Comparative effectiveness of surgery for traumatic acute subdural hematoma

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Chapter 10

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

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SUMMARY

Background

Despite being well-established, acute surgery in traumatic acute subdural hematoma (ASDH) 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 ASDH.

Methods

Using the observational, multicentre, European cohort CENTER-TBI, we conducted a prospective comparative effectiveness study among patients with ASDH, presenting within 24 hours after injury. In an instrumental variable analysis, we compared outcomes between centres according to treatment preference, measured by the case-mix adjusted proportion acute surgery per centre. The primary endpoint was functional outcome rated by the 6-months Glasgow Outcome Scale Extended, estimated with ordinal regression as a common odds ratio (OR), adjusted for prespecified confounders. Variation in centre preference was quantified with the median odds ratio (MOR).

Findings

We included 1407 patients with ASDH from 65 centres. Acute surgical evacuation was performed in 336 patients (24%), in 245 (73%) by craniotomy and in 91 (27%) by decompressive craniectomy. Delayed surgery after initial conservative treatment (n=982) occurred in 107 patients (11%). The proportion acute surgery ranged from 6 to 52% (IQR 12-36%) between centres with a twofold higher probability of receiving acute surgery for an identical patient in one versus another random centre (adjusted MOR for acute surgery 1·8 [$p < 0·0001$]). Centre preference for acute surgery over initial conservative treatment was not associated with better outcome (OR per 24% (IQR) more acute surgery in a centre 0·92 [95% CI 0·77-1·09]). This was consistent in the group of patients without unreactive pupils or a GCS of 15.

Interpretation

Similar patients with ASDH, without an extremely poor or good prognosis at presentation, were treated differently due to 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 ASDH for whom a clinician sees no clear superiority in acute surgery vs. conservative strategy, initial conservative treatment may be considered.

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Introduction

Acute subdural hematoma (ASDH) is the most prevalent focal lesion in traumatic brain injury (TBI) and is associated with high mortality and long-term neurocognitive morbidity.[1] One of the cornerstones of treatment is immediate neurosurgical management: acute hematoma evacuation or initial conservative treatment with potential delayed surgery.[2,3]

In patients with rapid neurological deterioration due to a large ASDH the decision to operate in the acute phase is clear: without acute surgery a high intracranial pressure (ICP) will persist and the patient will die. In most cases however, the benefit of acute surgery is less clear and patients may - at least initially - be safely managed conservatively. It requires balancing surgery with potential complications against initial conservative treatment with a risk of early death and disability due to irreversible deterioration.

Current Brain Trauma Foundation (BTF) guidelines advise acute surgery for ASDHs thicker than 10 mm or with midline shift greater than 5 mm, irrespective of clinical condition or patient characteristics,[4] but the strength of underpinning evidence is low, with only non-comparative studies in small, selected populations.[5-9] In the emergency setting, 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 ASDH surgical evacuation varies substantially between centres.[10,11,12] Strong treatment preferences deeply rooted in centres seem to underlie this practice variation and reflect a lack of equipoise, a necessary premise for a randomised controlled trial (RCT).

Practice variation, however, provides opportunities to study the effectiveness of interventions in clinical reality by relating treatment variation to outcome.[13] Within the large observational cohort study 'Collaborative European NeuroTrauma Effectiveness Research in TBI' (CENTER-TBI), designed as comparative effectiveness study, preferred local treatment strategies were accepted and exploited to estimate their effectiveness in real-life practice.[14] Our aim was to compare the effectiveness of a strategy of acute surgical evacuation with one preferring initial conservative treatment in patients with ASDH.

METHODS

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology-statement with instrumental variable (IV) recommendations.[15,16] The research question, design, outcomes, analysis, subgroups and sample size calculations were defined before patient enrolment and have been published.[14] CENTER-TBI is registered with ClinicalTrials.gov, number NCT02210221, and the Resource Identification Portal (RRID: SCR_015582). This study corresponds to Stage A in the IDEAL Framework.[17]

Study population

Patients with TBI, presenting within 24 hours after trauma, with a brain CT and without pre-existing severe neurological disorders were included in CENTER-TBI, from 2014 through 2017, in centres across Europe and Israel.[18,19] For this study, we selected patients with ASDH regardless of size and presumed necessity for surgical treatment. We excluded brain dead patients and those considered by the treating physician to be not salvageable due to injury deemed unsurvivable, in whom active treatment was not indicated. Due to the design of comparing treatment preferences, the study population inherently reflects the "real-life" clinical dilemma who to surgically treat acutely (appendix p 16). However, for interpretation purposes, we restricted the main analysis also to those "clinical equipoise" patients, being those without an extreme prognosis on either side of the spectrum. Specifically, patients with one or two unreactive pupils (poor prognosis) and patients with a GCS 15 (relatively good prognosis) were excluded for this main analysis.

