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Review

Complications following cranioplasty and relationship to timing: A systematic review and meta-analysis

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ABSTRACT

The optimal timing of cranioplasty after decompressive craniectomy has not been well established. The purpose of this study was to evaluate the relationship between timing of cranioplasty and related complications. A systematic search of MEDLINE, Scopus, and the Cochrane databases was performed using PRISMA guidelines for English-language articles published between 1990 and 2015. Case series, case–control and cohort studies, and clinical trials reporting timing and complication data for cranioplasty after decompressive craniectomy in adults were included. Extracted data included overall complications, infections, reoperations, intracranial hemorrhage, extra-axial fluid collections, hydrocephalus, seizures, and bone resorption for cranioplasty performed within (early) and beyond (late) 90 days. Twenty-five of 321 articles met inclusion criteria for a total of 3126 patients (1421 early vs. 1705 late). All were retrospective observational studies. Early cranioplasty had significantly higher odds of hydrocephalus than late cranioplasty (Odds Ratio [OR] 2.38, 95% Confidence Interval [CI] 1.25–4.52, $p = 0.008$). There was no difference in odds of overall complications, infections, reoperations, intracranial hemorrhage, extra-axial fluid collections, seizures, or bone resorption. Subgroup analysis of trauma patients revealed a decreased odds of extra-axial fluid collection (OR 0.30, $p = 0.02$) and an increased odds of hydrocephalus (OR 4.99, $p = 0.05$). Early cranioplasty within 90 days after decompressive craniectomy is associated with an increased odds of hydrocephalus than with later cranioplasty, but no difference in odds of developing other complications. Earlier cranioplasty in the trauma population is associated with fewer extra-axial fluid collections.

1. Introduction

Cranioplasty after decompressive craniectomy is a common neurosurgical procedure that carries known perioperative risks and complications [1]. The initial decompressive procedure is often performed to relieve elevated intracranial pressure in the setting of traumatic brain injury [2], ischemic [3,4] or hemorrhagic stroke [5,6], or aneurysmal subarachnoid hemorrhage [7–9]. Subsequent cranioplasty to repair the skull defect is typically delayed several months to years after craniectomy to allow the patient to convalesce from the acute phase of illness and ensure resolution of elevated intracranial pressure. The goals of cranioplasty are to restore cerebral protection and craniofacial cosmesis [10]. Cranioplasty may also address post-craniectomy complications such early pseudomeningocele collection [1,11] and delayed paradoxical herniation (sinking skin flap syndrome) [12], and has been shown to improve patients' neurological status [13–17]. Furthermore, a recent systematic review showed no significant difference in infectious and overall complications between early and late cranioplasty [18]. For these reasons, earlier cranioplasty has been advocated in some patients, though optimal timing has yet to be determined.

The purpose of this study was to evaluate the relationship between cranioplasty timing (early versus late) after decompressive craniectomy, and the rate and type of related complications via a systematic review and meta-analysis of the literature. By identifying complications related to timing of cranioplasty, it may be possible to improve neurologic outcome and minimize complication risk by varying the delay between craniectomy and cranioplasty for select patients.

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2. Methods

2.1. Search strategy

A systematic review of the literature adherent to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was performed for published articles reporting on timing of cranioplasty after craniectomy [19]. PubMed/MEDLINE, Scopus, and the Cochrane Database of Systematic Reviews were searched using the keywords "cranioplasty, early" or "cranioplasty, timing" included in the title, abstract, or keyword list. The search was restricted to original clinical studies published between January 1990 and December 2015. Thorough bibliographic searches of qualifying articles and relevant medical journals were also performed to identify additional articles for inclusion.

2.2. Study selection

Articles reporting on the relationship between timing of cranioplasty (early versus late) after decompressive craniectomy, and type and rate of related complications in human adults were included in the analyses.

Case–control studies, cohort studies, or clinical trials that directly compared complication rates between early and late cranioplasty time-points were included. Case series that reported enough raw timing and outcome data to allow authors to make the necessary computations for at least 10 patients were also included. Case reports, technical notes, letters, and editorials were excluded. Meta-analyses and reviews were also excluded; however, referenced articles were thoroughly screened for possible inclusion [1,18,20–24]. Non-English articles were excluded, unless the article had been previously included in a related systematic review [25,26]. Studies that involved animals, included non-calvarial or maxillofacial procedures, or focused exclusively on the pediatric population were excluded [21]. Studies were excluded if a significant proportion of patients underwent non-decompressive craniectomy (for example, for resection of skull tumor). For articles that mentioned collection but no report of timing or complication data, attempts were made to contact authors for further details and potential inclusion.

The search results were independently screened by two authors (JGM and RSR); disagreements were resolved by consensus.

2.3. Data extraction

The following data were extracted from each article, if reported: number of patients, indication for initial craniectomy, anatomic location of procedure, time interval between craniectomy and cranioplasty, incidence and types of cranioplasty-associated complications. Complications were grouped into the following categories: total overall complications; infection requiring treatment (antibiotics, drainage, or reoperation); reoperations (e.g. for infection, resorption, or drainage of fluid collection); intracranial hemorrhage (intracerebral hemorrhage, subdural hematoma, epidural hematoma); extra-axial fluid collection (non-hemorrhagic collections, subdural effusions, cerebrospinal fluid leaks, or hygroma); hydrocephalus (treated with or without a ventriculoperitoneal shunt); new-onset seizures; and bone resorption (by clinical exam or imaging).

Seventeen authors were contacted for further information regarding missing data [15,25,27–41]. Five authors responded and provided data that had not been included in the original publication [15,28,29,34,36]. These data were included in pooled analyses.

Study quality of individual articles was determined according to the Oxford Center for Evidence-Based Medicine (OCEBM) guidelines [42]. Risk of bias was assessed by the Newcastle-Ottawa Scale, which is a three-category, 9-point scale assessing cohort selection, comparability, and outcome [43]. A higher score indicates higher quality.

2.4. Data analysis

Data were analyzed using Review Manager 5.3.5 (The Cochrane Collaboration). Complications were first grouped by specific type (e.g. overall complications, infection, seizure, etc.). If overall complications were not reported in a study, individual complications were summed. Complications were then grouped by "early" and "late" cranioplasty time-points. "Early" cranioplasty was defined as less than or equal to 90 days after craniectomy. The 90-day timepoint was chosen for several reasons: (1) in the authors' experience, cranioplasty procedures often occur around 90 days after initial craniectomy; (2) several studies utilized the median time to cranioplasty in their data as a cutoff for defining early/late time-points, which was around 90 days; (3) grouping around 90 days allowed for inclusion of more studies in the pooled analysis. Studies that provided raw timing data were dichotomized at this time-point for analysis. For studies that did not provide raw data or used a different time-point than 90 days, the study's reported definition was accepted, and the results were pooled in the overall analyses.

Odds ratios (OR) and 95% confidence intervals (CI) for each outcome were then calculated by "early" and "late" time-points. Odds ratios were pooled by using the Mantel–Haenszel method with fixed-effects model, except where the chi-squared test indicated significant heterogeneity among studies, in which case a random-effects model was used. The I^2 metric was reported to further quantify heterogeneity (0% = no heterogeneity, 100% = maximal heterogeneity) [44]. P values of less than 0.05 were considered statistically significant.

For each complication, a subgroup analysis comparing trauma and mixed populations was performed in addition to the overall analysis. The chi-squared test was used to evaluate significant differences between subgroups.

3. Results

Literature review results are depicted in the PRISMA flow diagram (Fig. 1). Three hundred twenty-one non-duplicate studies were screened. This included 309 articles from the database search, three articles identified from review of relevant journals [28,37,45], and nine articles identified from bibliographic review [25,26,36,46–51]. Two of these were non-English articles, but were included because they appeared in a previous meta-analysis on cranioplasty [18,25,26]. Thirty three articles were excluded after full-text review. Reasons for exclusion were as follows: review article [18,20–24], lack of craniectomy to cranioplasty timing data [12,41,52–58], all procedures within 90 days [59,60], significant proportion of non-decompressive craniectomies [31], insufficient data (i.e. authors unreachable or unable to provide) [11,27,35,38,39,61–66], or cranioplasty complications not reported [67–69].

