Prognostic value of major extracranial injury in traumatic brain injury: an individual patient data meta-analysis in 39,274 patients

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ABSTRACT

Introduction

Major extracranial injury (MEI) is common in Traumatic Brain Injury (TBI) patients, but the effect on outcome is controversial.

Objective

To assess the prognostic value of MEI on mortality after TBI in an individual patient data meta-analysis of three observational TBI studies (IMPACT), a randomized controlled trial (CRASH), and a trauma registry (TARN).

Methods

MEI (extracranial injury with an AIS ≥ 3 or "requiring hospital admission") was related to mortality with logistic regression analysis, adjusted for age, GCS motor score and pupil reactivity, stratified by TBI severity. We pooled odds ratios (ORs) with random effects meta-analysis.

Results

We included 39,274 patients. Mortality was 25% and 32% had MEI. MEI was a strong predictor for mortality in TARN, with adjusted ORs and 95% confidence intervals (95%CI) of 2.81 (2.44-3.23) in mild, 2.18 (1.80-2.65) in moderate and 2.14 (1.95-2.35) in severe TBI patients. The prognostic effect was smaller in IMPACT and CRASH with pooled adjusted ORs and 95%CIs of 2.14 (0.93-4.91) in mild, 1.46 (1.14-1.85) in moderate and 1.18 (1.03-1.55) in severe TBI. When patients who died within 6 hours after injury were excluded from TARN, the effect of MEI was comparable with IMPACT and CRASH.

Conclusion

MEI is an important prognostic factor for mortality in TBI patients. However, the effect varies by population, which explains the controversy in the literature. The strength of the effect is smaller in patients with more severe brain injury, and depends on time of inclusion in a study.

INTRODUCTION

Major extracranial injury (MEI) is frequently present in patients with traumatic brain injury (TBI). The prevalence differs from 23%(1) to 41%(2) dependent on study population and definition of MEI. Relatively few studies have however focused on the effect of MEI on mortality after TBI. Most studies concerning TBI and MEI have investigated patients with extracranial trauma, with or without TBI. These studies show that the coexistence of traumatic brain injury with extracranial injury is associated with both increased mortality and morbidity.(3-6)

In contrast, there is no consensus on the degree to which the presence of MEI worsens outcome in TBI patients. Some studies demonstrate that outcome mainly depends on the severity of the primary cerebral damage and is not worsened by the presence of extracranial injuries.(2, 7) Other studies suggest that the presence of MEI carries a poorer outcome in TBI patients.(1, 8-10) Differences between studies might be due to patient population, setting and study design. Determining the importance of MEI in outcome after TBI has relevance for understanding and potentially improving the patient pathway, and for improving prognostic models that might be used to benchmark care(6), or to inform relatives and medical decisions.

We report a collaborative analysis on a large number of TBI patients with and without documented MEI, including data from the International Mission on Prognosis and Clinical Trial design in TBI (IMPACT) study, the Medical Research Council Corticosteroid Randomization after Significant Head Injury (MRC CRASH) trial, and the Trauma Audit & Research Network (TARN) registry. Our aim was to determine the role of MEI as a prognostic factor for mortality after TBI and to solve the current disagreement in the literature. We hypothesize that the presence of MEI is associated with higher mortality in patients with TBI.

METHODS

Patient population and data collection

We included individual patient data from the International Mission on Prognosis and Clinical Trail design in TBI (IMPACT) study, the Medical Research Council Corticosteroid Randomization after Significant Head Injury (MRC CRASH) trial, and the Trauma Audit & Research Network (TARN).

IMPACT combines individual patient data from randomized controlled trials (RCTs) and three observational studies in moderate and severe TBI, mainly from the US and Europe. Here we focused on the three observational studies (the European Brain Injury Consortium core data survey (EBIC), the UK four centre study (UK4), and the Traumatic

Coma Databank (TCDB)), as the presence of MEI was not an exclusion criterium for these studies. Patients were enrolled in these studies between 1984 and 1995.

