INJURIES AND VIOLENCE

Patient outcome after traumatic brain injury in high-, middle- and low-income countries: analysis of data on 8927 patients in 46 countries

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Background Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide. The burden of TBI is greatest in low- and middle-income countries (LAMIC), yet little is known about patient outcomes in these settings.

Methods Complete data on 8927 patients from 46 countries from the corticosteroid randomization after significant head injury (CRASH) trial were analysed to explore whether outcomes 6 months after TBI differed between high-income countries and LAMIC.

Results Just under half of patients experienced a good recovery, one-third moderate or severe disability and one-quarter died within 6 months of their injury. Univariate analyses showed that patients in LAMIC were more likely to die following severe TBI, but were less likely to be disabled following mild and moderate TBI. These results were confirmed in multivariate analyses. Compared to patients in high-income countries, patients in LAMIC have over twice the odds of dying following severe TBI (OR 2.23, 95% CI 1.51–3.30) but half the odds of disability following mild (OR 0.41, 95% CI 0.23–0.72) and moderate TBI (OR 0.53, 95% CI 0.35–0.81). There were no differences between settings in the odds of death following either mild or moderate TBI.

Conclusions Reduced death rates following severe TBI in patients from high-income countries may be due to differences in medical care which may result in a higher proportion of patients surviving with a disability. Socio-cultural factors may explain the lower levels of disability after mild and moderate TBI in LAMIC.

Keywords Traumatic brain injury, Glasgow Outcome Score, high-income countries, middle-income countries, low-income countries

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Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Every year, millions of people receive emergency medical treatment for TBI and an estimated 1.5 million die. TBI is the leading cause of disability in people under 40, severely disabling 150–200 people per million annually. The burden of TBI is greatest in low- and middle-income countries (LAMIC), where 85% of the world’s population live. The World Health Organization (WHO) estimates that almost 90% of deaths due to injuries occur in these settings. Despite this, very little is known about patient outcomes after TBI in LAMIC. For example, a systematic review of prognostic models after TBI found that only 7% of the 102 included models were based on data from LAMIC. This may be a consequence of the 10/90 gap whereby <10% of worldwide expenditure on health research is devoted to the health problems that account for 90% of the global burden of disease. In this paper we attempt to address this gap.

There are some reasons to suspect that outcomes after TBI may differ between high-income countries and LAMIC. Patterns of injury observed in LAMIC are different from those seen in high-income countries, while treatment differences including standards of intensive care may affect outcomes. In addition, socio-cultural differences such as welfare provision and cultural norms may affect levels of disability following TBI.

This paper explores whether outcomes 6 months after TBI differ between high-income countries and LAMIC. The MRC corticosteroid randomization after significant head injury (CRASH) trial contains information on outcomes 6 months after TBI for 10 008 patients from 48 countries and was therefore used in a post hoc analysis to explore differential outcomes between settings.

Patients and methods

The CRASH trial is a large international double-blind randomized placebo-controlled trial of the effect of early administration of a 48-h infusion of a corticosteroid (methylprednisolone) on the risk of death and disability after TBI. The background, methods, baseline characteristics of the patients randomized and results of the trial have already been reported in detail. Briefly, adults (aged 16 years or older) with a head injury and a Glasgow Coma Score (GCS) of 14 or less were randomly allocated to commence either a 48-h infusion of methylprednisolone or matching placebo within 8 h of injury. A total of 10 008 patients from 239 hospitals in 48 countries were randomized. The same inclusion criteria and recruitment procedure were used in all countries. The study conformed to Good Clinical Practice (GCP) guidelines in all countries. Primary outcomes were all-cause mortality within 14 days and death and disability 6 months after injury. Treatment allocation remained concealed from patients, clinical staff and interviewers. Local ethics or research committee approval was obtained by all trial collaborators.

