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Surgical Treatment of Intracerebral Hemorrhage: A meta analysis of recent RCT's

Χειρουργική αντιμετώπιση Ενδοεγκεφαλικής Αιμορραγίας: μετα-ανάλυση πρόσφατων κλινικών μελετών

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ABSTRACT

INTRODUCTION: Intracerebral hemorrhage (ICH) is a disease that accounts for 10-15% of all strokes with 30% 1-month mortality, while most survivors are left with severe disabilities. Many factors have been associated with ICH. The effect of surgery on the outcome still remains controversial.

OBJECTIVES: Our objective was to combine data of recent Randomised Clinical Trials (RCT's) in order to generate an overall estimate of the effect of surgery on the outcome.

METHODS: We searched for recent RCT's regarding spontaneous supratentorial ICH with no underlying entities treated surgically. We used the modified Rankin Score (mRS) to dichotomize into favorable (mRS 0-3) and unfavorable (mRS 4-6) outcome.

RESULTS: The pooled result of our analysis showed a statistically significant positive effect of surgery on favorable outcome. On subgroup analysis we did not detect a significant impact of age and total ICH volume on outcome.

CONCLUSION: ICH remains a deadly disease and more data is needed to form a gold standard method of treatment.

Keywords: intracerebral hemorrhage, surgical treatment, outcome, meta-analysis

ΠΕΡΙΛΗΨΗ:

ΕΙΣΑΓΩΓΗ: Η ενδοεγκεφαλική αιμορραγία είναι μια νόσος που αφορά το 15-20% όλων των εγκεφαλικών επεισοδίων, με θνητότητα 30% τον πρώτο μήνα, και σοβαρού βαθμού αναπηρία στους επιζήσαντες. Ο ρόλος της χειρουργικής αντιμετώπισης στο κλινικό αποτέλεσμα παραμένει αμφιλεγόμενος.

ΣΤΟΧΟΙ: Στόχος μας είναι να συνδυάσουμε τα δεδομένα πρόσφατων κλινικών μελετών με σκοπό να παράξουμε μια συνολική εκτίμηση της επίδρασης της χειρουργικής αντιμετώπισης στο κλινικό αποτέλεσμα.

ΜΕΘΟΔΟΙ: Αναζητήσαμε πρόσφατες κλινικές μελέτες που αφορούν αυτόματες υπερσκηνιδιακές εγκεφαλικές αιμορραγίες χωρίς υποκείμενες οντότητες οι οποίες αντιμετωπίστηκαν χειρουργικά. Χρησιμοποιήσαμε την τροποποιημένη Rankin κλίμακα για να διχοτομήσουμε τις κατηγορίες των ασθενών σε ωφέλιμο (mRS 0-3) και μη ωφέλιμο κλινικό αποτέλεσμα (mRS 4-6).

ΑΠΟΤΕΛΕΣΜΑΤΑ: Το συγκεντρωτικό αποτέλεσμα των κλινικών μελετών έδειξε μια στατιστικά σημαντική θετική επίδραση στο κλινικό αποτέλεσμα. Στην

υποκατηγορική ανάλυση δεν ανιχνεύτηκε σημαντική επίδραση της ηλικίας και του συνολικού όγκου αιματώματος στο κλινικό αποτέλεσμα.

ΣΥΜΠΕΡΑΣΜΑ: Η ενδοεγκεφαλική αιμορραγία παραμένει μια νόσος με υψηλή θνητότητα και βαριά πρόγνωση και χρειάζονται περισσότερα δεδομένα και μελέτες για να καταλήξουμε στην «χρυσή» μέθοδο αντιμετώπισης.

Λέξεις-κλειδιά: ενδοεγκεφαλική αιμορραγία, χειρουργική αντιμετώπιση, κλινικό αποτέλεσμα, μετα-ανάλυση

INTRODUCTION

Epidemiology

Intracerebral Hemorrhage (ICH) is a medical condition concerning a large portion of the global population with high mortality rates and still remains to this day poorly studied [6].

ICH accounts for 10-15% of all strokes [7]. It is estimated that each year over 2 million new cases of ICH are recorded worldwide [1]. The 30-day mortality still remains at 30%, while many of the survivors are left with important disabilities [1], [2].

