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# Surgery versus conservative treatment for traumatic acute subdural haematoma: a prospective, multicentre, observational, comparative effectiveness study

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## Summary

**Background** Despite being well established, acute surgery in traumatic acute subdural haematoma is based on low-grade evidence. We aimed to compare the effectiveness of a strategy preferring acute surgical evacuation with one preferring initial conservative treatment in acute subdural haematoma.

**Methods** We did a prospective, observational, comparative effectiveness study using data from participants enrolled in the Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) cohort. We included patients with no pre-existing severe neurological disorders who presented with acute subdural haematoma within 24 h of traumatic brain injury. Using an instrumental variable analysis, we compared outcomes between centres according to treatment preference for acute subdural haematoma (acute surgical evacuation or initial conservative treatment), measured by the case-mix-adjusted percentage of acute surgery per centre. The primary endpoint was functional outcome at 6 months as rated with the Glasgow Outcome Scale Extended, which was estimated with ordinal regression as a common odds ratio (OR) and adjusted for prespecified confounders. Variation in centre preference was quantified with the median OR (MOR). CENTER-TBI is registered with ClinicalTrials.gov, number NCT02210221, and the Resource Identification Portal (Research Resource Identifier SCR\_015582).

**Findings** Between Dec 19, 2014 and Dec 17, 2017, 4559 patients with traumatic brain injury were enrolled in CENTER-TBI, of whom 1407 (31%) presented with acute subdural haematoma and were included in our study. Acute surgical evacuation was done in 336 (24%) patients, by craniotomy in 245 (73%) of those patients and by decompressive craniectomy in 91 (27%). Delayed decompressive craniectomy or craniotomy after initial conservative treatment (n=982) occurred in 107 (11%) patients. The percentage of patients who underwent acute surgery ranged from 5·6% to 51·5% (IQR 12·3–35·9) between centres, with a two-times higher probability of receiving acute surgery for an identical patient in one centre versus another centre at random (adjusted MOR for acute surgery 1·8; p<0·0001). Centre preference for acute surgery over initial conservative treatment was not associated with improvements in functional outcome (common OR per 23·6% [IQR increase] more acute surgery in a centre 0·92, 95% CI 0·77–1·09).

**Interpretation** Our findings show that treatment for patients with acute subdural haematoma with similar characteristics differed depending on the treating centre, because of variation in the preferred approach. A treatment strategy preferring an aggressive approach of acute surgical evacuation over initial conservative treatment was not associated with better functional outcome. Therefore, in a patient with acute subdural haematoma for whom a neurosurgeon sees no clear superiority for acute surgery over conservative treatment, initial conservative treatment might be considered.

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## Introduction

Acute subdural haematoma is the most prevalent focal lesion in traumatic brain injury and is associated with high mortality and long-term neurocognitive morbidity.<sup>1</sup> One of the cornerstones of treatment is immediate neurosurgical management, with either acute haematoma evacuation or initial conservative treatment with potential delayed surgery.<sup>2,3</sup>

In patients with rapid neurological deterioration because of a large acute subdural haematoma, the decision to operate in the acute phase is clear; without acute surgery, high intracranial pressure will persist and the patient will die. In most cases however, the benefit of acute surgery is less clear, and patients might, at least initially, be safely managed conservatively. This strategy requires balancing potential complications of

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## Research in context

### Evidence before this study

The only existing guidelines on the optimal immediate treatment strategy for acute subdural haematoma, from the Brain Trauma Foundation, were published in 2006, and consisted of a thorough systematic review of the empirical evidence. The conclusions for acute subdural haematoma were based on the lowest grade on the effectiveness evidence hierarchy (merely case series, comparative studies with historical controls, case reports, and expert opinions). Since then, no update has been published. Therefore, in preparation for the present comparative effectiveness study we also systematically reviewed the evidence on the surgical indication for acute subdural haematoma. The protocols of this assessment are available online (PROSPERO registration numbers CRD42015025491 and CRD42019125336). We searched English and Dutch publications in the databases IndexCAT, PubMed, Embase (OVID-version), Web of Science, Cochrane library, CENTRAL, Academic Search Premier, Google Scholar, ScienceDirect, and CINAHL. The search string focused on traumatic acute subdural haematoma, cranial surgery, conservative management, and outcome, and was devised with a trained librarian (appendix pp 43–49). We did not restrict the search to a publication date. This initial search was completed in Sept 19, 2019, and updated for this report to Nov 24, 2021. After risk of bias evaluation, no comparative studies with a low risk of bias were found.

### Added value of this study

We report, to our knowledge, the largest effectiveness study on acute subdural haematoma. The study was done across

several centres in Europe, and is thus generalisable to a broad population. We found substantial practice variation in the treatment of acute subdural haematoma, reflecting the scarcity of strong evidence. In an instrumental variable analysis, this variation in treatment strategy did not result in differences in outcome for acute surgery versus initial conservative treatment. Extensive sensitivity analyses, including propensity score matching and multivariable regression, showed the results were robust.

### Implications of all the available evidence

The strong curative potential of surgery in acute subdural haematoma is well established in patients who are comatose. By showing large practice variation, our study confirms the uncertainty among neurosurgeons in the optimal immediate treatment strategy for all other patients with acute subdural haematoma. By exploiting strong and consistent treatment preferences by centre, our study provides a real-world estimate of effectiveness for patients with acute subdural haematoma for whom the neurosurgeon sees no clear superiority of acute surgery over conservative treatment. Furthermore, our findings, in combination with previous evidence, suggest a beneficial effect of acute surgery in older people. However, further research is needed to establish effectiveness in subgroups, preferably by pragmatic randomised trials.

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See Online for appendix

surgery against the risk of death or potential disability caused by irreversible deterioration with initial conservative treatment.

Current Brain Trauma Foundation guidelines advise acute surgery for acute subdural haematomas with a diameter greater than 10 mm or with a midline shift greater than 5 mm, irrespective of clinical condition or patient characteristics,<sup>4</sup> but the strength of underpinning evidence is low, with only non-comparative studies in small, selected populations.<sup>5–9</sup> In emergency settings, without high-level evidence, neurosurgeons are left with intuition and experience, formed by regional training and centre treatment culture, to guide their decision.

Consequently, the threshold for acute subdural haematoma surgical evacuation varies substantially between centres.<sup>10–12</sup> Strong treatment preferences deeply rooted in centres seem to underlie this practice variation and reflect an absence of equipoise, a necessary premise for a randomised controlled trial.

Practice variation, however, provides opportunities to study the effectiveness of interventions in clinical reality by relating treatment variation to outcome.<sup>13</sup> Within the large Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI)

observational cohort study, designed as a comparative effectiveness study, preferred local treatment strategies were accepted and exploited to estimate their effectiveness in real-life practice.<sup>14</sup> Our aim was to compare the effectiveness of a strategy of acute surgical evacuation with one preferring initial conservative treatment in patients with acute subdural haematoma.

