JNS

CLINICAL ARTICLE

J Neurosurg 141:895–907, 2024

Early versus delayed cranioplasty after decompressive craniectomy in traumatic brain injury: a multicenter observational study within CENTER-TBI and Net-QuRe

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OBJECTIVE The aim of this study was to compare the outcomes of early (≤ 90 days) and delayed (> 90 days) cranioplasty following decompressive craniectomy (DC) in patients with traumatic brain injury (TBI).

METHODS The authors analyzed participants enrolled in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) and the Neurotraumatology Quality Registry (Net-QuRe) studies who were diagnosed with TBI and underwent DC and subsequent cranioplasty. These prospective, multicenter, observational cohort studies included 5091 patients enrolled from 2014 to 2020. The effect of cranioplasty timing on functional outcome was evaluated with multivariable ordinal regression and with propensity score matching (PSM) in a sensitivity analysis of functional outcome (Glasgow Outcome Scale–Extended [GOSE] score) and quality of life (Quality of Life After Brain Injury [QOLIBRI] instrument) at 12 months following DC.

RESULTS Among 173 eligible patients, 73 (42%) underwent early cranioplasty and 100 (58%) underwent delayed cranioplasty. In the ordinal logistic regression and PSM, similar 12-month GOSE scores were found between the two groups (adjusted odds ratio [aOR] 0.87, 95% CI 0.61–1.21 and 0.88, 95% CI 0.48–1.65, respectively). In the ordinal logistic regression, early cranioplasty was associated with a higher risk for hydrocephalus than that with delayed cranioplasty (aOR 4.0, 95% CI 1.2–16). Postdischarge seizure rates (early cranioplasty: aOR 1.73, 95% CI 0.7–4.7) and QOLIBRI scores (β −1.9, 95% CI −9.1 to 9.6) were similar between the two groups.

CONCLUSIONS Functional outcome and quality of life were similar between early and delayed cranioplasty in patients who had undergone DC for TBI. Neurosurgeons may consider performing cranioplasty during the index admission (early)

ABBREVIATIONS aOR = adjusted odds ratio; DC = decompressive craniectomy; CENTER-TBI = Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; ECI = extracranial intervention; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale–Extended; ICP = intracranial pressure; IMPACT = International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury; IQR = interquartile range; Net-QuRe = Neurotraumatology Quality Registry; PSM = propensity score matching; QOL = quality of life; QOLIBRI = Quality of Life after Brain Injury; RCT = randomized controlled trial; TBI = traumatic brain injury.

SUBMITTED September 20, 2023. **ACCEPTED** January 26, 2024.

INCLUDE WHEN CITING Published online April 26, 2024; DOI: 10.3171/2024.1.JNS232172.

to simplify the patient's chain of care and prevent readmission for cranioplasty but should be vigilant for an increased possibility of hydrocephalus.

Clinical trial registration nos.: CENTER-TBI, NCT02210221 (clinicaltrials.gov); Net-QuRe, NTR6003 (trialsearch.who.int) and NL5761 (onderzoekmetmensen.nl)

https://thejns.org/doi/abs/10.3171/2024.1.JNS232172

KEYWORDS cranioplasty; traumatic brain injury; timing; complication; early; delayed; trauma

Each year in Europe, severe traumatic brain injury (TBI) causes an estimated 82,000 deaths with current trends indicating consistent annual increases despite widespread efforts and awareness to combat this "silent epidemic."[1–3] An important complication of severe TBI is increased intracranial pressure (ICP) due to severe brain swelling posttrauma or the mass effect arising from the primary lesion. Decompressive craniectomy (DC) is the treatment of last resort for medically refractory ICP and can be performed as part of a primary procedure (after immediate evacuation of a mass lesion) or as a secondary procedure (to treat medically refractory ICP elevation).[4] As a secondary treatment, it allows immediate outward expansion of brain tissue, lowers ICP, and consequently improves cerebral blood flow.[5–10] The surgical approach is usually a hemicraniectomy but can be a bifrontal craniectomy.[11]

After a DC, neurosurgeons must determine when to reconstruct the bone defect by cranioplasty. There are no widely accepted guidelines to facilitate this decision, although the timing of cranioplasty has been abundantly discussed in the literature.[12–19] In general, a pragmatic approach is employed; once the brain is sufficiently sunken, the skull is rebuilt. Cranioplasty is associated with high rates (10%–40%) of complication, including postoperative infection, bone resorption, hydrocephalus, and seizures.[20,21] Some studies have suggested a benefit if cranioplasty is performed within 90 days after DC to potentially reverse cognitive, language, and motor deficits, referred to as "syndrome of the trephined,"[22] as delayed reconstruction can impact the type and intensity of rehabilitation services.[12,13] Conversely, early cranioplasty has been associated with higher risks for hydrocephalus and surgical site infection,[14] and not all patients are sufficiently stable to undergo the procedure in this period. A recent consensus statement on post-TBI cranioplasty recommended further prospective research on the timing of cranioplasty and subsequent neurological outcomes.[23] We aimed to determine the comparative effectiveness of early versus delayed cranioplasty after DC in TBI patients. In keeping with the artificial nature of the 90-day (3-month) cutoff, we also assessed different predefined cutoffs, namely ultra early (< 6 weeks), early (6 weeks–3 months), intermediate (3–6 months), and late (> 6 months).

Methods

Study Design and Population

This observational cohort study used data obtained from two prospective, multicenter, observational cohorts: the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) and the Neurotraumatology Quality Registry (Net-QuRe) studies.[24] CENTER-TBI is registered with ClinicalTrials.gov (registration no. NCT02210221). Net-QuRe is registered with the International Clinical Trials Registry (registration no. NTR6003, trialsearch.who.int) and the Dutch National Trial Register (registration no. NL5761, onderzoekmetmensen.nl). These parent studies were conducted in accordance with Good Clinical Practice (CPMP/ICH/135/95). The current study was predefined in a protocol.[25] Participants in CENTER-TBI were enrolled between 2014 and 2017 from 65 centers across Europe and Israel. Participants in Net-QuRe were enrolled between 2015 and 2020 from 8 centers in the Netherlands. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology statement and corresponds to stage 3 in the IDEAL framework (Idea, Development, Exploration, Assessment, and Long-term study).[26] The study was planned to use the convenience sample provided by the CENTER-TBI.

