clear selection bias toward healthy or active older patients for performing the surgical procedure. Also, findings of our study could be limited by the inclusion of published data only, such as, DEMITUR, a RCT involving 151 patients with malignant infarction of MCA carried from January 2003 to December 2007, has not published yet[37]. Finally, a language bias might have been introduced because only studies in English were included.

In conclusion, despite these limitations, our study demonstrated that early DC was effective in lowering mortality and improving functional outcome in patients with malignant MCA infarction. Although higher age was an important predictor of unfavorable outcome in patients underwent decompressive surgery, early DC did increase the probability of survival and reduce poor functional outcome in patients >60 years of age. Finally, large, multicenter RCTs comparing the efficacy of decompressive surgery and conservative treatment are required, especially in older patients.

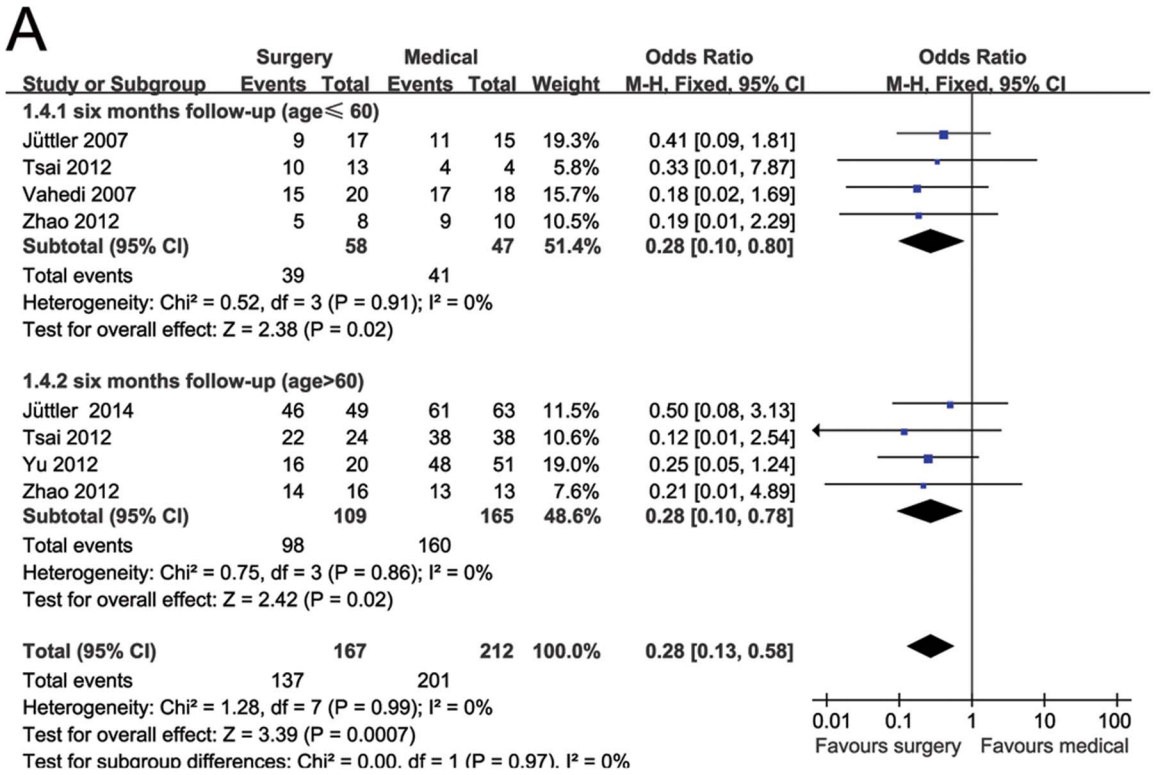

Figure 4 | Forest plot with OR estimating with the corresponding 95% CI for (A) unfavourable outcome (defined as mRS>3) or (B) the proportion of survivors with moderately severe or severe disability (defined as mRS=4 or 5) associated with early DC versus medical treatment for individual trials and the subgroup population stratified by age at 6 months follow-up. CI, confidence interval; DC: decompressive craniectomy; OR, odds ratio; mRS: modified Rankin scale.