## Methods

### Study design

This prospective, multicentre, observational, comparative effectiveness study is reported in keeping with the Strengthening of Reporting of Observational Studies in Epidemiology with instrumental variable recommendations.<sup>15,16</sup> The research question, design, outcomes, analysis, subgroups, and sample size calculations were defined before patient enrolment and have been published.<sup>14</sup> CENTER-TBI is registered with ClinicalTrials.gov, number NCT02210221, and the Resource Identification Portal (Research Resource Identifier SCR\_015582). This study corresponds to stage A in the IDEAL framework.<sup>17</sup> The CENTER-TBI study was approved by the medical ethics committees of all participating centres.

### Study population

The CENTER-TBI cohort includes patients with traumatic brain injury and no pre-existing severe neurological disorders who presented to one of 65 centres across Europe and in Israel within 24 h of the trauma and who have a brain CT.<sup>18,19</sup> For our current study, we selected patients from the CENTER-TBI cohort with acute subdural haematoma, regardless of acute subdural haematoma size, and a presumed necessity for surgical treatment. We excluded patients who were brain dead and those who were considered by the treating doctor to have an injury that was not survivable, for whom active treatment was not indicated. Because of the study design that compared treatment preferences, the study population inherently reflected the real-life clinical dilemma of who to treat with acute surgery (appendix p 16).

CENTER-TBI was done in accordance with Good Clinical Practice (CPMP/ICH/135/95). Informed written or oral consent by patients or legal representatives was obtained according to local legislation.

### Centre characteristics and data management

Centre characteristics were collected in previous surveys.<sup>12,20</sup> Questions included the policy of the centre towards the threshold for acute surgery, which was used in sensitivity analyses (appendix pp 13–14). Other treatment decisions possibly related to surgical threshold (eg, prehospital care) could affect the internal validity of our study. We therefore did an extensive cluster analysis, part of which was separately published.<sup>21</sup> The main conclusion was that treatment preferences within centres were unrelated.

Data were collected by trained personnel using web-based case-report forms (QuesGen Systems, Burlingame, CA, USA), coded with the Common Data Elements scheme. Complete CENTER-TBI methods have been published separately.<sup>22</sup>

### Interventions

Acute surgery was defined as surgery directly after the first CT scan, and conservative treatment was defined as best medical management (after the first CT scan) with potential delayed surgery. Neurosurgeons were asked at each CT scan if and why surgery was indicated, checked by actual operating room transfer and by surgery codes or description. Surgical treatment was at the discretion of the treating neurosurgeon and consisted of acute subdural haematoma evacuation by craniotomy or by additionally doing a (primary) decompressive craniectomy, defined as craniotomy without bone-flap replacement to allow for current or near-future brain swelling. If deemed necessary, surgery of concomitant skull or brain lesions was done simultaneously. The initial conservative approach consisted of best medical management after the first CT scan, with clinical monitoring on either the hospital ward, medium care unit, or (neurocritical) intensive care unit (ICU), with possible intracranial pressure monitoring and delayed surgical evacuation.

### Outcomes

The primary outcome was the Glasgow Outcome Scale Extended (GOSE), an eight-point scale ranging from 1 (death) to 8 (upper-good recovery), at 6 months.<sup>23</sup> The use of the GOSE as a core global outcome measure is recommended by the interagency Traumatic Brain Injury Outcomes Workgroup and the International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury group (IMPACT Common Data Elements). Secondary outcomes included in-hospital mortality, progression on CT or MRI scan (defined as an increase in the initial lesion, the development of a new lesion, or both), hospital length of stay (days), discharge destination, and 6 month quality of life assessed with the brain injury-specific Quality of Life after Brain Injury Questionnaire (Qolibri).<sup>24</sup> Outcome assessments were standardised and administered by interview or postal questionnaire.<sup>18</sup>

### Statistical analysis

Outcomes were analysed with respect to centre treatment strategy (and not actual treatment) using instrumental variable analyses.<sup>25–27</sup> Specifically, these analyses are a comparison of centres with different preferences for acute surgical evacuation, quantified by the case-mix-adjusted probability of acute surgery (as opposed to initial conservative treatment) as observed per centre. To minimise the influence of chance, only centres with at least 15 patients were included in analyses. We presented baseline characteristics and the Corticosteroid Randomisation after Significant Head Injury (CRASH) CT score, a validated baseline prognostic model,<sup>28</sup> across quartiles of the instrumental variable (ie, the case-mix-adjusted probability of acute surgery). The first quartile contained centres least likely to perform acute surgery, and the fourth quartile contained centres most likely to perform acute surgery. The instrumental variable analysis was based on preference for acute surgery as a continuous variable; the quartiles were presented to provide insight into the comparability of patient populations across the instrument, which allowed the reader to evaluate how similar patient characteristics were (instrumental variable assumption, the instrument is independent of confounders).<sup>16,29</sup>

Baseline characteristics were presented using descriptive statistics, and differences between quartiles were compared with standardised mean differences and p values. Practice variation was described as the percentage (IQR) of patients undergoing acute surgery per centre. To quantify and compare the between-centre differences in acute surgery, we calculated the median odds ratio (MOR). The MOR quantifies treatment variation between centres that is not attributable to chance and not explained by other (case-mix) factors. The primary effect estimate was the adjusted common odds ratio (OR) for a shift in the direction of a better outcome on the GOSE (proportional odds). This ratio was estimated with random-effects ordinal regression with the instrumental

For the Common Data Elements scheme see <https://commondataelements.ninds.nih.gov>

variable, referred to henceforth as the instrument (adjusted probability of acute surgery) as a continuous treatment variable. Random effects accounted for other between-centre differences compared with the factors included in the model. Confounding was further addressed by adjusting for predefined variables: age, GCS, pupil reactivity, acute subdural haematoma size, and midline shift.<sup>14</sup> The common OR was presented as an increase from the first to the fourth quartile (IQR) of the (continuous) instrument variable (the adjusted probabilities for undergoing acute surgery) and can be interpreted as the odds for a more favourable outcome when comparing centres favouring a strategy of acute surgery versus those favouring initial conservative treatment. Power calculations showed that the inclusion of 1000 patients with acute subdural haematoma would provide 80% power to detect an OR of 0.6.<sup>14</sup> ORs and betas were presented with 95% CIs calculated by bootstrapping with 500 samples. To assess the consistency of the (ordinal) estimate and the plausibility of proportionality of the OR, we presented ORs for all possible cutoff values on the GOSE. The association between surgical preferences and outcome was also estimated by linear regression with the fixed-effect centre coefficients as an independent variable and the (continuous) mean GOSE per centre as a dependent variable. These results are graphically represented in scatterplots. Secondary outcomes were analysed with random-effects logistic and linear regression.

