



Middle meningeal artery embolization for chronic subdural hematoma: a systematic review and meta-analysis

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ABSTRACT

Middle meningeal artery (MMA) embolization has been proposed as a minimally invasive treatment for chronic subdural hematoma (cSDH). The aim of this systematic review and meta-analysis is to compare outcomes after MMA embolization versus conventional management for cSDH. We performed a systematic review of PubMed, Embase, Oxford Journal, Cochrane, and Google Scholar databases from April 1987 to October 2020 in accordance with PRISMA guidelines. Studies reporting outcomes after MMA embolization for ≥ 3 patients with cSDH were included. A meta-analysis comparing MMA embolization with conventional management was performed. The analysis comprised 20 studies with 1416 patients, including 718 and 698 patients in the MMA embolization and conventional management cohorts, respectively. The pooled recurrence, surgical rescue, and in-hospital complication rates in the MMA embolization cohort were 4.8% (95% CI 3.2% to 6.5%), 4.4% (2.8% to 5.9%), and 1.7% (0.8% to 2.6%), respectively. The pooled recurrence, surgical rescue, and in-hospital complication rates in the conventional management cohort were 21.5% (0.6% to 42.4%), 16.4% (5.9% to 27.0%), and 4.9% (2.8% to 7.1%), respectively. Compared with conservative management, MMA embolization was associated with lower rates of cSDH recurrence (OR=0.15 (95% CI 0.03 to 0.75), $p=0.02$) and surgical rescue (OR=0.21 (0.07 to 0.58), $p=0.003$). In-hospital complication rates were comparable between the two cohorts (OR=0.78 (0.34 to 1.76), $p=0.55$). MMA embolization is a promising minimally invasive therapy that may reduce the need for surgical intervention in appropriately selected patients with cSDH. Additional prospective studies are warranted to determine the long-term durability of MMA embolization, refine eligibility criteria, and establish this endovascular approach as a viable definitive treatment for cSDH.

INTRODUCTION

Chronic subdural hematomas (cSDH) are a common intracranial pathology, with an incidence of approximately 1 to 5.3 cases per 100 000 people.¹ The incidence of cSDH is highest in elderly patients (age >65 years), with a range of 8.2 to 18.8 per 100 000 people in this subgroup.²⁻⁴ As the population ages worldwide, cSDH prevalence is expected to rise.¹ Surgical drainage, either with burr hole(s) or craniotomy, is considered as the definitive management for cSDHs.⁵⁻⁸ However, recurrence rates after

surgical cSDH drainage range from 2% to 37%.⁹⁻¹⁴ Neurosurgical decision-making in this patient population frequently requires the practitioner to consider medical comorbidities and determine the necessity, as well as timing, of restarting anticoagulants or antiplatelets.^{5 9 10 15 16} Recently, efforts have been directed towards the identification of non-surgical treatment strategies for cSDH.¹⁷⁻²²

Accumulation of blood within the subdural space incites an inflammatory response, comprising fibroblast proliferation, granulation tissue formation, and release of angiogenic factors.²³ This results in formation of a neomembrane within 3–4 weeks of the primary injury.²⁴ It has been hypothesized that leakage from neomembrane capillaries, which contain highly permeable endothelial gap junctions, might contribute to cSDH enlargement and recurrence.^{25 26} Eliminating the blood supply to the neomembrane by embolization of the middle meningeal artery (MMA), either upfront or adjunctive to surgical evacuation, has been proposed as a minimally invasive treatment for cSDH.^{18 20 27-35} Established guidelines for the management of cSDH are lacking, and treatment practices are variable.^{12 36} Endovascular intervention for cSDH is a novel treatment with heterogeneous indications and techniques.³⁶ The aim of this systematic review and meta-analysis is to summarize the current literature comparing the outcomes after MMA embolization versus conventional management, including surgical drainage and observation, for patients with cSDH.

METHODS

Study design

No registered review protocol was used in this study. This review follows guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (online supplemental figure 1).

Inclusion and exclusion criteria

The systematic review used the following inclusion criteria: (1) ≥ 3 patients undergoing MMA embolization for cSDH; (2) post-embolization outcomes data describing cSDH recurrence were reported; and (3) the language is English. Review articles, letters, editorials, comments, case reports, and technical reports were excluded. Articles with



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Table 1 Study design, treatment characteristics, and follow-up durations of the overall cohort