Methods

Search Strategy. A comprehensive electronic search in PubMed, Medline, Embase, Cochrane library, Web of Science database was carried out using the following search terms: "hemicraniectomy" or "craniectomy" or "decompressive surgery" or "decompressive craniectomy" or "decompression", "middle cerebral artery" or "internal carotid artery", AND "stroke" or "infarction" or "infarct" (the last search update was 5 June 2014). In addition, the references of all retrieved articles were checked for additional potential studies.

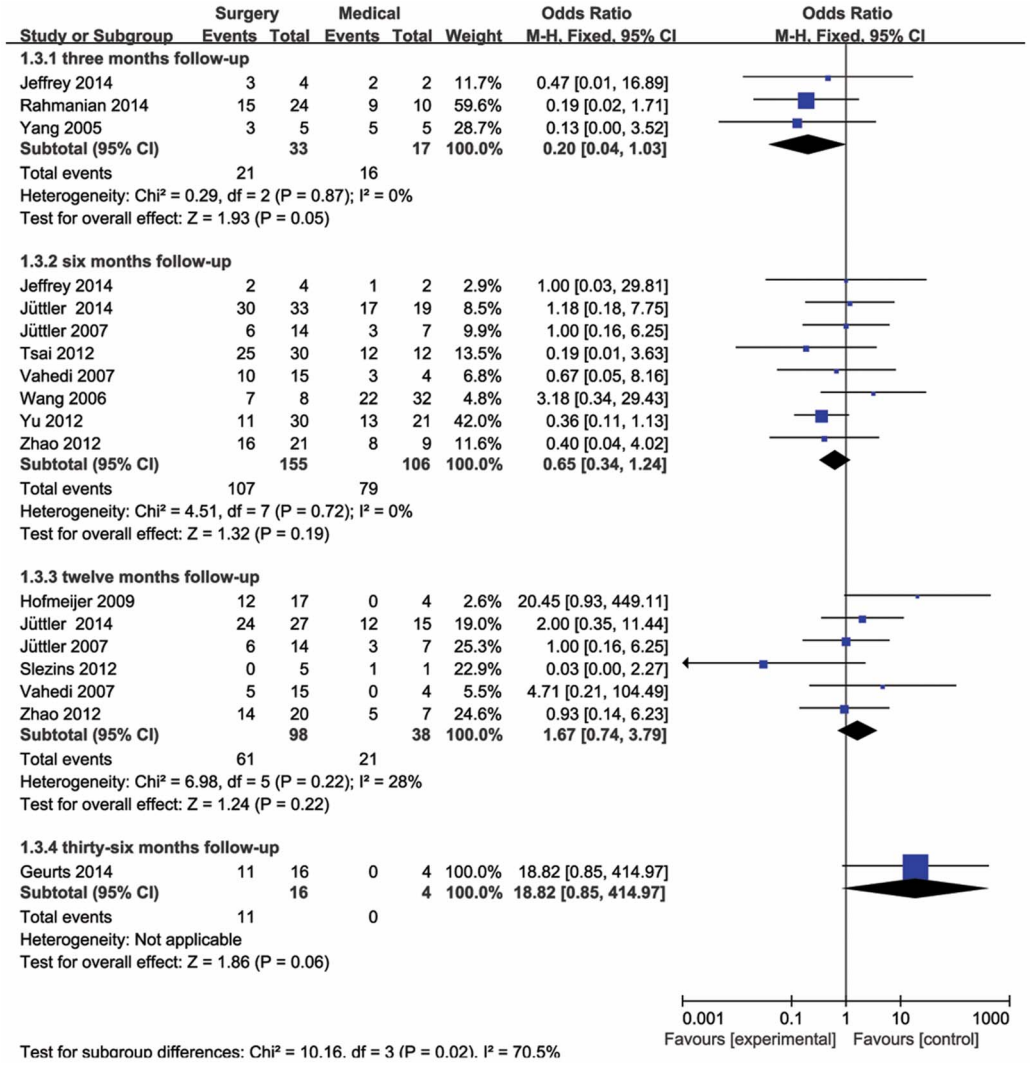

Figure 5 | Forest plot with OR estimating with the corresponding 95% CI for the proportion of survivors with moderately severe or severe disability (defined as mRS=4 or 5) associated with early DC versus medical treatment for individual trials and the pooled population at 3 months, 6 months, 12 months and 36 months follow-up (patients in all ages) CI, confidence interval; DC: decompressive craniectomy; OR, odds ratio; mRS: modified Rankin scale.