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

Centre characteristics and data management

Centre characteristics were collected in prior performed surveys.[12,20] Questions included the centre's policy towards the threshold for acute surgery, which was used in sensitivity analyses (appendix pp 13-14). Other treatment decisions, such as prehospital care, possibly related to the surgical threshold can impact the internal validity of our study. We have therefore performed extensive cluster analysis, of which part is separately published.[21] The main conclusion was that treatment preferences within a centres are unrelated.

Data were collected by trained personnel using web-based case report forms (QuesGen Systems Incorporated, Burlingame, CA, USA), coded with the Common Data Elements scheme.[22] Complete CENTER-TBI methodology was published separately.[23]

Interventions

Acute surgery was defined as surgery directly after the first CT-scan, conservative treatment was defined as best medical management (after the first scan) with potential delayed surgery. Neurosurgeons were asked at each CT if and why surgery was indicated, checked by actual operating room transferal and by surgery codes/description. Surgical treatment was at the discretion of the treating neurosurgeon and consisted of ASDH evacuation by craniotomy or by additionally performing a (primary) decompressive craniectomy (DC), 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 performed simultaneously. The initial conservative approach was defined as best medical management after the first scan, with clinical monitoring on the ward, medium-care- or (neurocritical) intensive care unit (ICU) and included possible ICP monitoring and delayed surgical evacuation).

Outcomes

The primary outcome was the Glasgow Outcome Scale Extended (GOSE), an 8-point scale ranging from 1 (death) to 8 (upper good recovery), at 6 months.[24] The use of the GOSE as a core global outcome measure is recommended by the interagency TBI Outcomes Workgroup and the International Mission for Prognosis and Analysis of Clinical Trials in TBI group (IMPACT Common Data Elements). Secondary outcomes included in-hospital mortality, progression on CT/MRI, hospital length of stay (days), discharge destination, and 6-months quality of life assessed with the brain injury-specific Quality of Life after Brain Injury Questionnaire (Qolibri).[25] Outcome assessments were standardized and administered by interview or postal questionnaire.[18]

Statistical analysis

Baseline characteristics are presented using descriptive statistics and compared between treatment groups with standardized mean differences. Practice variation was described as the proportion (%, interquartile range [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 outcomes were analysed with respect to centre treatment strategy (and not actual treatment) in instrumental variable (IV) analyses.[26-28] Specifically, this was a comparison of centres with different preferences for acute surgical evacuation, quantified by the case-mix adjusted probability of performing acute surgery (as

opposed to initial conservative treatment) as observed per centre. To minimize the influence of chance, only centres with at least 15 patients were included. We presented baseline characteristics and the Corticosteroid Randomization after Significant Head Injury (CRASH)-CT-score, a validated baseline prognostic model,[29] across quartiles of the instrumental variable, i.e. the case-mix adjusted probability of performing acute surgery. The first category contains centres least likely to perform acute surgery, fourth quartile contains centres most likely to perform acute surgery. The IV analysis is based on preference for acute surgery rates as a continuous variable, the quartiles are presented to provide insight in the comparability of patient populations across the instrument, which allows the reader to evaluate how comparable the patient characteristics are (IV assumption: the instrument is independent of confounders).[16,30]

The primary effect estimate was the adjusted common 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 instrument (adjusted probability of performing acute surgery) as a continuous treatment variable. Random-effect accounts for other between-centre differences than the factors included in the model. Confounding was further addressed by adjusting for the predefined variables age, GCS, pupil reactivity, ASDH size and midline shift.[14] The common OR is presented as a comparison between the first and the fourth quartile (IQR) of the instrument (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 to those favouring initial conservative treatment.

The main analysis was post-hoc repeated on those patients for whom clinical equipoise exists, as would have been done for a RCT. In this post-hoc analysis, we excluded patients without an extremely good (i.e. GCS 15) or an extremely poor (one or two unreactive pupils) prognosis. While most clinicians would agree that there is more equipoise in these patients, and thus intuitively feel that the results might be applicable to them, we did not define this analysis in the protocol and thus label it post-hoc.

To assess the consistency of the (ordinal) estimate and the plausibility of proportionality of the OR, we present ORs for multiple cut-offs on the GOSE.

The association of surgical preferences with outcome was also estimated by linear regression with the fixed effect centre coefficients as independent variable and the (continuous) mean GOSE per centre as dependent variable. These results are graphically represented in scatter plots.

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 surveyed centre's preference for the use of surgery, as captured through the prior performed provider profiling, as the instrumental variable. Additionally, we performed sensitivity and subgroup analyses on patient-level, with multivariable regression and propensity score matching. A consistency in estimates with the employed methods would strengthen our findings.[31] All sensitivity analyses were performed for the primary outcome.
The supplementary appendix provides additional methodological details for all analyses.
Power calculations showed that assuming inclusion of 1000 ASDH patients would provide 80% power to detect an OR of 0·6.[14]
Analyses were performed 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 (MICE) package (n=5), assuming to be missing at random.
Comparison of descriptive characteristics are presented with standardized mean differences (SMD) and p-values between compared groups. ORs and Beta's are presented with 95% confidence intervals (CIs) calculated by bootstrapping with 500 samples.