Inclusion criteria for the current study were adults with TBI who had undergone DC and subsequent cranioplasty. Patients were excluded if they met any of the following conditions: 1) missing time intervals between DC and cranioplasty, and 2) missing Glasgow Outcome Scale–Extended (GOSE) score data.

Interventions

Initial surgical treatment consisted of primary or secondary DC to decrease ICP. The DC did or did not include evacuation of a hematoma using a bifrontal craniectomy or hemicraniectomy approach. To restore the bone defect, a cranioplasty was performed as a secondary intervention. The timing of the cranioplasty and the materials used followed the treating neurosurgeon's preference, inherent to the observational nature of the study. Both autologous bone grafts and synthetic grafts were used to repair the cranial defect. Cranioplasty performed ≤ 90 days after DC was classified as early, and cranioplasty performed > 90 days after DC was classified as delayed, per the most widely accepted and published definition of early and delayed cranioplasty[12–19,27,28] and the definition used in the recent post-TBI cranioplasty consensus statement.[23] However, considering the relatively arbitrary nature of this stratification, we also performed sensitivity analyses with different thresholds.

Outcomes

The primary outcome was the GOSE score at 12 months. The GOSE is an internationally used measure for functional outcome and consists of an 8-point scale ranging from 1 (death) to 8 (upper good recovery).[29] The GOSE was applied mainly by interviews and was sometimes complemented with postal or web-based questionnaires.

Secondary outcomes were quality of life (QOL), as measured by the Quality of Life after Brain Injury (QOLIBRI) instrument at 12 months postinjury; occurrence of hydrocephalus (defined as the radiological appearance of enlarged ventricles or surgery to manage hydrocephalus); and post-TBI seizure at the 3-, 6-, and 12-month follow-ups and noted as having "occurred from TBI up until this follow-up time point."[30] Hydrocephalus and seizures were defined as binary variables (occurred vs did not occur).

Statistical Analysis

Baseline patient characteristics are reported using standardized mean differences between the early and delayed cranioplasty groups. We used model specifications as in the International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) models for the probability of death and an unfavorable outcome (in percentages) to correct for the severity of the initial injury. The IMPACT model has been extensively validated for TBI.[31–33] Random-effects proportional odds ordinal regression was used for the primary outcome (GOSE score). Age, baseline Glasgow Coma Scale (GCS) score, baseline pupil reactivity, and admission head CT findings (midline shift, acute subdural hematoma, epidural hematoma, and intracerebral hematoma) were considered confounders and were included as independent variables. Data on CT imaging variables were collected using the primary CT scan (per protocol, done within 24 hours of admission). Results of the regression yielded estimations for adjusted odds ratios (aORs) and 95% confidence intervals. The odds ratios regarding the GOSE score indicate the odds per 1-point increase on the GOSE, where early surgery was compared with delayed. Secondary outcomes were analyzed with random-effects logistic (hydrocephalus and seizures) and linear (QOLIBRI) regression.

To quantify and compare the between-center differences in early cranioplasty, we calculated the median odds ratio, which quantifies treatment variation between centers that is not attributable to chance and not explained by other (case-mix) factors. The effect of this intercenter variance of early cranioplasty on primary outcome was analyzed using an instrumental variable analysis. This analysis compared centers based on their various preferences for performing early cranioplasty, as measured by the case-mix–adjusted probability of undergoing early cranioplasty at each participating center.

Additional analyses of the GOSE score, hydrocephalus, and seizure occurrence were performed using the timing between DC and cranioplasty as a continuous variable rather than a binary one (early vs delayed). These odds ratios are expressed as per interquartile range (IQR) increase. Also, ultra-early cranioplasty (within 42 days, i.e., < 6 weeks) was compared to cranioplasty at or after 42 days. Exploratory subgroup analyses for the primary outcome were performed in 10 subgroups: age < 50 years, age ≥ 50 years, baseline GCS score < 9 (severe TBI), baseline GCS score ≥ 9 (moderate/mild TBI), location of DC (bifrontal craniectomy/hemicraniectomy), type of DC (primary/secondary), and whether any major extracranial intervention (ECI) was performed during the initial admission (yes/no). A major ECI was defined as any ECI that required hospitalization on its own (e.g., external fixation of a limb, damage control thoracotomy, damage control laparotomy, extraperitoneal pelvic packing, craniomaxillofacial reconstruction, tracheostomy, vertebrae fixation, and debridement of penetrating injuries). Undergoing a major ECI can interfere with the normal rehabilitation process and was therefore included as a subgroup. Primary DC was defined as initial surgical evacuation of a lesion within 24 hours of TBI. Secondary DC was defined as a preemptive approach to the treatment of suspected ICP or as a last-resort treatment for refractory ICP.

We performed a supplementary subgroup analysis, dividing the participating centers into three subgroups based on cranioplasty preference: preferring early cranioplasty, preferring delayed cranioplasty, and no clear preference. The three subgroups were based on the coefficients from a similar logistic regression model containing the same independent variables as the primary analysis.

Further sensitivity analyses were performed using propensity score matching (PSM). We aimed for balanced parallel groups (1:1) using a nearest-neighbor approach with a caliper of 0.16. Thus, participants who had undergone early cranioplasty were only matched to delayed cranioplasty patients if the maximum difference between propensity scores was < 0.16. Additionally, a similar sensitivity analysis was performed using the median timing between DC and cranioplasty, in days, as a cutoff to create two groups. These PSM models contained the same independent variables as the primary ordinal regression model.