The CRASH trial is a trial with broad inclusion criteria studying the effect of corticosteroids on death and disability after head injury. CRASH was conducted in both high and low/middle income countries. In CRASH we analyzed low/middle income countries and high income countries separately, as trauma organizations may be different.(1) CRASH enrolled 10,008 patients between 1999 and 2005, of which 9554 had complete outcome data.

TARN is a hospital based trauma registry in England and Wales including all patients with trauma resulting in immediate admission to hospital for three days or longer or death. From these, we selected TBI patients defined as having an Abbreviated Injury Scale for the Head Region of 3 or higher, which was not resulting from scalp laceration, scalp avulsion or penetrating injury. The patients from TARN included in this study were enrolled between 1990 and 2009.

Detailed descriptions of all the studies and data collection and management can be found in previous publications.(11-13)

Outcome and major extracranial injury

The primary outcome examined in this analysis was mortality at six months in IMPACT and CRASH and discharge mortality in TARN. In IMPACT, six-month mortality was missing in 3 patients who were excluded. CRASH had also 14 day mortality available. Major Extracranial Injury (MEI) was defined as "Abbreviated Injury Scale (AIS) ≥ 3" or "an injury requiring hospital admission on its own".

Statistical analyses

The strength of the association between MEI and mortality was analyzed univariably and multivariably using binary logistic regression models. We adjusted for core prognostic parameters: age, GCS motor score (1=makes no movements, 2=extension to painful stimuli, 3=abnormal flexion to painful stimuli, 4 =flexion/withdrawal to painful stimuli, 5=localizes painful stimuli, 6=obeys commands) and pupil reactivity (1= both responsive, 2=one responsive, 3=both unresponsive) at admission. We also adjusted for hypotension (prior to hospital admission) to better understand the pathway of the prognostic effect of MEI. When IMPACT was analyzed as a single study (in mild and moderate TBI), we additionally adjusted for study, since IMPACT actually consists of three studies. In CRASH we also adjusted for treatment by adding the treatment variable to the multivariable regression model, since there was a significant treatment effect. Since the patients in TARN and IMPACT were included in a wide time range, we tested for interaction between MEI and year of injury.

Results were expressed as odds ratio for mortality with MEI compared to absent MEI, with 95% confidence intervals. An overall summary measure was derived using random effects meta-analysis (Der Simonian-Laird pooling). We assessed the heterogeneity between the studies based on the between-study variance τ^2 and its p-value to test for heterogeneity.

TARN was not included in the pooled analysis because of the different nature of the study and the different time point of the outcome. Forest plots were used to display consistency of findings across the datasets. We calculated partial R^2 statistics to indicate the amount of variance explained by MEI, both univariable and multivariable. In CRASH and IMPACT we corrected the univariable and multivariable R^2s for the variance explained by study and treatment.

Absolute risks of patients with and without MEI were calculated from the models by taking the mean of the probabilities predicted by the multivariable models, stratified for brain injury severity.

Missing data is common in medical scientific research. One distinguishes three types of mechanisms leading to missing values. Missing completely at random (MCAR) are missing values due to for example administrative errors or accidents. Missingness related to known patient characteristics, time or place is called missing at random (MAR). The third mechanism, missing not at random (MNAR), is a problematic situation in which missingness is related to unknown predictors. In epidemiology, it is generally acknowledged that imputation is preferable over complete case analysis in case of missing values. (14-17) Estimating associations using complete case analysis is less efficient, since part of the data is not used. The simplest approach for imputation ('simple imputation') is imputing a fixed value for all patients with a missing value for a particular variable, e.g. the mean or the most common category. Such simple methods ignore the correlation between variables and are hence suboptimal. In 'single imputation', multivariable regression models are used to predict the missing value based on associations with other variables. In multiple imputation this procedure is repeated several times resulting in multiple datasets, all with slightly different imputed values. Subsequent analyses are performed on each dataset separately and summarized to obtain more precise standard errors and P-values.(15) The assumption underlying single and multiple imputation is that missing values are MAR.