Study, year	Country	Design	Patients n	F/U (months) mean (SD)	Total embolization patients n (%)	Total conventional management patients n (%)	Upfront embolization N (%)	Prophylactic embolization after surgical evacuation N (%)	Embolization for recurrent cSDH after surgical evacuation N (%)	Embolization material (N)
Mino, 2010	Japan	Retrospective	4	6 (0)	4 (100)	0 (0)	0 (0)	0 (0)	4 (100)	Gelatin sponge and Guglielmi detachable coils (4).
Hashimoto, 2013	Japan	Retrospective	5	3.5 (0.5) (2)	5 (100)	0 (0)	0 (0)	2 (40.0)	3 (60.0)	n-BCA (4), n-BCA+PVA (1)
Chihara, 2014	Japan	Retrospective	3	12 (8.5)	3 (100)	0 (0)	0 (0)	0 (0)	3 (100)	PVA +coil (3)
Tempaku, 2015	Japan	Retrospective	5	17.6 (21.4)	5 (100)	0 (0)	0 (0)	0 (0)	5 (100)	PVA (4), PVA+coil (1)
El Kim, 2017	Korea	Retrospective	43	3.45 (1.1)	20 (46.5)	Surgery 23 (53.5)	0 (0)	0 (0)	20 (100)	PVA (20)
Matsumoto, 2017	Japan	Retrospective	14	NR	4 (28.6)	Surgery 10 (71.4)	0 (0)	0 (0)	4 (100)	n-BCA (4)
Ban, 2018	Korea	Retrospective	541	6 (0)	72 (13.3)	Observation 67 (12.4), surgery 402 (74.3)	27 (37.5)	45 (62.5)	0 (0)	PVA (72)
Link, 2018	USA	Retrospective	49	At least 6 weeks	49 (100)	0 (0)	32 (65.3)	10 (20.4)	7 (14.3)	PVA (49)
Nakagawa, 2019	Japan	Retrospective	20	24 weeks after embolization	20 (100)	0 (0)	0 (0)	0 (0)	20 (100)	n-BCA (20)
Ng, 2018	France	Prospective, randomized	41	3 (0)	19 (46.3)	Surgery 22 (53.7)	0 (0)	19 (100)	0 (0)	PVA (19)
Okuma, 2019	Japan	Retrospective	17	26.3 (17.4)	17 (100)	0 (0)	0 (0)	0 (0)	17 (100)	n-BCA (11), embosphere (3), n-BCA+embosphere (2), coil (1)
Waqas, 2019	USA	Retrospective	8	3.3 (1.0)	8 (100)	0 (0)	6 (75.0)	0 (0)	2 (25.0)	Onyx (n=8)
Catapano, 2021	USA	Retrospective	35	3–4	35 (100)	0 (0)	24 (68.6)	2 (5.7)	9 (25.7)	Onyx (29), particles (7), n-BCA (5)
Fan, 2020	China	Retrospective	7	4–6	7 (100)	0 (0)	0 (0)	7 (100)	0 (0)	Absolute alcohol (7)
Joyce, 2020 *	USA	Retrospective	151	At least 6 weeks to 90 days	151 (100)	0 (0)	79 (52.3)	17 (11.3)	55 (36.4)	Coil (6), liquid (30), particles (38), liquid +coil (2), particles+coils (72), particles+liquid (1)
Kan, 2020	USA	Prospective	138	3.2 (2.5)	138 (100)	0 (0)	92 (66.7)	0 (0)	46 (33.3)	Coils (5), liquid (37), liquid+coil (2), particles (38), particles+coil (70)
Mureb, 2020	USA	Retrospective	8	3 (2 to 4 months)	8 (100)	0 (0)	8 (100)	0 (0)	0 (0)	PVA (8)
Rajah, 2020	USA	Prospective	46	2 (1)	46 (100)	0 (0)	37 (80.4)	4 (8.7)	5 (10.9)	Onyx (43), n-BCA (1)
Shotar, 2020	France	Retrospective	263	NR	89 (33.8)	174 (66.2)	0 (0)	89 (100)	0 (0)	Microsphere (81), n-BCA (5), coil (5)
Yajima, 2020	Japan	Retrospective	18	8 (2 to 53 months)	18 (100)	0 (0)	2 (11.1)	2 (11.1)	14 (77.8)	n-BCA (18)
Total			1416		718/1416 (50.7)	698/1416 (49.3)	307/718 (42.8)	197/718 (27.4)	214/718 (29.8)	
Pooled estimate†							28.4 (11.7 to 45.2)	23.2 (5.9 to 40.5)	47.8 (27.7 to 67.9)	

*Study reported outcome data using number of cases of cSDH instead of number of patients.

†Weighted pooled proportions in percentage (%) with 95% confidence intervals and weighted means with SD are presented. cSDH, chronic subdural hematoma; F/U, follow up; n-BCA, n-butyl cyanoacrylate; NR, not reported; PVA, polyvinyl alcohol particles.

insufficient surgical outcomes data or with overlapping published data in a more recent series were excluded.

Literature search

A systematic literature search was performed on October 2020 in the PubMed, Embase, Oxford Journal, Cochrane, and Google Scholar databases with the following search terms: ‘hematoma, subdural, chronic (MeSH)’ OR ‘chronic’ OR ‘subdural hematoma’ AND ‘meningeal arteries (MeSH)’ OR ‘middle meningeal artery’ AND ‘embolization, therapeutic’ (MeSH) OR ‘embolization’ AND ‘recurrence’. The literature search was performed by two reviewers (NI and CN). Articles were screened by title and

abstract. The remaining articles underwent a further detailed, full-text review for relevance and usable data that adhered to the inclusion criteria. The references of selected articles were manually screened for potentially relevant studies that had not previously been identified using the study search terms. Disagreement between reviewers was resolved by discussion until a consensus decision was reached.

Definitions

Indications for embolization were categorized as (1) upfront embolization in patients with a previously untreated cSDH; (2) prophylactic embolization after surgical evacuation without

evidence of interval postoperative cSDH recurrence; or (3) embolization for recurrent cSDH after previous surgical evacuation. Conventional management was defined as either observation with serial neuroimaging or surgical cSDH drainage (burr holes or craniotomy with or without drain placement). cSDH recurrence was defined as an increase of hematoma width on follow-up imaging compared with the immediate postoperative imaging.

In-hospital complications were defined as any adverse event related to the endovascular procedure, including new neurologic deficit or radiologic evidence of acute ischemic or hemorrhagic changes on post-embolization imaging. Surgical rescue was defined as the requirement for surgical evacuation for recurrent or persistent cSDH after MMA embolization. When reported, the modified Rankin Scale (mRS) was used to assess functional outcome, and favorable outcome was defined as mRS score 0–2 at the time of last follow-up.³⁷

Outcome measures and data extraction

The primary outcome was cSDH recurrence. Secondary outcomes included need for surgical rescue, in-hospital complications, and favorable outcome. Extracted patient demographic and study data included year of publication, study design, location of institution(s), age at presentation, sex, and mean follow-up duration. Clinical data included signs or symptoms of headache, speech disturbance, focal motor weakness, gait instability, altered mental status, seizure, and history of head trauma. Medical history data included history of congestive heart failure, hypertension, atrial fibrillation, diabetes mellitus, malignancy, coagulopathy, and antiplatelet or anticoagulant use at the time of presentation. Radiographic and treatment data included presence of bilateral cSDH, type of embolic agent used, indication for embolization, and history of surgical cSDH evacuation. A subgroup analysis was performed comparing the primary and secondary outcomes between patients who underwent upfront versus postoperative MMA embolization.

