Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients

MRC CRASH Trial Collaborators

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ABSTRACT

Objective To develop and validate practical prognostic models for death at 14 days and for death or severe disability six months after traumatic brain injury.

Design Multivariable logistic regression to select variables that were independently associated with two patient outcomes. Two models designed: “basic” model (demographic and clinical variables only) and “CT” model (basic model plus results of computed tomography). The models were subsequently developed for high and low-middle income countries separately.

Setting Medical Research Council (MRC) CRASH Trial.

Subjects 10,008 patients with traumatic brain injury. Models externally validated in a cohort of 8,509.

Results The basic model included four predictors: age, Glasgow coma scale, pupil reactivity, and the presence of major extracranial injury. The CT model also included the presence of petechial haemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, midline shift, and non-evacuated haematoma. In the derivation sample the models showed excellent discrimination (C statistic above 0.80). The models showed good calibration graphically. The Hosmer-Lemeshow test also indicated good calibration, except for the CT model in low-middle income countries.

External validation for unfavourable outcome at six months in high income countries showed that basic and CT models had good discrimination (C statistic 0.77 for both models) but poorer calibration.

Conclusion Simple prognostic models can be used to obtain valid predictions of relevant outcomes in patients with traumatic brain injury.

INTRODUCTION

Traumatic brain injury is a leading cause of death and disability worldwide. Every year, about 1.5 million affected people die and several millions receive emergency treatment. Most of the burden (90%) is in low and middle income countries.

Clinicians treating patients often make therapeutic decisions based on their assessment of prognosis. According to a 2005 survey, 80% of doctors believed that an accurate assessment of prognosis was important when they made decisions about the use of specific methods of treatment such as hyperventilation, barbiturates, or mannitol. A similar proportion considered that this was important in deciding whether or not to withdraw treatment. Assessment of prognosis was also deemed important for counselling patients and relatives. Only a third of doctors, however, thought that they accurately assessed prognosis.

Prognostic models are statistical models that combine data from patients to predict outcome and are likely to be more accurate than simple clinical predictions. The use of computer-based prediction of outcome in patients with traumatic brain injury increases the use of certain therapeutic interventions in those predicted to have a good outcome and reduces their use in those predicted to have a poor outcome.

Many prognostic models have been reported but none are widely used. A recent systematic review offers possible explanations. Most models were developed on small samples, most were methodologically flawed, and few were validated in external populations. Few were presented in a clinically practical way, nor were they developed in populations from low and middle income countries, where most trauma occurs.

The Medical Research Council (MRC) CRASH (corticosteroid randomisation after significant head injury) trial is the largest clinical trial conducted in patients with traumatic brain injury and presents a unique opportunity to develop a prognostic model. The trial prospectively included patients within eight hours of the injury, used standardised definitions of variables, and achieved almost complete follow-up at six months. Furthermore, the large sample size guarantees precise and valid predictions. The high recruitment of patients from low and middle income countries means that models developed with these data are relevant to these settings.

We have developed and validated prognostic models for death at 14 days and death and disability at six months in patients with traumatic brain injury.

METHODS

Patients—The study cohort was all 10,008 patients enrolled in the trial. Adults with traumatic brain injury, who had a score on the Glasgow coma scale of 14 or
Persistent vegetative state: unable to interact with environment; unresponsive
Severe disability: able to follow commands/unable to live independently
Moderate disability: able to live independently; unable to return to work or school

Good recovery: able to return to work or school
Moderate disability: able to live independently; unable to return to work or school
Severe disability: able to follow commands/unable to live independently
Persistent vegetative state: unable to interact with environment; unresponsive
Dead

Outcome—Death of a patient was recorded on an early outcome form that was completed at hospital discharge, death, or 14 days after randomisation (whichever occurred first). Unfavourable outcome (death or severe disability) at six months was defined with the Glasgow outcome scale (see box). The scale comprises five categories: death, vegetative state, severe disability, moderate disability, and good recovery. For the purpose of this analysis, we dichotomised outcomes into favourable (moderate disability or good recovery) and unfavourable (dead, vegetative state, or severe disability).

Prognostic variables—For the prognostic model we considered age, sex, cause of injury, time from injury to randomisation, Glasgow coma score at randomisation, pupil reactivity, results of computed tomography, whether the patient had sustained a major extracranial injury, and level of income in country (high or low-middle income countries, as defined by the World Bank) (see table A on bmj.com). We adjusted analyses for treatment within the trial as this was related to outcome, and we did not find interaction between treatment and the potential predictors.