In our study, missing data were imputed for the motor score of the Glasgow Coma Scale (GCS), pupil reactivity and MEI with single imputation using all relevant prognostic factors and outcome. We thus assume MAR. Imputations were done separately for TARN, CRASH and IMPACT, using the *AregImpute* function in R statistical software.

Analyses were performed with R statistical software 2.7.1 (R Foundation for Statistical Computation, Vienna) using packages *Rmeta*, *Hmisc* and *Design*, and SPSS 15.0 (SPSS Inc, Chicago).

Sensitivity analyses

In preliminary analysis we found a large difference between IMPACT and CRASH versus TARN in terms of the effect of MEI on outcome. We hypothesized that this might be due to the different setting (TBI studies versus a trauma registry), the different distribution of TBI severity across the studies (only moderate and severe TBI in IMPACT, many mild TBI patients in TARN), or the different time point of outcome assessment (discharge versus 6 month). We tested these hypotheses by three approaches.

1) We tested for interaction between MEI and brain injury severity (GCS), by adding an interaction term between MEI and GCS to the binary logistic regression model containing age, GCS motor score, pupil reactivity, MEI and GCS as main effects. We assessed the p-value of the interaction term and subsequently stratified the analyses for brain injury severity, defining mild TBI as Glasgow Coma Scale (GCS) 13-15, moderate TBI as GCS 9-12 and severe traumatic brain injury as GCS 3-8.
2) We excluded the patients from TARN who died within 6 hours after injury since the majority of these patients is not likely to be included in IMPACT or CRASH.
3) We analyzed in CRASH both 14 day and 6 month mortality.

RESULTS

Patient population

We included 2,216 patients from IMPACT (791 from UK4, 603 from TCDB, and 824 from EBIC), 9,554 from CRASH (7,205 from low/middle income countries, and 2,349 from high income countries), and 27,504 from TARN. This resulted in 39,274 patients for the analysis. For all variables missing was less than 10%, except for TARN where 90% of the pupil reactivity data was missing since this variable was only recorded from 2005 onwards.

Patient characteristics

The majority of the patients (17,136, 44%) had severe TBI. A total of 7,229 (18%) had moderate and 14,909 (38%) had mild TBI. The IMPACT studies included mainly severe TBI patients (81%) and TARN mainly mild (43%) and severe (42%) TBI patients. In CRASH the distribution of brain injury severity was more equal (30% mild, 30% moderate, 40% severe). In IMPACT, mortality was 41%, compared to 24% in CRASH and 28% in TARN. In IMPACT, 41% of the patients had MEI, in CRASH this was 23% and in TARN 34%. MEI was observed more frequently in patients with severe TBI (30-46%), than in those with mild TBI (14-41%). (Table 1)

Table 1. Patient Characteristics of 11 Studies in the IMPACT database, the CRASH trial and the TARN registry.