The primary centre-level analysis was supplemented with several sensitivity analyses, including predefined subgroup analyses. Specifically, one of the sensitivity analyses was an instrumental variable analysis using the preference of the surveyed centre for the use of surgery, as captured through the previously performed provider profiling, as the instrumental variable. Additionally, we did sensitivity and subgroup analyses at the patient level, with multivariable regression and propensity score matching. A consistency in estimates with the statistical methods that we used for this study would strengthen our findings.<sup>30</sup> All sensitivity analyses were done for the primary outcome. For our main patient-level analysis, we included all patients who met the inclusion criteria for our study. The appendix (pp 12–14) provides additional methodological details for all analyses.

The primary centre-level analysis and the multivariable-regression analysis was post hoc supplemented by repeating those analyses excluding individuals with one or two unreactive pupils (very poor prognosis) and those with a Glasgow Coma Scale (GCS) of 15 (relatively good prognosis). We did not define this analysis in the protocol, and thus label it as post hoc.

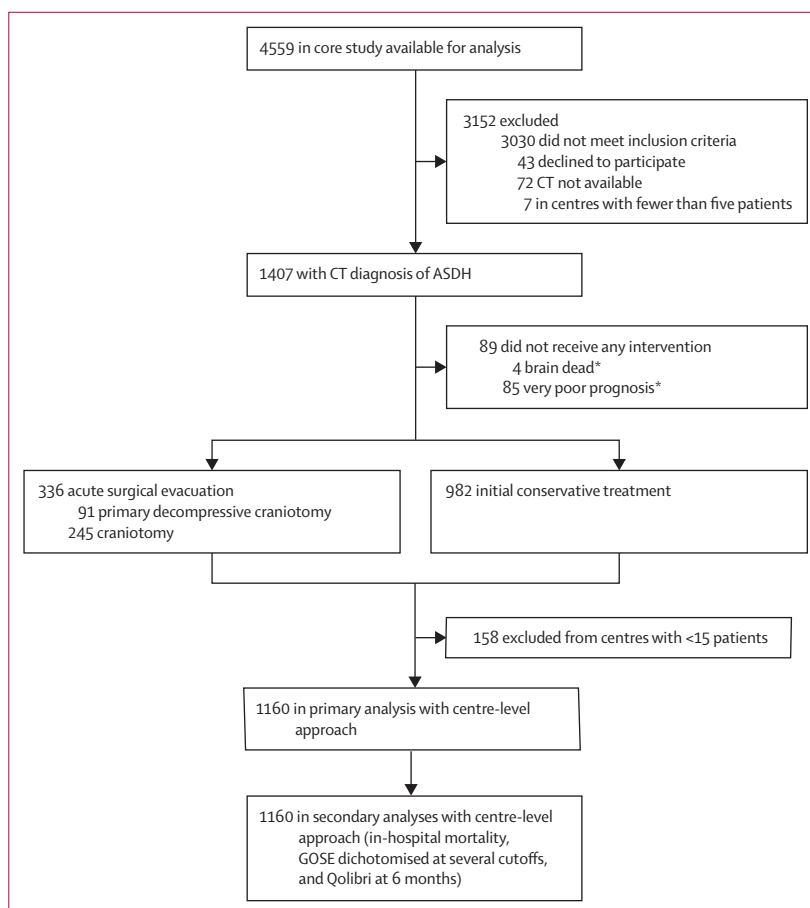
Analyses were done in R software, version 3.5.3, and RStudio, version 1.1.463. Missing data were multiply imputed with the Multiple Imputation by Chained Equations package, with the data assumed to be missing at random.

## Role of the funding sources

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

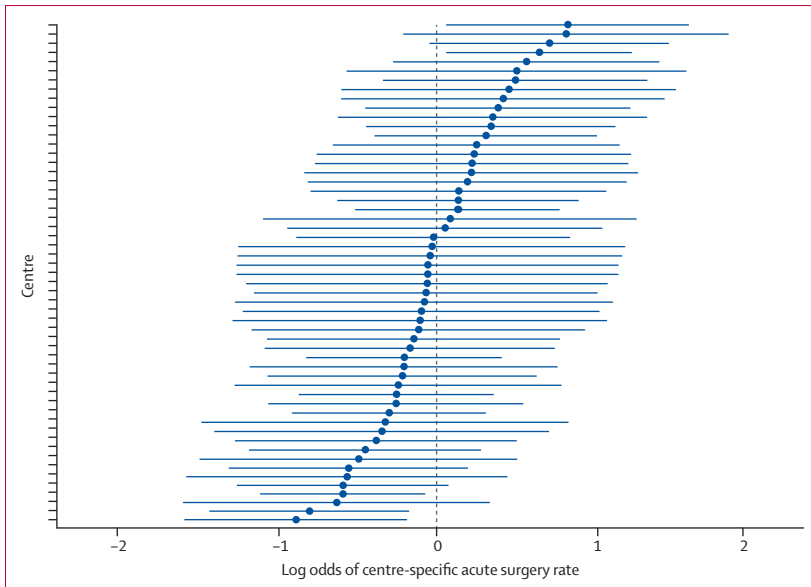
Between Dec 19, 2014, and Dec 17, 2017, 4559 patients with traumatic brain injury were enrolled in CENTER-TBI, of whom 1407 (31%) patients with acute subdural haematoma were included in our study. Acute surgery was done in 336 (24%) patients, at a median of 3.8 h (IQR 2.5–6.5) after injury (appendix pp 17–21). Of these patients who had acute surgery, 91 (27%) underwent a primary decompressive craniectomy (figure 1). Of the other 1071 patients, 89 (6%) had a very poor prognosis or were brain dead, resulting in 982 (92%) being treated conservatively. Of these patients, 313 (32%) subsequently had intracranial pressure monitoring, 107 (11%) underwent delayed decompressive craniectomy or craniotomy for an acute subdural haematoma or intracranial haemorrhage a median of 19.1 h (IQR 8.1–84.6) after injury, and 20 (2%) received delayed burr-hole drainage for a chronic subdural