The final twenty-five studies that met inclusion criteria for analysis represented 3126 cranioplasty procedures (1421 early, 1705 late) (Table 1). All were retrospective cohort studies with non-matched cohorts, with an OCEBM Level 4 evidence [14,27,33,70]. Indications for initial craniectomy included arteriovenous malformations, ischemic or hemorrhagic stroke, infection, ruptured aneurysm, trauma, or tumors. Cranial procedure locations, when specified, included unilateral, bilateral, and bifrontal. Six of twenty-five studies dichotomized early and late cranioplasty

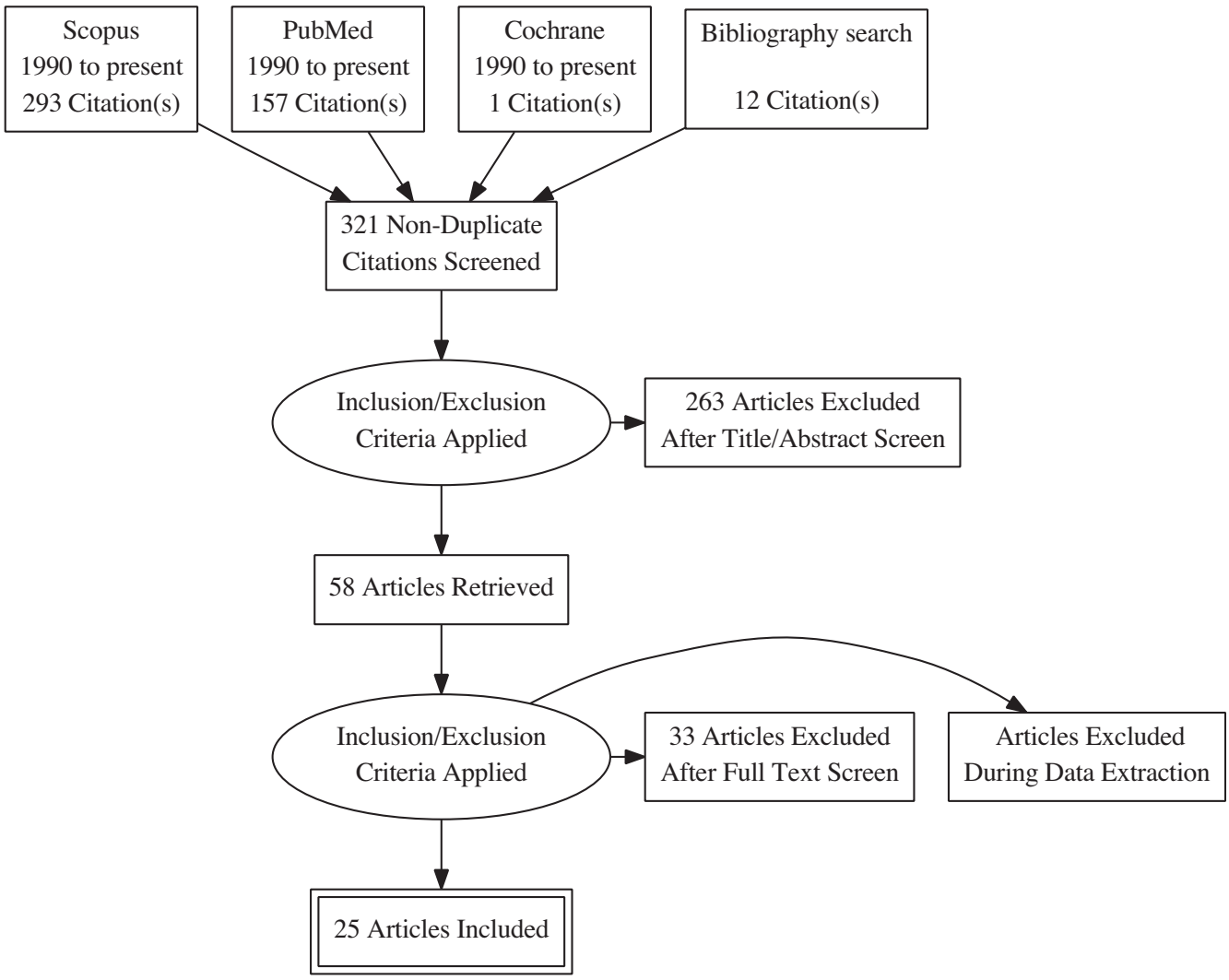

Fig. 1. PRISMA flow diagram.

at a time-point other than 90 ± 10 days (range 42–120 days), and the reported data did not allow for regrouping around 90 days [49–51,70–72]. Six studies included only trauma patients [27,29,30,33,49,73].

Study quality ranged from 3 to 6 out of 9 on the Newcastle–Ottawa Scale. None had matched cohorts, which significantly increases the risk of selection bias. Most had adequate time to follow-up with low loss to follow-up.

3.1. Overall complications

Overall complications included infections (n = 18 studies), complications requiring reoperation (n = 11), intracranial hemorrhage (n = 6), extra-axial fluid collections (n = 5), hydrocephalus (n = 6), seizures (n = 4), and bone resorption (n = 3; Fig. 2). The pooled rate of overall complications was 19.5% (n = 609/3126) across all studies, ranging from 3.9% to 45.3% [25,51]. There was no difference in odds of overall complications in the early cranioplasty group (n = 262/1421 procedures, 18.4%) compared with the late cranioplasty group (n = 347/1705, 20.3%; OR 1.15, CI 0.86–1.54, $p = 0.34$) using a random-effects model ($I^2 = 44\%$, $p = 0.010$). In the subgroup analysis, there was no difference in the odds of overall complications within either the trauma population (n = 425, OR 0.74, CI 0.30–1.83, $p = 0.51$) or mixed population (n = 2,701, OR 1.24, CI 0.92–1.66, $p = 0.16$).

3.2. Infection

Eighteen studies reported infectious complications that required antibiotic treatment with or without reoperation for abscess drainage or implant removal (Fig. 3). There was a wide range of definitions for infection, as follows: infection requiring bone removal [25,28,29,46,48,72,74]; fever, heat, swelling, elevated laboratory values [73] with drainage [33,70], with or without findings on CT scan [33,70]; purulent [50] or any fluid drainage [33,70]; superficial infection [37]; deep wound infection [13,37]; cellulitis [50]; osteomyelitis [13,14,34,50], bone necrosis or bone graft displacement [14]; bacterial meningitis [50], cerebrospinal fluid findings (leukocytosis, elevated protein) with fever and meningismus [14]; intracranial abscess [36], extra-axial empyema [36,50], expanding extra-axial fluid collection [45]; need for >2 weeks antibiotics [74], intravenous antibiotics [48,72]; wound dehiscence with flap exposure [45]; central nervous system infection [34]. Four studies reported an infection rate of 0%; these were listed in Fig. 3 for completeness, but were not included in the pooled calculations [11,27,30,49].

The pooled rate of infection was 7.7% (n = 165/2021), ranging from 1.4% to 24.4% [45,71]. There was no difference in odds of infection in the early cranioplasty group (n = 89/1003 procedures, 8.9%) compared with the late cranioplasty group (n = 76/1018, 7.5%; OR 1.21, CI 0.85–1.68, $p = 0.30$) using a fixed-effects model

Table 1
Characteristics of included studies reporting complications related to cranioplasty timing.