Role of the funding sources

The funding entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

RESULTS

Patient characteristics

Of 4559 patients with TBI, 1407 patients with ASDH were included. Acute surgery was performed in 336 patients (25%), at a median of 3·8 (IQR 2·5 – 6·5) hours after injury (appendix pp 17-21). Eighty-nine cases had an extremely poor prognosis or were brain dead, resulting in 982 out of 1071 patients treated conservatively, of which 107 patients (11%) receiving delayed surgery (craniotomy or DC), at a median of 19·1 (IQR 8·1 – 84·6) hours after injury. Of the 336 patients acutely operated, 91 (27%) underwent a primary DC (Figure 1). Of the initial conservatively treated by medical management, 313 patients (32%) received ICP monitoring, 107 patients (11%) underwent delayed DC or craniotomy for an ASDH or ICH and 20 patients (2%) received a (delayed) burr hole drainage for a chronic subdural hematoma (appendix pp 17-21). After excluding patients from centres with fewer than 15 patients (n = 158),

1160 patients were included in the IV analysis, 292 patients with acute surgery and 868 with (initial) conservative treatment (Figure 1).
The acute surgery cohort had a lower GCS at presentation, larger ASDHs, and a greater proportion of accompanying large contusions compared to the conservative cohort (appendix pp 17-21). The main reason for acute surgery was 'emergency' (57%), while in mild/moderate TBI, 'mass effect on CT' was relatively more often the motivation for surgery compared to severe TBI (appendix pp 26-27). Ninety-two percent of patients with 1 nonreactive pupil and large hematoma received acute surgery.
The main reasons for not performing acute surgery were that the lesion was considered not to benefit from surgery (considered 'no surgical lesion') or had little mass effect. The main reasons for secondary surgery after initial conservative treatment were '(suspicion of) raised ICP', 'mass effect on CT' and 'clinical deterioration' (appendix pp 26-27). Ninety-three percent of patients with a GCS of 15 received conservative treatment (initially).
In 89 patients, neither treatment was performed because these patients were considered not salvageable due to injury deemed unsurvivable (appendix pp 26-27). These patients had severe clinical and radiological characteristics and an in-hospital mortality of 96% with a median time to death of 21 hours, preceded by a multidisciplinary treatment limiting decision in most patients (79%, appendix pp 22-25).

Practice variation

The proportion of patients undergoing acute surgery per centre ranged from 5·6 to 51·5% (IQR, 12·3-35·9%) between centres (appendix p 28). Practice variation was low for patients with a GCS of 15, in whom initial conservative treatment varied between 91 and 100%, and for patients with one nonreactive pupil and a large hematoma of whom 100% received acute surgery in 13 out of 16 centres.
The MOR for acute surgery was 1·8 ($p < 0·0001$), reflecting a nearly twofold higher probability of receiving acute surgery for an identical patient in one versus another random centre (Figure 2). This remained consistent when restricting to patients with both reactive pupils and a GCS < 15: proportion acute surgery ranging from 3·1 to 47·6% (IQR, 14·3-36·2%) between centres with a MOR of 1·7 ($p = 0·0244$). Furthermore, the a-priori reported thresholds for acute surgery, i.e. the centre treatment policies, were associated with the casemix-adjusted (observed) acute surgery rates, confirming that surgery rates reflect centre treatment preferences (Table 1 and 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