**Figure 1: Flow diagram of study population and data analyses**

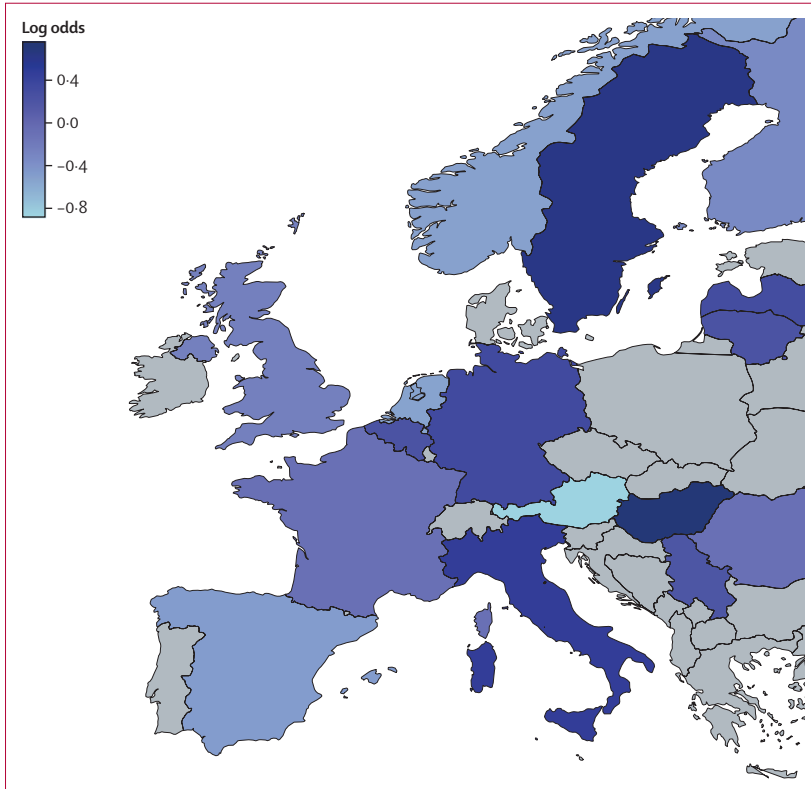
ASDH=traumatic acute subdural haematoma. GOSE=Glasgow Outcome Scale Extended. Qolibri=Quality of Life after Brain Injury scale. \*As judged by the treating doctor.





**Figure 2: Between-centre differences in acute surgery**

The x-axis presents the log odds of the adjusted acute surgery rates per centre. The number of centres reflects all centres that included patients with acute subdural haematoma. A logistic random-effects model, adjusted for the predefined confounders age, Glasgow Coma Scale, pupil reactivity, haematoma size, and midline shift, was used to estimate acute surgery preference per centre with corresponding 95% CIs. Dots represent the log odds per centre and the horizontal line the 95% CI.



**Figure 3: Between-country differences in acute surgery**

The colour coding in this geographical representation of Europe depicts the log odds of acute surgery per country compared with the overall average, adjusted for confounding, by means of the same model used for the centre analysis. The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

haematoma (appendix pp 17–21). After excluding patients from centres with fewer than 15 patients ( $n=158$ ), 1160 patients were included in the instrumental variable analysis, of whom 292 were treated with acute surgery and 868 with (initial) conservative treatment (figure 1).

The acute surgery cohort had a lower GCS at presentation, acute subdural haematomas with larger volumes, and a greater percentage had accompanying large contusions compared with the cohort treated conservatively (appendix pp 17–21). The main reason for acute surgery for acute subdural haematoma was that the patient was judged an emergency case ( $n=192$  [57%]), whereas for patients classified with a mild ( $n=67$ ) or moderate ( $n=57$ ) traumatic brain injury, mass effect on CT was most often the motivation for surgery (in 25 [37%] of patients with mild TBI, 18 [32%] of those with moderate TBI, and 54 [28%] of those with severe TBI; appendix pp 26–27). 33 (91%) of 35 patients with one non-reactive pupil and a large haematoma received acute surgery.

The main reasons for not doing acute surgery were that the lesion was considered by the neurosurgeon at the CT scan to be one that would not benefit from surgery (ie, considered a non-surgical lesion) or had little mass effect. The main reasons for secondary surgery after initial conservative treatment were raised intracranial pressure or suspicion of raised intracranial pressure, mass effect on CT, and clinical deterioration (appendix pp 26–27). 302 (93%) of 324 patients with a GCS of 15 initially received conservative treatment.

For 89 (6%) of 1071 patients, no treatment was given because they were considered to have injuries that were not survivable (appendix pp 22–25). These patients had severe clinical and radiological characteristics and an in-hospital mortality of 96% ( $n=85$ ) with a median time to death of 21 h (IQR 6–50), preceded by a multidisciplinary treatment-limiting decision in most ( $n=50$  [79%]) patients (appendix pp 22–25).

The percentage of patients undergoing acute surgery per centre ranged from 5.6% to 51.5% (IQR 12.3–35.9; appendix p 28). Practice variation was low for patients with a GCS of 15, with the percentage receiving initial conservative treatment varying between 91% and 100% per centre. For patients with one non-reactive pupil and a large haematoma, 100% received acute surgery in 13 of 16 centres.

The MOR for the between-centre difference in acute surgery was 1.8 ( $p<0.0001$ ), reflecting a nearly two-times higher probability of receiving acute surgery for an identical patient in one centre versus another centre at random (figures 2, 3). This finding remained consistent in the post-hoc analysis of only patients with both reactive pupils and a GCS less than 15, with the percentage of patients having acute surgery per centre ranging from 3.1% to 47.6% (IQR 14.3–36.2) between centres with a MOR of 1.7 ( $p=0.024$ ). Furthermore, the a-priori thresholds reported for acute surgery (ie, centre treatment policies) were associated with case-mix-adjusted