The methodological quality of the included studies was assessed using the Down's and Black checklist, in which each study was evaluated for sources of non-random error using a validated 32-point index (online supplemental table 1).³⁸

Statistical analysis

Statistical analysis of pooled data was performed using Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Meta-Essentials Software version 1.4 (Erasmus Research Institute of Management, 2017).³⁹ Patient demographic, clinical, medical history, radiographic, treatment, and outcomes data were summarized for the included studies using pooled weighted means with SD for continuous variables or pooled weighted proportions with corresponding 95% confidence intervals for categorical variables, as appropriate.⁴⁰

Among the double-arm studies comparing conventional management with MMA embolization, odds ratios (ORs) for the primary and secondary outcomes were computed using the Mantel-Haenszel test. Both fixed and random effects models were tested. Negligible differences were found between the two models, and the random effects model was implemented in the final analyses. Study heterogeneity was detected using the χ^2 and I^2 test statistics. Significant heterogeneity was considered to be present when both the χ^2 value was within a 10% level of significance ($p < 0.10$) and the I^2 value exceeded 50%.⁴¹ All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

Study characteristics

A total of 20 studies, comprising 1416 patients with cSDH, met the inclusion criteria for the study cohort (online supplemental figure 1). Five double-arm studies, comprising 902 patients with cSDH, compared outcomes between conventional management versus MMA embolization. Fifteen single-arm studies, comprising 514 patients with cSDH, reported outcomes after MMA embolization with or without surgical evacuation for cSDH. Table 1 summarizes the characteristics of the study cohort. The majority of studies originated from Japan ($n=8$), followed by USA ($n=7$), Korea ($n=2$), France ($n=2$), and China ($n=1$). MMA embolization was performed, for recurrent cSDH after previous surgical evacuation in 47.8%, prophylactically after surgical evacuation in 23.2%, and upfront in 28.4%. The mean follow-up duration ranged from 1.5 to 26.3 months. Embolization materials used were particles ($n=403$), liquid ($n=143$), coils ($n=171$), microspheres ($n=86$) and Onyx ($n=80$).

Patient demographic, clinical and radiographic characteristics

Table 2 summarizes the demographics and clinical characteristics of the 688 patients with cSDH treated with MMA embolization. The mean age was 72.7 ± 11.8 years, and 74% were male. There was a history of head trauma in 54.7%. Bilateral cSDHs were present in 17.5%. Presenting symptoms included focal motor weakness or gait instability in 51.8%, headache in 35.8%, speech disturbance in 5.5%, and seizure in 2.8%. Comorbidities included hypertension in 50.7%, diabetes mellitus in 23.2%, congestive heart failure in 14.7%, malignancy in 18.7%, and coagulopathy in 3.7%. Concurrent antiplatelet or anticoagulant use was reported in 47.2%.

Outcomes after MMA embolization versus conservative management for cSDH

Table 3 summarizes the outcomes after MMA embolization ($n=714$) versus conventional management ($n=698$) for cSDH. Following MMA embolization, the rates of cSDH recurrence, in-hospital complications, surgical rescue, and mRS score 0–2 at last follow-up were 4.8% (95% CI 3.2% to 6.5%), 1.7% (0.8% to 2.6%), 4.4% (2.8% to 5.9%), and 72.8% (46.3% to 99.2%), respectively. After conventional management, rates of cSDH recurrence, in-hospital complications, surgical rescue, and mRS score 0–2 at last follow-up were 21.5% (0.6% to 42.4%), 4.9% (2.8% to 7.1%), 16.4% (5.95% to 27.0%), and 92.3% (10.8% to 100%), respectively. Reported in-hospital complications in the conventional management cohort were epilepsy ($n=9$), cerebral infarction ($n=8$), acute epidural or subdural hematoma ($n=8$), surgical site infection ($n=8$), and intracerebral hemorrhage ($n=2$).

Meta-analysis of MMA embolization versus conventional management for cSDH

Five double-arm studies, comprising 902 patients with cSDH, compared outcomes between MMA embolization ($n=204$, 22.6%) versus conventional management ($n=698$, 77.4%), and these were included in the meta-analysis. MMA embolization was associated with a lower likelihood of cSDH recurrence (OR=0.15, 95% CI 0.03 to 0.75, $p=0.02$, $I^2=38\%$) and surgical rescue (OR=0.21, 95% CI 0.07 to 0.58, $p=0.003$, $I^2=19\%$; figure 1). In-hospital complication rates were comparable between the two cohorts (OR=0.78, 95% CI 0.34 to 1.76, $p=0.55$, $I^2=0\%$; figure 1).

Table 2 Demographics and clinical characteristics of the patients with cSDH treated with MMA embolization