Reference	Indication for DC	Location	Early CP cutoff (days)	Number of patients		Complications
				Early	Late	
Archavlis et al. (2012)	ICH, infection, ischemic stroke, rupture aneurysm, TBI	Unilateral	90*	147	53	Complication
Bender et al. (2013)	ICH, ischemic stroke, ruptured aneurysm, TBI	Bifrontal, unilateral	86	75	72	EDH, hydrocephalus, ICH, infection, ischemic stroke, local bone graft complication, seizure
Chang et al. (2010)	AVM, elective AVM/aneurysm, ICH, infection, ischemic stroke, other, ruptured aneurysm, TBI, tumor		90*	89	119	Complication
Chaturvedi et al. (2015)**	TBI	Bifrontal, unilateral	90	20	54	Complication
Cheng et al. (2008)	Arachnoid cyst, AVM, ICH, ischemic stroke, ruptured aneurysm, tumor, venous sinus thrombosis		90	41	43	Infection
Cho et al. (2011)	TBI		42	15	21	Infection, subdural fluid collection, ventriculomegaly
Chun et al. (2011)	TBI	Unilateral	90	30	15	Dural tear, infection, inadequate dissection, soft tissue injury, subdural fluid
Gooch et al. (2009)	Infection, intraoperative swelling, stroke, trauma	Bifrontal, bilateral, unilateral	100	31	31	Complication, reoperation
Hng et al. (2015)**	Infection, ruptured aneurysm, stroke, TBI, tumor	Bifrontal, unilateral	90	121	66	Complication, contour irregularity, extra-axial collections requiring evacuation, infection requiring removal, superficial infection, postop shunting, resorption requiring removal, seizures
Im et al. (2012)	TBI, tumor, vascular	Bifrontal, unilateral	90	84	47	Infection
Kim et al. (2001)	Trauma, non-trauma		90*	76	35	Infection
Kim et al. (2014)	ICH, infection, ischemic stroke, rupture aneurysm, TBI, tumor		60	23	83	Epidural fluid collection
Mukherjee et al. (2014)	AVM, ICH, intracranial infection, infected bone flap, ischemic stroke, ruptured aneurysm, TBI, tumor	Bifrontal, unilateral	120	29	145	Complication, post-op length of stay, removal
Nagayama et al. (2002)	ICH, ischemic stroke, ruptured aneurysm, TBI, other		90*	181	25	Infection
Paredes et al. (2015)**	AVM, ICH, ischemic stroke, reabsorption, ruptured aneurysm, TBI	Bifrontal, unilateral	85	10	45	Complication
Piedra et al. (2013)	Stroke		70	37	37	Complication, hematoma, hydrocephalus, infection, resorption
Piedra et al. (2014)	TBI		90*	78	79	Complication, hematoma, hydrocephalus, infection, resorption
Piitulainen et al. (2015)	infection, stroke, TBI		90	21	79	Reoperation
Rosetto et al. (2015)	infection, TBI, tumor		85	18	27	Infection
Schuss et al. (2012)	ICH, ischemic stroke, other, ruptured aneurysm, TBI	Bifrontal, unilateral	60	54	226	Abscess, cerebrospinal fluid fistula, EDH/SDH, hygroma, wound healing disturbance
Song et al. (2014)	TBI	Unilateral	90	25	18	infection, subdural fluid
Tsang et al. (2015)**	Cerebrovascular disease, infection, TBI, tumor		90*	60	102	Flap depression, infection
Walcott et al. (2013)**	Stroke, TBI	Convexity, bifrontal, bilateral convexity	90	71	168	Infection, seizure, wound healing disturbance, surgical site infection, hydrocephalus, hematoma
Yang et al. (2013)	ICH, ischemic stroke, SAH, TBI, tumor		60	62	68	infection
Zhang et al. (2010)	TBI	Unilateral	90	23	47	Epilepsy, infection, perioperative meninges breakdown, postoperative fluid below skin flap, wound healing
Total				*1421 3126*	*1705*	

Italics indicates a summed total for the column(s).
* Article reports individual case data or data at various time intervals. Patients were divided at a 90-day cutoff.
** Data obtained via correspondence with author.
AVM = arteriovenous malformation, CP = cranioplasty, DC = decompressive craniectomy, EDH = epidural hematoma, ICH = intracerebral hemorrhage, OCEBM = Oxford Center for Evidence-Based Medicine, SAH = subarachnoid.

(I^2 = 0%, p = 0.48). In the subgroup analysis, there was no difference in odds of infection within either the trauma population (n = 202, OR 0.46, CI 0.17–1.23, p = 0.12) or mixed population (n = 1,819, OR 1.38, CI 0.96–1.99, p = 0.09).

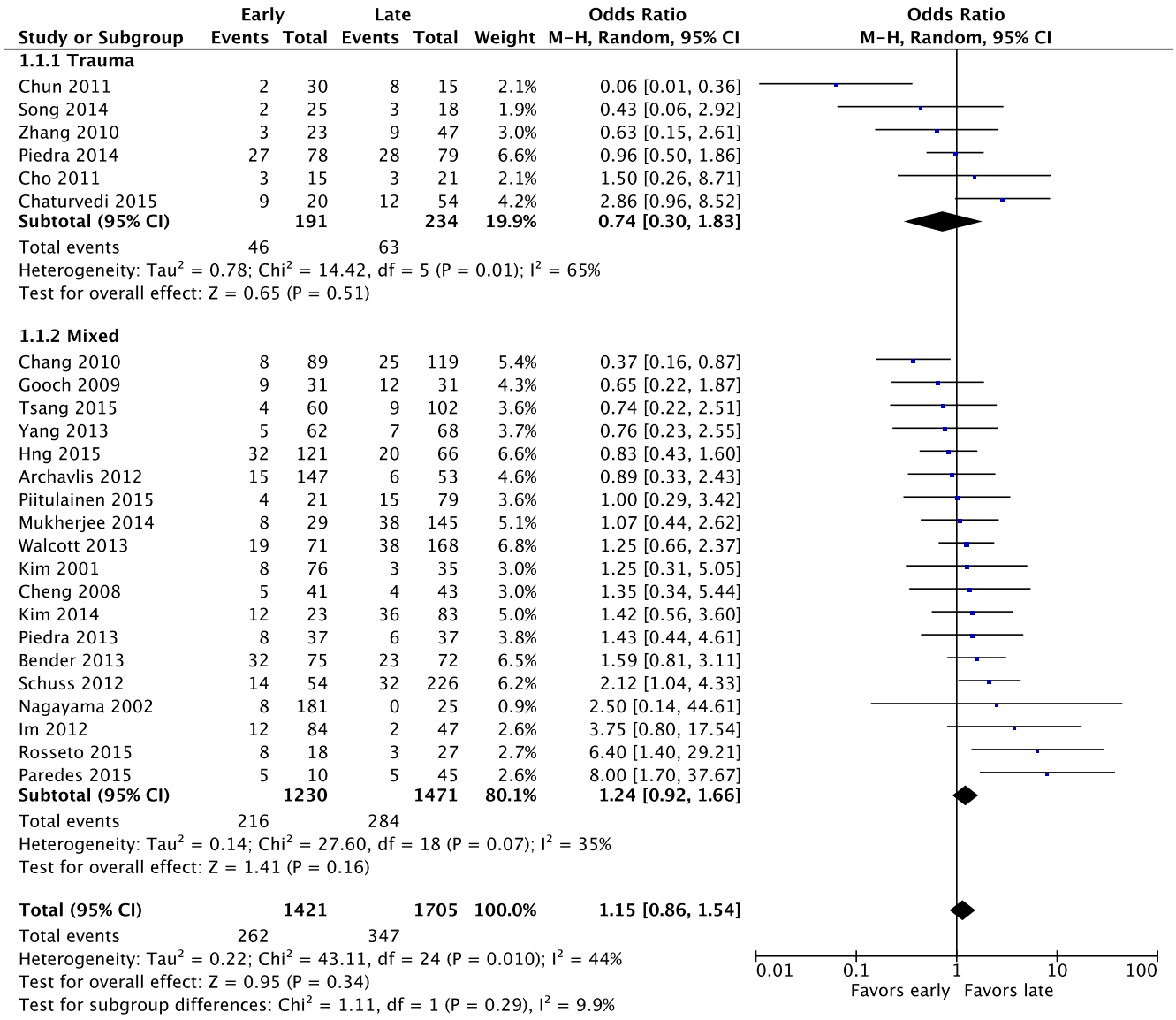

Fig. 2. Forest plot of studies reporting overall complications with early or late cranioplasty stratified by population type (trauma versus mixed). The blue square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% confidence intervals (CIs). The diamond data markers represent the subtotal and overall OR and 95% CIs. The vertical solid line indicates the line of no effect (OR 1). Results indicate no difference in odds of overall complications with early cranioplasty.

3.3. Reoperation

Eleven studies reported complications requiring reoperation for infection, resorption, or drainage of extra-axial fluid collection (Fig. 4). Placement of a ventriculoperitoneal shunt for post-cranioplasty hydrocephalus was not considered a reoperation in this review and is addressed separately. The pooled rate of reoperations was 13.2% (n = 191/1445), ranging from 3.9% to 25.8% [25,47]. There was no difference in odds of reoperation in the early cranioplasty group (n = 73/670 procedures, 10.9%) compared with the late cranioplasty group (n = 112/775, 14.5%; OR 0.78, CI 0.55–1.10, $p = 0.16$) using a fixed-effects model ($I^2 = 0\%$, $p = 0.63$). In the subgroup analysis, there was no difference in odds of reoperation within either the trauma (n = 157, OR 0.52, CI 0.18–1.47, $p = 0.22$) or mixed populations (n = 1288, OR 0.82, CI 0.57–1.18, $p = 0.29$).