	Treatment preference (percentages of patients having acute surgery per centre)*				p value	SMD
	Quartile 1 (<12%)	Quartile 2 (12–22%)	Quartile 3 (23–36%)	Quartile 4 (>36%)		
Patient characteristics						
Number	229	348	291	292	..	..
Age, median (IQR)	60 (43–75)	52 (35–66)	59 (36–72)	59 (43–71)	0.27	0.08
Sex	..	..	..	..	0.27	0.10
Female	77 (34%)	97 (28%)	117 (40%)	84 (29%)	..	..
Male	152 (66%)	251 (72%)	174 (60%)	208 (71%)	..	..
White European	195 (85%)	292 (84%)	248 (85%)	244 (84%)	0.51	0.28
Years of education, median (IQR)	12 (10–15)	12 (9–15)	12 (10–15)	12 (10–16)	0.36	0.09
College or university education	37 (16%)	83 (24%)	49 (17%)	55 (19%)	0.05	0.22
Married or living with partner	114 (50%)	174 (50%)	147 (51%)	149 (51%)	0.21	0.28
Working before injury	97 (42%)	138 (40%)	116 (40%)	125 (43%)	0.25	0.27
ASAPS	..	..	..	..	0.54	0.13
Healthy	106 (46%)	164 (47%)	157 (54%)	135 (46%)	..	..
Mild systemic disease	90 (39%)	129 (37%)	85 (29%)	111 (38%)	..	..
Severe systemic disease	27 (12%)	46 (13%)	42 (14%)	32 (11%)	..	..
Threat to life	0	1 (<1%)	3 (1%)	0	..	..
Unknown	6 (3%)	8 (2%)	4 (1%)	14 (5%)	..	..
History of cardiovascular disease	85 (37%)	109 (31%)	98 (34%)	118 (40%)	0.07	0.21
Alcohol consumption†	86 (38%)	93 (27%)	102 (35%)	77 (26%)	0.015	0.19
Injury mechanism and cause	..	..	..	..	0.57	0.28
High-velocity trauma	84 (37%)	110 (32%)	92 (32%)	87 (30%)	..	..
Incidental ground-level fall	104 (45%)	193 (55%)	151 (52%)	143 (49%)	..	..
Highest-trained bystander	..	..	..	..	0.55	0.23
None	15 (7%)	19 (5%)	17 (6%)	15 (5%)	..	..
Untrained person (bystander)	1 (<1%)	6 (2%)	6 (2%)	2 (1%)	..	..
Paramedic	57 (25%)	100 (29%)	56 (19%)	64 (22%)	..	..
Nurse	43 (19%)	43 (12%)	63 (22%)	46 (16%)	..	..
Doctor	59 (26%)	92 (26%)	72 (25%)	79 (27%)	..	..
Medical rescue team	53 (23%)	87 (25%)	73 (25%)	83 (28%)	..	..
Secondary referral	59 (26%)	85 (24%)	75 (26%)	65 (22%)	0.41	0.08
Arrival method	..	..	..	..	0.19	0.22
Ambulance	167 (73%)	268 (77%)	212 (73%)	216 (74%)	..	..
Helicopter	36 (16%)	36 (10%)	34 (12%)	35 (12%)	..	..
Medical mobile team	11 (5%)	23 (7%)	18 (6%)	26 (9%)	..	..
CPR	8 (3%)	12 (3%)	10 (3%)	4 (1%)	0.19	0.14
Instrumental variable fluids	86 (38%)	129 (37%)	121 (42%)	124 (42%)	0.30	0.10
Intubation	70 (31%)	97 (28%)	88 (30%)	97 (33%)	0.63	0.08
Supplemental oxygen	111 (48%)	170 (49%)	138 (47%)	144 (49%)	0.022	0.24
Ventilation	69 (30%)	87 (25%)	76 (26%)	88 (30%)	0.31	0.13
Hypoxia‡	..	..	..	..	0.54	0.13
No	204 (89%)	279 (80%)	263 (90%)	248 (85%)	..	..
Definite	9 (4%)	20 (6%)	19 (7%)	17 (6%)	..	..
Suspected	7 (3%)	9 (3%)	2 (1%)	10 (3%)	..	..

(Table 1 continues on next page)

(Table 1 continues on next page)

(observed) acute surgery rates, confirming that surgery rates reflect centre treatment preferences (table 1; appendix p 15).

Despite differences in baseline characteristics, the predicted 6 month functional outcome of the CRASH-CT score was similar across centres (table 1), reflecting a balance in patient populations between

centres with varying surgical preferences. Findings were consistent when analyses were restricted to patients with both reactive pupils and a GCS less than 15 (appendix pp 29–32).

Formally, testable assumptions for instrumental variable analyses were met (appendix p 33). Thus, the widely differing acute neurosurgical treatment strategies

	Treatment preference (percentages of patients having acute surgery per centre)*				p value	SMD
	Quartile 1 (<12%)	Quartile 2 (12–22%)	Quartile 3 (23–36%)	Quartile 4 (>36%)		
(Continued from previous page)						
Hypotension§	..	..	..	..	0.19	0.20
No	200 (87%)	301 (86%)	272 (93%)	246 (84%)	..	..
Definite	18 (8%)	12 (3%)	6 (2%)	18 (6%)	..	..
Suspected	2 (1%)	4 (1%)	7 (2%)	7 (2%)	..	..
Any major extracranial injury¶	82 (36%)	131 (38%)	128 (44%)	124 (42%)	0.15	0.14
GCS baseline, median (IQR)	13 (4–15)	12 (7–15)	10 (6–14)	11 (6–14)	0.05	0.10
GCS motor baseline, median (IQR)	6 (1–6)	6 (3–6)	5 (1–6)	5 (2–6)	0.31	0.02
Pupils	..	..	..	..	0.62	0.09
Both reacting	200 (87%)	305 (88%)	229 (79%)	243 (83%)	..	..
One reacting	12 (5%)	17 (5%)	22 (7%)	23 (8%)	..	..
Both not reacting	17 (7%)	26 (7%)	40 (14%)	26 (9%)	..	..
Any focal neurological deficit	..	..	..	..	0.29	0.14
No	149 (65%)	233 (67%)	190 (65%)	208 (71%)	..	..
Yes	36 (16%)	27 (8%)	31 (11%)	32 (11%)	..	..
Unknown	44 (19%)	88 (25%)	70 (24%)	52 (18%)	..	..
Anticoagulants or platelet-aggregation inhibitors	..	..	..	..	0.013	0.31
No	162 (71%)	271 (78%)	216 (74%)	205 (70%)	..	..
Anticoagulants	31 (14%)	20 (6%)	29 (10%)	18 (6%)	..	..
Platelet inhibitors	26 (11%)	42 (12%)	34 (12%)	44 (15%)	..	..
Both	2 (1%)	0	5 (2%)	3 (1%)	..	..
Unknown	8 (3%)	15 (4%)	7 (2%)	22 (8%)	..	..
Total volume of ASDH in cm <sup>3</sup> , median (IQR)	11 (3–25)	14 (4–31)	21 (6–55)	17 (5–53)	0.00041	0.39
Large ASDH on CT scan	44 (19%)	77 (22%)	88 (30%)	100 (34%)	0.00021	0.34
CT midline shift**	88 (38%)	139 (40%)	121 (42%)	106 (36%)	0.68	0.04
CT contusion	..	..	..	..	0.59	0.12
No	95 (41%)	122 (35%)	128 (44%)	104 (36%)	..	..
Small	105 (46%)	187 (54%)	126 (43%)	148 (51%)	..	..
Large	28 (12%)	38 (11%)	30 (10%)	39 (13%)	..	..
Unknown	1 (<1%)	1 (<1%)	7 (2%)	1 (<1%)	..	..
Subarachnoid haemorrhage on CT	..	..	..	..	0.10	0.22
No	76 (33%)	117 (34%)	101 (35%)	104 (36%)	..	..
Basal	13 (6%)	31 (9%)	23 (8%)	26 (9%)	..	..
Cortical	115 (50%)	158 (45%)	132 (45%)	118 (40%)	..	..
Basal and cortical	25 (11%)	42 (12%)	35 (12%)	44 (15%)	..	..
Basal cisterns absent or compressed on CT scan	37 (16%)	66 (19%)	64 (22%)	54 (18%)	0.56	0.06

(Table 1 continues on next page)

(Table 1 continues on next page)

are practiced in centres that on average treat patients with similar characteristics.

Centre preference for acute surgery over initial conservative treatment was not associated with better outcome according to GOSE at 6 months (adjusted common OR per 23.6% [IQR increase] more acute surgery in a centre 0.92, 95% CI 0.77–1.09; table 2; appendix p 34). ORs were consistent across several GOSE dichotomisations (table 2). In the post-hoc analysis, excluding patients with one or two unreactive pupils and patients with GCS 15, the OR remained consistent with the main analysis (adjusted common OR

per 23.6% [IQR increase] more acute surgery in a centre 0.91, 0.72–1.18; appendix p 35). Subgroup analyses showed considerable variation in acute surgery, but consistent ORs for functional outcome, according to age, TBI severity, and haematoma size (appendix p 36). Centre preference for acute surgery showed a large effect size that was not significant on GOSE in large haematomas (OR 2.7, 0.86–8.32). None of the secondary outcomes were different between groups (table 2; appendix p 41).