Last, a supplementary sensitivity analysis was done using intensive care discharge variables (neuroworsening, time to obey commands [days], ventilation duration [days], and GCS score) and hospital length of stay (days) as confounders.

Statistical analysis was performed using R version 4.0.3 (The R Foundation for Statistical Computing). Missing data were imputed using the mice package. Data were accessed with a bespoke data management tool, Neurobot (research resource identifier: SCR_01700).

Results

The CENTER-TBI cohort consisted of 4509 participants and the Net-QuRe cohort of 937 (355 patients were included in both studies). These cohorts combined yielded 363 unique patients who had undergone DC for intractable ICP after TBI, 97 of whom died before undergoing cranioplasty. For 39 participants, it was unknown whether a cranioplasty was performed within the follow-up period. The remaining 227 participants underwent subsequent cranioplasty, and 54 were excluded because the time between DC and cranioplasty was unknown (n = 48) or a GOSE score was missing (n = 6). Accordingly, 173 patients were available for primary and secondary outcome analyses. Of those, 73 underwent early cranioplasty and 100 delayed cranioplasty (Fig. 1). The median time between DC and cranioplasty between the groups was 101 days (IQR 42–116 days; Supplemental Fig. 1). The median time in the early group was 36 days; in the delayed group, 116 days.

The two cranioplasty groups were comparable in terms

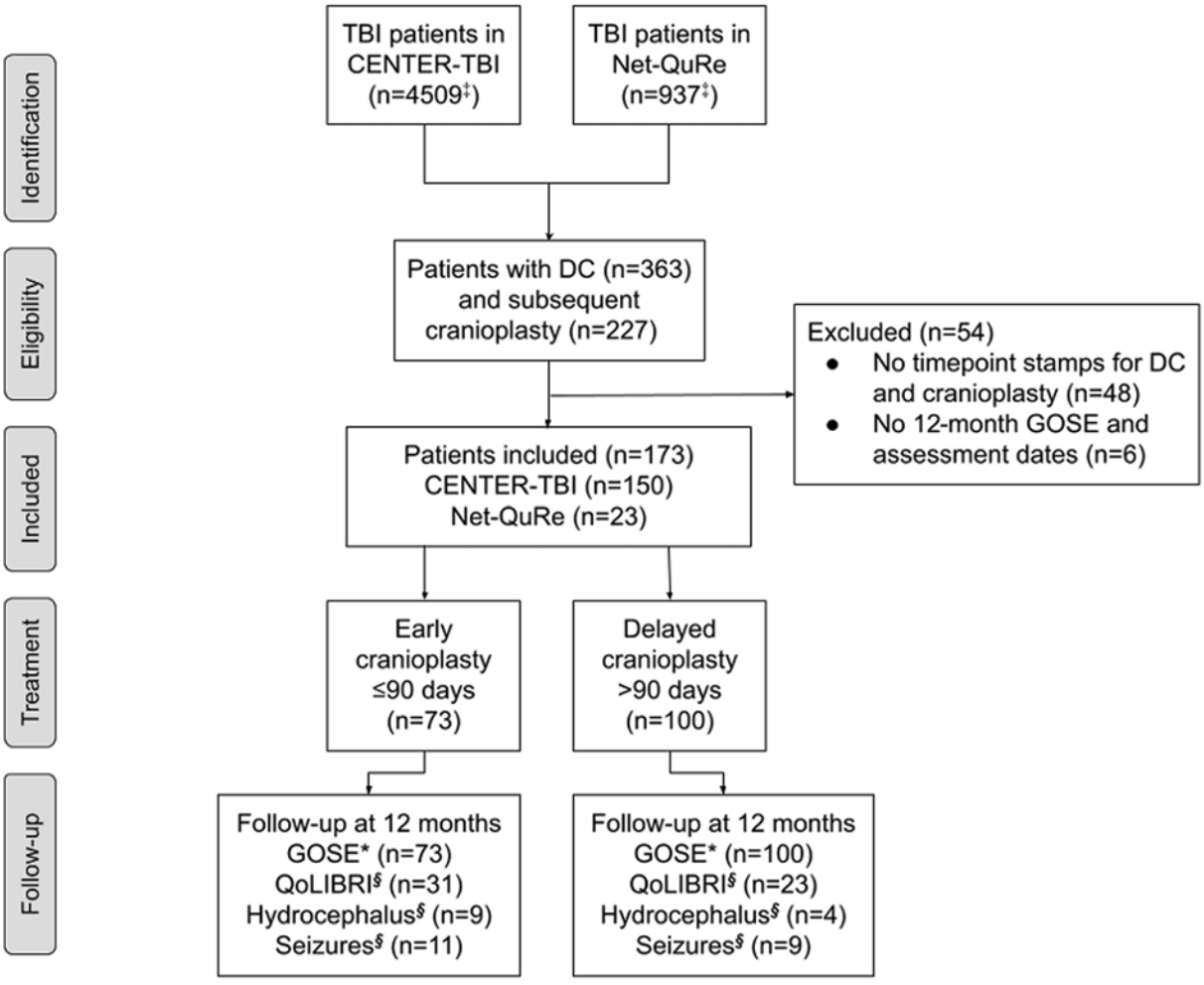

FIG. 1. Flow diagram of study population and data analysis. ‡532 patients were included in both studies, *primary outcome, §secondary outcome. Figure is available in color online only.

of age, sex, time between injury and DC, median GCS score (overall and motor), American Society of Anesthesiologists physical classification status, DC location, and presence of head CT variables (Table 1). IMPACT scores (core model for death and unfavorable outcome, respectively) provided a summary measure for baseline prognosis and were similar for the two groups (median 35, IQR 25–58 vs 33, IQR 22–55; median 57, IQR 39–73 vs 52, IQR 36–68, respectively). Patients in the early cranioplasty group were hospitalized longer than those in the delayed group (median 37 days, IQR 19–65 days vs 25 days, IQR 10–51 days), though the difference between the two was not statistically significant. Baseline characteristics were similar between the propensity score–matched groups (63 in both groups; Supplemental Table 1).