3.4. Intracranial hemorrhage

Six studies reported hemorrhagic complications that included epidural hematoma, subdural hematoma, intracerebral hemorrhage, and extra-axial fluid collections requiring evacuation [28] (Fig. 5). The pooled rate of hemorrhagic complications was 4.9% (n = 53/1084) ranging from 2.5% to 7.5% [14,33]. There was no difference in odds of intracranial hemorrhage in the early cranioplasty group (n = 18/436 procedures, 4.1%) compared with the late cranioplasty group (n = 35/648, 5.4%; OR 0.73, CI 0.40–1.36, $p = 0.33$) using a fixed-effects model ($I^2 = 0\%$, $p = 0.53$). In the subgroup analysis, there was no difference in the odds of hemorrhage within either the trauma (n = 157, OR 3.12, CI 0.32–30.66, $p = 0.33$) or mixed populations (n = 927, OR 0.64, CI 0.33–1.23, $p = 0.18$).

3.5. Extra-axial fluid collection

Five studies reported non-infectious, non-hemorrhagic extra-axial fluid collections, including epidural and subdural fluid collections [27,49,51,73], hygroma [71], dural tears [73], and CSF fistulas [71] (Fig. 6). The pooled rate of extra-axial fluid collections was 13.9% (n = 71/510), ranging from 2.11% to 45.3% [51,71]. There was no difference in odds of fluid collection in the early cranioplasty group (n = 19/147 procedures, 12.9%) compared with the

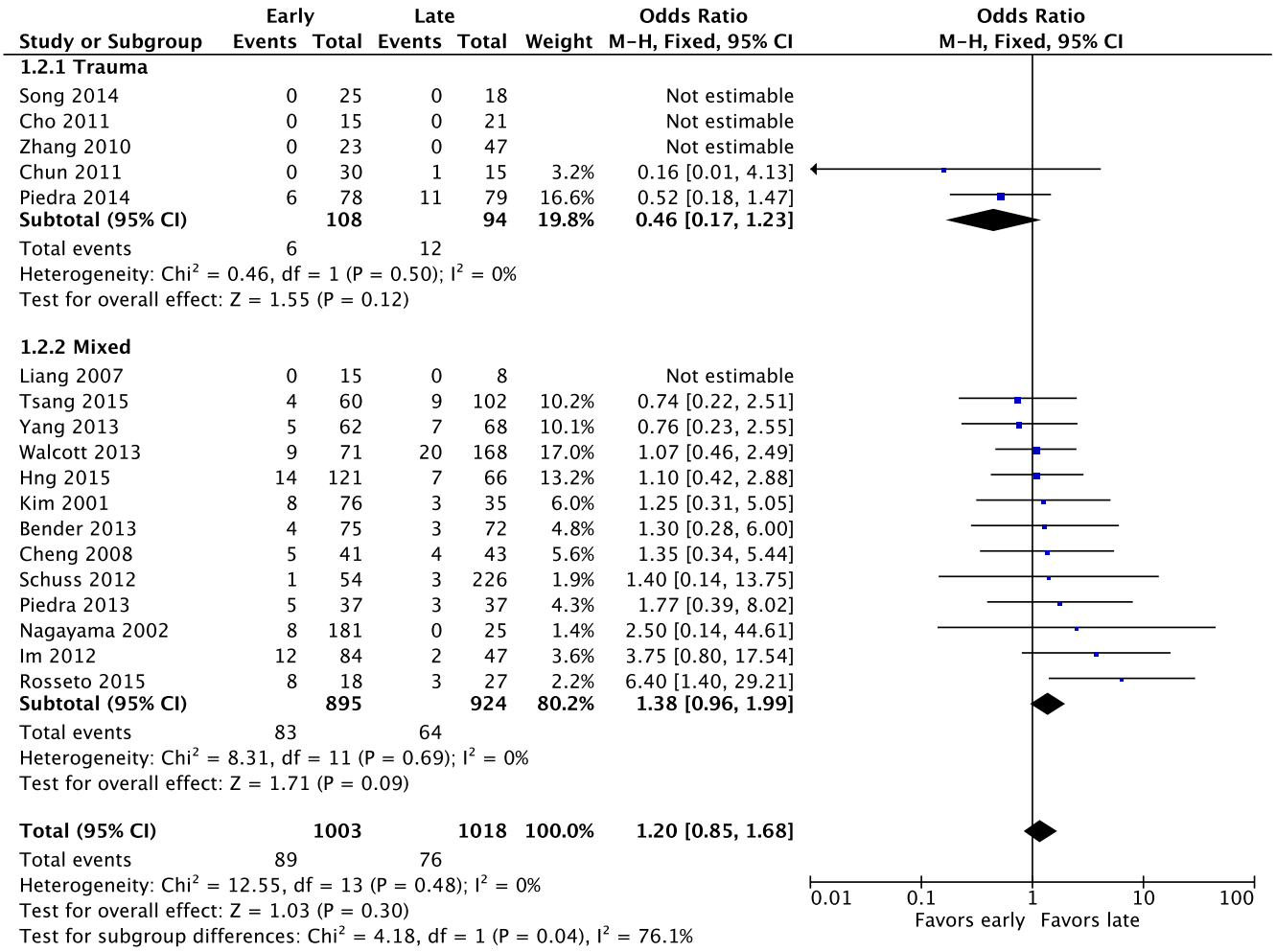

Fig. 3. Forest plot of studies reporting infectious complications with early or late cranioplasty stratified by population type. Results indicate no difference in odds of infection with early cranioplasty.

late cranioplasty group (n = 52/363, 14.3%; OR 0.64, CI 0.20–2.05, $p = 0.46$) using a random-effects model ($I^2 = 59\%$, $p = 0.05$). In the subgroup analysis, odds of fluid collection with early cranioplasty were significantly decreased within the trauma population (n = 124, OR 0.24, CI 0.07–0.88, $p = 0.03$), whereas there was no difference within the mixed population (n = 386, OR 1.56, CI 0.69–3.53, $p = 0.29$).

3.6. Hydrocephalus

Six studies reported post-cranioplasty hydrocephalus (Fig. 7). Four of these studies specifically defined hydrocephalus as requiring placement of a ventriculoperitoneal shunt [28,33,36,70]. The remaining two studies defined hydrocephalus by presence of enlarged ventricles on CT scan with [14] or without [49] neurological deterioration or lack of improvement. The pooled rate of hydrocephalus was 5.6% (n = 47/840) ranging from 1.4% to 12.2% [14,70]. There was a significant increase in odds of hydrocephalus in the early cranioplasty group (n = 31/397, 7.8%) compared with the late cranioplasty group (n = 16/443, 3.6%; OR 2.40, CI 1.28–4.52, $p = 0.006$) using a fixed-effects model ($I^2 = 0\%$, $p = 0.88$). In the subgroup analysis, odds of hydrocephalus with early cranioplasty were increased within both the trauma (n = 193, OR 4.99, CI 1.00–24.88, $p = 0.05$) and mixed populations (n = 647, OR 2.03, CI 1.01–4.07, $p = 0.05$). Odds were also higher in the trauma subgroup compared with the overall population.

3.7. Seizures

Four studies reported new-onset seizures (Fig. 8). The pooled rate of seizures was 6.1% (n = 39/643) ranging from 2.7% to 15.0% [14,28]. There was no difference in odds of seizure in the early cranioplasty group (n = 18/290 procedures, 6.2%) compared with the late cranioplasty group (n = 21/353, 5.9%; OR 0.98, CI 0.49–1.95, $p = 0.96$) using a fixed-effects model ($I^2 = 0\%$, $p = 0.94$). In the subgroup analysis, there was no difference in odds of seizures within either the trauma (n = 70, OR 0.67, CI 0.07–6.79, $p = 0.73$) or mixed populations (n = 573, OR 1.02, CI 0.50–2.11, $p = 0.95$).