Analysis—Most of the variables collected in the CRASH trial have been previously associated with prognosis in traumatic brain injury, so we included all of them in a first multivariable logistic regression analysis. We excluded variables that were not significant at 5% level. We quantified each variable’s predictive contribution by its z score (the model coefficient divided by its standard error). We explored linearity between age and mortality at 14 days and Glasgow coma score and mortality at 14 days. Interactions between country income level and all the other predictors were evaluated with a likelihood ratio test. Because there were few data missing, we performed a complete case analysis.

Prognostic models—We developed different models for each of the two outcomes: a basic model, which included only clinical and demographic variables, and a CT model, which also included results of computed tomography.

Performance of the model—We assessed performance of the models in terms of calibration and discrimination. Calibration was assessed graphically and with the Hosmer-Lemeshow test. Discrimination was assessed with the C statistic (an equivalent concept to area under the receiver operator characteristic curve).

Internal validation—The internal validity of the final model was assessed by the bootstrap re-sampling technique. Regression models were estimated in 100 models. For each of 100 bootstrap samples we refitted and tested the model on the original sample to obtain an estimate of predictive accuracy corrected for bias. This showed no overoptimism in any of the final model’s predictive C statistics.

External validation—A good prognostic model should be generalisable to populations different to those in which it was derived. We externally validated the models in an external cohort of 8509 patients with moderate and severe traumatic brain injury from 11 studies conducted in high income countries (the IMPACT (international mission for prognosis and clinical trial) dataset).

Score development—We developed a clinical score based on regression coefficients. A web based version of the model was developed to be accessible to clinicians internationally.
RESULTS

General characteristics

Table 1 shows the characteristics of the patients. More of the patients were men (81%) and more came from low-middle income countries (75%). More than half (58%) of participants were included within three hours of injury. Road traffic crashes were the most common cause of injury (65%) and 79% of the participants underwent computed tomography. A total of 1948 patients (19%) died in the first two weeks, 2323 patients (24%) were dead at six months, and 3556 patients (37%) were dead or severely dependent at six months.

The relation between age and the log odds of death within 14 days showed no association until the age of 40 and a linear increase afterwards. The relation between Glasgow coma score and mortality at 14 days was reasonably linear and we therefore included the coma score as a continuous variable (figs 1 and 2). The relation with unfavourable outcome at six months showed similar patterns.

Low-middle v high income countries

In comparison with patients from high income countries, those from low-middle income countries were younger, more likely to be male, were recruited later, had less severe traumatic brain injury (as defined by Glasgow coma score and pupil reactivity), and more often had abnormal results on computed tomography. Road traffic crashes were a more common cause of traumatic brain injury. Although patients from low-middle income countries experienced higher mortality at 14 days (odds ratio 1.94, 95% confidence interval 1.64 to 2.30), there was no significant difference in unfavourable outcome at six months.

There were significant interactions between the country’s income level and several predictors and so we developed two models, one for low-middle income countries and another for high income countries. Older age was a stronger predictor of 14 day mortality in high income countries (interaction P=0.003), and lower Glasgow coma score was a stronger predictor in low-middle income countries (interaction P=0.001). Obliteration of the third ventricle and a non-evacuated haematoma were both associated with a higher risk in high income countries (interaction P<0.001 and P=0.03, respectively).

Multivariable predictive models

We developed eight models altogether: basic and CT models for predicting two outcomes in two settings (low-middle and high income countries).

**Basic models**—We included four predictors in the basic model: age, Glasgow coma score, pupil reactivity, and the presence of major extracranial injury (table 2). Glasgow coma score was the strongest predictor of outcome in low-middle income countries and age was the strongest predictor in high income countries, while the absence of pupil reactivity was the third strongest predictor in both regions.

**CT models**—The following characteristics on computed tomography were strongly associated with the outcomes in addition to the predictors included in the basic models: presence of petechial haemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, midline shift, and non-evacuated haematoma (table 3). Obliteration of the third ventricle and midline shift were the strongest
Performance of models—All models showed excellent discrimination, with C statistics over 0.80 (tables 2 and 3). Calibration in all models was adequate and six out of the eight models had good calibration when evaluated with the Hosmer-Lemeshow test (figs 3 and 4).