The proportional distribution of GOSE scores showed no consistent shift in functional outcome by either early or delayed cranioplasty (Fig. 2). The median QOLIBRI scores were 68 (IQR 56–75) and 64 (IQR 53–74) in the early and delayed cranioplasty groups, respectively. Following cranioplasty, 13 cases of hydrocephalus were reported, 9 (12%) in the early group and 4 (4%) in the delayed group. Seizures were reported in 20 participants, 11 (15%) in the early and 9 (9%) in the delayed cranioplasty groups. Importantly, the occurrence of seizures was sometimes only noted as having "occurred from TBI up until this follow-up time point" without an actual occurrence date (before or after some cranioplasty dates). A total of 7 patients died between cranioplasty and the 12-month follow-up, 4 (5%) in the early group and 3 (3%) in the delayed group.

The ordinal logistic regression model showed no statistically significant difference in 12-month GOSE scores between early and delayed cranioplasty groups (aOR 0.87, 95% CI 0.61–1.21). Similarly, no statistically significant difference was found in 3- and 6-month GOSE scores (aOR 0.95, 95% CI 0.6–1.2 and aOR 1, 95% CI 0.6–1.9, respectively; Supplemental Table 2).

Early cranioplasty was associated with a higher incidence of hydrocephalus (aOR 4, 95% CI 1.2–16; Table 2). No statistical difference was found in postdischarge seizure occurrence between the two groups, but the point estimate suggested a higher seizure risk for early cranioplasty (aOR 1.7, 95% CI 0.67–4.7).

TABLE 1. Baseline and treatment characteristics of study population

Variable	Early	Delayed	Standardized Mean Difference	p Value	Missing Data (%)
No. of patients	73	100			
Age in yrs	44 (29, 58)	44 (24, 56)	0.09	0.52	0
Male sex	51 (70)	72 (72)	0.05	0.89	0
GCS score	6 (3, 10)	7 (4, 14)	0.25	0.12	20 (12)
GCS motor score	3 (1, 5)	4 (1, 6)	0.16	0.24	5 (3)
Severity of TBI			0.29	0.34	12 (7)
Mild, GCS score 13–15	11 (16)	27 (29)			
Mod, GCS score 9–12	10 (15)	11 (12)			
Severe, GCS score <9	46 (69)	56 (60)			
Pupils			0.22	0.37	10 (6)
Both reacting	51 (73)	76 (82)			
One reacting	8 (11)	6 (6)			
Both unreactive	11 (16)	11 (12)			
ASA status			0.16	0.80	4 (2)
I, healthy	43 (60)	58 (60)			
II, mild systemic illness	19 (26)	28 (29)			
III, severe systemic illness	8 (11)	7 (7)			
IV, severe systemic illness that is constant threat to life	2 (3)	4 (4)			
Cause of injury			0.51	0.11	4 (2)
Road traffic incident	22 (31)	36 (37)			
Incident fall	26 (37)	42 (43)			
Other nonintentional	7 (10)	5 (5)			
Violence or assault	9 (13)	3 (3)			
Act of mass violence	2 (3)	1 (1)			
Suicide attempt	4 (6)	5 (5)			
Unknown	1 (1)	6 (6)			
Major ECI*	19 (26)	31 (31)	0.11	0.59	0
Epidural hematoma	20 (29)	20 (22)	0.18	0.52	13 (8)
SDH, acute	47 (68)	54 (59)	0.22	0.39	13 (8)
SDH, subacute/chronic	6 (9)	3 (3)	0.24	0.30	13 (8)
Cerebral contusion	46 (67)	61 (67)	0.07	0.92	13 (8)
Traumatic SAH	53 (77)	64 (70)	0.20	0.47	13 (8)
Skull fracture	41 (68)	55 (66)	0.11	0.81	26 (15)
Midline shift†	34 (68)	39 (43)	0.16	0.61	13 (8)
Compressed basal cisterns	36 (52)	48 (53)	0.06	0.92	13 (8)
Diffuse axonal injury	5 (29)	6 (46)	0.35	0.58	143 (83)
IMPACT unfavorable outcome score‡	57 (39, 73)	52 (36, 68)	0.12	0.49	
IMPACT death score‡	35 (25, 58)	33 (22, 55)	0.14	0.43	
DC location			0.35	0.46	83 (48)
Bifrontal craniectomy	6 (14)	9 (19)			
Lt hemicraniectomy	14 (33)	17 (36)			
Rt hemicraniectomy	23 (53)	21 (45)			
Time btwn injury & DC in days	1 (0, 1)	1 (0, 1)	0.13	0.92	75 (43)
DC reason			0.55	0.22	69 (40)
Preemptive approach for raised ICP	11 (22)	13 (24)			
Raised ICP (last resort)	14 (29)	19 (35)			
CT evidence of raised ICP	12 (24)	11 (20)			

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TABLE 1. Baseline and treatment characteristics of study population

Variable	Early	Delayed	Standardized Mean Difference	p Value	Missing Data (%)
DC reason (*continued*)					
Not planned but decided due to intraop brain swelling	12 (24)	7 (13)			
Routinely performed w/ acute SDH or contusion evacuation	0 (0)	4 (7)			
Development of cerebral infarction	0 (0)	1 (2)			
DC type			0.61	0.06	81 (47)
Isolated procedure	12 (28)	9 (18)			
Association w/ acute SDH removal	27 (63)	24 (49)			
Association w/ contusion/ICH removal	1 (2)	6 (12)			
Association w/ acute SDH & contusion/ICH removal	3 (7)	10 (20)			
Hospital length of stay	37 (19, 65)	25 (10, 51)	0.34	0.34	9 (5)

ASA = American Society of Anesthesiologists; ICH = intracranial hemorrhage; Mod = moderate; SAH = subarachnoid hemorrhage; SDH = subdural hematoma.
Values are expressed as the median (IQR) or number (%), unless indicated otherwise.
* An ECI requiring a hospital admission/intervention on its own, for example, external fixation of a limb, damage control thoracotomy, etc.
† Defined as midline shift more than 5 mm.
‡ Scores give the probability of an unfavorable outcome or death at 6 months postinjury.