3.8. Bone resorption

Three studies reported bone graft resorption, which was determined either by clinical exam or imaging (Fig. 9). The pooled rate of bone resorption was 9.3% (n = 39/418) ranging from 2.7% and 17.2% [28,70]. There was no difference in odds of graft resorption in the early cranioplasty group (n = 20/236 procedures, 8.5%) compared with the late cranioplasty group (n = 19/182, 10.4%; OR 0.90, CI 0.45–1.78, $p = 0.76$) using a fixed-effects model ($I^2 = 0\%$, $p = 0.82$). In the subgroup analysis, there was no difference in odds of resorption within either the trauma (n = 157, OR 0.78, CI 0.34–1.79, $p = 0.55$) or mixed populations (n = 261, OR 1.23, CI 0.36–4.24, $p = 0.74$).

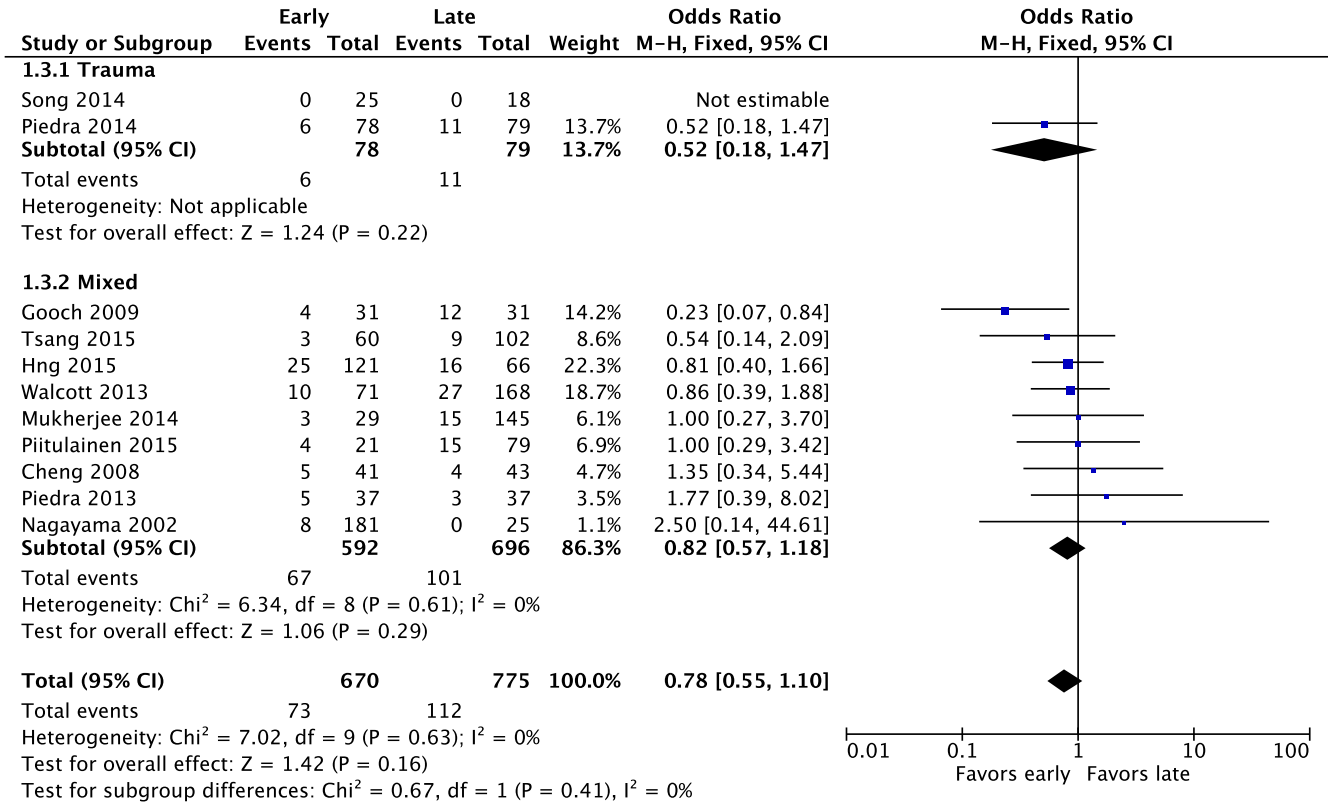

Fig. 4. Forest plot of studies reporting reoperations with early or late cranioplasty stratified by population type. Results indicate no difference in odds of reoperations with early cranioplasty.

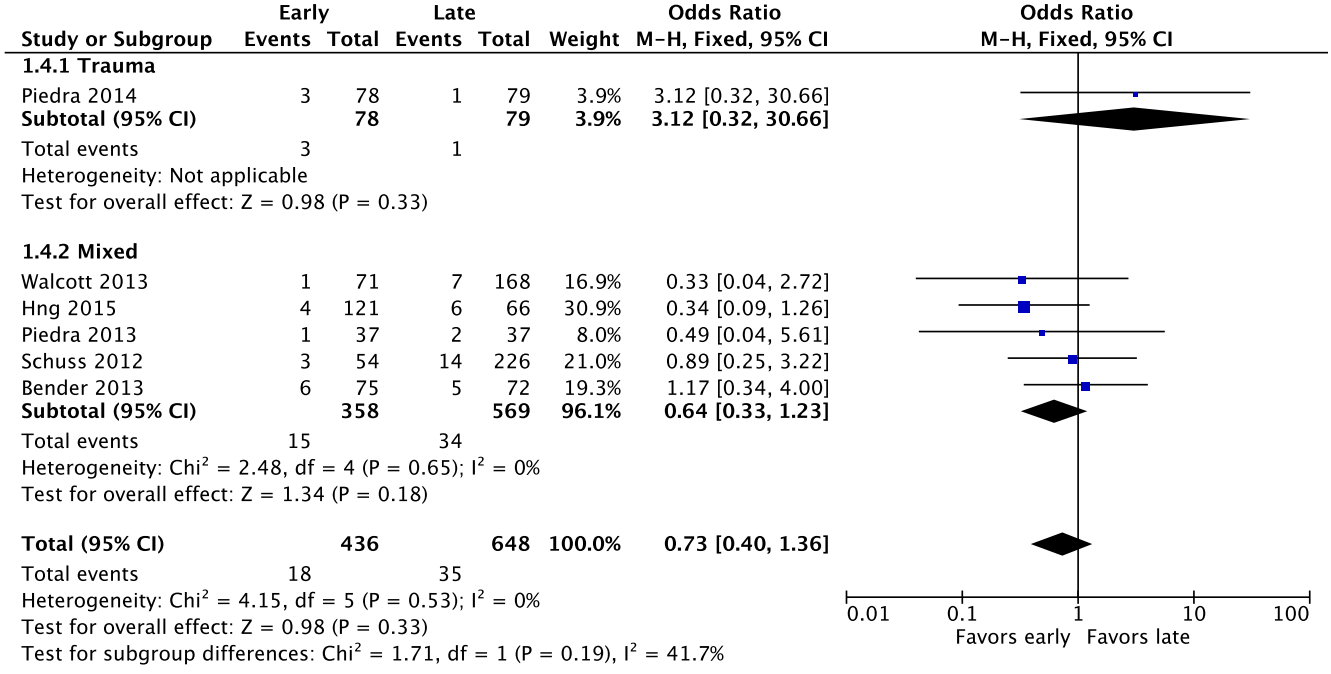

Fig. 5. Forest plot of studies reporting intracranial hemorrhage with early or late cranioplasty stratified by population type. Results indicate no difference in odds of hemorrhage with early cranioplasty.