Clinical score—Individual scores and their respective probability of outcome can be obtained from our web based calculator (www.crash2.lshtm.ac.uk/). By entering the values of the predictors, we can obtain the expected risk of death at 14 days and of death or severe disability at six months. Figure 5 shows a sample screenshot of the predictions for a 26 year old patient from a low and middle income country (Argentina), with a Glasgow coma score of 11, one pupil reactive, and absence of a major extra cranial injury. According to the basic model this patient has a probability of death at 14 days of 10% and a 23.9% risk of death or severe disability at six months. A good agreement is evident between observed and predicted outcome by the web calculator (figs 3 and 4).

External validation—Because an external cohort of patients from low-middle income countries was not available, we validated the models in patients from high income countries only. The IMPACT dataset used for the validation did not include mortality at 14 days and so we could validate only models for unfavourable outcome at six months. We validated the basic model with the variables age, Glasgow coma score, and pupil reactivity. We did not include the variable “major extracranial injury” as it was not available in the validation sample. For the CT models, we added obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, midline shift, and non-evacuated haematoma to the basic model. Similarly, we excluded the variable “petechial haemorrhages” as this was not available in the validation sample. We validated the models in all patients from high income countries only. The IMPACT dataset available in the validation sample. For the CT models, we added obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, midline shift, and non-evacuated haematoma to the basic model. Similarly, we excluded the variable “petechial haemorrhages” as this was not available in the validation sample.

Table 2 | Multivariable basic predictive models (excluding data from computed tomography*). Figures are odds ratios (95% confidence intervals) with z scores

<table>
<thead>
<tr>
<th>Prognostic variables</th>
<th>Mortality at 14 days</th>
<th>Death or severe disability at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High income countries (n=2294)</td>
<td>Low-middle income countries (n=7412)</td>
</tr>
<tr>
<td>Age†</td>
<td>1.72 (1.62 to 1.83), 14.08</td>
<td>1.47 (1.40 to 1.54), 14.10</td>
</tr>
<tr>
<td>GCS‡</td>
<td>1.24 (1.19 to 1.29), 10.22</td>
<td>1.39 (1.35 to 1.42), 25.60</td>
</tr>
<tr>
<td>Pupil reactivity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>One</td>
<td>2.57 (1.65 to 4.00), 4.17</td>
<td>1.91 (1.53 to 2.39), 5.69</td>
</tr>
<tr>
<td>None</td>
<td>5.49 (3.70 to 8.15), 8.45</td>
<td>3.92 (3.14 to 4.90), 12.07</td>
</tr>
<tr>
<td>Major extracranial injury:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>1.53 (1.11 to 2.09), 2.62</td>
<td>1.15 (0.99 to 1.34), 1.78</td>
</tr>
</tbody>
</table>

GCS=Glasgow coma scale.
*Includes age, GCS, sex, hours since injury, cause of injury, pupil reactivity, and presence of major extracranial injury.
†Per 10 year increase after 40 years.
‡Per decrease of each value of GCS.
1.0
[28x81]C statistic 0.88 0.84 0.83 0.84
[28x127]basal cisterns
[28x159]Findings on computed tomography:
[28x240]Pupil reactivity:

‡
†
GCS

Table 3 Multivariable predictive models with computed tomography*. Figures are odds ratios (95% confidence intervals) with z scores

Mortality at 14 days

High income countries (n=2030)  Low-middle income countries (n=5635)

Age† 1.73 (1.62 to 1.84), 13.33  1.46 (1.39 to 1.54), 12.54  1.73 [1.63 to 1.83], 14.94  1.72 [1.64 to 1.81], 17.74
GCS‡ 1.18 (1.12 to 1.23), 6.87  1.27 (1.24 to 1.31), 16.68  1.18 [1.14 to 1.22], 9.83  1.34 [1.30 to 1.37], 22.32

Pupil reactivity:

Both 1.00
One 2.00 (1.25 to 3.20), 2.88  1.45 (1.14 to 1.86), 2.97  2.12 [1.39 to 3.24], 3.47  1.54 [1.20 to 1.99], 3.35
None 4.00 (2.58 to 6.20), 6.21  3.12 (2.46 to 3.97), 9.31  2.83 [1.84 to 4.35], 4.73  3.56 [2.60 to 4.87], 7.92

Major extracranial injury:

No 1.00
Yes 1.53 (1.10 to 2.13), 2.53  1.08 (0.91 to 1.28), 0.89  1.55 [1.20 to 1.99], 3.37  1.61 [1.38 to 1.88], 6.03

Findings on computed tomography:

Petechial haemorrhages 1.15 [0.83 to 1.59], 0.84  1.26 (1.07 to 1.47), 2.82  1.21 [0.95 to 1.55], 1.56  1.49 [1.29 to 1.73], 5.33
Obliteration of 3rd ventricle or basal cisterns 4.46 [2.97 to 6.68], 7.23  1.99 (1.69 to 2.35), 8.25  2.21 [1.49 to 3.30], 3.95  1.53 [1.31 to 1.79], 5.30
Subarachnoid bleed 1.48 (1.09 to 2.02), 2.51  1.33 (1.14 to 1.55), 3.60  1.62 [1.26 to 2.08], 3.79  1.20 [1.04 to 1.39], 2.49
Midline shift 2.77 (1.82 to 4.21), 4.77  1.78 (1.44 to 2.21), 5.35  1.93 [1.30 to 2.87], 3.24  1.86 [1.48 to 2.32], 5.42
Non-evacuated haematoma 2.06 (1.49 to 2.84), 4.40  1.48 (1.24 to 1.76), 4.43  1.72 [1.33 to 2.23], 4.15  1.68 [1.43 to 1.97], 6.34

C statistic 0.88 0.84 0.83 0.84

GCS=Glasgow coma scale.

*Includes age, GCS, pupil reactivity, presence of major extra cranial injury, and all findings on computed tomography.

†Per 10 year increase after 40 years.

‡Per decrease of each value of GCS.

DISCUSSION

We have developed web based prognostic models for predicting two clinically relevant outcomes in patients with traumatic brain injury using variables that are available at the bedside. The models have excellent discrimination and good fit with both internal and external validation. We have reported on differences in outcomes and on the strength of predictors of outcomes, according to whether patients are from high or low-middle income countries.

Older age, low Glasgow coma score, absent pupil reactivity, and the presence of major extracranial injury predict poor prognosis. All of these variables have been previously identified as prognostic factors for poor outcome in traumatic brain injury.12 Glasgow coma score showed a clear linear relation with mortality. Our finding that mortality in patients with Glasgow coma score of 3 was lower than in patients with a score of 4 may be because scores of sedated patients are reported as 3. Increasing age was associated with worse outcomes but this association was apparent only after age 40. A similar threshold has been reported elsewhere.16 17 Plausible explanations for this include extracranial comorbidities, changes in brain plasticity, or differences in clinical management associated with increasing age. The presence of “obliteration of third ventricle or basal cisterns” on the corresponding coefficients in the validation sample. Although discrimination was, as expected, lower than in the original data, it was still quite good for both the basic and CT models (C statistic 0.77 for both models). The calibration was excellent for the CT model but poorer for the basic model (figs 6 and 7).

Fig 4 | Calibration of computed tomography models using expected and observed probabilities of mortality at 14 days (top) and death or severe disability at six months (bottom) in patient with traumatic brain injury according to income level of country. P value is for Hosmer-Lemeshow test.
computed tomography was associated with the worst prognosis at 14 days. This is supported by recent findings that absence of basal cisterns is the strongest predictor of six month mortality.\textsuperscript{18} We also found—as previously reported—the independent prognostic value of traumatic subarachnoid haemorrhage.\textsuperscript{19}

Patients from low-middle income countries had worse early prognosis than those from high income countries. Regional differences in outcome after traumatic brain injury have previously been reported between Europe and North America, but the difference in mortality between low-middle and high income countries has not been explored.\textsuperscript{20}

The strength of association between some predictors and outcomes differed by region. A low Glasgow coma score had an even worse prognosis in patients from low-middle income countries compared with patients from high income countries. This might relate to quality of care or it could be that low Glasgow coma score in high income countries is associated with greater use of sedation, rather than to severity of traumatic brain injury. Increasing age had a worse prognosis in high income countries compared with low-middle income countries. This is because of even lower risks at younger ages in high income countries, while both have similar risks at older ages. Regarding computed tomography, some abnormal findings were stronger predictors in high income countries. This could be because of better technology and therefore more accurate diagnosis with computed tomography.