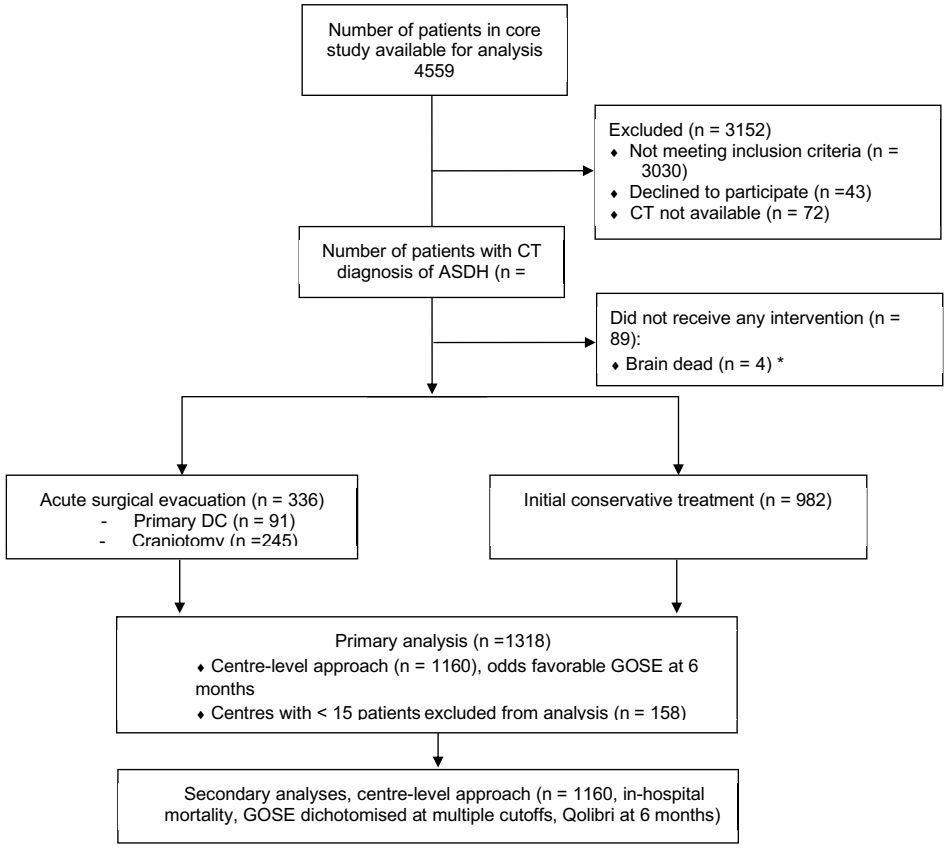

Figure 1. Flow diagram of study population and data analyses

* As judged by the treating physician.

DC indicates decompressive craniectomy, GOSE Glasgow Outcome Scale Extended and Qolibri Quality of Life after Brain Injury Scale.

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 < 15 (appendix pp 29-32).

Formally, the testable assumptions for IV analyses were met (appendix p 33).

Thus, the widely differing surgical practices arise from centres that on average treat similar patients.

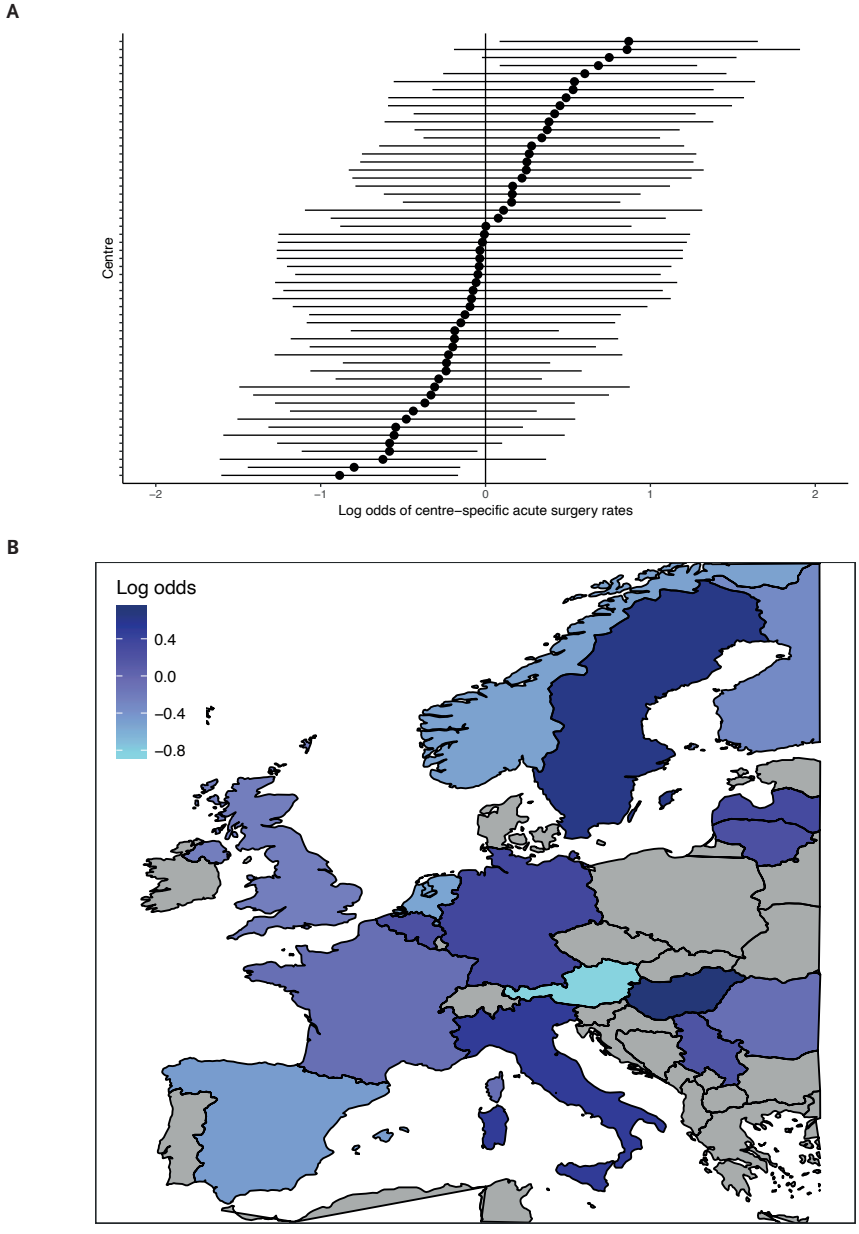

Figure 2. Between-centre (A) and between-country (B) differences in acute surgery

(A) The x-axis presents the log odds of the adjusted acute surgery rates per centre. A logistic random-effects model, adjusted for the predefined confounders age, GCS, pupil reactivity, hematoma size and midline shift, was used to estimate acute surgery preference per centre with corresponding 95% CIs. (B) 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.