4. Discussion

This systematic review investigated the difference in odds of complications between early and late cranioplasty following decompressive craniectomy. The results suggest that early cranioplasty (⩽90 days) is associated with greater odds of hydrocephalus than late cranioplasty (>90 days), without difference in odds of other complications. These findings suggest that early cranioplasty,

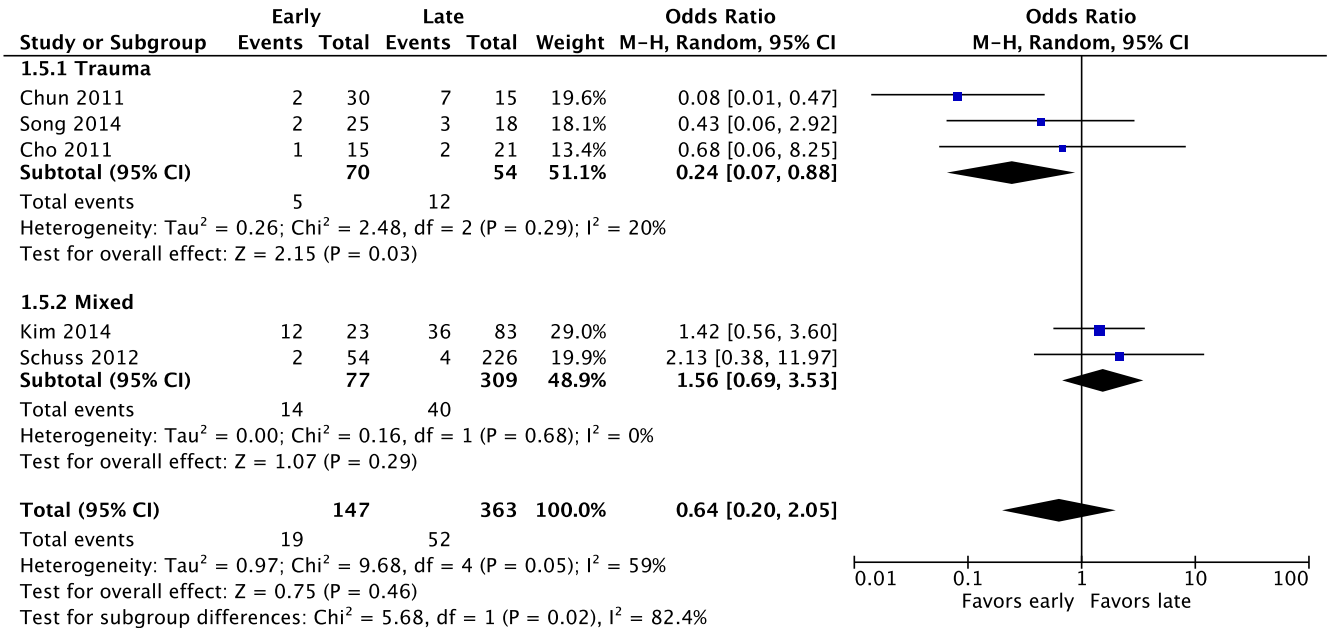

Fig. 6. Forest plot of studies reporting non-hemorrhagic extra-axial fluid collections with early or late cranioplasty stratified by population type. Results indicate no difference in odds of extra-axial fluid collection with early cranioplasty. The trauma subgroup had significantly decreased odds of fluid collection with early cranioplasty.

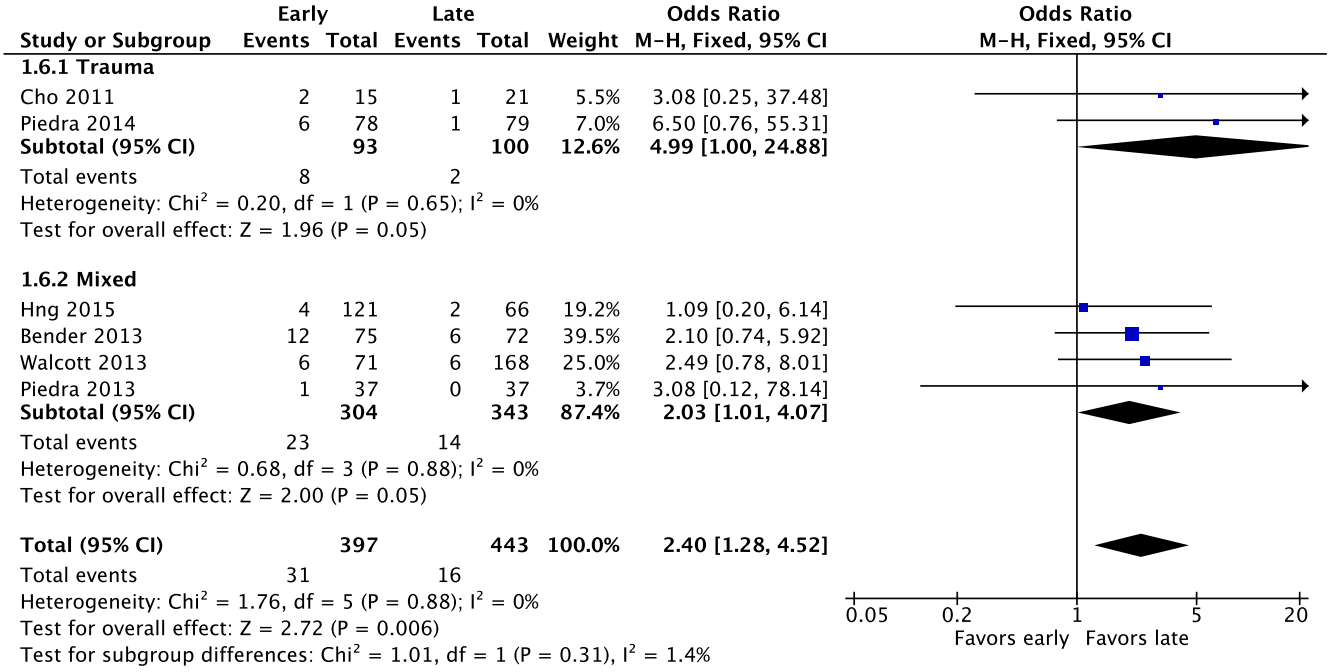

Fig. 7. Forest plot of studies reporting hydrocephalus with early or late cranioplasty stratified by population type (trauma versus mixed). Results indicate a significant increase in odds of hydrocephalus with early cranioplasty in the overall population, as well as trauma and mixed subgroups.

with expectant management of hydrocephalus, is otherwise as safe as late cranioplasty.

4.1. Comparison with previous reviews

The current review includes articles spanning the last twenty-five years of published literature, with the majority from the last five years, indicating increasing interest in this topic. Despite being one of the most common neurosurgical procedures, cranioplasty timing has not been the focus of any prospective studies until recently, with the planned German Cranial Reconstruction Registry [75]. Four other reviews have recently examined complication rates associated with timing of cranioplasty [18,20–22]. Yadla et al. performed a systematic review and meta-analysis evaluating overall complications and infections associated with the timing of cranioplasty (early defined as occurring within three months). It also compared infection rates by material (autogenous bone graft or allograft) and by bone graft storage method (subcutaneous pocket or extracorporeal) [18]. Their review included only five studies examining timing (671 procedures), all of which are also included in our review [25,26,46–48]. In the complications analysis, there appears to be a discrepancy in total counts for Gooch

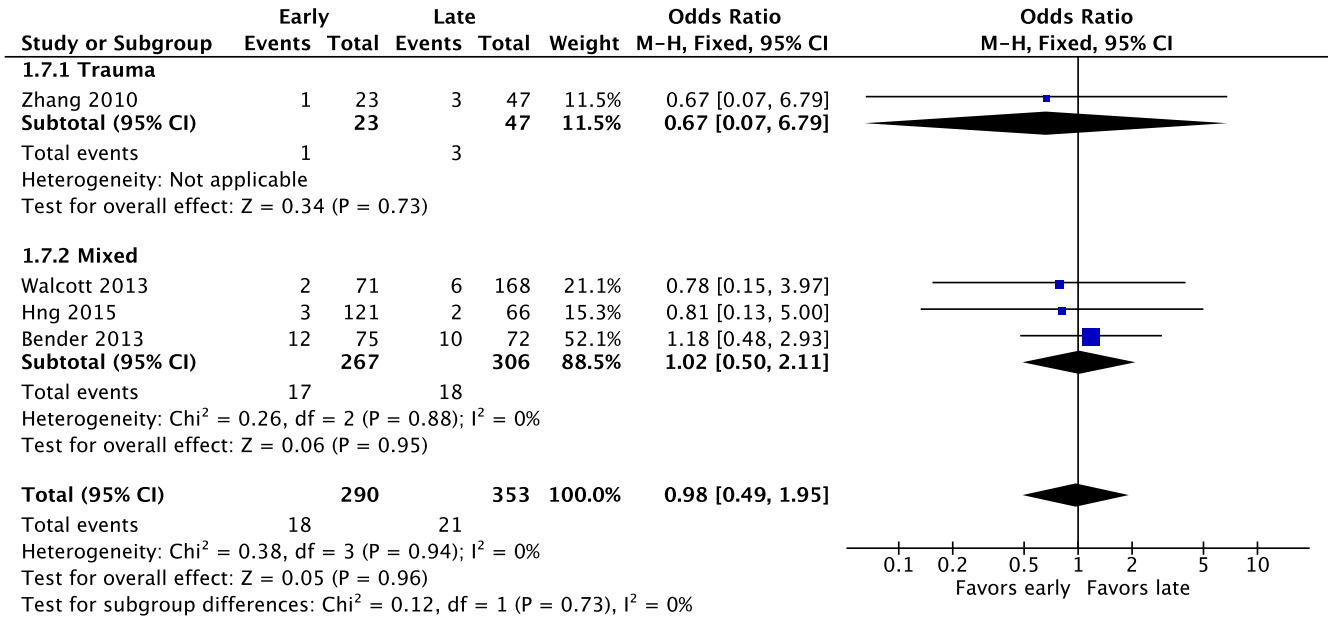

Fig. 8. Forest plot of studies reporting seizures with early or late cranioplasty stratified by population type. Results indicate no difference in odds of seizures with early cranioplasty.

