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

# 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 7 to 52% (IQR 13-35%) 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 22% (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 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 18-22). 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 acute surgery ranged from 6·7 to 51·5% (IQR, 13·4-35·1%) 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 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.

**Association with outcome**

Centre preference for acute surgery over initial conservative treatment was not associated with better outcome (adjusted common OR per 22% (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 non-salvageable patients (with a poor prognosis deemed unsurvivable) (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 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 TBI is amenable to a neutral result due to averaging heterogeneous effects.[33] In acute neurosurgery several RCTs and comparative observational studies have stumbled over such 'negative' findings.[34-37]

Second, the interpretation of IV effect estimates differs from that of conventional analyses. The instrument is the centre treatment rate 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 predefined 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 vs. 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, 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. 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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570 **Table 1. Baseline characteristics and prognostic risk across centres with different preferences**

571 **for immediate treatment of acute subdural hematoma**

572

| | Treatment preference (observed acute surgery rates) [a] | | | | | |
|---|---|---|---|---|---|---|
| | **1 (<13%)** | **2 (13 – 24%)** | **3 (24 – 35%)** | **4 (> 35%)** | **p value** | **SMD** |
| n | 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 (44) | 97 (28) | 117 (40) | 84 (28) | | |
| 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) | | |
| 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) | | |
| 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) | | |
| 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 | | | | | | |
| Academic hospital (vs. non-academic) | 229 (100) | 348 (100) | 210 (72) | 292 (100) | NA | <0·0001 |
| Number of beds (%) | 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 PaO2 < 8 kPa (60 mmHg)/SaO2 < 90%. "Suspected" was scored if the patient did not have documented hypoxia by PaO2 or SaO2, 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] |
|---|---|---|---|---|---|---|
| | 1 (<13%) | 2 (13 – 24%) | 3 (24 – 35%) | 4 (> 35%) | | |
| 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.

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

***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.

***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, %).

# Supplementary appendix

**Table of contents**

## 1. The CENTER-TBI participants and investigators

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## 2. Additional methods

**Instrumental variable analysis**

The main analysis associates centre-level treatment strategies to functional outcome to deduce effectiveness. This natural experiment, in which patients are 'allocated' to one or another treatment strategy based on where the accident occurred, leads to considerable reduction of (unmeasured) confounding because patients are brought to hospitals without knowledge of neurosurgical treatment preference. This is an instrumental variable (IV) analysis, a quasi-experimental approach, where the IV centre 'allocates' patients to be exposed to different likelihoods of receiving acute surgical evacuation. IV analysis is less biased by (unmeasured) confounding by indication and is the preferred analytical method in observational studies on acute neurosurgical decisions in traumatic brain injury.[1-3] The validity depends on 1) the extent to which the instrument is associated with the intervention under study and 2) the absence of independent association with the outcome under study, so that the IV is not associated with the measured or unmeasured patient health status.

To test assumption 1, the association of the instrument with acute surgery was modelled. We calculated adjusted probabilities of surgery with a fixed-effects logistic regression model with the potential confounders age, GCS, pupil reactivity, hematoma size and midline shift as covariables. This model was extended with random intercepts for centre, and centre conditional on country to estimate centre effects on the probability of surgery. To quantify this regional surgical variation, the median odds ratio (MOR) was calculated which is a measure of treatment variation between centres that is not explained by other factors in the model or attributable to chance. The models with and without random-effects for centre were compared with the likelihood ratio test to determine the significance of the between-centre variation. Lastly, we added the neurosurgical treatment policy characteristics from the provider profiling to the model, to determine whether the variation attributable to centre is actually explained by neurosurgical policy characteristics. The fit of the models was compared using the Nagelkerke $R^2$ as a measure for explained outcome variance.[4] Also, we included the partial F statistic as in our previous publication.[3,5]

Assumption 2 was evaluated by comparing the baseline prognosis, quantified by the CRASH-CT score, across the instrument. The CRASH-CT head injury model is a validated prognostic model based on the variables age, GCS, pupil reactivity to light, major extracranial injury, midline shift > 5mm, traumatic subarachnoid haemorrhage, and obliteration of the basal cisterns.[6] Additionally, we checked associations with measured confounders by calculating Spearman's correlation coefficients between the IV and the prognostic scores of unfavourable outcomes. The IV was thereby checked according to recommendations.[5]

For the actual IV analyses, the centre coefficients from fixed-effects models, representing adjusted geographic treatment probabilities of acute surgery, were modelled in a random-effects ordinal regression with the aforementioned confounders as covariables. In this model, the random intercept represents the unexplained hospital effect (beyond all factors included in the model, including the instrument treatment preference) and should capture the measured and unmeasured hospital-level confounders, resulting in unbiased treatment effect estimates. To minimize the influence of chance, only hospitals that enrolled at least 15 patients (at least 10 patients in sensitivity analyses) were included in the IV analyses.

**Sensitivity analyses**

The primary analysis was replicated 1) using a predefined IV for acute surgery from the provider profiling survey (dichotomized threshold for acute ASDH surgery policy: low vs high surgical threshold),[7] 2) without centres providing less than 10 patients, 3) with non-salvageable patients included,[8] 4) without patients with unreactive pupils (poor prognosis) and patients with GCS 15 (excellent prognosis) and 5) by restricting to patients meeting Brain Trauma Foundation (BTF)-guideline criteria for surgical evacuation, i.e. ASDH thickness greater than 10 mm and/or midline shift greater than 5 mm irrespective of the clinical condition. The first sensitivity analysis, using the predefined instrument from the provider profiling surveys, serves the goal to use another proxy for centre preference to function as an IV. In these provider profiling (before patient enrolment), centres reported whether their management protocol follows the BTF recommendation that every ASDH with a thickness > 10 mm or midline shift > 5 mm should be evacuated irrespective of clinical condition. The threshold for acute ASDH surgery was dichotomized accordingly: 'Yes', acute surgery following BTF guideline/low threshold for surgery; 'No', no management according to BTF guideline/high threshold for surgery). The predefined IV for acute surgery arises from this policy.

Additional analyses were performed with treatment defined at patient-level (exposed to intervention, yes/no), unadjusted, with multivariable regression and propensity score matching (PSM) and restricting to the BTF-guideline subgroup. The propensity of being exposed to the intervention was computed using multivariable logistic regression with acute surgery as the dependent variable. PSM was used to match exposed patients with non-exposed patients. The maximum difference between propensity scores was set at 0·10 (the caliper) using a nearest neighbour approach in 1:1 balance. For both the propensity score model and the covariable-adjusted

model, the aforementioned confounding variables of the primary analysis were considered independent variables. We used random-effects models with centre as the clustering variable for all patient-level analyses.

Subgroup analyses were performed for age (< 65 or ≥ 65 years), TBI severity (mild, moderate and severe TBI, corresponding to a Glasgow Coma Scale of 13-15, 9-12 and 3-8 respectively) and hematoma size (large vs small; 25 $cm^3$ cut-off) and presented in forest plots. No adjustments for multiple tests were made. The subgroup analyses were performed on centre-level, with IV analysis per subgroup, and on patient-level, with multivariable regression.

## 3. Additional results

**Quantification of practice variation and instrumental variable assumptions**

Including the variable centre, in addition to patient characteristics, in a model predicting treatment increased the explained variance (Nagelkerke R2) from 54 to 63%. Furthermore, the acute surgical practice was partially explained by predefined neurosurgical treatment policies of the provider profiling. The reported policy of a low threshold for acute surgery was associated with (actual) acute surgery over and above most confounders (OR 2·14, 95% CI 1·09 – 4·11). For comparison, the variable 'one nonreactive pupil' was less strongly correlated with acute surgery (OR 1·90, 95% CI 1·01 – 3·60).

Also, the instrument was strongly associated with the intervention under study (partial F statistic 62). The correlation between instrument and prognosis was small (Supplemental Table 3). Thus, the testable assumptions for IV analyses were met.

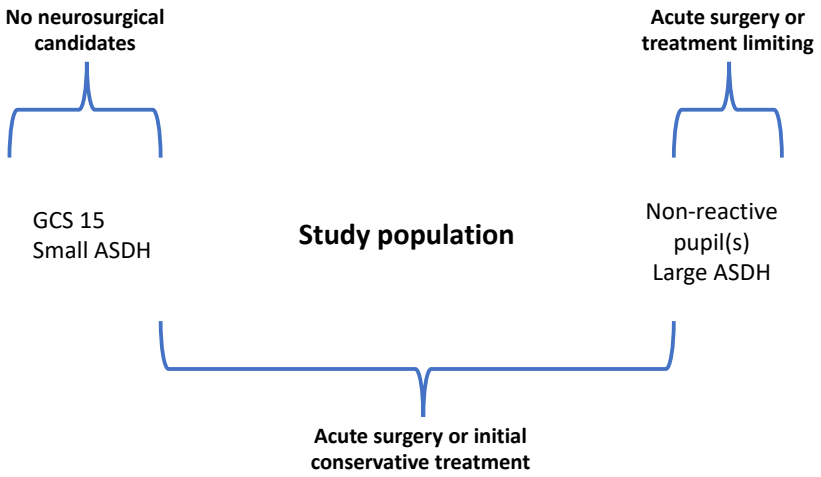
**Sensitivity analyses**

On a continuous outcome scale in linear regression, higher adjusted surgical rates per centre were not associated with higher mean GOSE scores: for an increase from the 25th percentile to the 75th percentile of the range in exposure to the regional intervention preferences for acute surgery, the mean GOSE non-significantly decreased with 0·13 (95% CI: -0·36 – 0·09; Supplemental Figure 5).

Finally, to further test the consistency of the IV approach, we used other instrumental variables. The policy of a 'low threshold for ASDH evacuation', as reported in the prior performed provider profiling survey, was associated with similar GOSE as the 'high threshold for surgery' policy (common OR 1·05 [95% CI 0·85 – 1·32], Supplemental Table 4).

## 4. Supplemental tables and figures

**Supplemental Figure 1. Sliding scale representation of clinical decision and inherent study population**




The scale depicts characteristics of clear-cut cases at either end of the clinical spectrum along which the treatment preference for acute surgery vs (initial) conservative treatment for ASDH differs. The right - red - end, represents patients with poor clinical characteristics for whom clinicians may not perform surgery or conservative treatment on ethical grounds but instead start comfort measures in a treatment-limiting setting. At the left – green – end, all patients will not be operated upon due to an anticipated good prognosis without need for acute evacuation. The window between the artificial divides of both ends, represents the resulting study population. The cut-offs of these divides cannot be reliably characterized because the window is applicable to those patients for whom the neurosurgeon may hypothetically be in clinical equipoise. Because an identical patient may be operated upon in one centre but not in another, it naturally follows that there is more than one valid treatment option. The varying centre policies thus lead to a group of patients for whom we infer clinical equipoise. Because centre policies are not measured per patient, it is not immediately clear what patient population the equipoise actually pertains to.