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)	p value	SMD
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 (0)	1 (0)	3 (1)	0 (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 [b]	86 (38)	93 (27)	102 (35)	77 (26)	0·0150	0·19
Injury mechanism and cause					0·57	0·28
High velocity trauma	84 (37)	110 (32)	92 (32)	87 (30)		

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma (*continued*)

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)	p value	SMD
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 (0)	6 (2)	6 (2)	2 (1)		
Paramedic	57 (25)	100 (29)	56 (19)	64 (22)		
Nurse	43 (19)	43 (12)	63 (22)	46 (16)		
Physician	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
IV 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)	0·0221	0·24
Ventilation (%)	69 (30)	87 (25)	76 (26)	88 (30)	0·31	0·13
Hypoxia (%) [c]					0·54	0·13
No	204 (89)	279 (80)	263 (90)	248 (85)		

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma (*continued*)

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)	p value	SMD
Definite	9 (4)	20 (6)	19 (7)	17 (6)		
Suspect	7 (3)	9 (3)	2 (1)	10 (3)		
Hypotension (%) [d]					0·19	0·20
No	200 (87)	301 (86)	272 (93)	246 (84)		
Definite	18 (8)	12 (3)	6 (2)	18 (6)		
Suspect	2 (1)	4 (1)	7 (2)	7 (2)		
Any major extracranial injury (%) [e]	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 unreacting	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)		
Anti-coagulants or platelet aggregation inhibitors (%)					0·0128	0·31
No	162 (71)	271 (78)	216 (74)	205 (70)		
Anti-coagulants	31 (14)	20 (6)	29 (10)	18 (6)		

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma (*continued*)

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)	p value	SMD
Platelet inhibitors	26 (11)	42 (12)	34 (12)	44 (15)		
Both	2 (1)	0 (0)	5 (2)	3 (1)		
Unknown	8 (3)	15 (4)	7 (2)	22 (8)		
Total volume of ASDH (cm3, median [IQR])	11 [3, 25]	14 [4, 31]	21 [6, 55]	17 [5, 53]	0·0001	0·39
CT ASDH = large (%) [f]	44 (19)	77 (22)	88 (30)	100 (34)	0·0002	0·34
CT midline shift (%) [g]	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 (0)	1 (0)	7 (2)	1 (0)		
CT subarachnoid haemorrhage (%)					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)		
CT basal cisterns absent/compressed (%)	37 (16)	66 (19)	64 (22)	54 (18)	0·56	0·06
Mean predicted 6-month unfavourable outcome (GOS ≤ 3, %, median [IQR]) [h]	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)	229 (100)	348 (100)	210 (72)	292 (100)	NA	<0·0001

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma (*continued*)

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	**Quartile 2 (12 – 22%)**	**Quartile 3 (23 – 36%)**	**Quartile 4 (>36%)**	**p value**	**SMD**
Number of beds (median (IQR))	925 [448, 1238]	841 [721, 1160]	953 [710, 1448]	898 [711, 1271]	0·59	0·43
Residency program neurosurgery	229 (100)	348 (100)	291 (100)	292 (100)	NA	<0·0001
Trauma centre designation					<0·01	0·58
- Level I	129 (70)	316 (95)	272 (100)	203 (100)		
- Level II	0 (0)	17 (5)	0 (0)	0 (0)		
- Level III	54 (30)	0 (0)	0 (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]	0·08	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 [i]	46 (20)	66 (19)	170 (58)	179 (61)	<0·0001	0·92

Abbreviations: AIS, Abbreviated Injury Scale; ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; FTE, full time equivalent; GCS, Glasgow Coma Scale; GOS(E), Glasgow Outcome Scale Extended; IQR, interquartile range.

[a] Treatment preference as defined by the case-mix adjusted probability of undergoing acute surgery (as opposed to initial conservative treatment) based on the observed acute surgery rates per centre. The first category is less aggressive than the second and the second is less aggressive than the third and so forth. Importantly, the IV analysis used the acute surgery rates as continuous preference, the quartiles are presented for purposes of interpretability of baseline comparability.

[b] On presentation the behavioural history of the patient was recorded. This variable reflects the past three months consumption of alcoholic beverages (beer, wine, spirits) (>2/day).

[c] Second insult during the pre-hospital or ER phase, defined as partial pressure of oxygen (PaO_2) < 8 kPa (60 mmHg) or oxygen saturation of the arterial blood (SaO_2) < 90%. "Suspected" was scored if the patient did not have documented hypoxia by PaO_2 or SaO_2, but there was a clinical suspicion, as evidenced by for example cyanosis, apnoea or respiratory distress.