A systematic review identified over 100 prognostic models for patients with traumatic brain injury, but methodological quality was adequate in only a few.\textsuperscript{7} As with our models, two of the more methodologically robust models showed similarly good discrimination but worse calibration.\textsuperscript{17,21} They too included Glasgow coma score, age, pupil reactivity, and results of computed tomography as predictors, but, unlike our models, they did not include the presence of major extracranial injury, and none of them included patients from low-middle income countries.

**Strengths and weakness of the study**

Our study’s strengths are the use of a well described cohort of patients, prospective and standardised collection of data on prognostic factors, low loss to follow-up, and the use of a validated outcome measure at a fixed time after the injury. All of these factors provide reassurance about the internal validity of our models. The large sample size in relation to the number of prognostic variables examined is another particular strength. In relation to its external validity, only a few prognostic models have been developed from patients in low-middle income countries, and to the best of our knowledge the models we developed are the first with a large sample size and adequate methods.\textsuperscript{7} The external validation confirmed the discriminatory ability of the models in patients from high income countries and showed good calibration for the computed tomography model. Unlike most published prognostic models,
we included the complete spectrum of patients with traumatic brain injury, ranging from mild to severe. Finally, the data required to make predictions with the model are easily available to clinicians, and we have developed a web based risk calculator.

There are some limitations. The data from which the models were developed come from a clinical trial and this could therefore limit external validity. For example, patients were recruited within eight hours of injury and we cannot estimate the accuracy of the models for patients evaluated beyond this time. Nevertheless, the CRASH trial was a pragmatic trial that did not require any additional tests and therefore included a diversity of “real life” patients. Another limitation was that for the validation we were forced to exclude the variables major extracranial injury and petechial haemorrhages because they were not available in the IMPACT sample. Neither of these variables, however, was among the stronger predictors. The external validation showed good discriminatory ability, but this was somewhat lower than in the original data. This may be explained by a more homogeneous selected case mix in these other trials, which included only patients with moderate and severe Glasgow coma score.

Implications of the study
Most of the burden of traumatic brain injury is in low-middle income countries, where case fatality is higher and resources are limited. We found that several predictors differed in their strength of association with outcome according to income level of country, suggesting that it may be inappropriate to extrapolate from models for high income countries to poorer settings. We have developed a methodologically valid, simple, and accurate model that may help decisions about health care for individual patients. It is important to emphasise, however, that while prognostic models may complement clinical decision making they cannot and should not replace clinical judgment. This is particularly important in the context of judgments about the withdrawal of care or clinical triage. These prognostic models can also help in the design and analysis of clinical trials, through prognostic stratification, and can be used in clinical audit by allowing adjustment for case mix.

Future research
The differences found between the prognostic models for low-middle and high income countries are important. Although most of the burden of trauma occurs in low-middle income countries, most research takes place in high income countries. A recent systematic review found that few prognostic models for traumatic brain injury were developed in low-middle income countries. More research is therefore needed to obtain reliable data from these settings. An improved understanding of the differences between these regions might also clarify the mechanisms of predictors that are not immediately obvious when we analyse a homogeneous population. Because our models were developed with data from a clinical trial, and validated only in patients from high income countries, further prospective validation in independent cohorts is needed to strengthen the generalisability of the models. Future research could also evaluate different ways, or formats, for presenting the models to physicians; their use in clinical practice; and whether ultimately they have any

Fig 7 External validation of CT model for death or severe disability at six months in IMPACT database

What is already known on this topic
Traumatic brain injury is a leading cause of death and disability worldwide with most cases occurring in low-middle income countries
Prognostic models may improve predictions of outcome and help in clinical research
Many prognostic models have been published but methodological quality is generally poor, sample sizes small, and only a few models have included patients from low-middle income countries

What this study adds
In a basic model prognostic indicators included age, Glasgow coma scale, pupil reactivity, and the presence of major extracranial injury
In a CT model additional indicators were the presence of petechial haemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, mid-line shift, and non-evacuated haematoma
The strength of predictors of outcomes varies according to whether patients are from high or low-middle income countries
These prognostic models, that include simple variables, are available on the internet (www.crash2.lshtm.ac.uk/)
impact on the management and outcomes of patients with traumatic brain injury.