In sensitivity analyses, the association between centre preference for acute surgery and outcome remained



	Treatment preference (percentages of patients having acute surgery per centre)*				p value	SMD
	Quartile 1 (<12%)	Quartile 2 (12–22%)	Quartile 3 (23–36%)	Quartile 4 (>36%)		
(Continued from previous page)						
Mean predicted 6-month unfavourable outcome (GOS ≤3), median (IQR)††	59% (31–77)	48% (26–65)	56% (31–75)	56% (28–73)	0.28	0.10
Centre characteristics						
Number of patients in academic hospital (vs non-academic hospital)	229 (100%)	348 (100%)	210 (72%)	292 (100%)	<0.0001	0.44
Number of beds, median (IQR)	925 (448–1238)	841 (721–1160)	953 (710–1448)	898 (711–1271)	0.59	0.43
Neurosurgery residency programme	229 (100%)	348 (100%)	291 (100%)	292 (100%)	NA	<0.0001
Trauma centre designation	..	..	..	..	<0.0001	0.58
Level 1	129 (70%)	316 (95%)	272 (100%)	203 (100%)	..	..
Level 2	0	17 (5%)	0	0	..	..
Level 3	54 (30%)	0	0	0	..	..
Urban location (vs suburban and rural location)	229 (100%)	348 (100%)	291 (100%)	292 (100%)	NA	<0.0001
Neurosurgeon staffing (FTE)	12 (10–14)	12 (11–12)	10 (8–14)	7 (6–11)	0.076	0.49
Number of surgeries for ASDH in 2013	62 (20–99)	20 (14–35)	24 (24–25)	24 (8–42)	0.16	0.60
Low threshold policy for acute surgery in ASDH‡‡	46 (20)	66 (19)	170 (58)	179 (61)	<0.0001	0.92
ASAPS=American Society of Anesthesiologists classification system. ASDH=acute subdural haematoma. FTE=full-time equivalent. CPR=cardiopulmonary resuscitation. GCS=Glasgow Coma Scale. GOS=Glasgow Outcome Scale. GOSE=Glasgow Outcome Scale Extended. SMD=standardised mean difference. *Treatment preference as defined by the case-mix-adjusted probability of undergoing acute surgery (as opposed to initial conservative treatment) on the basis of the observed acute surgery rates per centre. The first quartile contains centres least likely to perform acute surgery and the fourth quartile contains centres most likely to perform acute surgery. Importantly, the instrumental variable analysis used acute surgery rates as continuous preference, the quartiles are presented for purposes of interpretability of baseline comparability. †On presentation, the behavioural history of the patient was recorded. This variable reflects the past 3 months consumption of alcoholic beverages (beer, wine, or spirits; more than two alcoholic beverages per day). ‡Second insult during the prehospital or emergency-room phase, defined as partial pressure of oxygen lower than 8 kPa (60 mm Hg) or oxygen saturation of the arterial blood lower than 90%. The suspected category was chosen if the patient did not have documented hypoxia by partial pressure of oxygen or oxygen saturation of the arterial blood, but there was clinical suspicion of hypoxia, as evidenced by, for example, cyanosis, apnoea, or respiratory distress. §Second insult during the prehospital or emergency-room phase, defined as systolic blood pressure lower than 90 mm Hg. The suspected category was chosen if the patient did not have a documented blood pressure, but was reported to be in shock or to have an absent brachial pulse (not related to injury of the extremity). ¶Abbreviated Injury Scale of 3 or higher.   Large is defined as larger than 25 cm³. **Midline shift being present is classified as being more than 5 mm. ††Traumatic brain injury severity as summarised in the predicted unfavourable outcome, percentage with a GOS of 3 or lower, on the basis of Corticosteroid Randomisation after Significant Head Injury CT variables. ‡‡Before patient inclusion in the CENTER-TBI study, treatment policies per centre were captured by provider profile surveys, including the policy towards acute surgery. The resulting threshold for acute ASDH surgery is dichotomised on the basis of this distinction; low being low threshold for surgery and high being high threshold for surgery.						
Table 1: Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural haematoma						

**Table 1: Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural haematoma**

consistent when using the predefined instrumental variable (high vs low threshold surgical centres OR 1.05, 0.85–1.32), including centres with more than ten patients instead of 15 (n=1227; OR 0.87, 0.66–1.00), including the patients with a poor prognosis deemed to have a non-survivable injury (OR 1.01, 0.87–1.27), or excluding patients with unreactive pupils or GCS 15 (n=730; OR 0.94, 0.85–1.12; appendix p 37).

Adjustment with multivariable regression and propensity-score matching gave similar estimates to the primary analysis (appendix pp 37–40). Specifically, excluding patients with one or two unreactive pupils and patients with GCS 15, the ORs from the multivariable regression and the propensity-score matching remained consistent (appendix 37). In patient-level subgroup analyses, surgery was associated with worse outcome for patients younger than 65 years. Acute surgery in older patients and in patients with moderate traumatic brain injury was not significantly associated with better outcome (figure 4).

## Discussion

In this comparative effectiveness study, we found that patients with acute subdural haematoma with similar characteristics were treated differently because of surgical treatment preferences that varied across centres. A treatment strategy preferring an approach of acute surgical evacuation over initial conservative treatment was not associated with a better outcome according to GOS-E at 6 months. Results were consistent in a post-hoc analysis of patients without one or two unreactive pupils (probably poor prognosis) or a GCS of 15 (relatively good prognosis).