**Supplemental Table 1. Baseline and treatment characteristics of patients with traumatic acute subdural hematoma, comparing acute surgical evacuation and conservative treatment**

| | ASDH treatment (n = 1318) | | | | |
|---|---|---|---|---|---|
| | **Acute surgery** | **Conservative treatment** | | | |
| n | 336 | 982 | **p value** | **SMD** | **Missing (%)** |
| Age (median [IQR]) | 56 [40, 67] | 58 [38, 72] | 0·08 | 0·08 | 0·0 |
| Sex (%) | | | 0·06 | 0·12 | 0·0 |
| Female | 94 (28) | 331 (34) | | | |
| Male | 242 (72) | 651 (66) | | | |
| White European | 280 (83) | 832 (85) | 0·37 | 0·25 | 0·0 |
| Years of education (median [IQR]) | 12 [10, 14] | 12 [10, 15] | 0·0301 | 0·20 | 42·1 |
| Highest level of education | | | 0·96 | 0·08 | 34·1 |
| College or university | 38 (19) | 140 (20) | | | |
| Married or living with partner | 174 (52) | 485 (49) | 0·13 | 0·21 | 0·4 |
| Employment status before injury | | | 0·10 | 0·27 | 17·2 |
| Working (%) | 127 (49) | 358 (43) | | | |
| Pre-injury ASAPS (%) | | | 0·0252 | 0·20 | 0·2 |
| Healthy | 159 (47) | 469 (48) | | | |
| Mild systemic disease | 106 (32) | 370 (38) | | | |
| Severe systemic disease | 49 (15) | 111 (11) | | | |
| Threat to life | 2 (1) | 2 (0) | | | |
| Unknown | 19 (6) | 29 3) | | | |
| History of cardiovascular disease | 116 (35) | 359 (37) | 0·11 | 0·12 | 0·2 |
| History of neurological disease | 39 (12) | 112 (11) | 0·07 | 0·13 | 0·2 |
| History of psychiatric disease | 57 (17) | 132 (13) | 0·0062 | 0·19 | 0·4 |
| History of oncological disease | 20 (6) | 58 (6) | 0·0313 | 0·15 | 0·2 |
| History of endocrine disease | 41 (12) | 164 (17) | 0·0120 | 0·18 | 0·2 |
| Injury area | | | 0·0250 | 0·18 | 0·1 |
| Urban (city) | 278 (83) | 749 (76) | | | |
| Rural | 44 (13) | 193 (20) | | | |
| Injury cause (%) | | | <0·0001 | 0·31 | 0·1 |
| Road traffic incident | 101 (30) | 331 (34) | | | |
| Incidental fall | 165 (49) | 496 (51) | | | |
| Other non-intentional injury | 11 (3) | 41 (4) | | | |
| Violence | 22 (7) | 44 (4) | | | |

| | | | | | |
|---|---|---|---|---|---|
| Suicide attempt | 6 (2) | 9 (1) | | | |
| Unknown | 26 (8) | 24 (2) | | | |
| Other | 5 (1) | 36 (4) | | | |
| Injury mechanism | | | 0·42 | 0·10 | 0·1 |
| High velocity trauma (acceleration/deceleration) | 80 (24) | 255 (26) | | | |
| Direct impact: blow to head | 32 (10) | 95 (10) | | | |
| Direct impact: head against object | 64 (20) | 167 (17) | | | |
| Ground level fall | 105 (31) | 325 (33) | | | |
| Fall from height > 1 meter/5 stairs | 88 (26) | 234 (23) | | | |
| Alcohol consumption [a] | | | 0·0002 | 0·27 | 6·7 |
| No | 114 (36) | 456 (50) | | | |
| Yes | 114 (36) | 263 (29) | | | |
| Unknown | 86 (27) | 199 (22) | | | |
| Hypoxia (%) [b] | | | 0·0049 | 0·21 | 0·8 |
| No | 267 (80) | 854 (88) | | | |
| Definite | 24 (7) | 51 (5) | | | |
| Suspect | 16 (5) | 19 (2) | | | |
| Unknown | 25 (8) | 52 (5) | | | |
| Hypotension (%) [c] | | | 0·0013 | 0·22 | 0·8 |
| No | 281 (85) | 865 (89) | | | |
| Definite | 15 (5) | 52 (5) | | | |
| Suspect | 14 (4) | 10 (1) | | | |
| Unknown | 22 (7) | 49 (5) | | | |
| Any major extracranial injury (%) [d] | 137 (41) | 393 (40) | 0·86 | 0·02 | 0·0 |
| Face (%) | 66 (20) | 160 (16) | 0·19 | 0·09 | 0·0 |
| Thorax and chest (%) | 76 (23) | 225 (23) | 0·97 | 0·01 | 0·0 |
| Abdomen and pelvis (%) | 33 (10) | 109 (11) | 0·58 | 0·04 | 0·0 |
| Extremities (%) | 23 (7) | 124 (13) | 0·0050 | 0·20 | 0·0 |
| External (%) | 9 (3) | 16 (2) | 0·32 | 0·07 | 0·0 |
| Spine (%) | 42 (12) | 114 (12) | 0·73 | 0·03 | 0·0 |
| GCS (median [IQR]) | 7 [3, 11] | 13 [8, 15] | <0·0001 | 0·86 | 4·3 |
| GCS motor (median [IQR]) | 3 [1, 5] | 6 [4, 6] | <0·0001 | 0·79 | 1·9 |
| TBI severity (%) | | | <0·0001 | 0·82 | 4·3 |
| Mild | 67 (21) | 537 (57) | | | |

| | | | | | |
|---|---|---|---|---|---|
| Moderate | 56 (18) | 141 (15) | | | |
| Severe | 196 (61) | 267 (28) | | | |
| Pupils (%) | | | <0·0001 | 0·62 | 4·8 |
| Both reacting | 215 (67) | 847 (91) | | | |
| One reacting | 44 (14) | 31 (3) | | | |
| Both unreacting | 62 (19) | 53 (6) | | | |
| Any focal neurological deficit (%) | | | <0·01 | 0·55 | 0·2 |
| No | 157 (47) | 713 (73) | | | |
| Yes | 55 (16) | 89 (9) | | | |
| Unknown | 123 (37) | 178 (18) | | | |
| Anti-coagulants or platelet aggregation inhibitors (%) | | | 0·0335 | 0·19 | 0·2 |
| No | 235 (70) | 734 (75) | | | |
| Anti-coagulants | 33 (10) | 75 (8) | | | |
| Platelet inhibitors | 38 (11) | 126 (13) | | | |
| Both | 3 (1) | 8 (1) | | | |
| Unknown | 26 (8) | 38 (4) | | | |
| Total volume of ASDH ($cm^3$, median [IQR]) | 58 [28, 96] | 9 [3, 23] | <0·0001 | 1·33 | 38 |
| CT ASDH = large (%) [e] | 252 (75) | 100 (10) | <0·0001 | 1·2 | 0·1 |
| CT SDH of mixed density (%) | 22 (8) | 43 (5) | | 0·1 | 12 |
| CT midline shift (%) [f] | 287 (85) | 219 (22) | | 1·0 | 0·1 |
| CT DAI (%) | | | 0·81 | 0·04 | 0·1 |
| No | 268 (80) | 797 (81) | | | |
| Yes | 43 (13) | 123 (13) | | | |
| Unknown | 24 (7) | 61 (6) | | | |
| CT depressed skull fracture (%) | | | 0·0203 | 0·17 | 0·1 |
| No | 260 (78) | 825 (84) | | | |
| Closed | 62 (19) | 123 (13) | | | |
| Open | 13 (4) | 33 (3) | | | |
| CT contusion (%) | | | <0·0001 | 0·34 | 0·2 |
| No | 134 (40) | 375 (38) | | | |
| Small | 132 (39) | 506 (52) | | | |
| Large | 60 (18) | 95 (10) | | | |
| Unknown | 9 (3) | 5 (1) | | | |
| CT SAH (%) | | | 0·0312 | 0·18 | 0·1 |
| No | 117 (35) | 329 (34) | | | |

| | | | | | |
|---|---|---|---|---|---|
| Basal | 26 (8) | 76 (8) | | | |
| Cortical | 135 (40) | 462 (47) | | | |
| Basal and Cortical | 58 (17) | 114 (12) | | | |
| CT basal cisterns absent/compressed (%) | 156 (47) | 97 (10) | <0·0001 | 0·90 | 0·3 |
| | | | | | |
| Treatment characteristics during primary admission | | | | | |
| Surgery type | | Na | | | |
| DC | 91 (27) | | | | |
| Craniotomy | 245 (73) | | | | |
| Time injury to surgery (min, median [IQR]) | 230 [152, 391] | | | | 4·8 |
| Secondary or delayed surgery (%) | 93 (28) | 107 (11) | | | |
| DC | 51 (55) | 52 (49) | | | |
| ASDH | 32 (34) | 41 (38) | | | |
| Contusion/ICH | 10 (11) | 14 (13) | | | |
| Time injury to secondary or delayed surgery (min, median [IQR]) | 1115 [360, 6057] | 1149 [486, 5077] | | | 23 |
| Other surgery (during admission, after primary surgery or initial conservative treatment, %) | | | | | |
| Chronic subdural hematoma | 1 (0) | 8 (1) | | | |
| Epidural hematoma | 11 (3) | 8 (1) | | | |
| Cranioplasty | 22 (7) | 2 (0) | | | |
| Extracranial surgery (%) | 69 (21) | 200 (20) | 1·0 | <0·01 | 0·0 |
| ICP monitor (%) | 236 (70) | 313 (32) | <0·0001 | 0·83 | 0·0 |
| ICP device (%) | | | 0·37 | 0·12 | 0·0 |
| Ventricular | 33 (14) | 47 (15) | | | |
| Parenchymal | 184 (79) | 252 (81) | | | |
| Other | 17 (7) | 14 (4) | | | |
| ICP (median [IQR]) | 12 [8, 15] | 12 [9, 15] | 0·37 | 0·07 | |
| CPP (median [IQR]) | 73 [67, 77] | 74 [68, 80] | 0·10 | 0·19 | |
| TIL (median [IQR]) | 5 [2, 9] | 2 [0, 6] | <0·0001 | 0·49 | |
| | | | | | |
| Discharge destination (%) | | | 0·0120 | 0·81 | 10 |
| Other hospital | 63 (30) | 158 (21) | | | |

| | | | | | |
|---|---|---|---|---|---|
| Rehabilitation unit | 84 (41) | 162 (22) | | | |
| Nursing home | 16 (8) | 28 (4) | | | |
| Home | 35 (17) | 389 (52) | | | |
| Unknown | 0 (0) | 1 (0) | | | |
| Other | 9 (4) | 12 (2) | | | |
| | | | | | |
| Treatment during follow-up (after discharge) | | | | | |
| Hydrocephalus | 9 (3) | 5 (1) | | | |
| Chronic subdural hematoma | 2 (1) | 12 (1) | | | |
| Cranioplasty | 25 (7) | 17 (2) | | | |

Abbreviations: AIS, Abbreviated Injury Scale; ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; CPP, cerebral perfusion pressure; DAI, diffuse axonal injury; DC, decompressive craniectomy; GCS, Glasgow Coma Scale; ICP, intracranial pressure; IQR, interquartile range; Na, not applicable; SAH, subarachnoid hemorrhage; SMD, standardized mean difference; TIL, Therapy Intensity Level.

[a] On presentation the behavioral history of the patient was recorded. This variable reflects his/her use in the past three months of alcoholic beverages (beer, wine, spirits) (>2/day).

[b] Second insult during the pre-hospital or ER phase, defined as PaO2 < 8 kPa (60 mmHg)/SaO2 < 90%. 'Suspected' was scored if the patient did not have documented hypoxia by PaO2 or SaO2, but there was a clinical suspicion, as evidenced by for example cyanosis, apnoea or respiratory distress.

[c] 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).

[d] AIS ≥ 3.

[e] Large is defined as larger than 25 cm3.

[f] Midline shift present is classified as being more than 5 mm.