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Egypt (775 patients): Hussein Khamis (national coordinator), Abdal Hamid Abaza, Abdalla Fekky, Salah El Kordy, Tarek Shawky (Materna Teaching Hospital, 364); Hesham El-Sayed (national coordinator), Nabi Khalil, Nader Negm, Salem Faez (Suez Canal University, 180); Mamdouh Alamin, Hany Shokry (Axwan Teaching Hospital, 160); Aida Madrazo Carnero, Boris Zurita Cueva (Hospital de la Golicia, 13). Ghana (7 patients): Nii Andrews (Narh-Bita Hospital, 7). Greece (20 patients): George Nakos (University Hospital of Ioannina, 8); Antonios Karavelis (University General Hospital of Larissa, 5); George Archontakis (Charita General Hospital “St George,” 4); Pavlos Myrianthefs (KAT Hospital of Athens, 3). India (973 patients): Yadav Yadav, Sharda Yadav, R. K. Avin Baghel (NSCB Medical College, 177); Mazhar Husain (national coordinator for north India), Deepak Jha (King George Medical College, 105); Wu Hoong Chiang, Manohar Dhandhania, Choden Fonning (North Bengal Neuro Research Center, 655); S Niyeng, Sanjay Gupta (GR Medical College, 51); R R Ravi, K S Bopiah, Ajay Herur (Medical Trust Hospital Kochi, 51); N K Venkataratnam (national coordinator for south India), A Satish (Manipal Hospital, 50); K Bhavadasan, Raymond Morris, Samesh S (Medical College Hospital Trivandrum, 50); A Satish (Abhaya Hospital, 42); Yashbir Dewan, Yashpal Singh (Christian Medical College, 36); Rajesh Bhagchandani, Sanjana Bhagchandani (Apex Hospital Bhopal, 32); Vijaya Ushanthan Sethurayan (Meenakshi Mission Hospital and Research Centre, 32); Sojan Ipe, G Sreekumar (MOSC Medical College Hospital, 32); Parag Parvate, Sreejith, Agasti Reddy (Nizam’s Institute of Medical Sciences, 28); Venind Khosla, Sunil Gupta (Postgraduate Institute of Medical Education and Research, 28); Haroon Pillay, Nisha Thomas (Baby Memorial Hospital, 25); Krishnamurthy Sridhar, Bobby Joseph (V H S Hospital, 22); Namadakavakkkan Kuriy (Jubilee Mission Hospital, 20), Shanti Pratihar, Shibu Pillai (National Institute of Mental Health and Neurosciences, 17); Ramana (Case Hospital, 16); Sanjay Gupta, Smita Gupta (N Sai Hospital, 16); Dilip Kyawat (Hirabi Cowasji Jhargir Medical Research Institute, 15); Kishor Mashewrhi (Mashrewthi Orthopaedic Hospital, 13); Dilip Panikar (Ambita Institute of Medical Sciences, 11); Jayaant Chawla (Hartaje Maternity and Nursing Home, 7); Satyanarayana Shenoy, Armswamy Raja (Kasturba Medical College and Hospital, 7); Yeshomaran Rayapay (Chotram Hospital and Research Centre, 6); Suryaranyay Reddy (Gonw Gopal Superspeciality Hospital, 6); Nelanathula Mohan (Apex Hospital Vikashpatnam, 3); Shailesh Kelkar (Central India Institute of Medical Sciences, 3); Yadav Yadav (Marble City Hospital and Research Centre, 3); Jayaant Chawla (Government Medical College Amritsar, 1); Mukesh John (John Hospital, 1); Yadav Yadav (National Hospital Jaipur, 1). Indonesia (238 patients): Nyoman Golden (national coordinator), Sri Malawian (Sanglah General Hospital, 222); Achmad Fauzi, Umur Farouk (Sidoarjo General Hospital, 14). Iran (233 patients): Esmael Fakharian, Amir Aramesh (Naghi University Hospital, 110); Maasoumeh Ehtedari, Farhad Ahmadzadeh, Alireza Gholi (Fatemeh Zahra Hospital, 85); Maasoumeh Ehtedari, Farhad Ahmadzadeh (Social Security Hospital, 38); Ireland (113 patients): Patrick Plunkett, Catherine Redican, Geraldine McMahon (St James’s Hospital, 113). Italy (9 patients): Maria Giuseppina Annetta (Università Cattolica del Sacro Cuore, 4); Moneré Mouchayt (Università di Firenze, 3); Eros Bruzzone (Osedeale San Martino, 2). Ivory Coast (3 patients): Béatrice Harding (CHU de Cocody, 3). Kenya (2 patients): Mahmood Qureshi (Aga Khan Hospital, 2). Malaysia (176 patients): Zainuddi Idris, Jafri Abdullah NC, Ghazimee Ghaizali, Abdul Rahman Izaini Ghani (University Hospital Science Malaysia, 162); Fadzi Cheeh (Iphot Specialist Hospital, 14). Mexico (17 patients): Alfredo Cabrera (national coordinator), José Luis Mejia González (Hospital General Regional No 1, 12), José Luis Mejía (Hospital General Regional No 1, 12).