[d] Second insult during the pre-hospital or ER phase, defined as systolic BP < 90 mmHg. "Suspected" was scored if the patient did not have a documented blood pressure, but was reported to be in shock or have an absent brachial pulse (not related to injury of the extremity).

[e] AIS □ 3.
[f] Large is defined as larger than 25 cm3.
[g] Midline shift present is classified as being more than 5 mm.
[h] TBI severity as summarized in predicted unfavourable outcome, proportion with a Glasgow Outcome Scale ≤ 3, based on CRASH-CT variables.
[i] Before patient inclusion in CENTER-TBI, treatment policies per centre were captured by provider profile surveys, including the policy towards acute surgery. The resulting threshold for acute ASDH surgery is dichotomized based on this distinction: 'Low', low threshold for surgery; 'High', high threshold for surgery).

Table 2. Primary and secondary outcomes and association with acute surgery

	Treatment preference (observed acute surgery rates)				Effect variable	Adjusted value (95% CI) [a]
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)		
Primary outcome: GOSE at 6 months (median [IQR])	5 [3 to 8)	6 [3 to 7]	5 [3 to 7]	5 [3 to 7)	Common odds ratio	0·92 (0·77 – 1·09)
Secondary outcomes						
In-hospital mortality	37 (16)	42 (12)	56 (19)	52 (18)	Odds ratio	1·04 (0·78 – 1·40)
GOSE of 7 or 8 (%)	92 (40)	128 (37)	88 (30)	96 (33)	Odds ratio	0·95 (0·76 – 1·12)
GOSE of 5-8 (%)	141 (57)	231 (66)	158 (54)	153 (53)	Odds ratio	0·88 (0·74 – 1·10)
GOSE of 4-8 (%)	163 (67)	249 (71)	183 (63)	165 (57)	Odds ratio	0·76 (0·61 – 0·99)
Qolibri (median [IQR]) at 6 months [b]	80 [64 to 92]	74 [62 to 83]	66 [51 to 86]	76 [64 to 85]	Beta	0·92 (-1·05 – 2·89)

Abbreviations: CI, confidence interval; GOSE, Glasgow Outcome Scale Extended; IQR, interquartile range; Qolibri, Quality of Life after Brain Injury Scale;

[a] Estimates from random-effects multivariable logistic regression with the instrument, adjusted probability of performing acute surgery as treatment variable. Confounding was furthermore addressed by adjusting for the a-priori defined variables age, GCS, pupil reactivity, hematoma size and midline shift. The (common) odds ratio are presented as comparisons between the first quartile and the fourth quartile (IQR) of the instrument (the adjusted probabilities for undergoing acute surgery).

[b] Qolibri is a standardized health specific quality of life measure specifically designed for and validated for outcome assesment in patients with brain injury. It 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 of the acute surgery group, 596 patients of the conservative management group.

Association with outcome

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) more acute surgery in a centre 0·92 [95% CI 0·77-1·09], Table 2; appendix p 34). The ORs were consistent across multiple GOSE dichotomizations (Table 2). In the post-hoc analysis, excluding patients with one or two unreactive pupils and patients with GCS 15, the OR remained consistent (adjusted common OR per 22% (IQR) more acute surgery in a centre 0·91 [95% CI 0·72-1·18], appendix p 35). Subgroup analyses showed considerable practice variation and consistent ORs (appendix p 36). Centre preference for acute surgery was strongly, but non-significantly, associated with better outcomes in large hematomas (OR 2·7 [95% CI 0·86-8·32].

In sensitivity analyses, the association remained consistent when using the predefined instrumental variable (high vs low threshold surgical centres OR 1·05 [95% CI 0·85 – 1·32]), including centres with more than 10 patients instead of 15 (n = 1227, OR 0·87 [95% CI 0·66 – 1·0]), including the patients with a poor prognosis deemed to have an non-survivable injury (OR 1·01 [95% CI 0·87 – 1·27]) or excluding patients with unreactive pupils or GCS 15 (n = 730, OR 0·94 [95% CI 0·85 – 1·12], appendix p 37).

Adjustment in multivariable regression and propensity score matching gave comparable 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 age under 65. Acute surgery in the elderly and in patient with moderate TBI was non-significantly associated with better outcome (Figure 3). None of the secondary outcomes were different between groups (Table 2, appendix p 41).

DISCUSSION

In this comparative effectiveness study, similar patients with ASDH were treated differently due to varying surgical treatment preferences, and therefore, clinical equipoise can be inferred. A treatment strategy preferring an aggressive approach of acute surgical evacuation over initial conservative treatment was not associated with a better outcome. Results were consistent when targeting patients in whom equipoise likely existed for surgical vs. conservative treatment.