Measures

All-cause mortality within 14 days of the injury was obtained from a single-sided early outcome form completed at death, discharge or 14 days after injury, whichever occurred first. Data on deaths after 14 days and within 6 months were obtained by contact with patients’ general practitioners, and by access to death certification records.

Disability at 6 months was assessed using a simple questionnaire version of the Glasgow Outcome Scale (GOS), commonly used to assess outcome in head injury clinical trials. Pre-trial testing demonstrated that the questionnaire provided a reliable and valid assessment of disability. The GOS consists of six questions, three dealing with functional disability (ability to shop, travel and extent of help needed in the home), and three addressing psychosocial disability (ability to work, to take part in social and leisure activities and relationship problems). Patients were classified as having a good recovery, moderate disability, severe disability, a disability not due to their TBI or having died at 6 months. The questionnaire was either posted to patients, administered by telephone interview, or administered during a home visit or hospital appointment 6 months post-injury. The questionnaire was completed by the patient or carer, either alone or jointly.

Countries were classified using the World Bank Atlas method according to 2004 Gross National Income (GNI) per capita as either a high- (GNP of $10 066 or more) or a middle-/low-income country (GNI of $10 065 or less). The full list of countries included in the analysis by Glasgow outcome scale is listed as Supplementary Data.

A number of demographic, injury-related and treatment factors may confound the relationship between country-income group and 6-month outcome and were therefore included in the analysis. Figure 1 lists these factors and how they were coded in the analysis. Age, gender, time between injury and treatment, severity of TBI measured by the GCS and pupil reactivity were collected via the trial entry form. This form was completed before randomization by the treating clinician either on a paper form or over the phone with the central randomization service provided by the Clinical Trial Service Unit (CTSU) in Oxford, UK. Cause of injury, major extra-cranial injury, CT scan results and number of complications were collected using an early outcome form which was completed at death, discharge, or at 2 weeks, which ever occurred first. These data were obtained electronically, and by fax and post.
multiple imputation. This allows the incorporation of uncertainty of the missing data was explored using the consequence of departures from complete randomness of the key assumptions on the conclusions reached. First, the demographic, injury-related and treatment factors included in the analysis displayed the expected association with the GOS. As the association between these variables and the GOS has already been presented elsewhere, these results will not be discussed in detail here.

Results
Sample selection and description of sample
Figure 2 outlines the sample selection of patients for the analysis. A total of 10,008 patients from 239 hospitals in 48 countries were enrolled in the trial. In order to restrict the analysis to adults, 67 patients who were under 16 were excluded. In addition, 270 patients who had a disability which was not caused by their TBI were excluded as these patients cannot inform us about outcomes caused by TBI. In total, 7.5% of the sample was excluded due to missing data. A total of 8927 patients from 46 countries were included in the final analysis. Due to differences between countries in the numbers and sizes of participating hospitals, the numbers of patients from each country ranged from 1 to 1044 (mean 194; see Supplementary Data).

A full description of the sample has been provided elsewhere. The mean age of the patients is 37, and over 81% are male. Patients from LAMIC were younger and more likely to be male than patients from high-income countries (Table 1). Three-quarters live in LAMIC, and roughly a third suffered mild, moderate or severe TBI respectively. Patients in high-income countries suffered more mild and severe TBIs, but fewer moderate TBIs. One-fifth of patients suffered a major extra-cranial injury in addition to a TBI. Just under half of patients experienced a good recovery, one-third moderate or severe disability and one-quarter died within 6 months of their injury. Patients were more likely to experience a good recovery but were also more likely to die following TBI in LAMIC compared with high-income countries.

The demographic, injury-related and treatment factors included in the analysis displayed the expected association with the GOS. As the association between these variables and the GOS has already been presented elsewhere, these results will not be discussed in detail here.