González (Hospital General de Queretaro, 4); Jorge Loría-Castellanos (Hospital General Regional No 25, 1).
New Zealand (43 patients): Suzanne Jackson, Robyn Hutchinson (Dunedin Hospital, 43).
Nigeria (180 patients): Edward Komolafe (national coordinator), Augustin Adeolu, Moremike Komolafe (Obafemi Awolowo University Teaching Hospital, 77); Olusanya Adeyemi-Chido, Femi Bankole (Lagos University Teaching Hospital, 43); Bello Shuaibu, Victoria Danlami (Usmanu Danfodiyo University Teaching Hospital, 36); Olubunmi Adeboye (University of Ibadan Teaching Hospital, 15); Kehinde Oluwadara (Lautech Teaching Hospital, 7); Ahmed Sanni (Lagos State University Teaching Hospital, 1); Herb Giebel (Seventh Day Adventist Hospital, 1); Sushi Kamar (Seventh Day Adventist Hospital, 1).
Pakistan (17 patients): Rashid Jooma (Innarah Postgraduate Medical Centre, 17).
Panama (7 patients): Jose Eduardo Mezquita (Complejo Hospitalario M A Guerrero, 7).
Paraguay (10 patients): Carlos Ortiz Ovelar (Instituto de Previsión Social, 10).
Peru (8 patients): Marco Gonzales Portillo (Hospital Nacional "Dos de Mayo", 6); Diana Rodriguez (national coordinator) (Hospital Nacional Arzobispo Loayza, 2).
Romania (319 patients): Laura Balica (national coordinator), Bogdan Oprea, Mircea Skirniscu, Luiza Steifele, Laura Bandul (Spatulă Clinic de Urgență București, 162); Adam Danil, Remus Iliescu (Sfântu Pantelimon Hospital, 28); Jean Cureau (Prof D Dr Gagdashar Clinical Emergency Hospital, 9).
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Serbia (23 patients): Ranka Kunic-Protic, Vesna Janosevic (Klinicki Centar Zvezdara, 23).
Singapore (23 patients): James Tan (national coordinator) (National Neuroscience Institute, 21); Charles Seah (Changi General Hospital, 2).
Slovenia (179 patients): Stefan Trenkler (national coordinator), Matija Humenjak, Tatjana Stanjovanov (Reiman Hospital, 71); Ivan Schwendt, Anton Laimc (NIS Pospodni, 2); Zoran Julius, Stano Maros (Nemocnica Bajnice, 25); Izet Fermet (FSF Kosice, 12); Maria Cifranicova (NIS P Trebic, 15); Beata Sandomova (Faculty Hospital in Martin, 10); Karol Kalig (NIS Ruzinov, 4); Sofia Medekova (NIS Novy Zamek, 3); Radovan Wisz (NIS Liptovsky Mikulas, 2); NP D Roosevelt, 1); Ivan Mozga (NP Zilina, 1).
South Africa (366 patients): Bennie Hartzenberg (national coordinator), Grant du Plessis, Zelide Hallie (Tygerberg Academic Hospital, 307); Narendra Nathoo, Sphi Khumalo (Wentworth Hospital, 57); Ralph Tracey (GBW, 83).
Switzerland (160 patients): Reto Stocker (national coordinator), Silke Ludwig (national coordinator) (University Hospital of Zurich, 133); Heinz Zimmermann (University Hospital Zurich, 93); Urs Dendler (Kantonsspital Schaffhausen, 12).
Thailand (579 patients): Surakant Yuthaksasemsut (national coordinator), Warawut Kittiwattanaporn, Purnama Prayachevirat, Pojana Tapsai, Achara Namuangajan (Khon Kaen Regional Hospital, 355); Upapat Chantapimput (Chiangra Prachanuk Hospital, 12); Chanokhan Watanasri, Phut Subsomsong (Rayong Hospital, 11); Wipat Pusasukawatwan, Pensri Khunjan (Khrap Hospital, 10); Sakchai Tangtivivataya, Somklk Popleng (Suratthani Hospital, 8); Tanagorn Klangsang, Wibul Taechakosol (Roi Et Hospital, 11); Atitrat Srinat (Lampang Hospital, 1).