The exact term of ICH is spontaneous Intracerebral Hemorrhage, meaning it is not associated with a specific cause, or one may be assumed. While the mortality of ICH remains the same more or less over the years worldwide, in Netherlands, UK and France, where special stroke units have been established, survival tends to be favorable [2].

In the meantime, in other high-income countries the incidence of ischemic stroke seems to have dropped over the years, while the incidence of ICH remains at the same levels [1].

Cost

The total cost of strokes in the EU is estimated to be 27 billion € and the additional cost of ICH is estimated to be 30.000 - 45.000 € per survivor per year [1]. In addition, since ICH concerns mostly working adults the loss of productive life years has a social and economic impact [2].

Factors

Many factors have been associated with the incidence of ICH, among which is male gender, increasing age, arterial hypertension, excessive use of alcohol, smoking, diabetes mellitus, low-quality dietary habits and obesity [1].

Moreover the use of anticoagulant and antiplatelet drugs has been associated with ICH, which seems to be more common in patients under anticoagulation/antiplatelet treatment [5]. At the same time mortality risk is further affected in this group since the 6-month mortality reaches up to 67% while it ranges from 30% to 55% in the general population [6].

Pathophysiology

A general insight in the pathophysiologic mechanisms of ICH, derived from macroscopic autopsy studies, show neural damage from hydrostatic pressure of ICH. In most cases ICH is the result of small penetrating artery rupture with subsequent leaking of arterial blood into the parenchyma. Damage of neural tissue is due to the mass effect of the hematoma to the surrounding parenchyma as well as to remote regions due to midline shift or herniation, if any [1].

The parenchyma around the hematoma may be ischemic.

The aftermath of an ICH starts when the toxic (to the brain) effects of blood products start to take place [1].

This cascade constitutes secondary brain damage. The neural tissue is normally protected by the Blood-Brain-Barrier which ruptures when ICH occurs causing oedema, hence more damage. The cascade of thrombus lysis accelerates neurotoxic and apoptotic mechanisms and more inflammation occurs due to leukocyte activation [1].

Bio-predictors

High glucose levels on admission independently of diabetes mellitus have been associated with poorer outcomes and higher mortality rates. Also, the appearance of fever, which is frequent in ICH, is also associated with worse outcome [4].

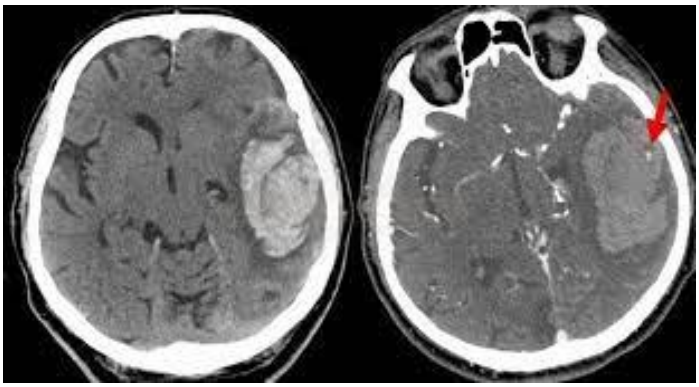
Finally, the total clot volume on admission as measured on imaging is a predictor of the 3-month functional outcome [7]. In general, a total clot volume of 150 ml or higher, almost inevitably leads to death [1].

Diagnosis

Diagnosis of ICH mostly relies on Computed Tomography (CT) imaging, due to its easier access and lower cost than MRI. Clinical examination is important but cannot differentiate from an ischemic stroke [2].

Also CT can help detect other probable underlying causes of ICH such as, an AVM, aneurysm, dural fistulas (which altogether account for 15% of all ICH), thrombosis or tumor [2].

Several CT markers have been described that can help predict potential rebleeding, hence worse outcome, such as the CT-Angiography (CTA) spot sign [2].



Picture 1: Frontotemporal ICH-CT (left)-CTA spot sign (right) [14].