**Supplemental Table 2. Baseline and hospital characteristics of non-salvageable patients**

| **Patient characteristic** | |
|---|---|
| | |
| n | 89 |
| Age (median [IQR]) | 74 [57, 79] |
| Sex = male (%) | 61 (69) |
| ASAPS (%) | |
| Healthy | 23 (26) |
| Mild systemic disease | 39 (44) |
| Severe systemic disease | 16 (18) |
| Threat to life | 1 (1) |
| Unknown | 9 (10) |
| Injury cause (%) | |
| Road traffic incident | 26 (29) |
| Incidental fall | 55 (62) |
| Other non-intentional injury | 1 (1) |
| Violence | 1 (1) |
| Suicide attempt | 2 (2) |
| Unknown | 3 (3) |
| Other | 1 (1) |
| Hypoxia (%) [a] | |
| No | 66 (75) |
| Definite | 15 (17) |
| Suspect | 3 (3) |
| Unknown | 4 (5) |
| Hypotension (%) [b] | |
| No | 63 (72) |
| Definite | 17 (19) |
| Suspect | 3 (3) |
| Unknown | 5 (6) |
| Any major extracranial injury (%) [c] | 34 (38) |
| GCS (median [IQR]) | 3 [3, 5] |
| GCS motor (median [IQR]) | 1 [1, 2] |
| TBI severity (%) | |
| Mild | 2 (2) |
| Moderate | 8 (10) |
| Severe | 73 (88) |

| | |
|---|---|
| Pupils (%) | |
| Both reacting | 21 (24) |
| One reacting | 7 (8) |
| Both unreacting | 59 (68) |
| Any focal neurological deficit (%) | |
| No | 38 (43) |
| Yes | 11 (12) |
| Unknown | 40 (45) |
| Anti-coagulants or platelet aggregation inhibitors (%) | |
| No | 46 (52) |
| Anti-coagulants | 20 (23) |
| Platelet inhibitors | 13 (15) |
| Both | 2 (2) |
| Unknown | 7 (8) |
| Total volume of ASDH ($cm^3$, median [IQR]) | 67 [18, 111] |
| CT ASDH = large (%) [d] | 68 (76) |
| CT SDH of mixed density (%) | 10 (12) |
| CT midline shift = yes (%) [e] | 63 (71) |
| CT DAI (%) | |
| No | 71 (80) |
| Yes | 9 (10) |
| Unknown | 9 (10) |
| CT depressed skull fracture (%) | |
| No | 62 (70) |
| Closed | 23 (26) |
| Open | 4 (4) |
| CT contusion (%) | |
| No | 34 (39) |
| Small | 22 (25) |
| Large | 29 (33) |
| Unknown | 3 (3) |
| CT SAH (%) | |
| No | 21 (24) |
| Basal | 9 (10) |

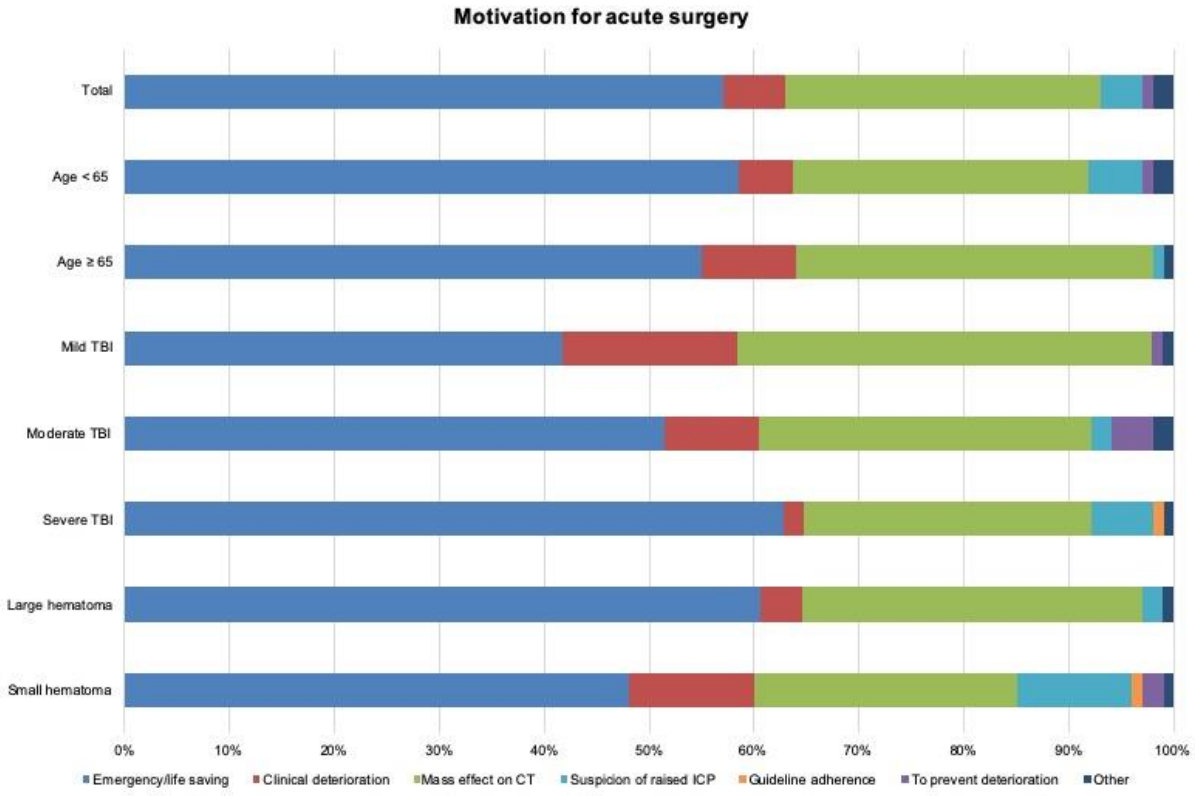
| | |
|---|---|
| Cortical | 31 (35) |
| Basal and Cortical | 28 (31) |
| CT basal cisterns absent/compressed = yes (%) | 55 (62) |
| In-hospital mortality (%) | 85 (96) |
| Time admission to death (hours, median [IQR]) | 21 [6, 50] |
| Decision to withdraw active treatment (%) | 67 (79) |
| Multidisciplinary | 50 (75) |
| By a single physician | 11 (16) |
| With relatives | 6 (9) |
| Withdrawal of life-sustaining measures[a] | |
| For severity of TBI | 45 (51) |
| For reason of age | 9 (10) |
| For reason of co-morbidities | 3 (4) |
| On request of relatives | 6 (7) |
| Following living will of patient | 5 (6) |
| Time injury to decision of withdrawal of care (hours, median [IQR]) | 6 [3, 27] |
| Discharge destination (%) | |
| Home | 1 (1) |
| Nursing home | 2 (2) |
| Other hospital | 1 (1) |
| GOSE 6-months (%) | |
| 1=Dead | 88 (99) |
| 2=Vegetative state/3=Lower severe disability | 0 |
| 4=Upper severe disability | 0 |
| 5=Lower moderate disability | 0 |
| 6=Upper moderate disability | 0 |
| 7=Lower good recovery | 0 |
| 8=Upper good recovery | 0 |

Abbreviations: GOS(E), Glasgow Outcome Scale Extended; IQR, interquartile range; TBI, traumatic brain injury.

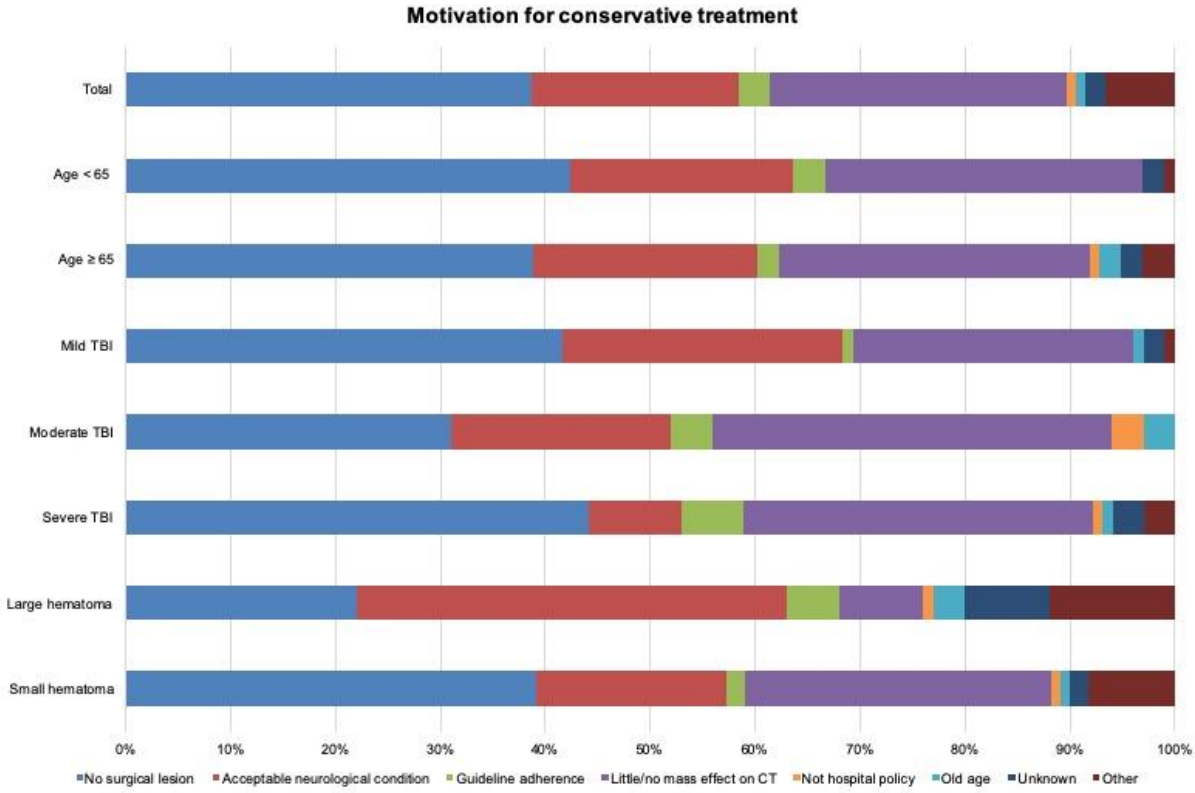
[a] Mechanical ventilation; vaso-active medication; continuous veno-venous hemofiltration; intravenous fluids.

**Supplemental Figure 2. Motivations for acute surgery, conservative treatment, and secondary surgery after initial conservative treatment**