Uganda (43 patients): Hussein Ssenyonyo, Olive Kubosingye (Makerere Medical School, 43).
UK (191 patients): Gabrielle Lomas, David Yates, Fiona Lecky (Hope Hospital, 209); Anthony Bletterman, Alan Baldwin, Emma Jenkinson, Sheila Pantrini (Birmingham Heartlands Hospital, 123); James Stewart, Nasreen Contractor, Trudy Roberts, Jim Butler (North Manchester General Hospital, 85); Alan Pinto, Diane Lee (Royal Albert Edward Infirmary, 83); Nigel Brayley, Karly Robbshaw, Clare Dix (Colchester General Hospital, 79); Sarah Graham, Sue Pey (Whiston Hospital, 69); Marcus Green, Annie Kellins (Selly Oak Hospital, 61); Chris Mouton, Barbara Fogg (Royal Bolton Hospital, 51); Rowland Cottingham, Sam Funnell, Utham Shanker (Eastbourne District General Hospital, 50); Claire Summers, Louise Maleik (Trafford General Hospital, 41); Rowland Cottingham (national coordinator), Christopher Ashcroft, Jacky Powell (Royal Sussex County Hospital, 38); Steve Moore, Stephanie Buckley (Countess of Chester Hospital, 36); Mandy Grocott, Steve Chambers (Worthing Hospital, 34); Amanda Morris, Helen Marshall (Medway Maritime Hospital, 29); Julia Harris, Wendy Matthews, Jane Tippett (Chelseia and Westminster Hospital, 28); Simon Mardell, Fiona MacMillan, Anita Shaw (Furness General Hospital, 27); Pramod Luthra, Gill Dixon (Royal Oldham Hospital, 26); Mohammed Ahmed, John Butler, Mike Young (Stepping Hill Hospital, 26); Susan Mason, Ian Loveday (Northern General Hospital, 25); Christine Clark, Sam Taylor (Blackburn Royal Infirmary, 23); Paul Wilson (Cheltenham General Hospital, 23); Kassim Ali, Stuart Greenwood (Fairfield General Hospital, 23); Martin White, Rosa Perez (Queen Elizabeth the Queen Mother Hospital, 21); Sam Elamit (Nineveh Hospitals and Medical School, 19); Jonathan Wasserberg, Helen Shale (Queen Elizabeth Hospital Birmingham, 18); Colin Read, John McCarron (Russell’s Hall Hospital, 18); Aaron Pennell (Princess Alexandra Hospital, 16); Gautam Ray (Princess Royal Hospital, 14); John Thurston, Emma Brown (Darent Valley Hospital, 13); Lawrence Jaffey, Michael Graves (Royal Liverpool University Hospital, 12); Richard Bailey, Nancy Loveridge (Chesterfield and North Derbyshire Royal Hospital, 10); Geraint Evans, Shireen Hughes, Majid Kafeel Ahmed (Withybush General Hospital, 10); Jeremy Richardson, Claire Gallagher (Aberdeen Royal Infirmary, 8); Titus Odedun, Karen Lees (Omskirk and District General Hospital, 8); David Foley, Nick Payne (Queen Mary’s Hospital, 8); Alan Pennycook, Carl Griffths (Arrow Park Hospital, 6); David Moore, Denise Byrne (City Hospital Birmingham, 5); Sulis Dusan (St Helier Hospital, 4); Ashley Banerjee, Steve McQuirness (Whittington Hospital, 4); Claude Chikha (Doncaster Royal Infirmary, 2); Nigel Zoltie, Ian Barlow (Leeds General Infirmary, 2); Ian Stell (Bromley Hospital, 1); William Hulse, Jacqueline Crossley (Harrogate District General Hospital, 1); Laurence Watkins (Institute of Neurology, 7); Balu Donai (Queen Elizabeth Hospital Gateshead, 7).
Vietnam (2 patients)—Truong Van Viet (Cho Ray Hospital, 2).
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9 MRC CRASH trial investigators. CRASH trial: a randomised placebo controlled trial of intravenous corticosteroids in adults with severe head injury on death and dependency at 1 month. BMJ 2008;337:a1603.


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