	Age	**GCS score**	**Motor score**	**Pupillary reactivity**	**Major extracranial injury**	**Mortality**
	median (25^{th}-75^{th} percentile)	*Mild - GCS 13-15* *Moderate - GCS 9-12* *Severe - GCS 3-8*	*none extension* *abnormal flexion* *normal flexion* *localize/obeys* *untestable/ missing*	*both responsive* *one responsive* *both unresponsive*	*yes*	*dead*
UK4 (n=791)	36 (22-55)	24 (3%) 83 (11%) 684 (87%)	113 (14%) 85 (11%) 37 (5%) 141 (18%) 221 (28%) 194 (26%)	434 (55%) 113 (14%) 244 (31%)	303 (38%)	359 (45%)
TCDB (n=603)	26 (21-40)	22 (4%) 45 (8%) 536 (89%)	136 (23%) 107 (18%) 74 (12%) 121 (20%) 134 (22%) 31 (5%)	299 (50%) 55 (9%) 249 (41%)	280 (46%)	264 (44%)
EBIC (n=822)	37.5 (24-59)	73 (9%) 168 (20%) 581 (71%)	150 (18.2%) 80 (10%) 55 (7%) 113 (14%) 281 (34%) 143 (17%)	532 (65%) 80 (10%) 210 (26%)	316 (38%)	281 (34%)
CRASH LOW/ MIDDLE INCOME (n=7,205)	32 (24-45)	2108 (29%) 2331 (32%) 2766 (38%)	356 (5%) 403 (6%) 531 (7%) 891 (12%) 5024 (70%) 0 (0%)	6135 (85%) 450 (6%) 620 (9%)	1694 (23%)	1854 (26%)
CRASH HIGH INCOME (n=2,349)	37 (24-54)	760 (32%) 551 (24%) 1038 (44%)	429 (18%) 112 (5%) 128 (5%) 290 (12%) 1390 (59%) 0 (0%)	1965 (84%) 147 (6%) 237 (10%)	522 (23%)	469 (20%)
TARN (n=27,504)	39 (24-60)	11922 (43%) 4051 (15%) 11531 (42%)	4117 (15%) 838 (3%) 973 (4%) 1449 (5%) 11892 (43%) 8235 (30%)	21548 (78%) 1630 (6%) 4326 (16%)	9452 (34%)	7673 (28%)

Major Extracranial Injury and mortality

We found a moderate prognostic effect of MEI in IMPACT and CRASH with pooled adjusted ORs and 95% confidence intervals (95%CIs) of 2.14 (0.93-4.91) in mild, 1.46 (1.14-1.85) in moderate and 1.18 (1.03-1.55) in severe TBI patients. The between-study variances τ^2 and p-values for heterogeneity were 0.39 (p=0.02) for the mild, 0.11 (p=0.10) for the moderate and 0.0 (p=0.98) for the severe TBI studies. In TARN MEI was a strong prognostic factor for mortality, with adjusted odds ratios (OR) and 95%CIs of 2.81 (2.44-3.23) in mild, 2.18 (1.80-2.65) in moderate and 2.14 (1.95-2.35) in severe TBI patients (Figure 1 and Table 2). The unadjusted ORs were all smaller than adjusted ORs, indicating that the effect of MEI on mortality was independent of other predictors of mortality.

Adjusting the effect of extracranial injury for hypotension led to a small decrease of the prognostic effect (ORs decreasing by 0.1-0.4) of MEI, indicating that hypotension indeed explains part of the relationship between extracranial injury and outcome. Hypotension itself was a strong prognostic factor for mortality, independent of MEI (adjusted ORs 2.9 to 3.6).