In settings where RCTs are difficult to conduct and strong confounding by indication exists, observational studies using robust quasi-experimental approaches are a

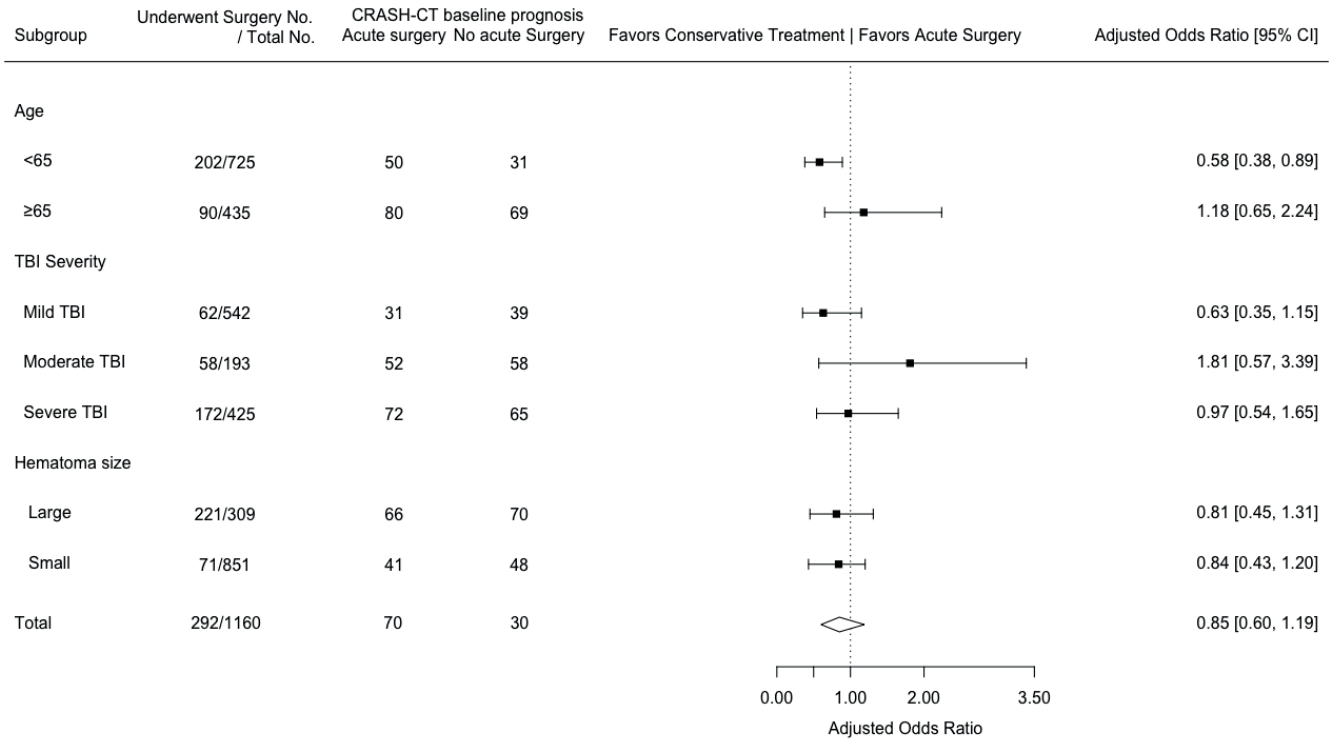

Figure 3. Subgroup analyses of the primary outcome for acute surgery, on patient-level

The panel shows the common odds ratio for an improvement on the ordinal Glasgow Outcome Scale Extended for acute surgery, stratified for subgroups, using ordinal logistic regressions with random-effects adjusted for predefined confounders. Baseline prognosis is summarized in the mean CRASH-CT predicted 6-month unfavourable outcome (GOS ≤ 3, %).

promising alternative.[26,27] The validity of our conclusions relies on whether the centre treatment rate is an appropriate instrumental variable. Our instrument was strongly associated with acute surgery and not associated with baseline prediction of outcome. The balanced confounding between centres allows to reliably infer a reasonable balance in the distribution of unmeasured confounding.[27] Yet, the observed practice variation might still partly result from residual prognostic differences. Therefore, we compared observed rates of surgery to centre policies captured during provider profiling and confirmed that the between-centre variation actually arises from provider preferences.[12] An a-priori reported low threshold for acute surgery was strongly associated with centres actually performing acute surgery more frequently for similar patients. Moreover, we showed that the organization of TBI care (in the same centres of the current study) was homogeneous, making residual confounding due to other local practice variations unlikely. To further disentangle the effect of the ASDH 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.[27]

The findings were robust in predefined sensitivity analyses and subgroups. By excluding patients who, in the acute phase, did not receive active treatment due to poor prognosis, the results could have suffered from selection bias. Similar to cross-over in as-treated analysis in a RCT, the inclusion of this cohort for the effectiveness analyses may not have been independent from confounding.[32] However, we performed 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 the treatment groups after the first CT (showing the ASDH), 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.[33] In acute neurosurgery, several randomised controlled trials and comparative observational studies have found such negative findings. The reasons are multiple and might also be a variable response to treatment because of the complexity and variability of the injury.[34-37]

Second, the interpretation of IV effect estimates differs from that of conventional analyses. The instrument is the proportion surgically treated per centre as a proxy for the surgeon's treatment preference. Because an identical patient may 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 may be

in equipoise, judging that more than one valid treatment option exists (appendix p 17). As this equipoise differs per centre, we cannot readily identify the relative contribution of each subgroup.[38] Some authors suggest that IV analysis provides information on whether patients' outcome will improve when centres change their policy with respect to a specific intervention, rather than estimating an effect in individual patients.[39,40] In this study some extrapolation to patient-level effects may be appropriate, because the multivariable regression and propensity score matching resulted in similar estimates to the IV approach and all methods were reliable and implemented correctly.[31] The results should be appreciated in light of the conceptual difference between the employed methods.