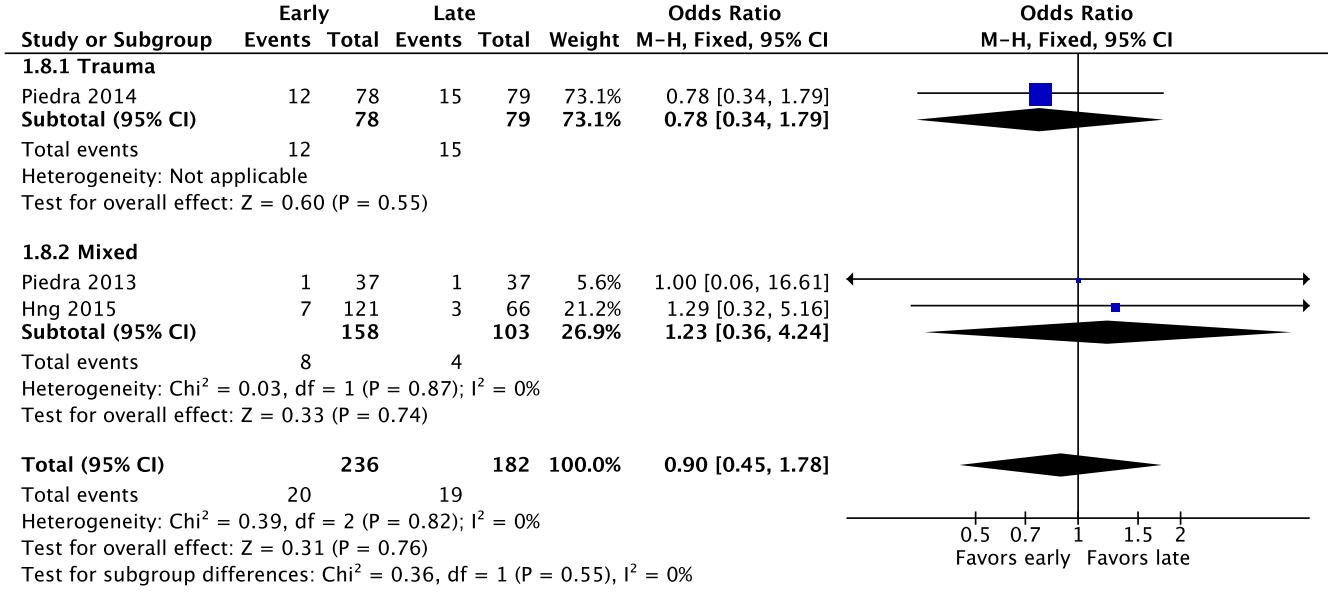

Fig. 9. Forest plot of studies reporting resorption with early or late cranioplasty stratified by population type. Results indicate no difference in odds of resorption with early cranioplasty.

et al.: Yadla et al. reported 17 complications among 47 patients in the "0–3 month" group, and four among the 15 patients in the ">3 months group," whereas Gooch et al. reported 9/31 and 12/31 respectively (Fig. 2) [18,47]. We were able to contact the primary authors who confirmed this discrepancy, although recalculation does not change the ultimate study conclusion.

Rocque et al. performed a systematic review of four articles reporting infection and resorption rates associated with timing in the pediatric population [21]. These studies, however, were not included in the present review because they included solely pediatric patients.

Tasiou et al. performed a qualitative systematic review of ten studies evaluating timing of cranioplasty after closed head injury [22]. Four of these were included in our review, but the remaining six were excluded due to unavailable timing data [11,32,38,60,63] or significant proportion of non-decompressive craniectomy cases [31]. Reported complications included infection, hydrocephalus, and subdural fluid collections. Neurological outcome was also evaluated to determine safety for early procedures [11,60]. There was a general trend for early cranioplasty to improve cerebrospinal fluid (CSF) dynamics and perfusion, while reducing the risk of a sunken flap; however, no comparative analyses were reported.

Finally, Xu et al. performed a systematic review and meta-analysis of nine studies (1209 procedures) evaluating various complications and procedure duration related to timing of cranioplasty also using a threshold of 90 days [20]. They evaluated differences in operative time in addition to other outcomes included in our study (overall complications, infections, hydrocephalus, hematoma, and subdural fluid collections). Several data extraction errors were identified in this study resulting in conclusions different from

those published. Specifically, a revised analysis found no difference in operative time and a decreased incidence of subdural fluid collections with early cranioplasty [76]. We identified additional errors affecting the analyses for overall complication [48,73], infection [73], and hydrocephalus [14]. Given these errors, it is difficult to draw reliable conclusions from their review. All nine studies included in Xu et al. were included in our analysis, along with sixteen additional studies from the literature search to make for a comprehensive review to date.

4.2. Overall complications

The overall complication rate in this study was 19.5%, and ranged widely across studies (3.9–45.3%).[25,51] Kurland et al. reported a lower overall complication rate of 6.4% [1]. Similar to our study, Yadla et al. reported no difference in odds of overall complications with early cranioplasty [47,48]; and the mathematical discrepancy described above did not appear to affect the ultimate study conclusions. Similarly, Rocque et al. identified three articles reporting no significant association between timing and overall complications in children (infection and resorption) [21]. Due to the varied reporting of complication types and their management, it may be useful for future studies to narrow the list of complications and differentiate those that resolved without intervention.

4.3. Infection

The pooled infection rate in this review (8.1%) is comparable to the combined infectious and inflammatory rate of 6.0% reported by Kurland et al. [1] Interestingly, there was a slightly increased rate of infection with trauma in their review (7.4% versus 5.8% for ischemic stroke, 5.1% for hemorrhagic stroke, and 5.6% for other/unspecified). Our analysis revealed no difference in overall odds of infection with early cranioplasty, which is consistent with Yadla et al.'s findings [18].

Several studies examined potential risk factors for infection. In patients that remained hospitalized in the time between the craniectomy and cranioplasty, infection rates were higher in those with a systemic infection within 30 days preceding cranioplasty, a low hemoglobin, or poor neurologic status (motor deficit, Glasgow Outcome Scale <4) [45]. However, these factors may simply be markers for the most debilitated patients [45]. Infection rates were also higher in patients that underwent an additional operation between the initial craniectomy and subsequent cranioplasty (OR 3.25, $p = 0.01$), or patients that had a stroke rather than a trauma that required craniectomy (OR 2.45, $p = 0.03$) [36]. These factors are certainly worth closer attention when choosing timing of cranioplasty for specific populations to control the infectious risk.

4.4. Reoperation

Reoperations for complications lead to longer hospital stays, additional surgical risk, and increased cost. Many studies report complications that often resolve with antibiotics or watchful waiting; however, few distinctly report those that require a return to the operating room, and no previous reviews have systematically investigated this question. The reoperation rate in our review was high at 12.9%, nearing the overall complication rate of 19.5%. We did not consider placement of a ventriculoperitoneal shunt for hydrocephalus as a reoperation, and it was evaluated separately. Of note, odds of reoperation with early cranioplasty was slightly lower than late cranioplasty and trended toward significance. It is possible that sicker patients require deliberate delay in their cranioplasty procedure, and harbor specific risk factors that increase their risk of complications requiring reoperation. However, this is only answerable with a prospective observational study. Additional risk factors for reoperation include bifrontal defects [47].