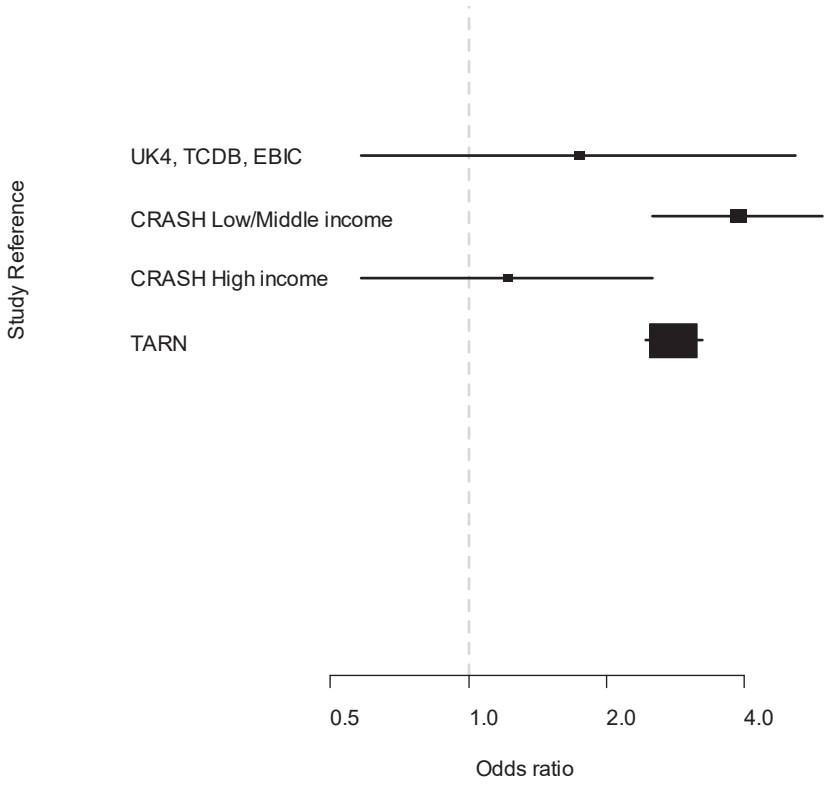

Figure 1. Forest plots showing the strength of the adjusted association between major extracranial injury and mortality in mild (left), moderate (middle) and severe (right) TBI patients

Table 2. Associations between major extracranial injury (versus no and minor extracranial injury) and mortality in the IMPACT, CRASH and TARN data in mild, moderate and severe TBI patients.

	Mild TBI (GCS 13-15)				**Moderate TBI** (GCS 9-12)				**Severe TBI** (GCS 3-8)			
	N Mortality (%)	*N Major extracranial injury (%)*	*Unadjusted*	*Adjusted*	*N Mortality (%)*	*N Major extracranial injury (%)*	*Unadjusted*	*Adjusted*	*N Mortality (%)*	*N Major extracranial injury (%)*	*Unadjusted*	*Adjusted*
UK4	10 (42)	9 (38)	1.14 (0.46-2.86)	1.75 (0.56-5.46)	34 (41)	33 (40)	0.70 (0.39-1.26)	1.15 (0.55-2.41)	315 (46)	261 (38)	0.90 (0.66-1.23)	1.21 (0.81-1.80)
TCDB	6 (27)	9 (41)	-	-	9 (20)	24 (53)	-	-	249 (47)	247 (46)	0.98 (0.70-1.38)	1.13 (0.74-1.73)
EBIC	11 (15)	19 (26)	-	-	26 (16)	51 (30)	-	-	244 (42)	246 (42)	0.79 (0.56-1.10)	1.12 (0.73-1.71)
CRASH L-M income	112 (5)	309 (14)	3.96 (2.64-5.94)	3.86 (2.52-5.91)	348 (15)	530 (22)	1.48 (1.15-1.92)	1.43 (1.09-1.88)	1393 (50)	852 (30)	1.16 (0.99-1.37)	1.24 (1.03-1.49)
CRASH High income	64 (8)	115 (15)	1.39 (0.73-2.64)	1.21 (0.58-2.52)	81 (15)	111 (20)	1.16 (0.66-2.04)	2.04 (1.01-4.12)	324 (31)	296 (30)	0.98 (0.73-1.31)	1.04 (0.75-1.44)
Overall	203 (7)	453 (15)	1.96 (0.84-4.59)	2.14 (0.93-4.91)	498 (16)	737 (23)	1.13 (0.73-1.75)	1.46 (1.14-1.85)	2525 (45)	1904 (34)	1.00 (0.86-1.15)	1.18 (1.03-1.55)
TARN	1132 (10)	3147 (26)	2.24 (1.98-2.54)	2.81 (2.44-3.23)	764 (19)	1178 (29)	1.68 (1.42-1.80)	2.18 (1.80-2.65)	5777 (50)	5127 (45)	1.92 (1.78-2.07)	2.14 (1.95-2.35)

In table: odds ratio (95% confidence intervals)

GCS = Glasgow Coma Scale

Adjusted analyses – adjusted for age, pupil reactivity and motor-score. In IMPACT and CRASH also adjusted for respectively study and treatment.

In mild and moderate TBI the logistic regression analyses were done together for UK4, TCDB and EBIC. The ORs are reported in the UK4 row.

In IMPACT there was no significant interaction between MEI and year of injury (p=0.618). In TARN there was a significant interaction between MEI and year of injury (p=0.000), with outcomes slightly improving over time and the effect of MEI slightly decreasing.