Thus, although the inherent heterogeneous treatment effects in TBI and the indefinable patient population in IV effect estimation preclude recognizing an average treatment effect, the results suggest, when in equipoise regarding the decision to evacuate or not, no difference in outcome due to a centre's treatment strategy.

Surgical evacuation of ASDH remains the cornerstone of treatment in life-threatening neurological deterioration.[2] All patients with one nonreactive pupil and a large hematoma were surgically treated acutely in nearly all participating centres, which had also been confirmed in our treatment preference surveys.[10,12] The strong – albeit non-significant – IV effect of surgery in the predefined subgroup with large hematoma is consistent with clinical experience that most patients would probably die if not operated, an effect that cannot be deduced from a RCT due to obvious constraints.

The estimates in the age subgroups were consistent in patient- and centre-level analyses. A suggestion of benefit in the elderly is consistent with other comparative studies, although pre-existent co-morbidities are major drivers of outcome in the elderly with TBI.[41-43] The negative effect of acute surgery in patients younger than 65 rather contrasts the consensus of benefit of acute surgery in young ASDH patients. In general, acute surgery may not always be necessary and a substantial proportion of patients initially managed conservatively have satisfactory outcomes.[5-7,9,44]

This study's strengths are the comparative effectiveness design using a contemporary, large cohort, with prospective, standardized data collection and predefined provider profiling. A limitation already discussed is the difficulty in interpretation of IV analysis. A RCT would obviously be ideal but is not easily feasible and also has methodological challenges.[33] Another limitation remains the possible residual confounding due to other local practice variations associated with surgical threshold, despite statistical adjustment (i.e. random effects term), despite the study design construction (IV analysis with a-priori confirmed neurosurgeon's preferences), and despite robust association estimates. We previously performed, a separate cluster analysis, with

a broader medical domain view than neurosurgical treatment alone, to explore if the assumption of the absence of correlation between treatment choices holds.[21] 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, is 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.

Limitation of the CENTER-TBI cohort in general is the focus on patients presenting to regional neurotrauma centres, with exclusion of pre-hospital deaths and patients with milder injuries. Participating institutions were mainly referral centres for neurotrauma and results might not be generalizable to other hospital settings and to every patient with a traumatic ASDH. For example, CENTER-TBI mainly included white males, reflecting the predominant white population of Europe and the fact that males are predominant in TBI, and thus the results are mostly applicable to white males.

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 0.6, deduced from the available evidence, suggesting comparable effect sizes for surgical ASDH evacuation.[4,41,45] Nevertheless, this assumed treatment effect is substantial and also smaller effects might be clinically relevant. However, all analyses show robust odds ratios close to 1. The uncertainty in these estimates is reported through confidence intervals; not by claiming non-significance in the p-values. So, while larger sample sizes are desirable to reduce statistical uncertainty, the current results are highly relevant for clinical practice and reflects "real life" care among patients with ASDH referred to a dedicated neurotrauma centre.

Subsequent studies of surgery in ASDH are advised to be pragmatic RCTs, specifically targeted at those subgroups of patients likely to benefit from acute surgery, as explored in our study, in combination with previous evidence.

In conclusion, similar patients with traumatic ASDH, without an extremely poor or good prognosis at presentation, were treated differently across different centres due to 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 ASDH for whom a clinician sees no clear superiority in acute surgery versus conservative strategy, initial conservative treatment may be considered.

Contributors

TvE conceptualised the study, curated the data, analysed the data and drafted the manuscript including all tables and figures. DP assisted in the data curation. GdR, HL, ES, AM and WP assisted in the interpretation of the data and helped drafting the manuscript. AM, RW, GdR, WP (the clinical supervisors) and HL, ES (the statistical supervisors) supervised the methodology of the study protocol and supervised the study. TvE, HL, RW, ES, AM, GdR, and WP reviewed the manuscript multiple times. TvE, HL, VV, HdB, DM, PH, BD, ES, AM, GdR and WP were involved in the design of CENTER-TBI. All authors reviewed and approved the final version of the manuscript. TvE, DP and HL 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

AM 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,
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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. The data that will be made available comprise de-identified participant data. The predefined study protocol is published.[14] 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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See Online for appendix:
https://ars.els-cdn.com/content/image/1-s2.0-S1474422220016 61-mmc1.pdf

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