4.5. Intracranial hemorrhage

Kurland et al. reported a rate of 3.6% for intracranial hemorrhage, which is consistent with our review (4.6%) [1]. Specific risk factors for intracranial hematoma that require reoperation include male sex, African-American race, and hypertension [56]. No other review has systematically evaluated the odds of intracranial hemorrhage in early versus late cranioplasty.

4.6. Extra-axial fluid collection

Kurland et al. reported a rate of 5.8% for subdural effusions/hygroma and 6.8% for CSF leaks/fistulas, for an overall rate of 6.1% [1]. In the corrected analysis of Xu et al. odds of subdural fluid collections were reduced in early cranioplasty [76]; however, in the overall analysis, this was true only in the trauma subpopulation (OR 0.24, $p = 0.03$). Among the studies included in this analysis, Chun et al. was the only one to find a significant decrease in collections with early cranioplasty [73]. It is possible that the potential space between the cranioplasty flap and brain is much smaller at earlier time points due to residual cerebral edema, which resolves and may even paradoxically sink at later time points.

4.7. Hydrocephalus

Our study revealed a relatively low rate of hydrocephalus (6.0%), similar to Kurland et al. (7.5%). However, our study found a significant increase in odds of hydrocephalus with early cranioplasty (OR 2.38, $p = 0.008$), which was even higher for the trauma subgroup (OR 4.99, $p = 0.05$). In contrast to our findings, Kurland et al. reported a similar rate of hydrocephalus for trauma (6.8%) and the overall population (7.5%) [1]. It is unclear whether hydrocephalus is a consequence of the initial brain insult, craniectomy, or cranioplasty itself. Other predictors of hydrocephalus independent of cranioplasty timing include age, subarachnoid hemorrhage and trauma [56]. Pre-existing hydrocephalus from the initial insult also increases the risk of persistent hydrocephalus despite simultaneous ventriculoperitoneal shunt placement at the time of cranioplasty [67]. Longer delays to cranioplasty in these patients also strongly correlate with persistent hydrocephalus. Early cranioplasty with simultaneous shunting might be beneficial for this population, but may also increase the risk of complications in simultaneous rather than staged procedures [69]. For trauma patients without pre-existing hydrocephalus, our results suggest an even greater risk of hydrocephalus and so later cranioplasty may prevent its occurrence. It will be important for future studies to assess out whether the presence of pre-existing hydrocephalus in different populations affects optimal cranioplasty timing.

4.8. Seizures

The rate of post-cranioplasty seizures is relatively low (6.1%) and has no association with the timing of cranioplasty. However, other factors, such as reoperation for an intracranial hematoma, may increase seizure risk [56]. Regardless of timing, peri-procedural anti-epileptic prophylaxis is a low risk and effective intervention to prevent the increased mortality risk associated with peri-operative seizures [36,56].

4.9. Bone resorption

Resorption is an often underappreciated complication, especially if asymptomatic or if serial imaging is not performed. Kurland et al. estimated incidence of aseptic bone flap resorption to be as high as 16% in adult patients, with flap depression or other cosmetic defects occurring at a rate of 3.1% [1]. This is higher than our rate of 10.8%. Resorption occurs significantly more frequently in the pediatric population, particularly if performed beyond six weeks [21,77]. Our study found no difference in odds of resorption in adults before and after 12 weeks. It is possible that younger age and ultra-early cranioplasty increases risk of resorption; however, this has not been specifically evaluated in adults.

4.10. Strengths and limitations

This study has both strengths and limitations. To our knowledge, it is the largest and most comprehensive systematic review and meta-analysis exploring the role of cranioplasty timing in complication rates. It builds upon and extends the findings from other systematic reviews addressing this question [18,20–22]. It also adds new data obtained through author correspondence from published articles. These factors strengthen the validity and generalizability of the findings and conclusions in this review.

There are also some limitations, particularly regarding the heterogeneity of the population. We were broad in our definition of "craniectomy," regarding both indication and anatomic location. Although many studies in this review performed decompressive craniectomies for the purpose of reducing intracranial pressure, it is possible that some non-decompressive indications were also included. We excluded any studies that explicitly described craniectomy for skull tumor if it comprised a significant portion of procedures [31]; however, we were unable to quantify the exact proportion of non-decompressive craniectomies in this review as these data were not always specified in the studies.

All but six studies in this analysis included a mix of indications for decompressive craniectomy [27,29,30,33,49,73]. These factors might have made the study population too heterogenous to find significant differences in complication rates. It has been suggested that optimal cranioplasty timing might be different for patients with discrete diseases due to unique disease pathophysiology [56,78]. For instance, it has been suggested that hemorrhagic complications after cranioplasty following large ischemic middle cerebral artery stroke could be related to the brain's natural inflammatory response to ischemic and necrotic tissue. This inflammation would increase tissue friability and, therefore, risk of hemorrhage when the cranial flap is replaced [78]. For these reasons, it may be advantageous to delay cranioplasty until the inflammatory process has resolved. Alternatively, patients that have undergone craniectomy for evacuation of subdural hematoma after trauma may benefit from early cranioplasty if no significant postoperative cerebral edema is present in order to reduce risk of pseudomeningocele or sinking skin flap syndrome [79]. Few studies have specifically compared complication rates of cranioplasty across craniectomy indications, and only a handful have stratified complication rates by both indication and cranioplasty timing. For instance, Kurland et al. reported differences in hemorrhagic complication rates by craniectomy indication, which surprisingly varied only slightly (hemorrhagic stroke 5.5%, ischemic stroke 4.6%, and trauma 5.4%) [1]. Only six studies in our review reported on a single patient population (traumatic brain injury) which allowed for a limited subgroup analysis [27,29,30,33,49,73]. It would be fruitful to further explore whether complications vary by both craniectomy indication and cranioplasty timing in future studies.

Anatomic heterogeneity of cranioplasty is another challenging factor to consider. This review pooled patients with unilateral, bilateral, and bifrontal craniectomies. Many studies did not specify cranioplasty location. Complications may vary by anatomical location due to differences in underlying cerebral anatomy, blood supply, cerebrospinal fluid circulation, and surface area of the defect. Bifrontal procedures have significantly higher infection rates[7] and increased risk for reoperation [47]. Size and location of craniectomy also depends significantly on the initial indication and goal of surgery, as discussed above. These factors should be further explored in future studies with subgroup analyses by anatomic location and craniectomy indication in order to evaluate whether optimal cranioplasty timing differs in these populations.

The definition of early and late cranioplasty has not been clearly established in the literature. Most studies in this review could be grouped around a 90-day time-point; however, five of the included studies used other time-points as dictated by institutional practices or to partition their patient population into two balanced cohorts (range 42–120 days) [49–51,71,72]. Some case series have shown that ultra-early cranioplasty (8–12 weeks) after trauma has low complication rates [11,60]. These were excluded in this present review since all procedures were early thus not allowing comparison. Including ultra-early cranioplasty in the early cranioplasty subgroup might have obscured important differences in complication rates between early and late time-points. The ultra-early time-point for cranioplasty is worth further exploration. Although most studies dichotomize timing data, it may be more appropriate to analyze data by month or perform regression analysis to prospectively identify the optimal time point.

Definitions of complications also varied across studies, particularly for infection. Some studies only considered infection a complication if it required reoperation [25,29], whereas others included wound dehiscence with flap exposure [45]. Others included various definitions for cellulitis, meningitis, osteomyelitis, intracranial abscess, or empyema. Given that these distinct infectious entities were grouped into a single category, it is impossible to parse any differences regarding severity of infection, the treatment of which might vary widely from a short antibiotic course to aggressive operative debridement with cranioplasty flap removal. The risk of specific infectious complications should be a focus of future prospective studies.

5. Conclusions

This systematic literature review investigated the difference in complication rates between early and late cranioplasty following decompressive craniectomy. The results suggest that early cranioplasty ($\leqslant$90 days) is associated with greater odds of developing hydrocephalus, particularly in the trauma population, but that the odds of other complications are no different from late cranioplasty (>90 days). These findings suggest that early cranioplasty, with expectant management of hydrocephalus, is otherwise as safe as late cranioplasty. Future studies should determine optimal cranioplasty timing for specific patient populations, as well as appropriate management of hydrocephalus after early cranioplasty.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication. Portions of this work will be presented in abstract and poster form as proceedings at the 84th AANS Annual Scientific Meeting at McCormick Place West in Chicago, Illinois April 30th–May 4th 2016.

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