Differences in 6-month outcomes by country-income group
There were significant differences according to injury severity in outcomes 6 months after TBI between high-income countries and LAMIC (Table 2). Twenty-one per cent more patients died following a severe TBI (GCS 3–8) in LAMIC compared with high-income countries (51%, n = 1347 vs 30%, n = 285; P < 0.001). However, patients in LAMIC had significantly better outcomes following mild (GCS 13–14) and moderate TBI (GCS 9–12) than patients in high-income countries. For example, 18% more patients had a good recovery following mild TBI in LAMIC compared with high-income countries (78%, n = 1557 vs 60%, n = 410; P < 0.001). Levels of moderate and severe disability were lower in LAMIC following severe TBI, though the proportion enjoying a good recovery did not differ between country groups.
Table 3 presents the results of the multivariate analysis of the association between country-income group and 6-month outcomes. As suggested by the descriptive analysis, a significant interaction was found between injury severity (GCS) and country-income group in the prediction of 6-month outcomes (Wald test $P < 0.001$). To account for this, separate models were fitted for each level of injury severity. Patients in LAMIC had over twice the odds (OR 2.23, 95% CI 1.15–3.30) of dying following severe TBI compared with patients in a high-income country. There was no significant difference in the odds of disability following severe TBI between settings. In contrast, patients in LAMIC had roughly half the odds of patients in high-income countries of being moderately or severely disabled following mild and moderate TBI. There was no difference between settings in the odds of death following either mild or moderate TBI.

**Additional analyses**

Using multiple imputation did not affect the direction of the effects reported above or the conclusions drawn from the analysis, though in some cases the magnitude of the difference between high-income countries and LAMIC was increased. Logistic regression with robust standard errors modelling the odds of a favourable vs unfavourable outcome also confirmed lower odds of an unfavourable outcome following mild TBI in LAMIC, but increased odds of death following severe TBI. Finally, the analysis based on a finer categorization of country-income group confirmed our decision to group LAMIC together as they displayed the same association with 6-month outcomes. Results for all additional analyses are available upon request.

**Discussion**

**Statement of principal findings**

Compared with patients in high-income countries, patients in LAMIC have increased odds of death following severe TBI and reduced odds of disability following mild and moderate TBI.

**Strengths and weaknesses of the study**

With data on 10008 patients from 46 countries, the CRASH data set is one of the largest longitudinal data sets of TBI in the world. There was very little missing data and multiple imputations showed that the exclusion of patients with missing observations did not materially affect the results.

This analysis is subject to a number of limitations. Countries included in the CRASH trial were not selected to be representative of the different country-income groups, nor were hospitals and patients selected to provide nationally representative samples. In order to be included in the trial, patients first had to be admitted to a hospital, and secondly to be treated within 8 h of their injury. Patients who did not have access to a hospital, or who had suffered a very mild TBI, were therefore less likely to be included.

It is unclear how valid the GOS is in different settings. Misclassification of outcome due to cultural differences in the interpretation of concepts such as ‘ability to work’ or ‘problems in how you get on with your friends or relatives’ may explain some of the differences between settings. Though studies from some high-income countries have shown the GOS to be valid and reliable in these settings, further studies are needed to assess the cross-cultural validity of the GOS. Attempts were made in the CRASH trial to ensure the linguistic validity of the GOS across countries by assigning an investigator in each country with responsibility for back-translating the GOS questionnaire. Where appropriate, culturally relevant
examples were used to ensure that the questions were interpreted appropriately.

Lastly, although a wide range of predictors of outcome following TBI were included in the analysis, residual confounding both by poorly measured and unmeasured confounders is possible. There may be residual confounding by injury severity as the mean GCS score among those classified as severely injured was higher in LAMIC compared with high-income countries. 

Residual confounding may also be caused by the severity of extra-cranial injuries which may affect both mortality and disability severity. Unmeasured variables (e.g. site of head injury, use of intoxicating substances; haemodynamic parameters, treatment received in hospital and socio-economic status) may have further confounded the association of interest.