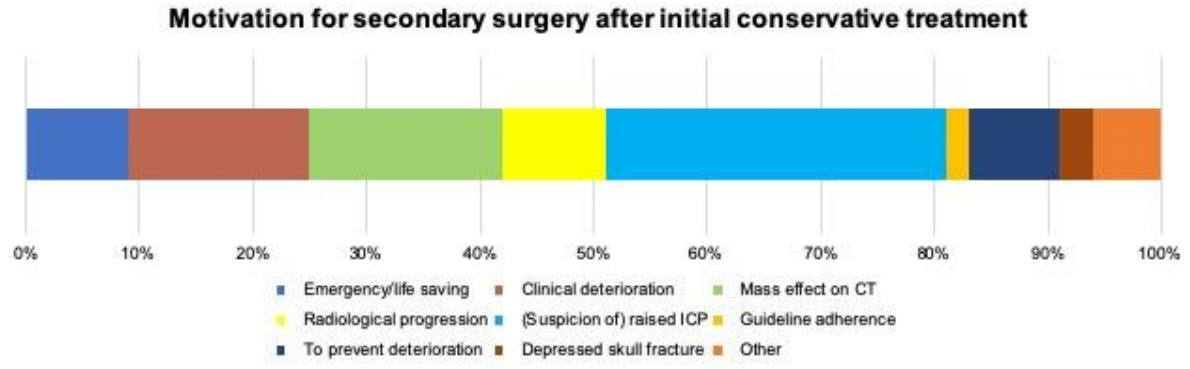
**A**



**B**

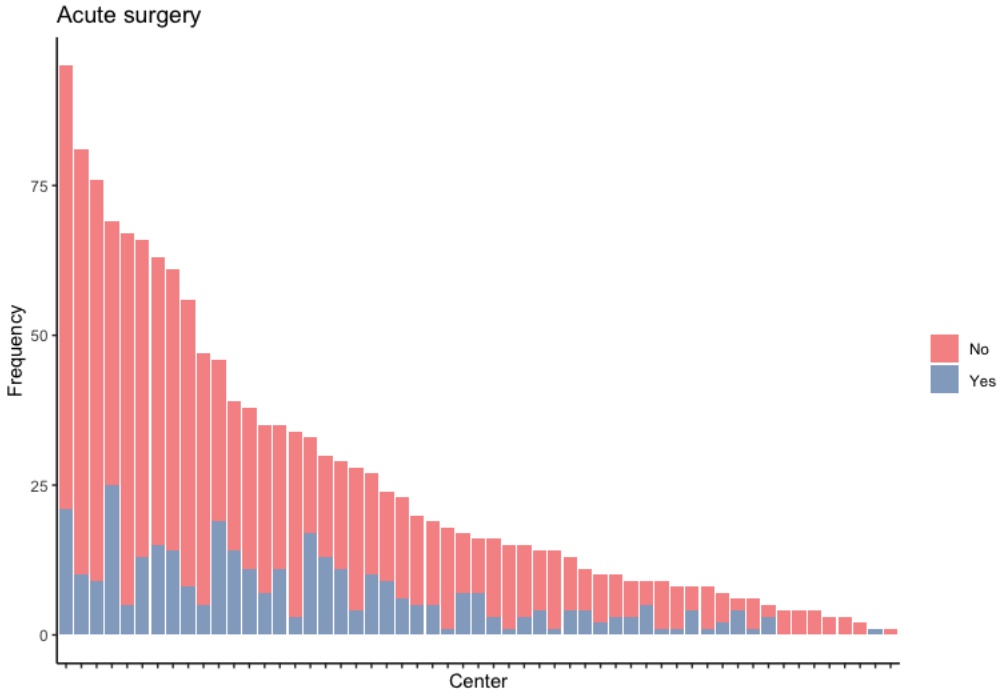



**C**




The graphs show the reasons for acute surgery (A), conservative treatment (B), and secondary surgery after initial conservative treatment (C), visually represented as proportions of the total (sub)group, as judged by the treating physician based on the first CT-scan (A,B and C) or a follow-up CT-scan (D). Definitions for clinical deterioration: a spontaneous decrease in the Glasgow Coma Scale motor score ≥ 2 points (compared with the previous examination), a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2 mm or any other deterioration in neurological status.

**Supplemental Figure 3. Proportions per centre with acute surgery of all ASDH patients**



**Supplemental Table 3. Baseline characteristics of the cohort for the post-hoc analysis, across centres with different preferences for immediate treatment of acute subdural hematoma**

| | Treatment preference (observed acute surgery rates) [a] | | | | | |
|---|---|---|---|---|---|---|
| | **1 (<14%)** | **2 (14 – 24%)** | **3 (24 – 36%)** | **4 (> 35%)** | **p value** | **SMD** |
| n | 140 | 134 | 152 | 125 | | |
| Age (median [IQR]) | 55 [40, 67] | 50 [32, 65] | 56 [38, 68] | 63 [42, 71] | 0·0332 | 0·18 |
| Sex | | | | | 0·96 | 0·02 |
| Female | 35 (25) | 45 (32) | 59 (39) | 30 (24) | | |
| Male | 105 (75) | 89 (66) | 93 (61) | 95 (76) | | |
| White European | 123 (88) | 111 (83) | 133 (88) | 109 (87) | 0·74 | 0·36 |
| Years of education (median [IQR]) | 13 [11, 16] | 12 [8, 14] | 12 [10, 14] | 12 [9, 14] | 0·0225 | 0·31 |
| College or university education | 35 (25) | 29 (22) | 22 (14) | 18 (14) | 0·06 | 0·35 |
| Married or living with partner | 72 (51) | 72 (54) | 84 (55) | 72 (57) | 0·21 | 0·28 |
| Working before injury (%) | 62 (44) | 51 (38) | 56 (36) | 47 (8) | 0·18 | 0·40 |
| ASAPS (%) | | | | | 0·81 | 0·12 |
| Healthy | 57 (41) | 88 (66) | 85 (56) | 50 (40) | | |
| Mild systemic disease | 64 (46) | 32 (24) | 45 (30) | 53 (42) | | |
| Severe systemic disease | 13 (9) | 14 (10) | 18 (12) | 14 (11) | | |
| Threat to life | 0 (0) | 0 (0) | 2 (1) | 0 (0) | | |
| Unknown | 6 (4) | 0 (0) | 2 (1) | 8 (6) | | |
| History of cardiovascular disease | 42 (30) | 33 (25) | 53 (35) | 53 (42) | 0·07 | 0·28 |
| Alcohol consumption [b] | 32 (23) | 49 (37) | 55 (36) | 19 (15) | 0·0340 | 0·32 |
| Injury mechanism and cause | | | | | 0·11 | 0·40 |
| High velocity trauma | 46 (33) | 44 (33) | 40 (26) | 33 (26) | | |
| Incidental ground level fall | 73 (52) | 71 (53) | 84 (55) | 65 (52) | | |
| Highest trained bystander (%) | | | | | 0·38 | 0·32 |
| None | 6 (4) | 10 (7) | 11 (7) | 9 (7) | | |
| Untrained person (bystander) | 2 (1) | 2 (1) | 3 (2) | 2 (2) | | |
| Paramedic | 41 (29) | 34 (25) | 28 (18) | 24 (19) | | |
| Nurse | 25 (18) | 23 (17) | 36 (24) | 19 (15) | | |
| Physician | 38 (27) | 26 (19) | 44 (29) | 40 (32) | | |
| Medical rescue team | 27 (19) | 38 (28) | 28 (18) | 31 (25) | | |
| Secondary referral (%) | 37 (26) | 40 (30) | 42 (28) | 27 (22) | 0·44 | 0·11 |
| Arrival Method (%) | | | | | 0·27 | 0·28 |
| Ambulance | 111 (79) | 97 (72) | 112 (74) | 88 (70) | | |
| Helicopter | 14 (10) | 15 (11) | 18 (12) | 18 (14) | | |
| Medical mobile team | 8 (6) | 8 (6) | 7 (5) | 9 (7) | | |
| CPR (%) | 5 (4) | 9 (7) | 6 (4) | 1 (1) | 0·27 | 0·19 |

| | | | | | | |
|---|---|---|---|---|---|---|
| IV Fluids (%) | 50 (36) | 47 (35) | 58 (38) | 52 (42) | 0·39 | 0·12 |
| Intubation (%) | 38 (27) | 34 (25) | 47 (31) | 41 (33) | 0·52 | 0·14 |
| Supplemental oxygen (%) | 60 (43) | 64 (48) | 67 (44) | 62 (50) | 0·11 | 0·26 |
| Ventilation (%) | 35 (25) | 33 (25) | 39 (26) | 40 (32) | 0·29 | 0·19 |
| Hypoxia (%) [c] | | | | | 0·71 | 0·15 |
| No | 121 (86) | 111 (83) | 138 (91) | 111 (89) | | |
| Definite | 5 (4) | 8 (6) | 10 (7) | 6 (5) | | |
| Suspect | 6 (4) | 3 (2) | 2 (1) | 3 (2) | | |
| Hypotension (%) [d] | | | | | 0·66 | 0·16 |
| No | 123 (88) | 107 (80) | 143 (94) | 104 (83) | | |
| Definite | 7 (5) | 8 (6) | 4 (3) | 10 (8) | | |
| Suspect | 1 (1) | 4 (3) | 2 (1) | 2 (2) | | |
| Any major extracranial injury (%) [e] | 50 (36) | 63 (47) | 63 (41) | 60 (48) | 0·07 | 0·25 |
| GCS baseline (median [IQR]) | 10 [5, 13] | 9 [5, 13] | 9 [6, 13] | 10 [7, 13] | 0·28 | 0·14 |
| GCS motor baseline (median [IQR]) | 5 [2, 6] | 5 [2, 6] | 5 [1, 6] | 5 [4, 6] | 0·37 | 0·14 |
| Any focal neurological deficit (%) | | | | | 0·0022 | 0·44 |
| No | 78 (56) | 82 (61) | 92 (61) | 92 (74) | | |
| Yes | 15 (11) | 23 (17) | 27 (18) | 14 (11) | | |
| Unknown | 47 (34) | 29 (22) | 33 (22) | 19 (15) | | |
| Anti-coagulants or platelet aggregation inhibitors (%) | | | | | 0·21 | 0·30 |
| No | 105 (75) | 111 (83) | 121 (80) | 80 (64) | | |
| Anti-coagulants | 8 (6) | 7 (5) | 11 (7) | 8 (6) | | |
| Platelet inhibitors | 15 (11) | 15 (11) | 16 (11) | 22 (18) | | |
| Both | 0 (0) | 0 (0) | 2 (1) | 2 (2) | | |
| Unknown | 12 (9) | 1 (1) | 2 (1) | 13 (10) | | |
| Total volume of ASDH (cm3, median [IQR]) | 14 [4, 29] | 10 [4, 28] | 23 [6, 58] | 20 [6, 48] | 0·10 | 0·25 |
| CT ASDH = large (%) [f] | 31 (22) | 36 (27) | 57 (38) | 36 (29) | 0·27 | 0·15 |
| CT midline shift (%) [g] | 74 (53) | 55 (41) | 68 (45) | 43 (34) | 0·0038 | 0·38 |
| CT contusion (%) | | | | | 0·0021 | 0·44 |
| No | 27 (19) | 53 (40) | 44 (29) | 46 (37) | | |
| Small | 91 (65) | 64 (48) | 79 (52) | 70 (56) | | |
| Large | 22 (16) | 16 (12) | 27 (18) | 9 (7) | | |
| Unknown | 0 (0) | 1 (1) | 2 (1) | 0 (0) | | |
| CT subarachnoid haemorrhage (%) | | | | | 0·32 | 0·23 |
| No | 31 (22) | 27 (20) | 43 (28) | 38 (30) | | |
| Basal | 9 (6) | 15 (11) | 18 (12) | 11 (9) | | |
| Cortical | 75 (54) | 75 (56) | 76 (50) | 55 (44) | | |
| Basal and Cortical | 25 (18) | 17 (13) | 15 (10) | 21 (17) | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| CT basal cisterns absent/compressed (%) | 30 (21) | 30 (22) | 37 (24) | 21 (17) | 0·42 | 0·12 |
| Mean predicted 6-month unfavourable outcome (GOS ≤ 3, %, median [IQR]) [h] | 57 [39, 74] | 52 [29, 73] | 60 [31, 78] | 63 [34, 76] | 0·90 | 0·05 |
| Centre characteristics | | | | | | |
| Academic hospital (vs. non-academic) | 140 (100) | 134 (100) | 130 (86) | 125 (100) | NA | <0·0001 |
| Number of beds (%) | 915 [632, 1158] | 1200 [882, 1300] | 924 [870, 1212] | 850 [665, 1213] | 1·00 | 0·11 |
| Residency program neurosurgery | 140 (100) | 134 (100) | 152 (100) | 125 (100) | NA | <0·0001 |
| Trauma centre designation | | | | | <0·01 | 0·48 |
| - Level I | 140 (70) | 92 (69) | 121 (100) | 106 (100) | | |
| - Level II | 0 (0) | 15 (11) | 0 (0) | 0 (0) | | |
| - Level III | 0 (0) | 27 (20) | 0 (0) | 0 (0) | | |
| Urban location (vs. suburban and rural location) | 134 (100) | 152 (100) | 125 (100) | 134 (100) | NA | <0·0001 |
| Neurosurgeon staffing (FTE) | 14 [14, 16] | 12 [11, 12] | 10 [8, 14] | 8 [7, 11] | 0·03 | 2·02 |
| Number of surgeries for ASDH in 2013 | 92 [68, 101] | 18 [13, 24] | 25 [24, 28] | 21 [10, 30] | 0·14 | 1·18 |
| Low threshold policy for acute surgery in ASDH [i] | 44 (31) | 20 (15) | 103 (68) | 64 (51) | 0·0017 | 0·41 |

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 PaO2 < 8 kPa (60 mmHg)/SaO2 < 90%. "Suspected" was scored if the patient did not have documented hypoxia by PaO2 or SaO2, 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).