In settings in which randomised controlled trials are difficult to do and strong confounding by indication exists, observational studies using robust quasi-experimental approaches are a promising alternative.<sup>25,26</sup> The validity of our conclusions relied on whether the percentage surgically treated per centre was an appropriate instrumental variable. Our instrument variable was strongly associated with acute surgery and not associated with baseline prediction of outcome. The balanced

	Treatment preference (percentages of patients having acute surgery per centre)				Effect variable	Adjusted value (95% CI)*
	Quartile 1 (<12%)	Quartile 2 (12–22%)	Quartile 3 (23–36%)	Quartile 4 (>36%)		
Primary outcome, GOSE at 6 months	5 (3–8)	6 (3–7)	5 (3–7)	5 (3–7)	Common odds ratio	0.92 (0.77 to 1.09)
Secondary outcomes						
In-hospital mortality	37 (16%)	42 (12%)	56 (19%)	52 (18%)	Odds ratio	1.04 (0.78 to 1.40)
GOSE of 7–8%	92 (40%)	128 (37%)	88 (30%)	96 (33%)	Odds ratio	0.95 (0.76 to 1.12)
GOSE of 5–8%	141 (57%)	231 (66%)	158 (54%)	153 (53%)	Odds ratio	0.88 (0.74 to 1.10)
GOSE of 4–8%	163 (67%)	249 (71%)	183 (63%)	165 (57%)	Odds ratio	0.76 (0.61 to 0.99)
Qolibri at 6 months, median (IQR)†	80 (64–92)	74 (62–83)	66 (51–86)	76 (64–85)	β	0.92 (–1.05 to 2.89)

Data are median (IQR) or number (%), unless otherwise indicated. More specific estimates of the quartile percentages are presented in the appendix (p 18). GOSE=Glasgow Outcome Scale Extended. Qolibri=Quality of Life after Brain Injury scale. \*Estimates from random-effects multivariable logistic regression with the instrument, with the adjusted probability of acute surgery as the treatment variable. Confounding was addressed by adjusting for the a-priori defined variables age, Glasgow Coma Scale, pupil reactivity, haematoma size, and midline shift. The (common) odds ratios are presented as comparisons between the first quartile and the fourth quartile (IQR) of the instrument (the adjusted probabilities for undergoing acute surgery). †Qolibri is a standardised health-specific quality-of-life measure specifically designed for and validated for outcome assessment in patients with brain injury. Qolibri is a numerical scale with scores ranging from 0 to 100, with higher scores indicating a better quality of life. The score was available for 130 patients in the acute surgery group and 596 patients in the conservative management group.

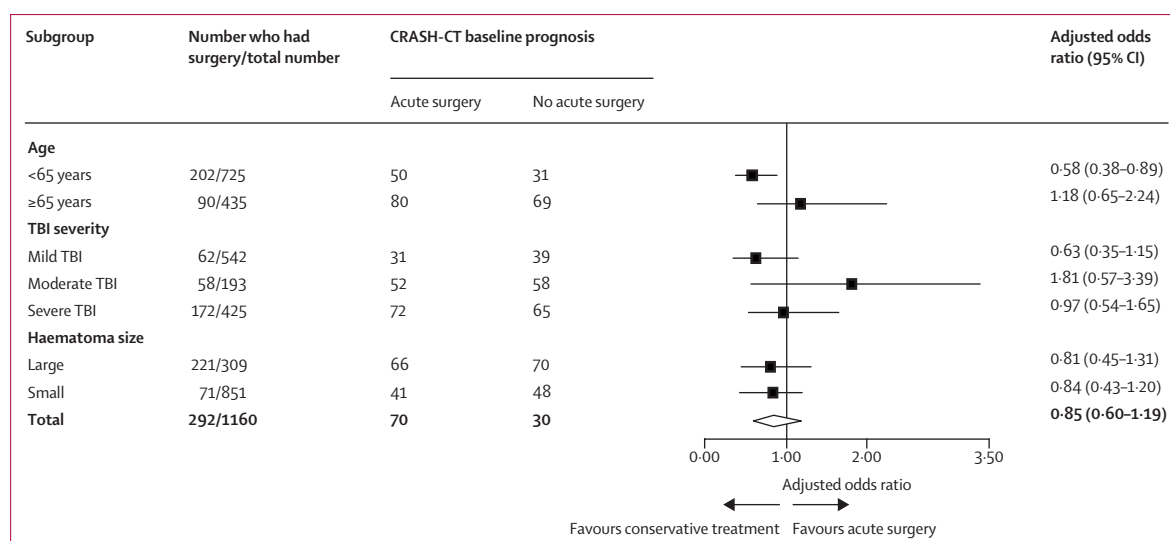
**Table 2: Primary and secondary outcomes and association with acute surgery**

confounding between centres allowed us to reliably infer a reasonable balance in the distribution of unmeasured confounding.<sup>26</sup> Yet, the observed variation in practice might still partly result from residual prognostic differences. Therefore, we compared observed rates of surgery to centre policies captured during provider profiling, and we confirmed that the between-centre variation arose from provider preferences.<sup>12</sup> An a-priori reported low threshold for acute surgery was strongly associated with centres performing acute surgery more frequently for patients with similar characteristics. Moreover, we showed that the organisation of traumatic brain injury care (in the same centres of the current study) was homogeneous, making residual confounding because of other local practice variations unlikely. To further disentangle the effect of the acute subdural haematoma treatment strategy in a centre from other between-centre variations in care associated with outcome, the effect of the current treatment strategy on outcome was modelled with adjustment for other between-centre differences using a random effect for centre.<sup>26</sup>

Our findings were robust in predefined sensitivity analyses and subgroups. By excluding patients who, in the acute phase, did not receive active treatment because of their poor prognosis, the results could have suffered from selection bias. Similar to crossover in an as-treated analysis in a randomised controlled trial, the inclusion of this cohort for the effectiveness analyses might not have been independent from confounding.<sup>31</sup> However, we did a sensitivity analysis on the entire cohort, thereby not selecting on treatment, and found a similar OR. Finally, immortal time bias has been addressed through the design, in which we defined treatment groups after the first CT scan (showing the acute subdural haematoma), thereby aligning the start of the follow-up with treatment assignment.

In terms of clinical implication, the results should be interpreted more carefully than concluding no effect of surgery. First, estimating an overall effect of any (surgical) intervention in traumatic brain injury is amenable to a neutral result, possibly because of averaging heterogeneous effects.<sup>32</sup> In acute neurosurgery, several randomised controlled trials and comparative observational studies have found such negative findings.<sup>33–36</sup> The reasons are multiple and might also be a variable response to treatment because of the complexity and variability of the injury.<sup>34–37</sup>

Second, the interpretation of instrumental variable effect estimates differs from that of conventional analyses. The instrument variable is the percentage surgically treated per centre as a proxy for the surgeon's treatment preference. Because patients with similar characteristics might be operated in one centre but not in another, it naturally follows that there is more than one valid treatment option. The results apply to patients for whom the neurosurgeon might judge that more than one valid treatment option exists among the expert neurosurgical community (appendix p 16). Because this equipoise differs per centre, we cannot readily identify the relative contribution of each subgroup.<sup>38</sup> Some authors suggest that instrumental variable analysis provides information on whether the outcomes of patients will improve when centres change their policy with respect to a specific intervention, rather than estimating an effect in individual patients.<sup>39,40</sup> In this study, some extrapolation to patient-level effects might be appropriate, because multivariable regression and propensity score matching resulted in similar estimates to the instrumental variable approach, and all methods were reliable and implemented correctly.<sup>31</sup> The results should be appreciated in light of the conceptual difference between the methods used.