Study, year	Total embolization patients, n	Age (years) mean±SD	History of head trauma			Headache N (%)	Speech disturbance N (%)	Focal weakness/ gait instability, N (%)	Altered mental status, N (%)	Seizure, N (%)	Asympto-matic N (%)	Bilateral N (%)	CHF N (%)	HTN N (%)	AF N (%)	DM N (%)	Malignancy N (%)	Coagulopathy, N (%)	Antiplatelet/ anticoagulant use N (%)
			Male N (%)	N (%)	N (%)														
Mino, 2010	4	73.0±5.9	4 (100)	3 (75.0)	0 (0)	1 (25.0)	3 (75.0)	1 (25.0)	0 (0)	0 (0)	0 (0)	1 (25.0)	NR	NR	NR	NR	NR	NR	NR
Hashimoto, 2013	5	73.5±7.8	3 (60.0)	NR	NR	NR	NR	NR	NR	NR	0 (0)	1 (20.0)	NR	NR	NR	NR	NR	NR	NR
Chihara, 2014	3	67.0±9.8	3 (100)	NR	NR	NR	NR	NR	NR	NR	0 (0)	NR	NR	NR	NR	NR	1 (33.3)	NR	NR
Tempaku, 2015	5	83.0±7.1	4 (80.0)	2 (40.0)	NR	NR	NR	NR	NR	NR	0 (0)	NR	NR	1 (20.0)	NR	2 (40.0)	NR	1 (20.0)	1 (20.0)
El Kim, 2017	20	73.7±7.1	14 (70.0)	8 (40.0)	NR	NR	NR	NR	NR	NR	0 (0)	6 (30.0)	NR	13 (65.0)	NR	7 (35.0)	4 (20.0)	5 (25.0)	9 (45.0)
Matsumoto, 2018	4	65.8±16.9	4 (100)	NR	1 (25.0)	0 (0)	1 (25.0)	2 (50.0)	0 (0)	0 (0)	0 (0)	NR	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)	1 (25.0)
Ban, 2018	72	69.3±10.5	48 (66.7)	45 (62.5)	NR	NR	NR	NR	NR	NR	27 (37.5)	19 (26.4)	NR	45 (62.5)	NR	16 (22.2)	NR	1 (1.4)	29 (40.3)
Link, 2018*	49**	69.0±13.0	32 (65.3)	NR	24 (49.0)	26 (53.1)	2 (4.1)	11 (22.4)	1 (2.0)	1 (2.0)	0 (0)	11 (22.4)	10 (20.4)	26 (52.1)	5 (10.2)	11 (22.4)	13 (26.5)	3 (6.1)	34 (69.4)
Nakagawa, 2019	20	78.3±11.4	14 (70)	NR	NR	NR	NR	NR	NR	NR	0 (0)	8 (40.0)	NR	NR	NR	NR	NR	NR	4 (20.0)
Ng, 2020	19	77.4±10.9	10 (52.6)	12 (63.2)	9 (47.4)	15 (78.9)	NR	NR	0 (0)	0 (0)	0 (0)	3 (15.8)	NR	NR	NR	NR	NR	NR	7 (36.8)
Okuma, 2019	17	76.5±12.5	12 (70.6)	NR	NR	NR	NR	NR	NR	NR	0 (0)	4 (23.5)	NR	NR	NR	NR	2 (11.8)	0 (0)	11 (64.7)
Waqas, 2019	8	63.6±10.9	5 (62.5)	2 (25.0)	2 (25.0)	6 (75.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)	NR	NR	NR	NR	NR	NR	6 (75.0)
Catapano, 2021	35	68.0 ± 12.0	25 (71.4)	23 (65.7)	14 (40.0)	21 (60.0)	3 (8.6)	7 (20.0)	3 (8.6)	3 (8.6)	3 (8.6)	6 (17.1)	NR	20 (57.1)	NR	12 (34.3)	NR	1 (2.9)	14 (40.0)
Fan, 2020	7	NR	NR	NR	5 (71.4)	2 (28.6)	NR	1 (14.3)	NR	NR	NR	0 (0)	NR	NR	NR	NR	NR	NR	NR
Joyce, 2020	121	77.5±7.6	99 (81.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	64 (52.9)	NR	23 (19.0)	NR	2 (1.7)	69 (57.0)
Kan, 2020	138	69.8±14.2	98 (71.0)	NR	NR	NR	NR	NR	NR	NR	NR	15 (10.9)	NR	NR	NR	NR	NR	NR	72 (52.2)
Mureh, 2020	8	75.4±7.9	7 (87.5)	NR	NR	NR	NR	NR	NR	NR	NR	0 (0)	NR	NR	NR	NR	NR	NR	NR
Rajah, 2020	46	71.7±14.4	31 (67.4)	10 (21.7)	NR	9 (19.6)	NR	NR	NR	NR	0 (0)	6 (13.0)	4 (8.7)	24 (52.2)	6 (13.0)	11 (23.9)	NR	NR	NR
Shroter, 2020	89	74.0 ± 13.0	68 (76.4)	NR	NR	NR	NR	NR	NR	NR	0 (0)	15 (16.9)	NR	NR	NR	NR	NR	2 (2.2)	71 (79.8)
Yajima, 2020	18	78.5±9.6	16 (88.9)	NR	NR	NR	NR	NR	NR	NR	NR	3 (16.7)	NR	NR	NR	NR	NR	3 (16.7)	3 (16.7)
Total n (%)	688	65/163 (88.7)	487/681 (70.8)	65/172 (37.8)	6/100 (6.0)	83/172 (48.3)	6/100 (6.0)	22/107 (20.6)	4/119 (3.4)	30/396 (7.6)	99/555 (17.8)	99/555 (17.8)	15/99 (15.2)	193/352 (54.8)	11/99 (11.1)	82/352 (23.3)	19/90 (21.1)	19/428 (4.4)	331/615 (53.8)
Pooled estimate†		72.7±11.8	74.0 (68.9 to 79.1)	54.7 (39.5 to 69.9)	35.8 (19.1 to 52.6)	5.5 (0.0 to 11.2)	51.8 (31.5 to 72.0)	19.5 (6.6 to 32.4)	2.8 (0.0 to 6.2)	3.8 (0.0 to 9.7)	17.5 (13.0 to 22.1)	14.7 (0.0 to 33.9)	50.7 (35.6 to 65.7)	10.9 (2.3 to 19.5)	23.2 (17.1 to 29.3)	18.7 (3.3 to 34.1)	3.7 (0.0 to 7.9)	47.2 (35.1 to 59.2)	

*Demographic data is based on 49 patients. Outcome data is based on 45 cases with >6 weeks follow-up information available. †Weighted pooled proportions in percentage (%) with 95% confidence intervals and weighted means with SD are presented.