The prognostic value of MEI in terms of univariable R^2 (Figure 2) varied from 0.0% (in severe patients in IMPACT and CRASH) to 3.4% (in severe patients in TARN), and was considerably smaller than the prognostic value of core predictors as age, GCS motor score and pupil reactivity.

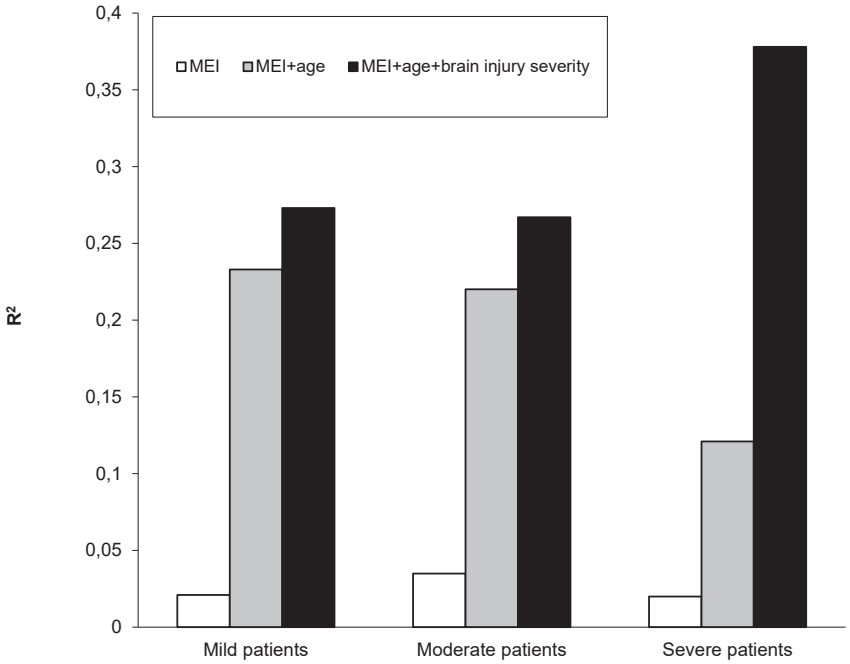

Figure 2. The prognostic value of major extracranial injury (MEI), univariable and in combination with age and brain injury severity (GCS motor score and pupil reactivity), expressed in percentage explained variance (R^2)

Absolute risks

In CRASH and IMPACT, the increase in absolute risk on mortality associated with MEI was 8% (6% vs. 14%) in mild, 4% (15% vs. 19%) in moderate and 1% (45% vs. 46%) in severe TBI patients. The prevalence of MEI in TBI patients was larger in TARN for all brain injury severities than in IMPACT and CRASH, as was the increase in absolute risks on mortality. The increase in absolute risk on mortality associated with MEI was 8% (7% vs. 15%) in mild, 9% (16% vs. 25%) in moderate and 16% (43% vs. 59%) in severe TBI patients in TARN (Table 3).

Table 3. Absolute risks of major extracranial injury and no and minor extracranial injury in different TBI severity groups on mortality in IMPACT& CRASH vs. TARN.

		Mild TBI patients	Moderate TBI patients	Severe TBI patients
IIMPACT & CRASH	**No major extracranial injury**	5.5 (5.2-5.8)	14.8 (14.2-15.3)	44.8 (44.1-45.6)
	Major extracranial injury	13.9 (12.6-15.2)	18.7 (17.7-19.8)	45.5 (44.5-46.6)
TARN	**No major extracranial injury**	7.4 (7.2-7.4)	16.4 (15.8-17.1)	42.9 (42.2-43.6)
	Major extracranial injury	15.3 (14.7-15.8)	24.8 (23.5-26.0)	59.1 (58.3-59.8)

Differences between CRASH, IMPACT and TARN

There was a significant interaction between MEI and brain injury severity in CRASH ($p<0.001$) and TARN ($p=0.029$) but not in IMPACT.