Treatment

The lack of a gold standard treatment for ICH impacts the urgent need for further research. On the one side the standard medical treatment is not clearly beneficial and on the other side the role of surgery to this day remains controversial [2].

The standard medical management aside from the initial ABC'S stabilization consists of arterial blood pressure management, although data remains unclear concerning the outcome. Medical management also includes the management of complications of ICH, e.g. seizures, oedema, Venous Thrombosis [2].

In addition to medical management, neurosurgical intervention is currently recommended when patients show neurologic deterioration. However, it is not clarified if surgery or even if early surgery can positively affect outcome [4].

When Intraventricular Hemorrhage is present along with ICH, an External Ventricular Drainage is recommended to treat underlying Hydrocephalus in deteriorating patients [7].

Plus, there is data showing decompressive craniectomy may decrease mortality in deteriorating patients with large hematomas. Finally the role of Minimally Invasive Surgery, using stereotactic or endoscopic techniques, is uncertain [7].

METHODS

Data search-inclusion criteria

We took a thorough insight in the existing published data in our effort to conduct a meta-analysis of recent Randomised Clinical Trials of surgical treatment of ICH.

We decided to search for RCTs studying the outcome of surgical treatment of supratentorial Intracerebral hemorrhage in adults (age > 18yo) with no underlying other causes of ICH, as explained above.

We used the Cochrane database, clinicaltrials.gov, and the National Library of Medicine and limited our search using the Boolean operators to RCTs listing all the above criteria with published results from 2012 to date, not using any language restrictions.

The 5 RCTs that were retrieved and included in the analysis are listed in Table 1, along with the surgical method that was used in each trial.

STUDY/*YEAR*	METHOD	N	S	C	mAgeS	mAgeC	mVS	mVC
ICES *2016* [8]	Intraoperative stereotactic computed tomography-guided endoscopic surgery	56	14	42	59,00	62,00	36,40	41,40
MISTIE *2016* [9]	Minimally invasive surgery plus alteplase	96	54	42	60,70	61,10	48,20	43,10
MISTIEIII *2019* [10]	Minimally invasive catheter evacuation plus alteplase	499	250	249	62,00	62,00	42,70	41,50
STICHII *2013* [11]	Early surgery-craniotomy –hematoma evacuation	597	305	292	65,00	65,00	41,40	41,00
BHASKAR *2017* [12]	Craniotomy-hematoma evacuation	61	34	27	55,90	53,33	66,70	61,96

Table 1: RCT's included in this study : Method: surgical method that was used, N: total number of participants , S: number of cases, C: number of controls , mAgeS : mean Age in surgical/case group , mAgeC : mean age in Control group , mVS : mean Volume of ICH in surgical/case group , mVC : mean Volume of ICH in Control group, measured in ml.

Data synthesis

We collected data from all 5 studies, including the total number of participants, the number of cases and controls, the mean age of each group, the mean Volume of ICH on admission as measured on CT Imaging, as shown in Table 1.

Primary efficacy outcome was good functional outcome. To address specifically good functional outcomes we used the modified Rankin Score. The mRS is a scoring system used in neurological/neurosurgical diseases and measures the degree of disability or dependence in daily activities. The score ranges from 0-6 as shown in (Picture 2). We dichotomized the score into 2 categories: 0-3 which was labeled as good functional outcome and 4-6 was labeled unfavorable functional outcome. We used data on outcome of the RCTs included in the 3-month follow-up since this timeframe was used in all 5 studies. Data on good functional outcome was collected for each group (case/control) of each study.

Score	Description
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, or unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

Picture 2: The modified Rankin Scale [13].