When using cranioplasty timing as a continuous variable, timing was not associated with differences in the GOSE score (aOR 1.1 for IQR increase of 74 days, 95% CI 0.88–1.3) or seizure occurrence (aOR 0.86, 95% CI 0.49–1.4), but a shorter time to cranioplasty was associated with a higher risk for hydrocephalus (aOR 2.5, 95% CI 1.1–7.1; Supplemental Table 3 and Supplemental Fig. 2).

There was no difference in QOLIBRI scores comparing the early and delayed cranioplasty groups (Table 2). Unadjusted analyses of early cranioplasty to all outcomes yielded comparable associations to the adjusted analyses. In a sensitivity analysis using PSM, incorporating baseline variables yielded an aOR for GOSE score of 0.88 (95% CI 0.48–1.65). Moreover, when using intensive care dis-

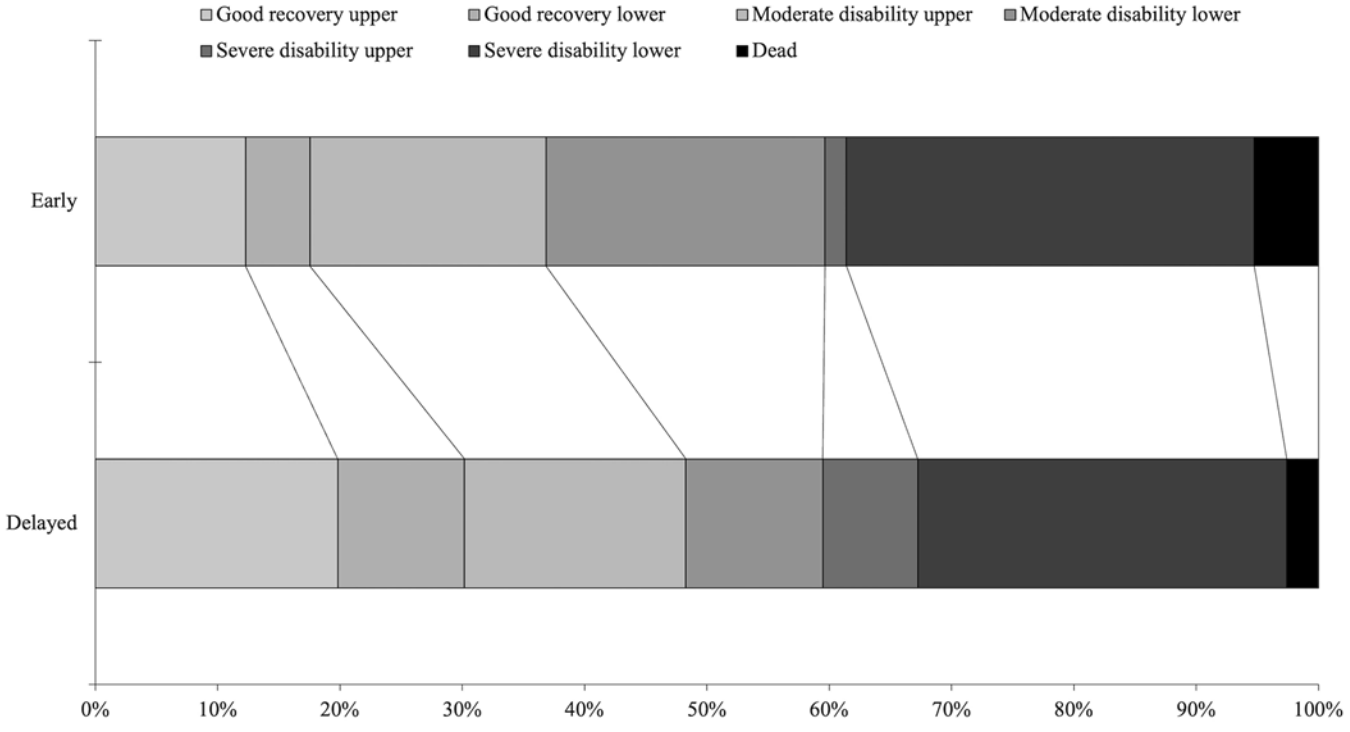

FIG. 2. Proportional distribution of GOSE scores between early and delayed cranioplasty groups. Figure is available in color online only.

TABLE 2. Associations of early cranioplasty with 12-month outcomes

Outcome	Early (n = 73)	Delayed (n = 100)	Effect Estimate	Unadjusted (95% CI)	Adjusted (95% CI)
GOSE score	4 (2, 5)	4 (2, 6)	OR	0.76 (0.56–1.1)	0.87 (0.61–1.21)
Hydrocephalus	9 (12)	4 (4)	OR	3.4 (1.1–13)	4 (1.2–16)
Seizures	11 (15)	9 (9)	OR	1.8 (0.7–4.7)	1.73 (0.67–4.7)
QOLIBRI	68 (56, 75)	64 (53, 74)	β	–1.9 (–10 to 14)	0.21 (–9.1 to 9.6)

Values are expressed as median (IQR) or number (%), unless indicated otherwise.

charge variables and length of stay, the aOR was 1.1 (95% CI 0.77–1.5; Supplemental Table 4). In PSM using the median timing as a cutoff point (101 days), the aOR for GOSE score was 1.1 (95% CI 0.79–1.6); for hydrocephalus, 4.8 (95% CI 1.1–34); and for seizure, 1.5 (95% CI 0.49–4.9; Supplemental Table 3).