**Figure 4: Subgroup analyses of the primary outcome for acute surgery, at the patient level**

Common odds ratio for an improvement on the ordinal GOS<sub>E</sub> for acute surgery, stratified by subgroups, using ordinal logistic regressions with random effects adjusted for predefined confounders. Baseline prognosis is summarised in the mean CRASH-CT-predicted 6-month unfavourable outcome (GOS<sub>E</sub> ≤3). Mild TBI severity corresponds to a GCS of 13–15, moderate TBI to a GCS of 9–12, and severe TBI to a GCS of 3–8. CRASH=Corticosteroid Randomization after Significant Head Injury. GCS=Glasgow Coma Scale. GOS=Glasgow Outcome Scale. GOS<sub>E</sub>=Glasgow Outcome Scale Extended. TBI=traumatic brain injury.

Thus, although the inherent heterogeneous treatment effects in traumatic brain injury and the indefinable patient population in the instrumental variable effect estimation preclude recognising an average treatment effect, the results suggest, when there is no clear superiority to evacuate the acute subdural haematoma, no difference in outcome from a centre's treatment strategy.

Surgical evacuation of acute subdural haematoma remains the cornerstone of treatment in life-threatening neurological deterioration.<sup>2</sup> All patients with one non-reactive pupil and a large haematoma were surgically treated acutely in nearly all participating centres, which had also been confirmed in our treatment preference surveys.<sup>10,12</sup> The noted instrumental variable effect of surgery in the predefined subgroup with large haematoma (although non-significant) supports clinical experience that most patients would probably die if not operated on, an effect that cannot be deduced from a randomised controlled trial because of obvious ethical constraints.

The estimates in the age subgroups were consistent in patient-level and centre-level analyses. A suggestion of benefit in older people is consistent with other comparative studies, although pre-existent comorbidities are major drivers of outcome in older people with traumatic brain injury.<sup>41–43</sup> The negative effect of acute surgery in patients younger than 65 years contrasts with the consensus of benefit of acute surgery in young patients with acute subdural haematoma. In general, acute surgery might not always be necessary and a substantial percentage of patients initially managed conservatively have satisfactory outcomes.<sup>5–7,9,44</sup>

The strengths of this study are the comparative effectiveness design using a contemporary, large cohort

with prospective, standardised data collection and predefined provider profiling. A limitation already discussed is the difficulty in interpretation of the instrumental variable analysis. A randomised controlled trial would obviously be ideal, but is not easily feasible and also has methodological challenges.<sup>32</sup> Another limitation remains the possible residual confounding caused by other local practice variations associated with surgical threshold, despite statistical adjustment (ie, the random effects term), despite the study design construction (instrumental variable analysis with a-priori confirmed neurosurgeon preferences), and despite robust association estimates. We previously did a separate cluster analysis, with a broader medical domain view than neurosurgical treatment alone, to explore whether the assumption of the absence of correlation between treatment choices was correct.<sup>21</sup> The main conclusion was that, although correlations between treatment policies within domains (intracranial pressure monitoring, coagulation and transfusion, neurosurgery, prophylactic antibiotics, and more general ICU treatment policies) were found, it was not possible to cluster hospitals. Thus, specific treatment choices within the cohort do not correlate with other treatment choices of another domain. Importantly, the absence of correlation between domains was most pronounced for surgical treatment.

A limitation of the CENTER-TBI cohort in general is the focus on patients presenting to regional neurotrauma centres, with exclusion of prehospital deaths and patients with milder injuries. Participating institutions were mainly referral centres for neurotrauma, and results might not be generalisable to other hospital settings and

to every patient with a traumatic acute subdural haematoma. For example, the CENTER-TBI cohort predominantly comprises white male individuals, reflecting the population of Europe and the fact that male individuals are most likely to have a traumatic brain injury.

An important power consideration is whether there could have been a clinically relevant treatment effect that was not detected with the current sample size. For power calculations, the treatment effect was based on an OR of 0.6, deduced from the available evidence, suggesting similar effect sizes for surgical acute subdural haematoma evacuation.<sup>4,41,45</sup> Nevertheless, this assumed treatment effect is substantial, and furthermore smaller effects might be clinically relevant. However, all analyses show robust ORs close to 1. The uncertainty in these estimates is reported through 95% CIs; not by claiming non-significance in the p values. Therefore, although larger sample sizes are desirable to reduce statistical uncertainty, the current results are highly relevant for clinical practice and reflect real-life care among patients with acute subdural haematoma referred to a dedicated neurotrauma centre.

Subsequent studies of surgery in acute subdural haematoma are advised to be pragmatic randomised controlled trials, specifically targeted at subgroups of patients likely to benefit from acute surgery, as explored in our study, in combination with previous evidence.

In conclusion, patients with traumatic acute subdural haematoma with similar characteristics, without a very poor or good prognosis at presentation, were treated differently across centres because of varying treatment preferences. A treatment strategy preferring an aggressive approach of acute surgical evacuation over initial conservative treatment was not associated with better outcome. Therefore, in a patient with an acute subdural haematoma for whom a neurosurgeon sees no clear superiority for acute surgery versus conservative treatment, initial conservative treatment might be considered.

#### Contributors

TAvE conceptualised the study, curated the data, analysed the data, and drafted the manuscript including all tables and figures. DP assisted in the data curation. GCWdR, HFL, EWS, AIRM, and WCP assisted in the interpretation of the data and helped drafting the manuscript. AIRM, RW, GdR, WP (the clinical supervisors), and HFL and EWS (the statistical supervisors) supervised the methodology of the study protocol and supervised the study. TAvE, HFL, RW, EWS, AIRM, GCWdR, and WCP reviewed the manuscript several times. TAvE, HFL, VV, HfDb, DKM, PH, BD, EWS, AIRM, GCWdR, and WCP were involved in the design of CENTER-TBI. All authors reviewed and approved the final version of the manuscript. TAvE, DP, and HFL accessed and verified the analyses. All authors guarantee that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. All authors had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

#### Declaration of interests

AIRM declares consulting fees from PresSura Neuro, Integra Life Sciences, and NeuroTrauma Sciences. DKM reports grants from the UK

National Institute for Health Research, during the conduct of the study; grants, personal fees, and non-financial support from GlaxoSmithKline; and personal fees from Neurotrauma Sciences, Lantmaanen AB, Pressura, and Pfizer, outside of the submitted work. EWS reports personal fees from Springer during the conduct of the study. All other authors declare no competing interests.

#### Data sharing

The datasets, which include individual participant data and a data dictionary defining each field in the set used or analysed during the current study, will be available upon reasonable request to the management committee of the CENTER-TBI study. Requests for data should be submitted online at <https://www.center-tbi.eu/data> or via email to [center-tbi@uza.be](mailto:center-tbi@uza.be). The data that will be made available comprise deidentified participant data. The predefined study protocol is published.<sup>14</sup> The statistical analysis plan, R syntax, and informed consent forms will be made available upon request. To access any other data from CENTER-TBI, a proposal should be submitted and approved by the management committees of the CENTER-TBI study. A data access agreement with the management team of CENTER-TBI should be signed before access to the data will be granted.

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