STUDY	OR	LL	UL	Var	Weight	θ
ICES	2,75	0,76	9,99	0,43	2,31	1,01
MISTIE	1,83	0,72	4,64	0,23	4,45	0,61
MISTIEIII	1,17	0,82	1,67	0,03	30,35	0,16
STICHII	1,21	0,88	1,67	0,03	37,13	0,19
BHASKAR2017	1,21	0,19	7,81	0,91	1,10	0,19

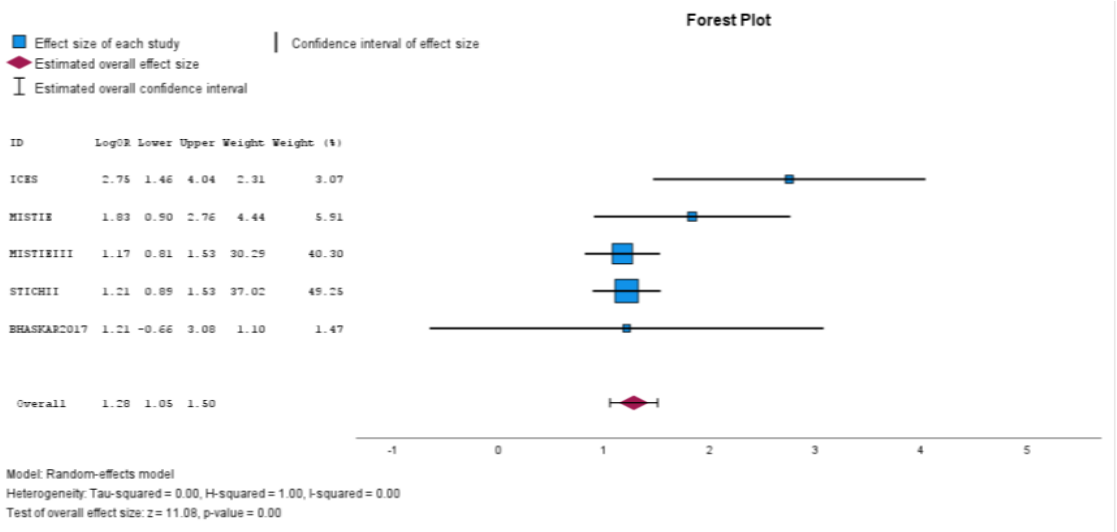
Table2: OR: odds ratio, LL: Lower limit of Confidence Interval, UL: Upper limit of Confidence Interval, Weight: the weight of each study, θ: ln(OR).

We used the odds ratio (OR) as the effect size to measure and compare the functional outcome. Since the trials included did not use the same effect size, and in some it was not specified, we calculated the odds ratio with the corresponding CIs using Microsoft excel (Table 2).

Statistical Analysis

We used IBM SPSS Statistics 29.0 for analysis.