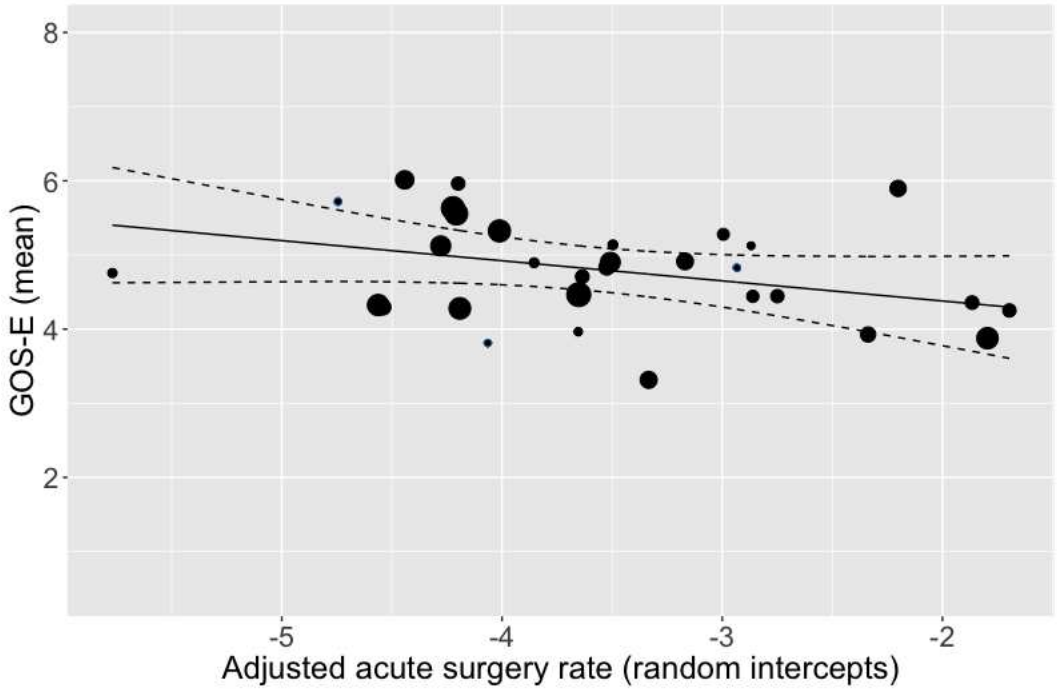
**Supplemental Table 4. Assumptions for instrumental variable analysis**

| IV assumptions | Acute surgery |
|---|---|
| Assumption 1: instrument association with intervention | |
| Partial F statistic | 61·8 |
| Assumption 2: instrument association with prognosis | |
| Spearman's Rho correlation with $P_{unfavourable}$ [a] | 0·02 |

Abbreviation: IV, instrumental variable

[a] Prognosis as summarized in CT-CRASH score, predicted unfavourable outcome (proportion with a Glasgow Outcome Scale ≤ 3)

**Supplemental Figure 4. Functional outcome with centres with different rates of acute surgery**




Graphical illustration to estimate the incremental effect of treatment preference (more acute surgery) on 6-months GOSE. Each circle represents a centre with area proportional to the number of patients. The fitted line is the result of a random-effects linear model with dotted lines reporting the 95% confidence interval with a Beta of -0·13 (95% CI: -0·36 – 0·09) for acute surgery, adjusted for confounders.

**Supplemental Table 5. Primary and secondary outcomes and association with acute surgery of the post-hoc analysis**

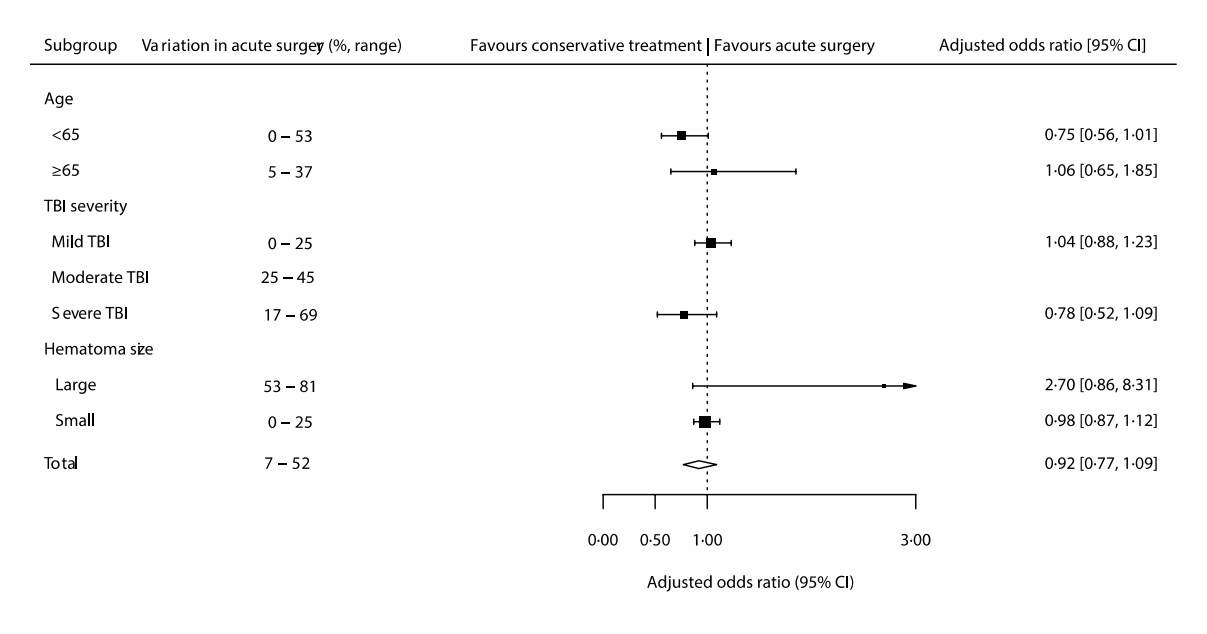
| | Treatment preference (observed acute surgery rates) | | | | Effect variable | Adjusted value (95% CI) [a] |
|---|---|---|---|---|---|---|
| | 1 (<14%) | 2 (14 – 24%) | 3 (24 – 36%) | 4 (> 35%) | | |
| Primary outcome: GOSE at 6 months (median [IQR]) | 5 [3 to 7) | 5 [3 to 7] | 5 [3 to 6] | 4 [3 to 7) | Common odds ratio | 0·91 (0·72 – 1·18) |
| Secondary outcomes | | | | | | |
| In-hospital mortality | 26 (19) | 24 (18) | 24 (16) | 28 (22) | Odds ratio | 0·99 (0·63 – 1·38) |
| GOSE of 7 or 8 (%) | 38 (27) | 42 (32) | 36 (23) | 33 (26) | Odds ratio | 0·87 (0·62 – 1·17) |
| GOSE of 5-8 (%) | 79 (57) | 88 (66) | 79 (51) | 55 (43) | Odds ratio | 0·83 (0·65 – 1·14) |
| GOSE of 4-8 (%) | 94 (68) | 95 (71) | 94 (61) | 67 (53) | Odds ratio | 0·81 (0·62 – 1·08) |
| Qolibri (median [IQR]) at 6 months [b] | 67 [54 to 89] | 74 [62 to 87] | 66 [51 to 86] | 76 [62 to 85] | Beta | 0·49 (-4·06 – 5·04) |

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, focal neurological deficit, 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 59 patients of the acute surgery group, 225 patients of the conservative management group.

**Supplemental Figure 5. Subgroup analyses for acute surgery in the instrumental variable cohort.**




The panel shows the common odds ratio for improvement on the ordinal Glasgow Outcome Scale Extended for acute surgery, stratified for subgroups, using ordinal logistic regressions with random-effects and adjustments for confounders (see 'Methods/Statistical Analysis').

The variation in acute surgery is presented as the range for centres providing at least 15 patients. Exploratory subgroup analyses were displayed as forest plots using the primary outcome as dependent variable without the subgroup-defining variable on categorized regression models. The moderate TBI subgroup only had 1 centre and, hence, no estimate could be calculated.

**Supplemental Table 6. Results of sensitivity analyses: comparing analytical methods to adjust for confounding by indication**

| Approach | Acute surgery (OR 95 % CI, number of patients) |
|---|---|
| Unadjusted model | 0·32 (0·26 - 0·40, n = 1318) |
| Covariable adjustment in multivariable regression [a] | 0·85 (0·60 - 1·19, n = 1318) |
| Patients with both reactive pupils and GCS < 15 | 0.87 (0.55 - 1.39, n = 665) |
| Restriction (to patients meeting BTF guidelines) [b] | 0·65 (0·48 - 1·28, n = 414) |
| Propensity score matching [c] | 0·89 (0·57 - 1·36, n = 332) |
| Patients with both reactive pupils and GCS < 15 | 0.87 (0.44 – 1.57, n = 184) |
| Instrumental variable [d] | |
| Patients with both reactive pupils and GCS < 15 [e] | 0·91 (0·72 - 1·18, n = 665) |
| Predefined instrument (of provider profiling) [f] | 1·05 (0·85 - 1·32, n = 1318) |
| With the cohort with centres < 10 patients excluded | 0·87 (0·66 - 1·0, n = 1227) |
| On BTF subgroup [g] | 0·82 (0·47 - 1·50, n = 414) |
| With the cohort including the non-salvageable patients (excluded in primary analysis) | 1·01 (0·87 - 1·27, n = 1407) |

Abbreviations: BTF, Brain Trauma Foundation; CI, confidence interval; GCS, Glasgow Coma Scale; OR, odds ratio.

All ORs represent the effect on the Glasgow Outcome Scale Extended estimated with proportional odds regression models

[a] Model was adjusted for the following confounders: age, GCS, pupillary reactivity, midline shift, hematoma size.

[b] This analysis is performed restricting to patients meeting the BTF guidelines for surgical evacuation, i.e. when ASDH thickness is greater than 10 mm and/or with midline shift greater than 5 mm irrespective of the clinical condition, in the covariable adjusted model.

[c] A propensity score was calculated based on the following variables: age, GCS, pupillary reaction, midline shift, hematoma size and concomitant contusion, including random-effects term for centre.

[d] In these instrumental variable analyses, the adjusted common OR indicates the odds of a more favourable outcome for an increase from the 25th percentile to the 75th percentile of the range in exposure to the regional intervention preferences for acute surgery, adjusted for age, GCS, pupillary reactivity, midline shift, hematoma size and random hospital effect.

[e] This analysis is performed without patients with one or both unreactive pupil(s) (poor prognosis) and patients with GCS 15 (excellent prognosis).

[f] Centres provided - before patient enrolment - whether their management protocol follows the Brain Trauma Foundation (BTF) recommendation: surgical evacuation in case of a hematoma > 10mm or midline shift > 5 mm, irrespective of clinical condition. The threshold for acute ASDH surgery was dichotomized accordingly: 'Yes', acute surgery following BTF guideline/ low threshold for surgery; 'No', no management according to BTF guideline/high threshold for surgery).

[g] This analysis is performed restricting to patients meeting the BTF guidelines for surgical evacuation, i.e. when ASDH thickness is greater than 10 mm and/or with midline shift greater than 5 mm irrespective of the clinical condition.