Study Eligibility. The inclusion criteria were the following: 1) studies comparing effects of DC and medical treatment alone as control on patients with MCA infarction; 2) assessing outcome as death and functional outcome defined by mRS or Glasgow outcome scale (GOS) score (if mRS score was unavailable) at 3 months, 6 months, 12 months or 36 months follow-up. Exclusion criteria for our primary analysis were as follows: 1) unavailability of a medical treatment comparison group 2) unavailability of numbers of patients survival or with functional outcome at 3 months, 6 months, 12 months or 36 months follow-up 3) review articles, meta-analysis, and guidelines

Data Extraction. The following data was extracted independently from each study by two authors using a standardized data extraction form: study design, patient eligibility criteria, duration of follow-up, sex and age of patients, National Institutes of Health stroke scale (NIHSS), vascular territories and side of the infarction, presence of preoperative clinical signs of herniation, time to surgery, mRS scores, GOS scores and mortality. Disagreements were resolved by consulting with a third author.

Quality Assessment. Quality assessment for included studies was assessed by 2 independent authors. Briefly, Cochrane Collaboration's tool were used for assessing quality according to the following domains: selection bias (random sequence generation and allocation concealment), attrition bias (incomplete outcome data), performance and detection bias (blinding of participants, personnel and outcome assessment), reporting bias (selective reporting), and other bias (other sources of bias)[38]. In addition, we used Newcastle–Ottawa Scale (NOS) to assess the quality in the non-randomized cohort studies[39].

Outcome. We assessed the following outcomes to explore the effect of DC on malignant MCA infarction: 1) death at 3 months, 6 months, 12 months, and 36

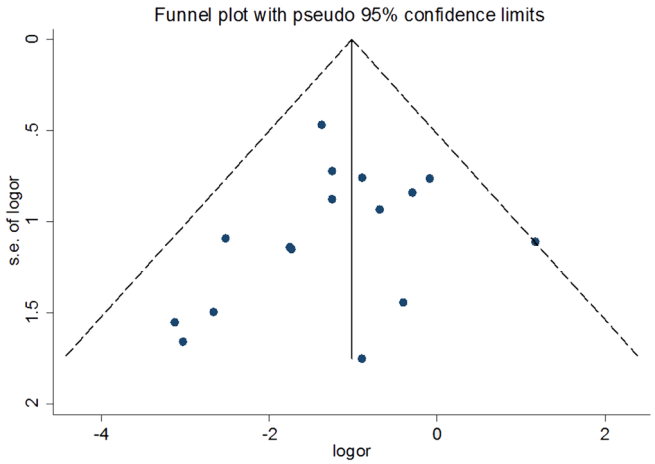

Figure 6 | Funnel plot to detect publication bias. No significant funnel asymmetry was observed which could indicate publication bias. (P value for Egger test was 0.38) logor Natural logarithm of the OR, s.e. of logor standard error of the logOR.

months follow-up, 2) a poor functional outcome (defined as mRS= 4 to 6 or GOS= 1 to 3) at 3 months, 6 months, 12 months, and 36 months follow-up 3) survival with moderately severe or severe disability defined as mRS 4 and 5 at 3 months, 6 months, 12 months, and 36 months follow-up. Pooled analyses of the association between DC and outcome adjusted by other variables were not carried out due to the unavailable data for individual subjects.

Statistical Analysis. Absolute risk reductions (ARRs), odds ratios (ORs), and 95% confidence intervals (CIs) were calculated for the specified outcome[15]. The significance of the pooled OR and ARR was determined by the Z-test, a P-value less than 0.05 was considered significant. The heterogeneity between studies was assessed by Chisquare based Q test and I^2 test[40]. Heterogeneity was considered significant when $P<0.10$, and pooled estimates were calculated using the random-effects (DerSimonian-Laird) model, otherwise, a fixed-effects (Mantel-Haenszel) model was used[41]. Publication bias was investigated using visual evaluation of funnel plots and Egger regression asymmetry test[42]. All statistical analyses were performed by Review Manager (RevMan) (Version 5.2) or STATA software (version 12).

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Author contributions

L.X.C. and L.L.X. designed the analysis. Z.J.Y., H.B.S., L.S. and Y.W. collected and abstracted the data. T.L.J., T.Y. and Z.R.L. carried out the statistical analysis. L.X.C. and L.L.X. drafted the manuscript. All authors reviewed and approved the final report.

Additional information

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