The median ORs were 2.3 and 2.1 for intercenter and intercountry random-effects variance, respectively (Supplemental Fig. 3), meaning that there is a 2 times greater probability of undergoing early cranioplasty for an identical patient in one center versus another random center or country. In an instrumental variable analysis, there were no evident disparities in treatment effect between the participating centers (aOR 0.96, 95% CI 0.86–1.1).

In a subgroup analysis, no difference in the GOSE score was found between early or delayed cranioplasty in patients with an age < 50 years or ≥ 50 years (n = 107, aOR 0.84, 95% CI 0.58–1.2; n = 66, aOR 1, 95% CI 0.7–1.5, respectively). Furthermore, cranioplasty timing did not result in a difference in GOSE scores when comparing participants with a GCS score < 9 or ≥ 9 (n = 105, aOR 0.96, 95% CI 0.64–1.3; n = 68, aOR 1.1, 95% CI 0.72–1.6, respectively). Cranioplasty performed ultra early (e.g., within 42 days, < 6 weeks) was also not associated with differences in the GOSE score (aOR 0.82, 95% CI 0.41–2.6). When comparing early to delayed cranioplasty in patients who had undergone a major ECI during the initial admission, early cranioplasty was associated with an improved functional outcome (n = 50, aOR 1.9, 95% CI 1.3–2.7). In those who did not undergo a major ECI, early cranioplasty was negatively associated with the GOSE score (n = 123, aOR 0.63, 95% CI 0.44–0.87). The median IMPACT death probability scores were lower in those who had undergone a major ECI at the initial admission than in those who had not (IMPACT score = 30, IQR 21–47 vs 36, IQR 24–58, respectively; Supplemental Table 5). Within the major ECI subgroup, median IMPACT scores for an unfavorable outcome appeared similar when comparing early versus delayed cranioplasty (IMPACT score = 48, IQR 42–73 vs 54, IQR 35–65, respectively; Supplemental Table 6). In the same subgroup, road traffic accidents were more common in the delayed cranioplasty group (19 [63%]) than in the early group (6 [32%]). There was no statistically significant difference between early and delayed cranioplasty in the patients who underwent either bifrontal craniectomy or hemicraniectomy (n = 15, aOR 0.79, 95% CI 0.21–27; n = 75, aOR 1.1, 95% CI 0.57–2.4, respectively). Moreover, early cranioplasty was not associated with an improved functional outcome in patients undergoing either primary (n = 62, aOR 0.62, 95% CI 0.39–1.1) or secondary (n = 52, aOR 1.2, 95% CI 0.81–1.7) DC (Fig. 3).

Lastly, in an additional subgroup analysis, there was no statistically significant difference between early and delayed cranioplasty in terms of centers preferring early over delayed cranioplasty or centers without a clear preference. In centers preferring delayed cranioplasty, early cranioplasty was associated with an improved functional outcome (aOR 2.7, 95% CI 1.1–7.1; Supplemental Fig. 4) but the subgroup sample sizes were small (early cranioplasty/total subgroup = 4/56).

Discussion

In this analysis of patients with TBI from two large observational European studies who had undergone DC and subsequent cranioplasty, we found similar functional outcomes and QOL regardless of whether the cranioplasty was performed early (≤ 90 days post-DC) or was delayed (> 90 days post-DC). There was a significant positive association of early cranioplasty with an increased risk of hydrocephalus, whereas the risk of seizure did not reach significance. Different categorizations of timing did not lead to a difference in outcome in the sensitivity analyses.

A recent systematic review and meta-analysis revealed a possible positive effect of performing cranioplasty within 90 days on functional outcome. Our study could not confirm this overall treatment effect, although comparisons are difficult because the review utilized outcome measures different from ours.[12] Another systematic review demonstrated a benefit in cognitive and motor function when performing cranioplasty within 90 days after DC.[13] Although we did not specifically evaluate cognitive and motor function, a potential difference in motor and cognitive function did not translate into a difference in functional outcome as measured with the GOSE between early and delayed cranioplasty. Furthermore, another review discussed the possible beneficial effect of early cranioplasty on functional outcome when performed as soon as brain edema had resolved.[34]

Hydrocephalus and Seizures

Early cranioplasty was associated with a higher risk of hydrocephalus. A recent systematic review described an increased risk of hydrocephalus after cranioplasty performed within 90 days.[35] A large retrospective study on the timing of cranioplasty also demonstrated an increased risk of hydrocephalus with early cranioplasty.[14] DC is known to alter CSF flow dynamics and cerebral blood flow dynamics, both of which change with replacement of the bone flap.[36–39] Replacement of the bone flap can be relatively premature, limiting swelling of the brain and therefore affecting intracranial CSF dynamics. Thus, although the