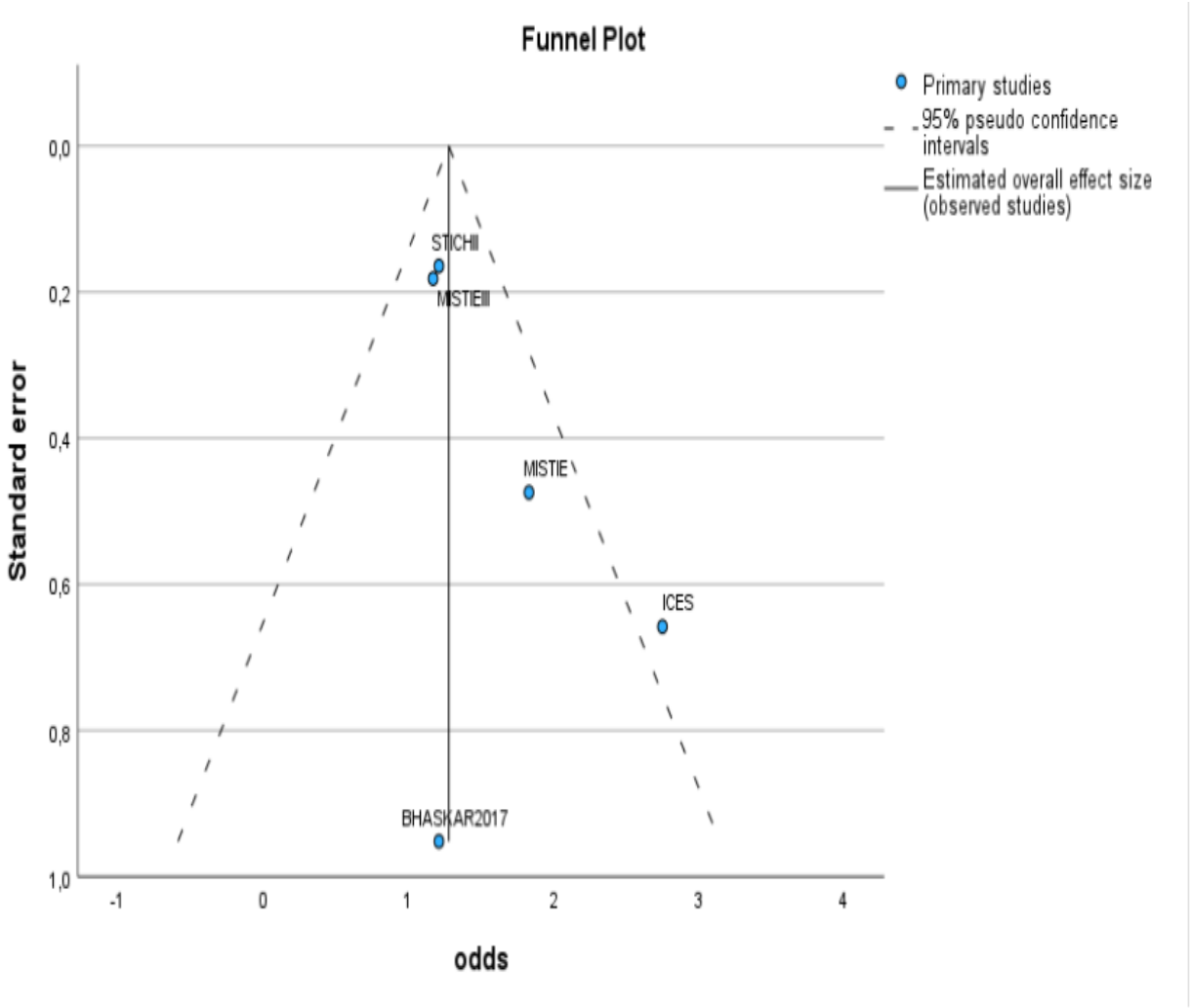
First we drew a forest plot to test the magnitude of each trial that we included in the analysis (picture 3).



Picture 3: The forest plot.

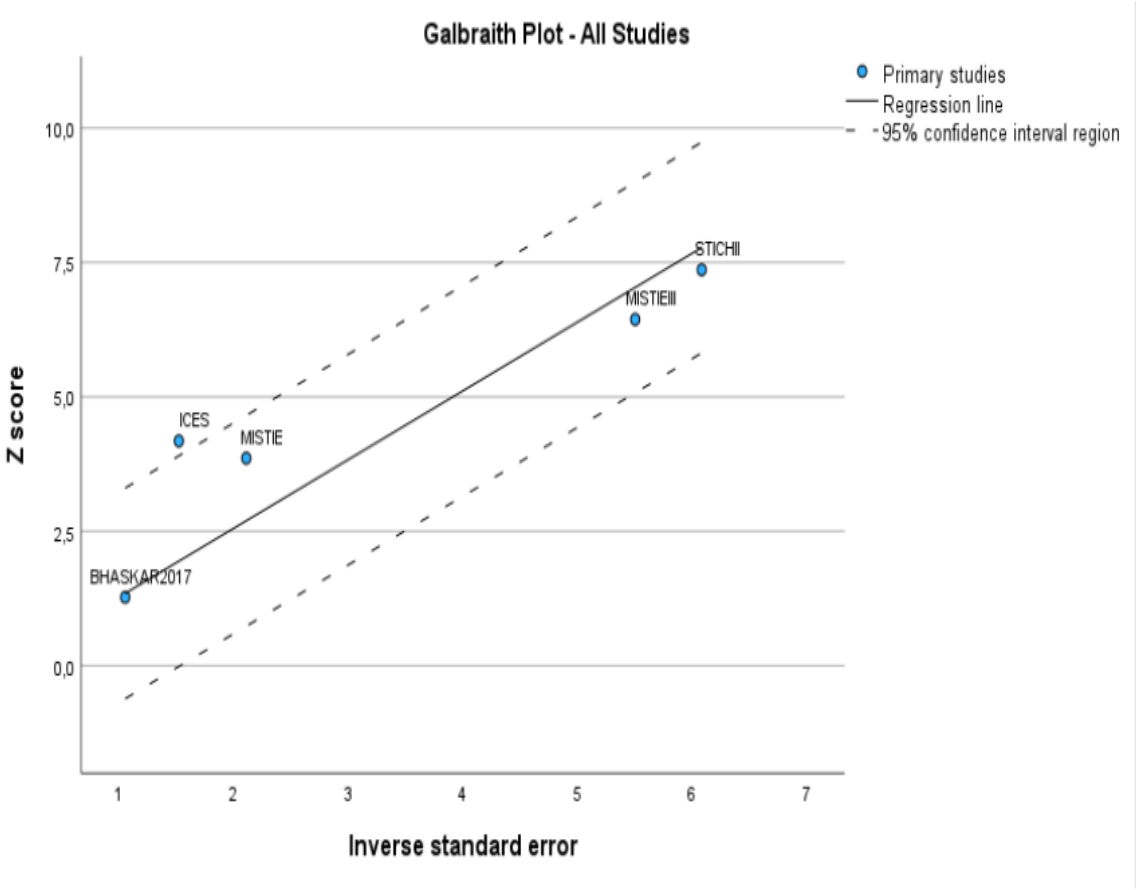
We performed a homogeneity test to examine if there is vast heterogeneity between studies and we proceeded to the appropriate model of analysis and measured a pooled OR.