Table 3 Primary and secondary outcomes after MMA embolization versus conventional management for cSDH

Study, year	Embolization N (%)	Recurrence N (%)	In-hospital complication N (%)	Surgical rescue N (%)	mRS score 0–2 at last F/U N (%)	Conventional management N (%)	Recurrence N (%)	In-hospital complication N (%)	Surgical rescue N (%)	mRS score 0–2 at last F/U N (%)
Mino, 2010	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR	NR	NR	NR
Hashimoto, 2013	5 (100)	0 (0)	0 (0)	0 (0)	NR	NR	NR	NR	NR	NR
Chihara, 2014	3 (100)	1 (33.3)	0 (0)	1 (33.3)	NR	NR	NR	NR	NR	NR
Tempaku, 2015	5 (100)	0 (0)	0 (0)	0 (0)	NR	NR	NR	NR	NR	NR
El Kim, 2017	20 (46.5)	1 (5)	2 (10)	0 (0)	17 (85)	23 (53.5)	8 (34.8)	2 (8.7)	8 (34.8)	20 (87.0)
Matsumoto, 2018	4 (28.6)	0 (0)	0 (0)	0 (0)	4 (100)	10 (71.4)	2 (20)	0 (0)	2 (20)	10 (100)
Ban, 2018	72 (13.3)	1 (1.4)	0 (0)	1 (1.4)	NR	469 (86.7)	129 (27.5)	20 (4.3)	88 (18.8)	NR
Link, 2018	45** (100)	4 (8.9)	0 (0)	4 (8.9)	NR	NR	NR	NR	NR	NR
Nakagawa, 2019	20 (100)	0 (0)	0 (0)	0 (0)	NR	NR	NR	NR	NR	NR
Ng, 2020	19 (46.3)	1 (5.3)	1 (5.3)	1 (5.3)	NR	22 (53.7)	1 (4.5)	1 (4.5)	1 (4.5)	NR
Okuma, 2019	17 (100)	0 (0)	0 (0)	0 (0)	9 (52.9)	NR	NR	NR	NR	NR
Waqas, 2019	8 (100)	0 (0)	0 (0)	0 (0)	8 (100)	NR	NR	NR	NR	NR
Catapano, 2021	35 (100)	1 (2.9)	1 (2.9)	1 (2.9)	25 (71.4)	NR	NR	NR	NR	NR
Fan, 2020	7 (100)	0 (0)	0 (0)	0 (0)	NR	NR	NR	NR	NR	NR
Joyce, 2020 *	151	8 (5.3)	3 (2.0)	9 (6.0)	NR	NR	NR	NR	NR	NR
Kan, 2020	138 (100)	10 (7.2)	2 (1.4)	9 (6.5)	90 (65.2)	NR	NR	NR	NR	NR
Mureb, 2020	8 (100)	0 (0)	0 (0)	0 (0)	8 (100)	NR	NR	NR	NR	NR
Rajah, 2020	46 (100)	5 (11.4)	1 (2.3)	5 (11.4)	NR	NR	NR	NR	NR	NR
Shotar, 2020	89 (33.8)	7 (7.9)	6 (6.7)	4 (4.5)	NR	174 (66.2)	NR	14 (8.0)	24 (13.8)	NR
Yajima, 2020	18 (100)	0 (0)	0 (0)	0 (0)	NR	NR	NR	NR	NR	NR
Total n (%)	714	39/714 (5.5)	16/714 (2.2)	35/714 (4.9)	161/234 (68.8)	698	140/524 (26.7)	37/698 (5.3)	123/698 (17.6)	30/33 (90.9)
Pooled estimate†		4.8 (3.2 to 6.5)	1.7 (0.8 to 2.6)	4.4 (2.8 to 5.9)	72.8 (46.3 to 99.2)		21.5 (0.6 to 42.4)	4.9 (2.8 to 7.1)	16.4 (5.9 to 27.0)	92.3 (10.8 to 100)

*Study reported outcome data using # of cSDH instead of # of patients.

†Weighted pooled proportions in percentage (%) with 95% confidence intervals are presented.

cSDH, chronic subdural hemorrhage; F/U, Follow up; MMA, middle meningeal artery; mRS, modified Rankin Scale; NR, not reported.

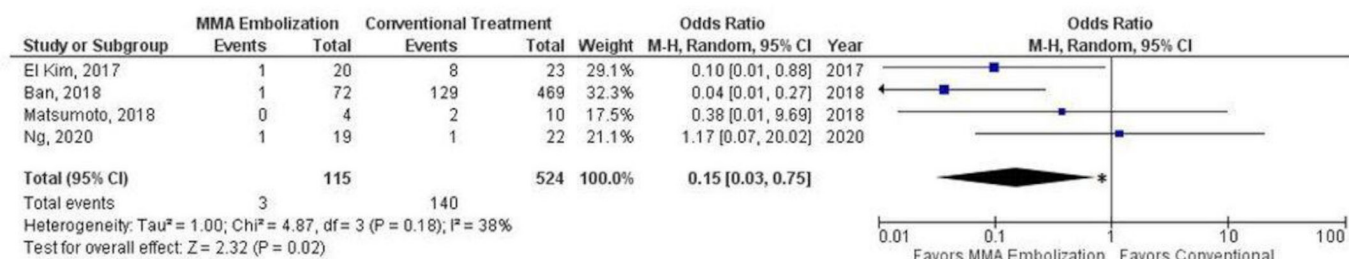
Subgroup analysis of upfront versus postoperative MMA embolization for cSDH

Online supplemental table 2 summarizes the outcomes after upfront (n=43) versus postoperative MMA embolization (n=256) for cSDH. Based on the four studies reporting outcomes after upfront MMA embolization, the rates of cSDH recurrence, in-hospital complications, and surgical rescue were each 0%. Based on the 15 studies reporting outcomes after postoperative MMA embolization, the rates of cSDH recurrence, in-hospital complications, and surgical rescue were 3.9% (95% CI 1.4% to 6.4%), 2.8% (0.7% to 4.8%), and 2.9% (0.8% to 5.0%), respectively.