**Supplemental Table 7: Baseline characteristics of propensity matched cohort, comparing acute surgical evacuation with conservative treatment**

| Patient characteristic | Treatment status (n = 332) | | |
|---|---|---|---|
| | Acute surgery | Conservative treatment | SMD |
| n | 166 | 166 | |
| Age (median [IQR]) | 56 [36, 66] | 57 [32, 72] | 0·1 |
| ASAPS (%) | | | 0·2 |
| Healthy | 76 (46) | 73 (44) | |
| Mild systemic disease | 64 (39) | 61 (37) | |
| Severe systemic disease | 17 (10) | 23 (14) | |
| Threat to life | 0 (0) | 1 (1) | |
| Unknown | 9 (5) | 8 (5) | |
| Hypoxia (%) [a] | | | 0·2 |
| No | 140 (84) | 132 (80) | |
| Definite | 10 (6) | 16 (10) | |
| Suspect | 5 (3) | 4 (2) | |
| Unknown | 11 (7) | 14 (8) | |
| Hypotension (%) [b] | | | 0·3 |
| No | 140 (84) | 142 (86) | |
| Definite | 7 (4) | 11 (7) | |
| Suspect | 9 (5) | 1 (1) | |
| Unknown | 10 (6) | 12 (7) | |
| Any major extracranial injury (%) [c] | 62 (37) | 68 (41) | 0·1 |
| GCS (median [IQR]) | 9 [4, 13] | 10 [5, 14] | 0·1 |
| GCS motor (median [IQR]) | 5 [1, 6] | 5 [1, 6] | 0·2 |
| Pupils (%) | | | 0·1 |
| Both reacting | 126 (76) | 131 (79) | |
| One reacting | 17 (10) | 14 (8) | |
| Both unreacting | 23 (14) | 21 (13) | |
| Any focal neurological deficit (%) | | | 0·2 |
| No | 88 (53) | 99 (60) | |
| Yes | 25 (15) | 17 (10) | |
| Unknown | 53 (32) | 50 (30) | |
| Anti-coagulants or platelet aggregation inhibitors (%) | | | 0·2 |

| | | | |
|---|---|---|---|
| No | 116 (70) | 114 (69) | |
| Anti-coagulants | 14 (8) | 17 (10) | |
| Platelet inhibitors | 21 (13) | 21 (13) | |
| Both | 1 (1) | 4 (2) | |
| Unknown | 14 (8) | 10 (6) | |
| CT ASDH = large (%) [d] | 85 (51) | 84 (51) | 0·0 |
| CT midline shift (%) e | 5 [0, 10] | 3 [0, 6] | 0·4 |
| CT contusion (%) | | | 0·2 |
| No | 63 (38) | 67 (40) | |
| Small | 65 (39) | 66 (40) | |
| Large | 31 (19) | 31 (19) | |
| Unknown | 7 (4) | 2 (1) | |
| GOSE 6-months (%) | | | 0·3 |
| 1=Dead | 43 (26) | 55 (33) | |
| 2=Vegetative state/3=Lower severe disability | 38 (23) | 24 (15) | |
| 4=Upper severe disability | 15 (9) | 8 (5) | |
| 5=Lower moderate disability | 24 (15) | 23 (14) | |
| 6=Upper moderate disability | 9 (5) | 12 (7) | |
| 7=Lower good recovery | 21 (13) | 19 (11) | |
| 8=Upper good recovery | 16 (10) | 25 (15) | |

Abbreviations: ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; GCS, Glasgow Coma Scale; GOS(E), Glasgow Outcome Scale Extended; IQR, interquartile range; SMD, standardized mean difference.

[a] Second insult during the pre-hospital or ER phase, defined as PaO2 < 8 kPa (60 mmHg)/SaO2 < 90%. 'Suspected' was scored if the patient did not have documented hypoxia by PaO2 or SaO2, but there was a clinical suspicion, as evidenced by for example cyanosis, apnoea or respiratory distress.

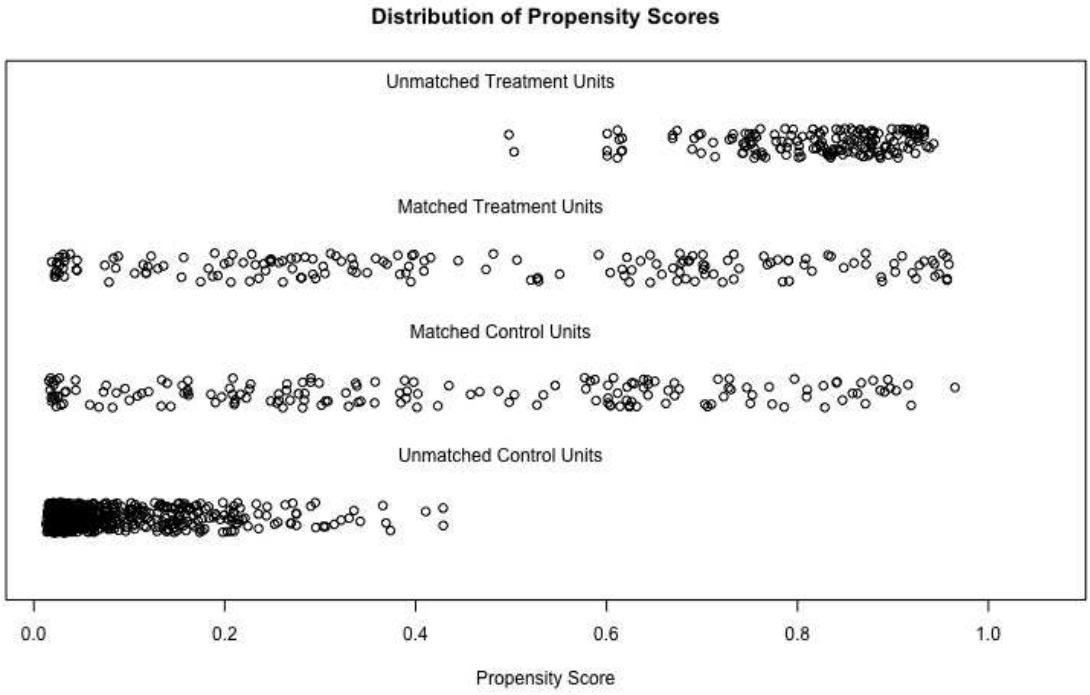
[b] Second insult during the pre-hospital or ER phase, defined as systolic BP < 90 mmHg. 'Suspected' was scored if the patient did not have a documented blood pressure, but was reported to be in shock or have an absent brachial pulse (not related to injury of the extremity).

[c] AIS ≥ 3.

[d] Large is defined as larger than 25 cm3.

[e] Midline shift present is classified as being more than 5 mm.

**Supplemental Figure 6. Propensity scores distribution of nonmatched cohorts and propensity matched cohorts for acute surgery**




The figure depicts the distribution of propensity scores between matched and unmatched patients treatment- (surgical hematoma evacuation) and control-units (conservative treatment)

**Supplemental Table 8. Hospital course and outcomes**

| Outcome | Treatment preference (observed acute surgery rates) | | | |
|---|---|---|---|---|
| | **1 (<13%)** | **2 (13 – 24%)** | **3 (24 – 35%)** | **4 (> 35%)** |
| n | 229 | 348 | 291 | 292 |
| Any neuroworsening = yes (%) [a] | 51 (22) | 113 (32) | 118 (41) | 91 (31) |
| Progression on CT = present (%) [b] | 42 (18) | 94 (27) | 91 (31) | 81 (28) |
| Length of hospital stay (days, [IQR])) | 10 [5, 21] | 12 [5, 28] | 14 [5, 28] | 16 [9, 29] |
| Decision to withdraw active treatment (%) | 15 (7) | 30 (9) | 41 (13) | 26 (9) |
| Discharge destination (%) | | | | |
| Other hospital | 51 (22) | 87 (25) | 62 (21) | 35 (12) |
| Rehabilitation unit | 18 (8) | 76 (22) | 59 (20) | 85 (29) |
| Nursing home | 14 (6) | 9 (3) | 25 (9) | 16 (5) |
| Home | 94 (41) | 130 (37) | 88 (30) | 94 (32) |
| Unknown | 12 (5) | 11 (3) | 13 (4) | 11 (4) |
| Other | 40 (17) | 35 (10) | 44 (15) | 51 (17) |
| GOSE 6-months (%) | | | | |
| 1=Dead | 45 (20) | 51 (15) | 65 (22) | 69 (24) |
| 2=Vegetative state/3=Lower severe disability | 31 (14) | 48 (14) | 43 (15) | 58 (20) |
| 4=Upper severe disability | 22 (10) | 18 (5) | 25 (9) | 12 (4) |
| 5=Lower moderate disability | 21 (9) | 53 (15) | 35 (12) | 32 (11) |
| 6=Upper moderate disability | 18 (8) | 50 (14) | 35 (12) | 25 (9) |
| 7=Lower good recovery | 30 (13) | 58 (17) | 48 (16) | 30 (10) |
| 8=Upper good recovery | 62 (27) | 70 (20) | 40 (14) | 66 (23) |

[a] Neuroworsening is defined as: a spontaneous decrease in the Glasgow Coma Scale motor score ≥ 2 points (compared with the previous examination), a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2 mm, and/or deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention.

[b] Progression on the CT scan during the hospital course is defined as an increase in initial lesion and/or the development of a new lesion.

## 5. Search string strategy and output

Total d.d. 24-11-2021: 2422 references, sourced from PubMed, Embase (OVID-version),Web of Science, Cochrane Library, CENTRAL, CINAHL (EbscoHOST), Emcare (OVID-version), Academic Search, ScienceDirect, Google Scholar.

P: Acute subdural haematoma, hematoma, haemorrhage, hemorrhage
I: Surgery/(neuro-)surgical intervention, evacuation/craniotomy/(decompressive) (hemi-)craniectomy
C: Expectant approach/medical treatment/steroids/mannitol/observation/non-surgical treatment
O: Survival/Glasgow Outcome Scale/Rankin score

Databases:

**PubMed**

((("Hematoma, Subdural"[majr:noexp] OR "Hematoma, Subdural, Acute"[majr] OR "subdural hematoma"[ti] OR "subdural hematomas"[ti] OR "subdural haematoma"[ti] OR "subdural haematomas"[ti] OR "sub dural hematoma"[ti] OR "traumatic subdural hematoma"[ti] OR "post-traumatic subdural hematoma"[ti] OR "subdural bleeding"[ti] OR "subdural haemorrhage"[ti] OR "subdural hemorrhage"[ti]) AND ("surgery"[Subheading] OR "surgery"[tiab] OR "surgical procedures, operative"[mesh] OR "surgical"[tiab] OR neurosurgical[tiab] OR "neurosurgical procedures"[mesh] OR "neurosurgery"[tiab] OR "neurosurgery"[mesh] OR evacuation[tiab] OR "craniotomy"[mesh] OR "craniotomy"[tiab] OR craniotom*[tiab] OR decompressive[tiab] OR "decompression"[mesh] OR "decompression"[tiab] OR hemicraniectomy[tiab] OR hemicraniectom*[tiab] OR haemicraniecto*[tiab] OR craniectomy[tiab] OR craniectom*[tiab]) AND (expectant[tiab] OR "medical treatment"[tiab] OR "medical therapy"[tiab] OR "drug therapy"[Subheading] OR "drug therapy"[tiab] OR "drug therapy"[mesh] OR "steroids"[mesh] OR "mannitol"[mesh] OR "mannitol"[tiab] OR "observation"[mesh] OR "observation"[tiab] OR "non-surgical"[tiab] OR "non-operative"[tiab] OR conservative[tiab] OR conservativ*[tiab] OR "wait and see"[tiab] OR "Unconsciousness"[mesh])) OR (("Hematoma, Subdural"[majr:noexp] OR "Hematoma, Subdural, Acute"[mesh] OR "subdural hematoma"[tiab] OR "subdural hematomas"[tiab] OR "subdural haematoma"[tiab] OR "subdural haematomas"[tiab] OR "sub dural hematoma"[tiab] OR "traumatic subdural hematoma"[tiab] OR "post-traumatic subdural hematoma"[tiab] OR "subdural bleeding"[tiab] OR "subdural haemorrhage"[tiab] OR "subdural hemorrhage"[tiab]) AND ("surgery"[Subheading] OR "surgery"[tiab] OR "surgical procedures, operative"[mesh] OR "surgical"[tiab] OR surgical*[tiab] OR neurosurgical[tiab] OR "neurosurgical procedures"[mesh] OR "neurosurgery"[tiab] OR "neurosurgery"[mesh] OR evacuation[tiab] OR "craniotomy"[mesh] OR "craniotomy"[tiab] OR craniotom*[tiab] OR decompressive[tiab] OR "decompression"[mesh] OR "decompression"[tiab] OR hemicraniectomy[tiab] OR hemicraniectom*[tiab] OR haemicraniecto*[tiab] OR craniectomy[tiab] OR craniectom*[tiab]) AND (expectant[tiab] OR "medical treatment"[tiab] OR "medical therapy"[tiab] OR "drug therapy"[Subheading] OR "drug therapy"[tiab] OR "drug therapy"[mesh] OR "steroids"[mesh] OR "mannitol"[mesh] OR "mannitol"[tiab] OR "observation"[mesh] OR "observation"[tiab] OR "non-surgical"[tiab] OR "non-operative"[tiab] OR conservative[tiab] OR conservativ*[tiab] OR "wait and see"[tiab]) AND ("mortality"[Subheading] OR "mortality"[tiab] OR "survival"[tiab] OR "survival"[mesh] OR "Survival Analysis"[Mesh] OR "glasgow outcome scale"[mesh] OR "glasgow outcome"[tiab] OR (Rankin[tiab] AND score[tiab]))) OR (("Hematoma, Subdural"[majr:noexp] OR "Hematoma, Subdural, Acute"[majr] OR "subdural hematoma"[ti] OR "subdural hematomas"[ti] OR "subdural haematoma"[ti] OR "subdural haematomas"[ti] OR "sub dural hematoma"[ti] OR "traumatic subdural hematoma"[ti] OR "post-traumatic subdural hematoma"[ti] OR "subdural bleeding"[ti] OR "subdural haemorrhage"[ti] OR "subdural hemorrhage"[ti] OR (("Hematoma, Subdural"[mesh:noexp] OR "Hematoma, Subdural, Acute"[mesh]) AND ("Hematoma"[majr:noexp] OR "Brain Injuries"[majr:noexp])) OR ("acute"[ti] AND ("subdural"[ti] OR "sub dural"[ti]) AND ("hematoma"[ti] OR "hematomas"[ti] OR "haematoma"[ti] OR "haematomas"[ti] OR "bleeding"[ti] OR "haemorrhage"[ti] OR "hemorrhage"[ti] OR "haemorrhages"[ti] OR "hemorrhages"[ti])) OR (("subdural hematoma"[ti] OR "subdural hematomas"[ti] OR "subdural haematoma"[ti] OR "subdural haematomas"[ti] OR "sub dural hematoma"[ti] OR "traumatic subdural hematoma"[ti] OR "post-traumatic subdural hematoma"[ti] OR "subdural bleeding"[ti] OR "subdural haemorrhage"[ti] OR "subdural hemorrhage"[ti]) AND ("acute subdural hematoma"[tiab] OR "acute subdural hematomas"[tiab] OR "acute subdural haematoma"[tiab] OR "acute subdural haematomas"[tiab] OR "acute sub dural hematoma"[tiab] OR "acute traumatic subdural

hematoma"[tiab] OR "acute post-traumatic subdural hematoma"[tiab] OR "acute subdural bleeding"[tiab] OR "acute subdural haemorrhage"[tiab] OR "acute subdural hemorrhage"[tiab]))) AND ("prognosis"[mesh] OR "prognosis"[tiab] OR "prognostic"[tiab] OR treatment outcome[tiab] OR "treatment outcome"[mesh] OR outcome[ti] OR outcomes[ti] OR diagnostic feature*[ti] OR "survival"[tiab] OR "survival"[mesh] OR "Survival Analysis"[Mesh] OR "glasgow outcome scale"[mesh] OR "glasgow outcome"[tiab] OR (Rankin[tiab] AND score[tiab])))) **NOT** ("acute spinal subdural"[ti] OR "acute spontaneous spinal subdural"[ti]) **NOT** (("Case Reports"[publication type] OR case report[ti]) NOT "Clinical Trial"[pt])

**EMBASE**

((((("Subdural Hematoma"/ AND acute.ti) OR "acute subdural hematoma".ti OR "acute subdural hematomas".ti OR "acute subdural haematoma".ti OR "acute subdural haematomas".ti OR "acute sub dural hematoma".ti OR "acute traumatic subdural hematoma".ti OR "acute post-traumatic subdural hematoma".ti OR "acute subdural bleeding".ti OR "acute subdural haemorrhage".ti OR "acute subdural hemorrhage".ti OR (("acute".ti OR acute*.ti OR *"Acute Disease"/) AND ("subdural".ti OR subdural*.ti OR "sub dural".ti) AND ("hematoma".ti OR "hematomas".ti OR "haematoma".ti OR "haematomas".ti OR hematoma*.ti OR haematoma*.ti OR "bleeding".ti OR "haemorrhage".ti OR "hemorrhage".ti OR "hemorrhages".ti OR "haemorrhages".ti)) OR (*"Subdural Hematoma"/ AND *"Acute Disease"/)) AND ("su".fs OR "surgery".mp OR exp "surgery"/ OR "surgical".mp OR neurosurgical.mp OR exp "neurosurgery"/ OR "neurosurgery".mp OR "evacuation".mp OR "craniotomy"/ OR "craniotomy".mp OR craniotom*.mp OR decompressive.mp OR exp "decompression surgery"/ OR exp "decompression"/ OR "decompression".mp OR hemicraniectomy.mp OR hemicraniectom*.mp OR craniectomy.mp OR craniectom*.mp) AND (expectant.mp OR "medical treatment".mp OR "medical therapy".mp OR "dt".fs OR "drug therapy".mp OR exp "drug therapy"/ OR exp "steroid"/ OR "mannitol"/ OR "mannitol".mp OR "observation"/ OR "observation".mp OR "non-surgical".mp OR "non-operative".mp OR conservative.mp OR conservativ*.mp OR "wait and see".mp OR exp "conservative treatment"/)) **OR** ((("Subdural Hematoma"/ AND acute.mp) OR "acute subdural hematoma".mp OR "acute subdural hematomas".mp OR "acute subdural haematoma".mp OR "acute subdural haematomas".mp OR "acute sub dural hematoma".mp OR "acute traumatic subdural hematoma".mp OR "acute post-traumatic subdural hematoma".mp OR "acute subdural bleeding".mp OR "acute subdural haemorrhage".mp OR "acute subdural hemorrhage".mp OR (("acute".mp OR acute*.mp OR "Acute Disease"/) AND ("subdural".mp OR subdural*.mp OR "sub dural".mp) AND ("hematoma".mp OR "hematomas".mp OR "haematoma".mp OR "haematomas".mp OR hematoma*.mp OR haematoma*.mp OR "bleeding".mp OR "haemorrhage".mp OR "hemorrhage".mp OR "hemorrhages".mp OR "haemorrhages".mp)) OR ("Subdural Hematoma"/ AND "Acute Disease"/)) AND ("su".fs OR "surgery".mp OR exp "surgery"/ OR "surgical".mp OR neurosurgical.mp OR exp "neurosurgery"/ OR "neurosurgery".mp OR "evacuation".mp OR "craniotomy"/ OR "craniotomy".mp OR craniotom*.mp OR decompressive.mp OR exp "decompression surgery"/ OR exp "decompression"/ OR "decompression".mp OR hemicraniectomy.mp OR hemicraniectom*.mp OR craniectomy.mp OR craniectom*.mp) AND (expectant.mp OR "medical treatment".mp OR "medical therapy".mp OR "dt".fs OR "drug therapy".mp OR exp "drug therapy"/ OR exp "steroid"/ OR "mannitol"/ OR "mannitol".mp OR "observation"/ OR "observation".mp OR "non-surgical".mp OR "non-operative".mp OR conservative.mp OR conservativ*.mp OR "wait and see".mp OR exp "conservative treatment"/) AND (exp "mortality"/ OR "mortality".mp OR "survival".mp OR exp "survival"/ OR exp "injury scale"/ OR "glasgow outcome".mp OR (Rankin.mp AND score.mp))) **OR** (((*"Subdural Hematoma"/ AND Acute.ti) OR "acute subdural hematoma".ti OR "acute subdural hematomas".ti OR "acute subdural haematoma".ti OR "acute subdural haematomas".ti OR "acute sub dural hematoma".ti OR "acute traumatic subdural hematoma".ti OR "acute post-traumatic subdural hematoma".ti OR "acute subdural bleeding".ti OR "acute subdural haemorrhage".ti OR "acute subdural hemorrhage".ti OR ("acute".ti AND ("subdural".ti OR "sub dural".ti) AND ("hematoma".ti OR "hematomas".ti OR "haematoma".ti OR "haematomas".ti OR "bleeding".ti OR "haemorrhage".ti OR "hemorrhage".ti OR "haemorrhages".ti OR "hemorrhages".ti)) OR (("subdural hematoma".ti OR "subdural hematomas".ti OR "subdural haematoma".ti OR "subdural haematomas".ti OR "sub dural hematoma".ti OR "traumatic subdural hematoma".ti OR "post-traumatic subdural hematoma".ti OR "subdural bleeding".ti OR "subdural haemorrhage".ti OR "subdural hemorrhage".ti) AND ("acute subdural hematoma".ti,ab OR "acute subdural hematomas".ti,ab OR "acute subdural haematoma".ti,ab OR "acute subdural haematomas".ti,ab OR "acute sub dural hematoma".ti,ab OR "acute traumatic subdural hematoma".ti,ab OR "acute post-traumatic subdural hematoma".ti,ab OR "acute subdural

bleeding".ti,ab OR "acute subdural haemorrhage".ti,ab OR "acute subdural hemorrhage".ti,ab))) AND (exp "prognosis"/ OR "prognosis".ti,ab OR "prognostic".ti,ab OR treatment outcome.mp OR exp "treatment outcome"/ OR outcome.ti OR outcomes.ti OR exp "mortality"/ OR "mortality".mp OR "survival".mp OR exp "survival"/ OR exp "injury scale"/ OR "glasgow outcome".mp OR (Rankin.mp AND score.mp))) OR ((*"head injury"/ AND *"intracranial pressure"/) AND ("surgery".mp OR exp "surgery"/ OR "surgical".mp OR neurosurgical.mp OR exp "neurosurgery"/ OR "neurosurgery".mp OR "evacuation".mp OR "craniotomy"/ OR "craniotomy".mp OR craniotom*.mp OR decompressive.mp OR exp "decompression surgery"/ OR exp "decompression"/ OR "decompression".mp OR hemicraniectomy.mp OR hemicraniectom*.mp OR craniectomy.mp OR craniectom*.mp) AND exp "clinical study"/ AND (exp "prognosis"/ OR "prognosis".ti,ab OR "prognostic".ti,ab OR treatment outcome.mp OR exp "treatment outcome"/ OR outcome.ti OR outcomes.ti OR exp "mortality"/ OR "mortality".mp OR "survival".mp OR exp "survival"/ OR exp "injury scale"/ OR "glasgow outcome".mp OR (Rankin.mp AND score.mp)))) NOT ("acute spinal subdural".ti OR "acute spontaneous spinal subdural".ti) NOT ("Case Report"/ OR case report.ti))