Then we tested for publication bias and drew a funnel plot (picture 4).



Picture 4: The funnel plot.

We also drew a Galbraith's plot in search of questionable studies (picture 5).



Picture 5: The Galbraith's plot.

Then we performed a sensitivity analysis in which we ran the model of analysis excluding the biggest trial (e.g. larger number of participants).

Finally we performed a subgroup analysis to test relationship patterns among outcome and other characteristics (mean age and mean Volume of ICH).

RESULTS

The forest plot gave us a visual representation about the size of each study.

The Q-test for homogeneity is not significant at 10% point of the x^2 distribution p=0.142, therefore we cannot reject the null hypothesis that homogeneity exists

among studies and data (picture 6) .Thus we used the fixed effect model in our analysis including the variance of each study. The model gave us a pooled OR of 1.278 p<0.001, CI [1.052, 1.504] which shows statistically significant increase in OR (picture 7). A pooled OR of 1.278 means that there was an increase of 27.8% in favorable outcome in the control group (surgically treated).

Test of Residual Homogeneity

Chi-square (Q statistic)	df	Sig.
6,890	4	,142

Tests the null hypothesis that the residuals are homogeneous.

Picture 6: Homogeneity test.

Effect Size Estimates

	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval	
					Lower	Upper
Overall	1,278	,1153	11,079	<,001	1,052	1,504

Picture 7: The pooled Odds Ratio with the corresponding limits of the Confidence Interval.

While testing for publication bias we drew the funnel plot and tested for asymmetry. The first visual assessment shows asymmetry, therefore publication bias (picture 4). The Egger's test showed a significance of 0.021 < 0.05 which dictates publication bias (picture 8).

Egger's Regression-Based Test[a]

Parameter	Coefficient	Std. Error	t	Sig. (2-tailed)	95% Confidence Interval	
					Lower	Upper
(Intercept)	,938	,2121	4,424	,021	,263	1,613
SE[b]	1,570	,8221	1,910	,152	-1,046	4,186

a. Random-effects meta-regression

b. Standard error of effect size

Picture 8: The Egger's test for publication bias.

Galbraith's plot shows one trial (ICES) exceeds the graphical limit of the plot, therefore could be considered questionable (picture 5).

In sensitivity analysis we excluded the larger trial (STICH II) and the results showed heterogeneity (p = 0.088) , as shown in picture 9, with 10% level of significance.

Test of Residual Homogeneity

Chi-square (Q statistic)	df	Sig.
6,551	3	,088

Tests the null hypothesis that the residuals are homogeneous.

Picture 9: Homogeneity test for sensitivity analysis.