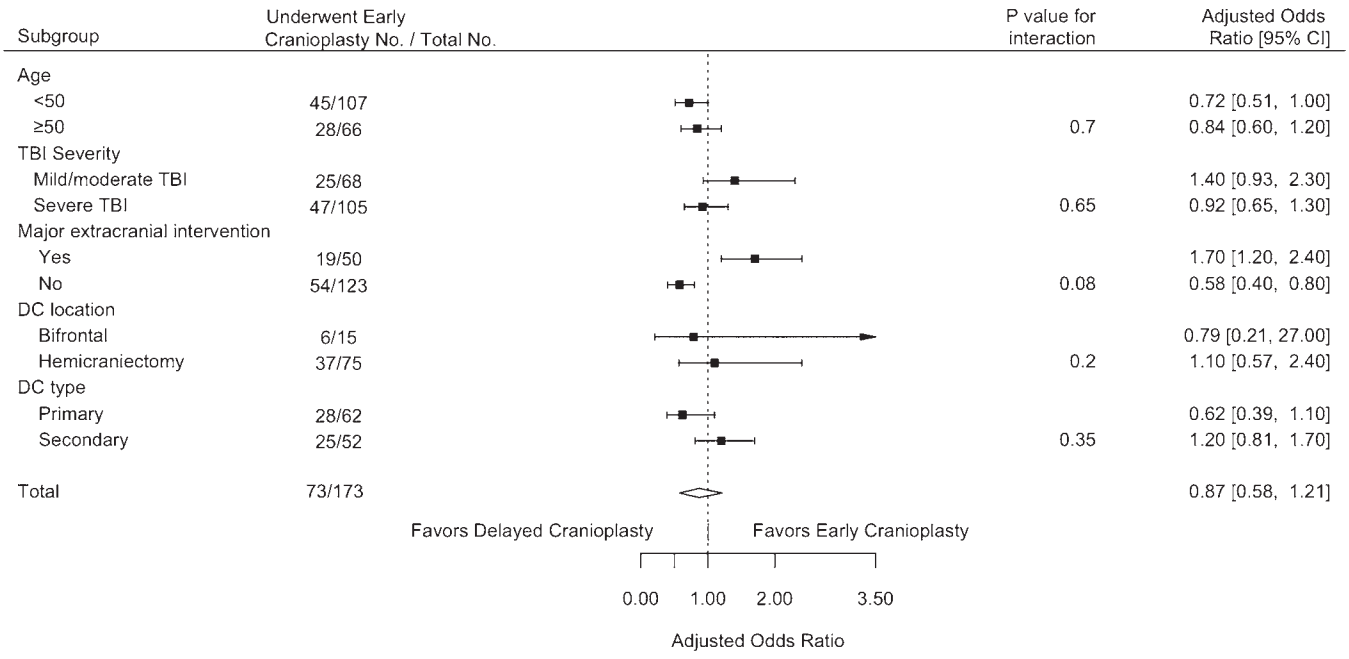

FIG. 3. Subgroup analyses of primary outcome for early cranioplasty. The figure shows common odds ratios with their corresponding confidence intervals for an improvement in the ordinal GOSE score for early cranioplasty. Adjusted odds ratios were calculated using multivariable ordinal logistic regression models.

higher hydrocephalus incidence did not translate to a difference in the GOSE score or QOL, early cranioplasty must be weighed against the potentially chronic need for shunts and their complications.

Furthermore, although 15% of patients in the early group experienced seizures as compared with 9% in the delayed group, we found no statistically significant association between timing of cranioplasty and seizure occurrence. This lack of a clear association is in line with other reports.[14,40]

Quality of Life

Studies have shown an increased QOL after cranioplasty, especially in patients harboring a large cranial defect; however, research on the effect of cranioplasty timing on QOL in TBI patients has been scant.[41] Our study found no difference in the QOLIBRI score according to the timing of cranioplasty.

Polytrauma

The lack of an overall treatment effect in our study may be attributable to the averaging of heterogeneous subgroup effects. Therefore, subgroup analyses may be informative. In patients who had undergone a major ECI, early cranioplasty was associated with a favorable functional outcome at 12 months after DC (Fig. 3). Rehabilitation decisions in TBI are mainly based on injury severity, but patients who undergo a major ECI may receive relatively more intensive inpatient rehabilitation before cranioplasty or may be selected for early cranioplasty to facilitate further effective rehabilitation. Additionally, patients who recover rapidly may also be selected for early cranioplasty. Finally, many rehabilitation physicians and physical therapists are cautious in designing rehabilitation programs for patients with a skull defect given the fear of falls and other injuries. Thus, appropriate rehabilitation in patients with delayed cranioplasty can vary, which may exert an impact on outcomes for this particular subgroup. The type, intensity, and level of rehabilitation services both pre- and postcranioplasty could significantly impact the short- and long-term trajectories of recovery and therefore have an impact on overall outcome. However, the exact explanation remains uncertain.[42,43]

Study Strengths and Weaknesses

We report on the timing of cranioplasty after DC in the largest international multicenter cohort sample to date. We used harmonized data from 65 centers across Europe and Israel with standardized data collection. The broad inclusion criteria ensured the incorporation of all TBI severities. Considering this and the international multicenter nature of our study, we believe the findings have broad generalizability.

The primary limitation of this study is its observational design. Patient characteristics rather than the intervention may determine the outcome. Confounding by indication plays a major role in determining validity to real-world clinical practice because residual confounding may persist.[44–47] Early cranioplasty patients exhibited lower median GCS scores, reduced pupil reactivity, and a higher incidence of midline shift, potentially indicative of more severe underlying injuries, although the differences were not statistically significant.

However, the risk of residual confounding was reduced because baseline prognoses were similar, and the discrepancy between the unadjusted and adjusted analyses was

minimal. To combat confounding, we used a multivariable regression model and PSM as sensitivity analysis. Our findings were robust since the sensitivity analysis yielded similar odds ratios (Supplemental Table 1). Also, immortal time bias may be an issue: certain patients will probably not undergo cranioplasty because of their persistently bad neurological condition and presumed very poor prognosis. This is unlikely to have led to discrepant inclusion between early and delayed cranioplasty groups because the inclusion is predominantly determined by whether brain edema has decreased sufficiently to technically allow for the procedure.

The difference in hospital length of stay may be explained by recording it only for the initial admission and may therefore be prolonged in patients undergoing cranioplasty during this initial admission. This could give a distorted image of the actual cumulative hospitalization duration. Nonetheless, the difference may also indicate potential selection bias. A prolonged hospital length of stay may influence surgical decision-making since the bony defect may become more and more apparent during daily rounds.