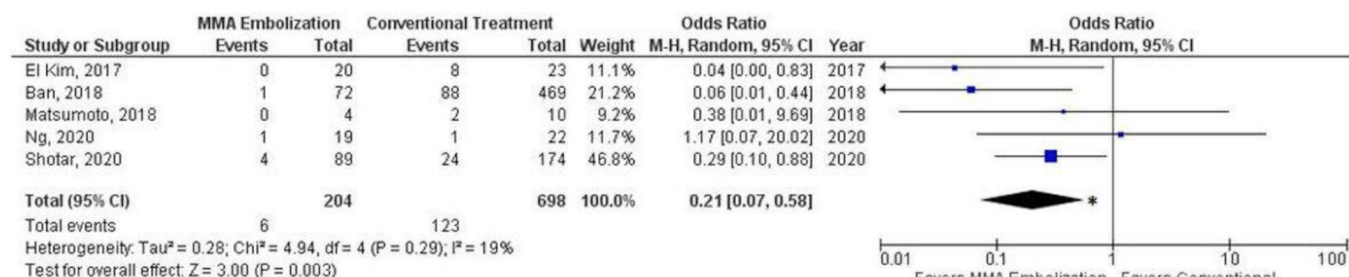
DISCUSSION

Formation of a vascular neomembrane derived from the dura mater is hypothesized to contribute to cSDH pathogenesis and recurrence, as the fragile neomembrane undergoes repetitive cycles of breakdown and reconstitution.^{24–26} MMA embolization targets the blood supply to the neomembrane, thereby eliminating the potential source of persistent bleeding.¹⁸ In this systematic review and meta-analysis, we pooled data from 20 studies reporting outcomes after MMA embolization for cSDH.^{18 20–22 27 29 31 32 34 42–52} The primary outcome of cSDH recurrence was observed in 4.8% of the MMA embolization cohort versus 21.5% of the conventional management cohort.

Recurrence



Surgical re-treatment



In-hospital complications

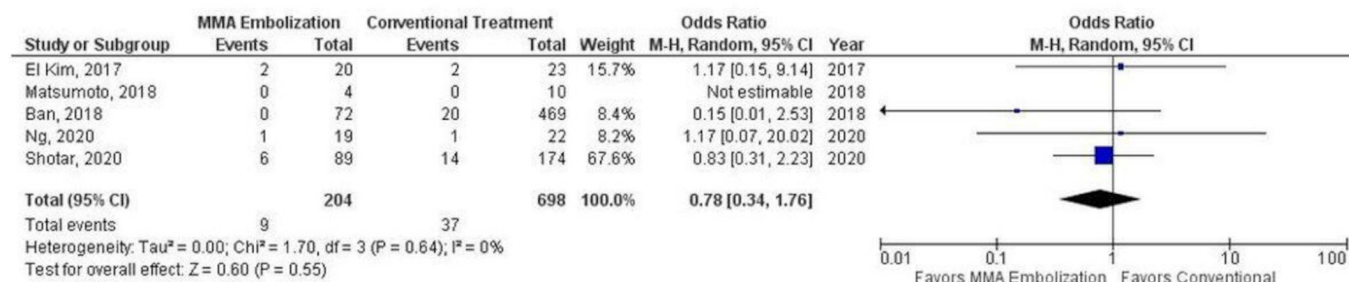


Figure 1 Forest plot showing rates of chronic subdural hematoma (cSDH) recurrence, surgical re-treatment, and in-hospital complication rate after middle meningeal artery (MMA) embolization versus conventional management for cSDH. *Indicates $p < 0.05$.

MMA embolization was associated with a lower rate of cSDH recurrence than conventional management ($OR = 0.15$; $p = 0.02$), and this corresponded to a reduced likelihood of surgical rescue ($OR = 0.21$; $p = 0.003$). The rates of in-hospital complications were similar between the two cohorts ($OR = 0.78$; $p = 0.55$). Our overall findings suggest that MMA embolization is a promising therapeutic strategy that can be employed as an adjunct or alternative to surgical drainage for judiciously selected patients with cSDH.

cSDH is a common neurosurgical pathology, and its worldwide incidence is expected to rise in tandem with the aging population.^{1–4} Although spontaneous resolution of cSDHs has been reported, conventional management of enlarging or symptomatic cSDHs requires surgical evacuation.^{53–55} Burr hole craniotomy and irrigation of the subdural space, with or without subdural or subgaleal drain placement, is the preferred technique for cSDH evacuation at many institutions, although miniature craniotomy

can be performed in cases of thick subdural membranes or those with a sizeable acute hematoma component.^{5–8 56} While cSDH drainage is not technically challenging, the overall management of these patients can be complicated, as affected patients frequently have multiple risk factors for poor postoperative and in-hospital outcomes.^{1 57 58} Increasing age, presence of comorbidities, and lower Glasgow Coma Scale score at presentation have been associated with increased disability and reduced survival after cSDH surgery.^{57 58}