**Web of Science**
http://isiknowledge.com/wos

((TI=(("Subdural Hematoma" AND acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR (("acute" OR acute* OR "Acute Disease") AND ("subdural" OR subdural* OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR hematoma* OR haematoma* OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "hemorrhages" OR "haemorrhages")) OR ("Subdural Hematoma" AND "Acute Disease")) AND TS=("surgery" OR "surgery" OR "surgical" OR neurosurgical OR "neurosurgery" OR "neurosurgery" OR "evacuation" OR "craniotomy" OR "craniotomy" OR craniotom* OR decompressive OR "decompression surgery" OR "decompression" OR "decompression" OR hemicraniectomy OR hemicraniectom* OR craniectomy OR craniectom*) AND TS=(expectant OR "medical treatment" OR "medical therapy" OR "drug therapy" OR "drug therapy" OR "steroid" OR "mannitol" OR "mannitol" OR "observation" OR "observation" OR "non-surgical" OR "non-operative" OR conservative OR conservativ* OR "wait and see" OR "conservative treatment")) **OR** (TS=(("Subdural Hematoma" AND acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR (("acute" OR acute* OR "Acute Disease") AND ("subdural" OR subdural* OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR hematoma* OR haematoma* OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "hemorrhages" OR "haemorrhages")) OR ("Subdural Hematoma" AND "Acute Disease")) AND TS=("surgery" OR "surgery" OR "surgical" OR neurosurgical OR "neurosurgery" OR "neurosurgery" OR "evacuation" OR "craniotomy" OR "craniotomy" OR craniotom* OR decompressive OR "decompression surgery" OR "decompression" OR "decompression" OR hemicraniectomy OR hemicraniectom* OR craniectomy OR craniectom*) AND TS=(expectant OR "medical treatment" OR "medical therapy" OR "drug therapy" OR "drug therapy" OR "steroid" OR "mannitol" OR "mannitol" OR "observation" OR "observation" OR "non-surgical" OR "non-operative" OR conservative OR conservativ* OR "wait and see" OR "conservative treatment") AND TS=("mortality" OR "mortality" OR "survival" OR "survival" OR "injury scale" OR "glasgow outcome" OR (Rankin AND score))) **OR** (TI=(("Subdural Hematoma" AND Acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR ("acute" AND ("subdural" OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "haemorrhages" OR "hemorrhages")) OR (("subdural hematoma" OR "subdural hematomas" OR "subdural haematoma" OR "subdural haematomas" OR "sub dural hematoma" OR "traumatic subdural hematoma" OR "post-traumatic subdural hematoma" OR "subdural bleeding" OR "subdural haemorrhage" OR "subdural hemorrhage") AND ("acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma"

OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage"))) AND TS=("prognosis" OR "prognosis" OR "prognostic" OR treatment outcome OR "treatment outcome" OR outcome OR outcomes OR "mortality" OR "mortality" OR "survival" OR "survival" OR "injury scale" OR "glasgow outcome" OR (Rankin AND score)))) NOT (TI=("acute spinal subdural" OR "acute spontaneous spinal subdural") OR TI=("Case Report"))

**Cochrane Library**

((((("Subdural Hematoma" AND acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR (("acute" OR acute* OR "Acute Disease") AND ("subdural" OR subdural* OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR hematoma* OR haematoma* OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "hemorrhages" OR "haemorrhages")) OR ("Subdural Hematoma" AND "Acute Disease")) AND ("surgery" OR "surgery" OR "surgical" OR neurosurgical OR "neurosurgery" OR "neurosurgery" OR "evacuation" OR "craniotomy" OR "craniotomy" OR craniotom* OR decompressive OR "decompression surgery" OR "decompression" OR "decompression" OR hemicraniectomy OR hemicraniectom* OR craniectomy OR craniectom*) AND (expectant OR "medical treatment" OR "medical therapy" OR "drug therapy" OR "drug therapy" OR "steroid" OR "mannitol" OR "mannitol" OR "observation" OR "observation" OR "non surgical" OR "non operative" OR conservative OR conservativ* OR "wait and see" OR "conservative treatment")) **OR** ((("Subdural Hematoma" AND acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR (("acute" OR acute* OR "Acute Disease") AND ("subdural" OR subdural* OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR hematoma* OR haematoma* OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "hemorrhages" OR "haemorrhages")) OR ("Subdural Hematoma" AND "Acute Disease")) AND ("surgery" OR "surgery" OR "surgical" OR neurosurgical OR "neurosurgery" OR "neurosurgery" OR "evacuation" OR "craniotomy" OR "craniotomy" OR craniotom* OR decompressive OR "decompression surgery" OR "decompression" OR "decompression" OR hemicraniectomy OR hemicraniectom* OR craniectomy OR craniectom*) AND (expectant OR "medical treatment" OR "medical therapy" OR "drug therapy" OR "drug therapy" OR "steroid" OR "mannitol" OR "mannitol" OR "observation" OR "observation" OR "non surgical" OR "non operative" OR conservative OR conservativ* OR "wait and see" OR "conservative treatment") AND ("mortality" OR "mortality" OR "survival" OR "survival" OR "injury scale" OR "glasgow outcome" OR (Rankin AND score))) **OR** ((("Subdural Hematoma" AND Acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR ("acute" AND ("subdural" OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "haemorrhages" OR "hemorrhages")) OR (("subdural hematoma" OR "subdural hematomas" OR "subdural haematoma" OR "subdural haematomas" OR "sub dural hematoma" OR "traumatic subdural hematoma" OR "post traumatic subdural hematoma" OR "subdural bleeding" OR "subdural haemorrhage" OR "subdural hemorrhage") AND ("acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage"))) AND ("prognosis" OR "prognosis" OR "prognostic" OR treatment outcome OR "treatment outcome" OR outcome OR outcomes OR "mortality" OR "mortality" OR "survival" OR "survival" OR "injury scale" OR "glasgow outcome" OR (Rankin AND score))):ti,ab,kw

**CENTRAL**

((((("Subdural Hematoma" AND acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR (("acute" OR acute* OR "Acute Disease") AND ("subdural" OR subdural* OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR hematoma* OR haematoma* OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "hemorrhages" OR "haemorrhages")) OR ("Subdural Hematoma" AND "Acute Disease")) AND ("surgery" OR "surgery" OR "surgical" OR neurosurgical OR "neurosurgery" OR "neurosurgery" OR "evacuation" OR "craniotomy" OR "craniotomy" OR craniotom* OR decompressive OR "decompression surgery" OR "decompression" OR "decompression" OR hemicraniectomy OR hemicraniectom* OR craniectomy OR craniectom*) AND (expectant OR "medical treatment" OR "medical therapy" OR "drug therapy" OR "drug therapy" OR "steroid" OR "mannitol" OR "mannitol" OR "observation" OR "observation" OR "non-surgical" OR "non-operative" OR conservative OR conservativ* OR "wait and see" OR "conservative treatment")) **OR** ((("Subdural Hematoma" AND acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR (("acute" OR acute* OR "Acute Disease") AND ("subdural" OR subdural* OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR hematoma* OR haematoma* OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "hemorrhages" OR "haemorrhages")) OR ("Subdural Hematoma" AND "Acute Disease")) AND ("surgery" OR "surgery" OR "surgical" OR neurosurgical OR "neurosurgery" OR "neurosurgery" OR "evacuation" OR "craniotomy" OR "craniotomy" OR craniotom* OR decompressive OR "decompression surgery" OR "decompression" OR "decompression" OR hemicraniectomy OR hemicraniectom* OR craniectomy OR craniectom*) AND (expectant OR "medical treatment" OR "medical therapy" OR "drug therapy" OR "drug therapy" OR "steroid" OR "mannitol" OR "mannitol" OR "observation" OR "observation" OR "non-surgical" OR "non-operative" OR conservative OR conservativ* OR "wait and see" OR "conservative treatment") AND ("mortality" OR "mortality" OR "survival" OR "survival" OR "injury scale" OR "glasgow outcome" OR (Rankin AND score))) **OR** ((("Subdural Hematoma" AND Acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR ("acute" AND ("subdural" OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "haemorrhages" OR "hemorrhages")) OR (("subdural hematoma" OR "subdural hematomas" OR "subdural haematoma" OR "subdural haematomas" OR "sub dural hematoma" OR "traumatic subdural hematoma" OR "post-traumatic subdural hematoma" OR "subdural bleeding" OR "subdural haemorrhage" OR "subdural hemorrhage") AND ("acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage")))) AND ("prognosis" OR "prognosis" OR "prognostic" OR treatment outcome OR "treatment outcome" OR outcome OR outcomes OR "mortality" OR "mortality" OR "survival" OR "survival" OR "injury scale" OR "glasgow outcome" OR (Rankin AND score)))) NOT ("Case Report")

**CINAHL**

Search in fields TI (title), MW (subject headings), SU (subject headings and descriptors)

((((("Subdural Hematoma" AND acute) OR "acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage" OR (("acute" OR acute* OR "Acute Disease") AND ("subdural" OR subdural* OR "sub dural") AND ("hematoma" OR "hematomas" OR "haematoma" OR "haematomas" OR hematoma* OR haematoma* OR "bleeding" OR "haemorrhage" OR "hemorrhage" OR "hemorrhages" OR "haemorrhages")) OR ("Subdural Hematoma" AND "Acute Disease")) AND ("surgery" OR "surgery" OR "surgical" OR neurosurgical OR "neurosurgery" OR "neurosurgery" OR "evacuation" OR "craniotomy" OR

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Search in fields TI (title), KW (key words), SU (subject headings)

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**ScienceDirect**

TITLE-ABSTR-KEY(("acute subdural hematoma" OR "acute subdural hematomas" OR "acute subdural haematoma" OR "acute subdural haematomas" OR "acute sub dural hematoma" OR "acute traumatic subdural hematoma" OR "acute post-traumatic subdural hematoma" OR "acute subdural bleeding" OR "acute subdural haemorrhage" OR "acute subdural hemorrhage") AND ("surgery" OR "surgery" OR "surgical" OR neurosurgical OR "neurosurgery" OR "neurosurgery" OR "evacuation" OR "craniotomy" OR "craniotomy" OR craniotom* OR decompressive OR "decompression surgery" OR "decompression" OR "decompression" OR hemicraniectomy OR hemicraniectom* OR craniectomy OR craniectom*) AND (expectant OR "medical treatment" OR "medical therapy" OR "drug therapy" OR "drug therapy" OR "steroid" OR "mannitol" OR "mannitol" OR "observation" OR "observation" OR "non-surgical" OR "non-operative" OR conservative OR conservativ* OR "wait and see" OR "conservative treatment"))

**Google Scholar**

allintitle: "treatment" "acute subdural hematoma"

allintitle: "surgery" "acute subdural hematoma"

allintitle: "therapy" "acute subdural hematoma"

**IndexCat**

"SUB-DURAL" OR SUBDURAL OR "intra dural" OR "INTRA-DURAL" OR intracranial AND hematoma OR intracranial AND haematoma OR intracranial AND hematoma OR intracranial AND haematoma OR intracranial AND hemorrhage OR intracranial AND haemorrhage OR intracranial AND bleeding OR intracranial AND hæmorrhage OR "intra-cranial" AND hematoma OR "intra-cranial" AND haematoma OR "intra-cranial" AND hematoma OR "intra-cranial" AND haematoma OR "intra-cranial"

AND hemorrhage OR "intra-cranial" AND haemorrhage OR "intra-cranial" AND bleeding OR "intra-cranial" AND hæmorrhage

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