The random effects model was used and the new pooled OR resulted in 1.646 p < 0.001, CI [0.937, 2.353] (picture 10). Thus the results are not statistically significant and we can no longer safely assume that the favorable outcome increases in the control group.

Effect Size Estimates

	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval	
					Lower	Upper
Overall	1,645	,3611	4,554	<,001	,937	2,353

Picture 10: Pooled OR with the corresponding limits of the Confidence Interval after excluding the largest trial

We could not perform meta-regression tests for our analysis since we included less than 10 studies in this analysis.

Finally, we performed a subgroup analysis. For this purpose, we calculated the ln(OR) which was labeled as ''θ'' for each study (as shown in Table 2) and performed a subgroup analysis comparing the impact of Age and Volume on θ, thus the ln(OR). This analysis did not detect a statistically significant relationship between age or volume and a favorable outcome, since p was 0,910 and 0,537 respectively (pictures 11, 12).

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	,004	3,503		,001	,999
	mAGE	,007	,058	,070	,122	,910

a. Dependent Variable: LN(OR)

Picture 11: Subgroup analysis for the effect of age.

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.
1	(Constant)	1,071	,936		1,144	,336
	mV	-,014	,020	-,373	-,695	,537

a. Dependent Variable: LN(OR)

Picture 12: Subgroup analysis of the effect of volume of ICH.

CONCLUSION

In conclusion, Intracerebral hemorrhage still remains a disease with high mortality rates and no clear guidance concerning treatment. Many studies have been conducted aiming to answer the question: to operate or not. The use of meta analysis provides us with an overall / pooled result.

Alongside the above analysis we included RCT's from the past decade that did not produce statistically significant results on whether surgery of ICH affects favorable outcome in a positive manner. When pooling all the data derived from different years, different countries with different sources we came to a significant positive effect.

More data derived from RCT's is needed to conclude to safer results, but we also need to continuously combine all the data.

Finally one may think that posing a single question, to operate or not, may not give us an answer or there may be no answer to that question. Maybe we should turn our focus or insight on who, or when or how or which ICH to operate on. Even those questions could only be answered with further research. The vast heterogeneity in results from previous RCT's could mean that we need to study several different variables in a wider range and then narrow down the range in order to define the group of patients that could benefit from the surgical treatment of ICH. This "needle in a haystack" effort may not even be cost effective or even achievable with all sources available, but would definitely be life changing.

REFERENCES

1. European Research Priorities for Intracerebral Haemorrhage, Thorsten Steiner

2. *Intracerebral haemorrhage: current approaches to acute management Charlotte Cordonnier, Andrew Demchuk, Wendy Ziai, Craig S Anderson*

3. Perihematomal Edema After Intracerebral Hemorrhage: An Update on Pathogenesis, Risk Factors, and Therapeutic Advances, Yihao Chenet et al.

4 Guidelines for the Management of Spontaneous Intracerebral Hemorrhage A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

5. Intracerebral haemorrhage associated with antithrombotic treatment: translational insights from experimental studies, Arne Lauer, Waltraud Pfeilschifter, Chris B Schaff er, Eng H Lo, Christian Foerch

6. Intracerebral haemorrhage: an often neglected medical emergency, M. Marietta, P. Pedrazzi, M. Girardis, G. Torelli

7. Spontaneous Intracerebral Hemorrhage Kevin N. Sheth, M.D.

8. ICES (Intraoperative Stereotactic Computed Tomography Guided Endoscopic Surgery) for Brain Hemorrhage A Multicenter Randomized Controlled Trial, Paul Vespa et al.

9. Safety and effi cacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial, Daniel Hanley et al.

10. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial, Daniel Hanley et al.

11. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial A David Mendelow, Barbara A Gregson, Elise N Rowan, Gordon D Murray, Anil Gholkar, Patrick M Mitchell, for the STICH II Investigator

12. A randomized controlled study of operative versus nonoperative treatment for large spontaneous supratentorial intracerebral hemorrhage Bhaskar et al.

13.www.researchgate.net/figure/The-modified-Rankin-Scale-mRS_tbl1_355682199

14. www.stroke-manual.com/spot-sign