Our findings are consistent with the current literature reporting cSDH recurrence rates after surgical evacuation in 2–37% of patients.^{9–14} Treatment for cSDH should account for the substantial overlap between risk factors for cSDH recurrence and those for perioperative morbidity and mortality.^{57–59} Recently, interest in MMA embolization for cSDH, both as an upfront definitive intervention and postoperative adjunctive therapy, has increased.^{18 21 29 35 60} In our pooled analysis, MMA

embolization was performed upfront in 28.4% of patients, as a post-surgical adjunct in 23.2%, and as rescue therapy following cSDH recurrence in 47.8%. No cases of cSDH recurrence or re-treatment were observed in patients who underwent upfront MMA embolization. However, patients treated with postoperative MMA embolization had cSDH recurrence and re-treatment rates of 3.9% and 2.9%, respectively. A two-arm open-label randomized controlled trial (NCT04065113) by Benitez *et al* is currently underway to compare outcomes between MMA embolization versus surgical evacuation for cSDH. The study, which includes patients with a new or recurrent cSDH, will assess cSDH persistence or recurrence as the primary outcome to inform the efficacy of MMA embolization as an upfront treatment. Another three-arm open-label randomized controlled trial (NCT04095819) has been designed by Osbun *et al* to compare change in cSDH size between upfront MMA embolization, surgery followed by MMA embolization, and surgery alone for cSDH. This study is expected to characterize differences between MMA embolization as an upfront versus adjuvant treatment. The findings of these trials may help to guide patient selection for MMA embolization and refine the management of cSDH.

Previous systematic reviews have evaluated MMA embolization for cSDH. Srivatsan *et al* reviewed three double-arm and six single-arm studies comprising 126 patients with cSDH, and they found lower recurrence (OR=0.087; $p<0.001$) and comparable complication (OR=0.563; $p=0.497$) rates after MMA embolization versus conventional management.³⁵ These findings were consistent with those from our study. Haldrup *et al* reviewed 18 single-arm studies comprising 191 patients with cSDH, and they reported recurrence rates of 4.1% and 2.4% after upfront and postoperative MMA embolization, respectively.⁶¹ The recurrence rate after upfront MMA embolization was higher than in the present study, although several case reports were included in prior analysis. The aforementioned reviews did not compare surgical rescue rates between MMA embolization versus conventional management, they lacked assessment of neurological and functional outcomes, and they were published before the dissemination of two recent multicenter studies. A recent single-center retrospective cohort study of 35 patients, which was published after completion of this systematic review, achieved complete cSDH resolution in 63% of patients. Although the authors did not report recurrence rates, surgical rescue (2%) and complication rates (3%) were comparable to the pooled data in the present study.⁴⁵

Limitations

We acknowledge that our analyses have several limitations. The majority of the included studies are retrospectively designed, and as such, the analyzed data are heterogeneous. The patient inclusion criteria varied across studies, and the relatively favorable outcomes in the MMA embolization cohort may reflect some degree of selection bias. Our subgroup analysis of upfront versus postoperative MMA embolization was limited by a paucity of data comparing the two treatment approaches in patient with similar baseline characteristics. Therefore, the usefulness of upfront MMA embolization could be limited for cSDHs causing significant mass effect for which urgent surgical evacuation is requisite.

Insufficient data were available to compare differences in outcomes between burr holes versus craniotomy for cSDH drainage, presence versus absence of a surgical drain, location of surgical drain (eg, subdural vs subgaleal), type of embolic materials, and techniques used for MMA embolization (eg, bilateral vs unilateral, complete vs partial embolization). Many studies did

not report long-term outcomes. Furthermore, the definition of cSDH recurrence might have been inconsistent across different studies, and the decision to perform surgical rescue was made at the discretion of the treating physician. The decision to perform MMA embolization might have necessitated withholding antiplatelet or anticoagulant agents, which can contribute to differences in outcomes and complications. Patient selection for MMA embolization was heterogeneous and varied between centers. Our inability to compare these variations in diagnosis and management between practitioners and institutions might have contributed to unmeasured confounding and significantly limits the generalizability of our results.

CONCLUSIONS

MMA embolization for the treatment of cSDH may be associated with lower probabilities of recurrence and surgical rescue than conventional management, with comparable in-hospital complication rates. MMA embolization is an emerging minimally invasive therapy that has the potential to reduce the requirement for surgical intervention in appropriately selected patients with cSDH. MMA embolization indications and techniques are heterogeneous, and there is a critical need to define appropriate patient selection criteria. Prospective randomized studies with predefined MMA embolization protocols are necessary to evaluate the long-term durability of MMA embolization and determine the efficacy of this endovascular approach as an upfront or adjunctive treatment for cSDH.

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Supplemental Table 1: Quality assessment of studies according to the Downs and Black checklist. Articles have been assigned points, out of a possible 32, according to the referenced criteria.

	Reporting										External validity			Internal validity – bias								Internal validity – confounding							Power	Σ
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24	Q25	Q26	Q27			
Mino, 2010	1	1	1	1	0	1	0	1	1	0	0	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	1	0	16	
Hashimoto, 2013	1	1	0	1	0	1	0	1	1	0	0	0	0	0	0	1	0	1	0	1	0	1	0	0	0	0	0	0	10	
Chihara, 2014	0	0	1	1	0	1	0	1	1	0	0	0	1	0	0	1	0	1	1	1	1	1	1	0	0	0	0	0	12	
Tempaku, 2015	1	1	1	1	0	1	0	1	1	0	0	0	1	0	0	1	0	1	1	1	1	1	1	0	0	0	1	0	15	
El Kim, 2017	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	1	0	18	
Matsumoto, 2017	1	1	1	1	0	1	1	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	1	0	17	
Ban, 2018	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	1	1	19	
Link, 2018	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	1	0	19	
Nakagawa, 2019	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	0	17	
Ng, 2019	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	20	
Okuma, 2019	1	1	1	1	0	1	1	1	0	0	0	0	1	0	0	1	0	1	1	1	1	1	1	0	0	0	0	0	14	
Waqas, 2019	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	10	
Catapano, 2020	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	1	0	19	
Fan, 2020	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	1	0	14	
Joyce, 2020	1	1	1	1	0	1	1	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	1	0	18	
Kan, 2020	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	1	0	19	
Mureb, 2020	1	1	0	1	0	1	0	1	0	1	0	0	0	0	0	1	1	1	1	1	1	0	1	0	0	0	0	0	12	
Rajah, 2020	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	1	0	19	
Shotar, 2020	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	1	0	18	
Yajima, 2020	1	1	1	1	0	1	0	1	1	0	0	0	1	0	0	1	0	0	1	1	1	1	0	0	0	0	1	0	13	