### Discussion of results

These results appear to show that patients in high-income countries are less likely to die following severe TBI than patients in LAMIC. This may be due to differences in medical care which may result in a higher proportion of patients surviving with a disability in high-income countries. Although reduced levels of disability in LAMIC may be partly explained by excess mortality following severe TBI, this cannot explain the finding that there are higher levels of disability following mild and moderate TBI in high-income countries, as patients in LAMIC do not suffer excess mortality at these injury severities.

Socio-cultural and environmental factors may partly explain the lower levels of disability following TBI in LAMIC. Previous research has indicated that considerable differences in patient characteristics and case management exist between continents and among countries, reflecting variations in social, cultural, environmental and organizational factors. 

The WHO International Classification of Functioning, Disability and Health (ICF) adopts a biopsychosocial model of disability which it defines as ‘the negative aspects of the interaction between an individual (with a
health condition) and that individual’s contextual factors (personal and environmental factors). Disability is a multi-faceted and dynamic phenomenon which is to a great extent determined by the social context in which an individual with an impairment lives. Additional analyses modelling each of the six domains of the GOS separately revealed that differences in disability levels between high-income countries and LAMIC are greater for the psychosocial (ability to work, socialize and relationship problems) than for the functional aspects of disability (extent of help in the home, help to shop and travel—results available on request), though all types of disability are less common in LAMIC. These results reflect the finding that the prevalence of disability is often lower in LAMIC than in high-income countries. This may be the result of differences in the definition of disability between settings, socio-cultural and environmental differences which affect how a society interprets and reacts to disability, and differences in medical care in high-income countries which may extend life expectancy.

For example, while social security or medical insurance is often available in high-income countries allowing those with even moderate disabilities to reduce or stop work, in LAMIC which lack a welfare system people may have no choice but to continue working. This is supported by our analysis whereby patients in high-income countries had greater odds of ceasing work than did patients in LAMIC, but the same odds of reducing the amount or type of work that they do. Similarly, cultural differences in patterns of socializing and norms of relationships may reduce the disabling impact of TBI in some settings. In LAMIC social life and leisure activities may often be centred on the family and home, and therefore functional disabilities which restrict travel may be less likely to lead to disruptions in an individual’s social life. In contrast, studies from high-income countries have shown a significant decrease in the social support network and pre-injury friendships of survivors of TBI. Lastly, the increased impact that TBI may have on an individual’s ability to work and socialize in high-income countries may have a correspondingly negative impact on their relationships with others. Changes in ability to work and socialize are associated with increased mental health problems including depression and anxiety, which may further increase the likelihood of relationship problems with friends and family.

**Implications**

This study has explored one aspect of the 10/90 gap—the lack of research into patient outcomes following TBI in LAMIC. Results indicate that outcomes following TBI are systematically different in high-income countries compared with LAMIC. As the vast body of research into the risk factors for, and treatment of, TBI has been conducted in high-income countries, it is questionable to what extent this research is applicable to LAMIC where the burden of death and disability due to TBI is greatest. Opportunities exist to improve patient outcomes by drawing on the experience of both contexts. For example, exploring the reasons for the lower levels of disability in LAMIC may provide opportunities for high-income countries to reduce the high level of disability resulting from mild and moderate TBI. Research into the prognostic factors and patterns of care which influence outcome following TBI in LAMIC is therefore needed.

**Supplementary data**

Supplementary data are available at *IJE* Online.

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**KEY MESSAGES**

- In a longitudinal analysis of nearly 9000 patients from 46 countries who had suffered a traumatic brain injury (TBI), patients in low- and middle-income countries (LAMIC) were more likely to die following severe TBI, but were less likely to be disabled following mild and moderate TBI compared with patients in high-income countries.

- This may be due to differences in medical care which results in a higher proportion of severely injured patients in high-income countries surviving with a disability. Socio-cultural factors may explain the lower levels of disability after mild and moderate TBI in LAMIC.
References