Since we found, also after stratification, a considerable difference in the prognostic effect of MEI between IMPACT-CRASH and TARN across all TBI severities, we excluded 912 patients from TARN who died within 6 hours after injury since the majority of these patients would not have been included in IMPACT or CRASH. This resulted in decreased ORs of MEI for mortality: 2.4 in mild, 1.8 in moderate and 1.6 in severe TBI (IMPACT and CRASH: 2.1 in mild, 1.6 in moderate and 1.2 in severe TBI).

To assess the difference between IMPACT-CRASH and TARN further, we analyzed 14 day mortality in CRASH. In low/middle income countries MEI was less strongly related to 14 day mortality than to 6 month mortality (ORs 0.1-1 point lower for 14 day mortality). In high income countries however, effects were opposite (ORs 0.1 to 0.4 points higher for 14 day mortality).

We performed all analyses also in a subset of the TARN collected after 2005 (n=6078) and found similar results.

DISCUSSION

Our study shows that MEI is a prognostic factor in patients with TBI. However, the effect varies by the population studied in two ways, which explains the disagreement in the literature. First the strength of the effect interacts with brain injury severity, with larger effects in milder TBI patient populations. Second the effect is dependent on the time of inclusion in a study. In TARN (a registry including all TBI patients form the time of injury) MEI is strongly associated with mortality after adjustment for age, GCS motor score and pupil reactivity. In IMPACT and CRASH (broadly selected observational studies and an RCT, including TBI patients surviving the early stage) the incremental prognostic value of MEI compared to known predictors of mortality is limited.

We found a large difference in prognostic effect between TARN and IMPACT / CRASH. The larger effect in TARN was largely explained by inclusion of patients who died before or shortly after admission. The ORs in IMPACT and CRASH thus could be interpreted as the effect of MEI when a TBI patient survives the early stage (first hours) after trauma. The effect in TARN could be interpreted as the effect of MEI in the unselected TBI population. For example: a victim of a road traffic accident with severe TBI and MEI has an odds for mortality 2.14 fold that of a similar patient without MEI. When this patient survives the early stage, the prognostic effect of MEI is reduced to a 1.18 fold increased risk.

Our study shows thus that the magnitude of the effect of MEI on mortality depends on the study design. This is also an explanation for the disagreement in the literature about the prognostic effect of MEI. Studies demonstrating that outcome is not worsened by MEI only included (often severe) patients admitted to an intensive-care unit.(2, 7) These studies are mostly comparable to IMPACT and CRASH with regard to study population and results. The studies showing an effect of MEI in TBI patients, obtained the data from a Trauma Registry like TARN.(8-10)

This means that prognostic effect of MEI is also dependent on the application of a prognosis in a clinical setting. For counseling of relatives of severe TBI patients in the hospital for example, MEI is more likely to be a highly relevant prognostic factor in the Emergency Department than a few hours later if the patient has survived the immediate risk of death from haemorrhage caused by major extracranial injury and has been admitted to intensive care. Thus, this study demonstrates that it is important not only to formulate a clear research question but also to define the specific patient population, which is often not done in prognostic research. To interpret results of a prognostic study and to determine applicability to a particular setting it is important to be aware of the study population and design.

We reported absolute risks in the different studies and the different strata of patients, which further provide some relevant clinical insights. For example, patients with mild TBI & MEI have a similar risk on mortality to one with moderate TBI and no MEI. Absolute risks on mortality were higher in TARN than in IMPACT and CRASH across all TBI severities. This is probably partly due to the previously mentioned difference in patient population. Further, differences in mortality between the studies might be caused by differences in health care system and resources (low/middle income countries in CRASH). Also, the time of data collection varied between the studies (1984 for TCDB and 2009 for the most recent patients in TARN), which might be considered a limitation, but we found that the effect of MEI was constant over time in IMPACT and slightly decreasing in TARN.