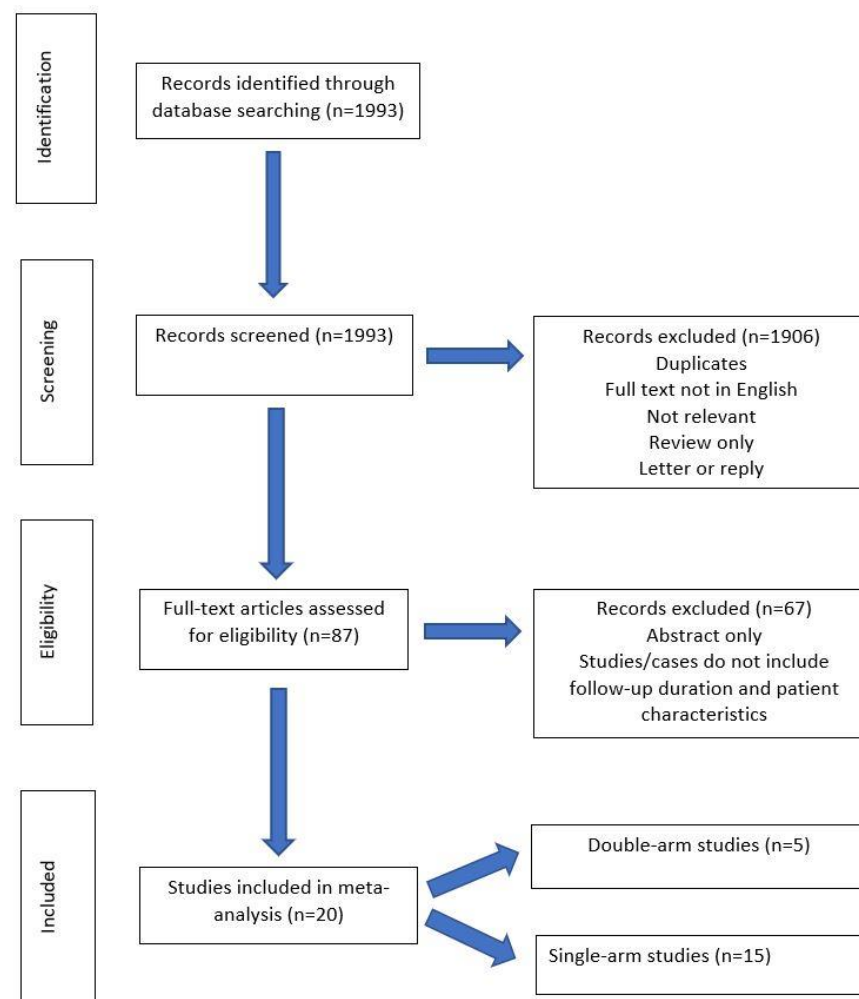
Supplemental Table 2. Subgroup analysis of primary and secondary outcomes after upfront versus postoperative MMA embolization for cSDH.

Abbreviations: n = number, NR = not reported, MMA=middle meningeal artery, cSDH=chronic subdural hemorrhage.

* Weighted pooled proportions in percentage (%) with 95% confidence intervals are presented.

Study, year	Upfront MMA embolization, n (%)	Recurrence, n (%)	In-hospital complication, n (%)	Surgical rescue, n (%)	Surgery with MMA embolization, n (%)	Recurrence, n (%)	In-hospital complication, n (%)	Surgical rescue, n (%)
Mino, 2010	0 (0)	0 (0)	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)	0 (0)
Hashimoto, 2013	0 (0)	0 (0)	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	0 (0)
Chihara, 2014	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)	1 (33.3)	0 (0)	1 (33.3)
Tempaku, 2015	0 (0)	0 (0)	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	0 (0)
El Kim, 2017	0 (0)	0 (0)	0 (0)	0 (0)	20 (100)	1 (5)	2 (10)	0 (0)
Matsumoto, 2017	0 (0)	0 (0)	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)	0 (0)
Ban, 2018	27 (37.5)	0 (0)	0 (0)	0 (0)	45 (62.5)	1	0 (0)	1
Nakagawa, 2019	0 (0)	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	0 (0)	0 (0)
Ng, 2019	0 (0)	0 (0)	0 (0)	0 (0)	19 (100)	1 (5.3)	1 (5.3)	1 (5.3)
Okuma, 2019	0 (0)	0 (0)	0 (0)	0 (0)	17 (100)	0 (0)	0 (0)	NR
Waqas, 2019	6 (75.0)	0 (0)	0 (0)	0 (0)	2 (25.0)	0 (0)	0 (0)	0 (0)
Fan, 2020	0 (0)	0 (0)	0 (0)	0 (0)	7 (100)	0 (0)	0 (0)	0 (0)
Mureb, 2020	8 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Shotar, 2020	0 (0)	0 (0)	0 (0)	0 (0)	89 (33.8)	7 (7.9)	6 (6.7)	4 (4.5)
Yajima, 2020	2 (11.1)	0 (0)	0 (0)	0 (0)	16 (88.9)	0 (0)	0 (0)	0 (0)
Total n (%)	43	0/43 (0)	0/43 (0)	0/43 (0)	256	11/256 (4.3)	9/256 (3.5)	7/239 (2.9)
Pooled estimate*		0 [0.0 to 0.0]	0 [0.0 to 0.0]	0 [0.0 to 0.0]		3.9 [1.4 to 6.4]	2.8 [0.7 to 4.8]	2.9 [0.8 to 5.0]



Supplemental Figure 1: PRISMA flow diagram outlining the study selection process.