Unfortunately, due to limitations in the available data, we were unable to analyze bone resorption, implant loosening/dislodgment, postoperative recurrent or new hemorrhage, and (surgical site) infection rates, which are among the most typical cranioplasty complications and commonly result in cranioplasty failure.[35] Other studies have suggested a possible benefit of early cranioplasty to prevent autologous bone flap resorption.[14] Bone resorption increases the risk of reoperation and therefore could have a biased overall effect on GOSE scores.[48] Infections are a rather common postcranioplasty complication and remain an important factor in the patient's rehabilitation period.[14,17,18,49]

A related limitation is the frequent unavailability of precise dates of the diagnosis of hydrocephalus and seizures. These complications could have occurred before the actual cranioplasty. As described, the early cranioplasty group had hydrocephalus more often and possibly also experienced seizures more frequently. A question remains as to whether those differences resulted from baseline discrepancies or from early cranioplasty. However, from a pragmatic point of view, it simply reveals which complications may occur more often for patients who have an early cranioplasty.

Furthermore, the GOSE remains a rather crude measure for overall functional outcome and cannot be used to evaluate cognitive and motor function. This should be considered when comparing the findings of this study to other related research.

Lastly, six GOSE scores at the 12-month follow-up were missing, which could lead to mild attrition bias. Moreover, in 48 patients, 6- or 12-month follow-up assessments indicated that a cranioplasty had been performed up until those time points. However, the exact date of surgery (i.e., before or after 90 days post-DC) was missing. Therefore, the patients were excluded from analysis. By excluding the patients with missing DC-to-cranioplasty timing intervals, the results could have suffered from selection bias. However, the bias should be minimal because the missing cranioplasty dates were probably random (i.e., not associated with the timing).

This study may reduce treatment variation, as it appears that delay in rebuilding the skull is likely not beneficial. However, a randomized controlled trial (RCT) with a health economic analysis must be performed to confirm our results. Specifically, the prospective nature of an RCT would permit more apposite data collection, and the randomization would be pivotal to mitigate confounding. The health economic component would test the hypothesis that earlier cranioplasty, while an inpatient, is more efficient and cost-effective but is offset by a higher rate of ventriculoperitoneal shunt placements. Still, performing RCTs in these settings is difficult because of, among other reasons, the varying treatment protocols and the perceived absence of equipoise in randomizing neurotrauma patients.[50]

Conclusions

We found comparable functional and QOL outcomes between early and delayed cranioplasty in patients who undergo DC for TBI. Accordingly, neurosurgeons may wish to perform cranioplasty shortly after or during the first index admission but should remain vigilant to the increased possibility of hydrocephalus.

Acknowledgments

We would like to gratefully thank Amy J. Markowitz, JD, for her editorial support and all CENTER-TBI participants and investigators.

CENTER-TBI was supported by the European Union 7th Framework Programme for Research (grant no. 602150; A.I.R.M.), Hannelore Kohl Stiftung (Germany), and OneMind (United States). Net-QuRe was supported by the Hersenstichting Nederland (Dutch Brain Foundation, grant no. ps2014.06). Dr. Korhonen reported research grants from the Finnish Cultural Foundation, Finnish Medical Foundation, and Orion Research Foundation outside the submitted work. Dr. Yue reported grants from the Neurosurgery Research and Education Foundation and Bagan Family Foundation Research Fellowship (award no. A139203, to the University of California, San Francisco) outside the submitted work. Dr. Maas reported grants from the European Union 7th Framework Programme for Research during the conduct of the study. Dr. Peul reported grants from European Committee Grant CENTER-TBI and grants from the Netherlands Brain Foundation during the conduct of the study. Dr. Posti reported funding from the Academy of Finland (grant no. 17379) and the Maire Taponen Foundation. Dr. van Essen reported grants from the European Union 7th Framework Programme for Research or CENTER-TBI and Hersenstichting Nederland (Dutch Brain Foundation) for Net-QuRe and the Niels Stensen Fellowship during the conduct of the study. Dr. Hutchinson is supported by the National Institute for Health and Care Research (Cambridge BRC, Brain Injury Medtech Co-operative, Global Health Research Group on Acquired Brain and Spine Injury, Senior Investigator Award) and the Royal College of Surgeons of England. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Appendix

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Vreeburg, Korhonen, Kolias, Hutchinson, de Ruiter, Maas, Peul, van Dijck, Posti, van Essen. Acquisition of data: Vreeburg, Singh, van Erp, Depreitere, Manley, Maas, van Dijck, van Essen. Analysis and interpretation of data: Vreeburg, Singh, van Erp, Korhonen, Yue, Hutchinson, Steyerberg, Maas, van Dijck, Posti, van Essen. Drafting the article: Vreeburg, Singh, Korhonen, Yue, Hutchinson, Peul, Posti, van Essen. Critically revising the article: Vreeburg, Singh, Korhonen, Yue, Mee, Timofeev, Kolias, Helmy, Depreitere, Moojen, Younsi, Hutchinson, Manley, Steyerberg, de Ruiter, Maas, Peul, van Dijck, den Boogert, Posti, van Essen. Reviewed submitted version of manuscript: Singh, van Erp, Korhonen, Yue, Mee, Timofeev, Kolias, Moojen, Younsi, Hutchinson, Manley, Steyerberg, de Ruiter, Maas, Peul, van Dijck, den Boogert, Posti, van Essen. Approved the final version of the manuscript on behalf of all authors: Vreeburg. Statistical analysis: Vreeburg, Steyerberg, van Essen. Administrative/technical/material support: Manley, van Essen. Study supervision: Moojen, Hutchinson, Manley, Peul, van Essen.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Tables and Figures. https://thejns.org/doi/suppl/10.3171/2024.1.JNS232172.

Previous Presentations

The abstract and figures were presented as an oral presentation at the European Association of Neurosurgical Societies (EANS) Annual Congress held in Barcelona, Spain, on September 24–28, 2023, and during the EANS cranioplasty webinar "Cranioplasty 2.0–Current Standards and Trends" on November 29, 2023.

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