It might be expected that MEI is more associated with early mortality than with late mortality. This is supported by our finding that ORs decrease when excluding early deaths in TARN. In CRASH we analyzed both 14 day and 6 month mortality, with inconsistent results. In high income countries the ORs for 14 day mortality were indeed higher

than those for 6 month mortality, in low/middle income countries it was the other way round. An explanation might be that within high income countries trauma deaths after 14 days are rare, while lack of resources and also a greater level of underlying comorbidity make late trauma deaths more prevalent in low/middle income countries. MEI will have an impact there because it will often cause immobility, resulting from e.g. limb and pelvic fractures, which may cause mortality in less resourced settings. In general, the prognostic effect of MEI was larger in low/middle income countries, which might be partly explained by structure and processes of care (e.g. longer times to admissions, less resources). These findings illustrate the necessity to take resources and post acute facilities into account when including patients in TBI studies from regions where resources may be more limited. This is particularly important as a tendency has been noted for pharmaceutical companies and researchers to involve centers from other regions of the world in TBI studies, because of higher patient potential and lower cost.(18)

The unadjusted ORs were all smaller than adjusted ORs. This means that the effect of MEI on mortality was not explained by other predictors of mortality. Adjusting only for brain injury severity led to a small decrease in the effect of MEI, since patients with MEI have more severe brain injury, which is also related to mortality. Adjusting for age led to an increase of the effect of MEI since patients with MEI are younger on average, which is related to less mortality.

Hypotension explained a small part of the association between MEI and mortality. This was expected since systemic injuries can cause major bleedings and thus hypotension. The finding that the ORs of MEI change only very little after adjustment for hypotension and that hypotension is also a strong predictor of mortality independent of MEI suggests that the threshold values for defining hypotension may be too restrictive, or that other mechanisms, such as inflammatory response to multiple injuries, play a role in the relationship between extracranial injury and mortality.

Previous studies have shown that TBI increases the risk of both mortality and morbidity in the general trauma population.(3-5) We find that the presence of MEI is also associated with increased mortality in patients with TBI. Whether this effect may be greater or smaller than in the general trauma population cannot be answered from our study, since we only included patients with TBI. Within the TARN registry work is currently ongoing to analyse the effect of TBI in the general trauma population. It is however an artificial distinction between patients with TBI and patients with MEI. In clinical practice there are patients with trauma and they have often multiple injuries, both extracranial and intracranial. Based on our results and findings from previous studies we would provisionally conclude that both MEI and TBI carry a high risk of mortality, and that a combination of both further increases this risk. The relation is however multidimensional and interaction effects exist with the severity of brain injury.

We used a very simple definition of MEI, since extracranial injury severity was reported differently in each dataset. Analysis of the prognostic value of the full AIS or Injury Severity Scale (ISS), and the different body parts in which the extracranial injury occurred may provide additional insights in the mechanism of effect. This would be of high interest, but unfortunately these data were not available in sufficient numbers to permit meaningful analysis. This represents a limitation of our study. On the other hand, the definition of AIS ≥ 3 we use is quite common, easy to use in practice and showed to discriminate well.

A second limitation of our study is the presence of missing values. We preformed imputation, which is better than deleting missing variables.(14-17) In TARN, where pupil reactivity was imputed in the majority of patients, we performed all analyses also in a subset of the TARN collected after 2005 (n=6078) with complete pupillary reactivity and found similar results.

It could be argued that another limitation is the heterogeneity between the three studies used in the meta-analysis, concerning patient population (enrollment criteria), setting and timing of outcome. However, this heterogeneity allowed us to disentangle the effects of MEI on mortality and to explain to some extent the conflicting results in the current literature. A strength of this study is obviously the many patients included in the study. Also, the meta-analysis is based on individual patient data.

In conclusion, this meta-analysis demonstrates that MEI is a prognostic factor for increasing mortality in patients with TBI. However, the strength of the effect is smaller in patients with more severe brain injury. Also, the strength of the effect decreases when only considering patients who survive the early phase after injury, instead of considering all patients, starting from the time of injury.

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