Risk Adjustment In Neurocritical care (RAIN) – prospective validation of risk prediction models for adult patients with acute traumatic brain injury to use to evaluate the optimum location and comparative costs of neurocritical care: a cohort study

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Executive summary

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Background

Where adult patients with traumatic brain injury (TBI) should be optimally managed is an important question for the NHS, both in terms of outcomes and costs. Notwithstanding the lack of evidence, it has been recommended that patients with a severe TBI should be managed within a neuroscience centre. Currently, many (particularly those without surgically remedial lesions) are neither treated in, nor transferred to, one. A combination of geography, bed availability, local variation and clinical assessment of prognosis can often determine the location of definitive critical care for adult patients with TBI.

Recent research has suggested benefit from managing severe head injury in specialist centres; however, the results are inconclusive owing to lack of adjustment for all known confounders, no data on costs of care, only having follow-up data to hospital discharge, and not addressing whether provision should be in dedicated neurocritical care units or combined neurocritical/general critical care units within neuroscience centres.

Variation in the way services are organised and delivered can allow them to be compared using observational methods. This is only possible; however, if a valid, reliable, appropriate and accurate risk prediction model exists. A number of specific models for TBI exist but these models require further prospective validation, and potentially recalibration, before they can be applied with confidence for research and audit in neurocritical care in the NHS.

The primary aim of the Risk Adjustment In Neurocritical care (RAIN) study was to validate risk prediction models for acute TBI and to use the best model(s) to evaluate the optimum location and comparative costs of neurocritical care in the NHS.

Objectives

Specific, detailed objectives to achieve this aims were to:

1. identify existing risk prediction models for acute TBI
2. collect data for the selected risk prediction models
3. describe the case mix and outcomes, to 6 months, from TBI
4. validate the selected risk prediction models
5. compare the relative costs, consequences and cost-effectiveness of care for adult patients with TBI admitted to dedicated neurocritical care units within a neuroscience centre, combined neuro/general critical care units within a neuroscience centre, and general critical care units outside a neuroscience centre
6. make recommendations for policy, practice and future research in the NHS.

Methods

Selection of candidate risk prediction models for acute TBI was conducted through a systematic review of the literature, consultation with clinical experts and methodological assessment. A detailed data set was produced (based on publications of the selected risk prediction models plus location of care details) to describe and cost the patient journey; short-term outcomes; and contact details, to provide the information required for 6-month follow-up.

All neurocritical care units in the UK and adult general critical care units participating in the Case Mix Programme (CMP) were invited to participate. Data set familiarisation courses were held to explain the background, aims and rationale for the study and provide a detailed explanation of the data set.

All adult patients admitted to participating critical care units following an actual or suspected TBI, and with a Glasgow Coma Scale (GCS) score of <15 following resuscitation were included. A sample size calculation indicated 3400 patients were required. Data were entered locally on to a dedicated, secure, web-based data entry system. To avoid duplication of data collection, the RAIN study was linked to two national clinical audits: the CMP for units in England and Wales and the Scottish Intensive Care Society Audit Group (SICSAG) for units in Scotland. Data validation was ongoing throughout and regular contact was maintained with all participating units.

Six-month patient follow-up was conducted centrally and was carefully conducted to prevent distress to either the patient or their carer(s). Surviving patients were sent, by post, an introductory letter, information sheet, consent form, questionnaires, freepost return envelope and pen. Carer(s) were asked to assist with completion of the consent form and, where relevant, questionnaires. Non-responders were followed up. Two questionnaires were included: one included the European Quality of life (EuroQol) 5-dimension, 3-level version (EQ-5D-3L) and the Glasgow Outcome Scale – Extended (GOSE) and the other included questions about use of health services following discharge from acute hospital.

Patients were included in the analysis if their last GCS score prior to sedation/admission to critical care was <15. Case mix, length of stay (LOS) and outcomes were summarised overall and for subgroups defined by the cause of TBI – road traffic accident (RTA), fall or assault. GOSE responses were used to assign each patient to a GOSE category.

With respect to model validation, the case mix and outcomes of patients for each family of models was compared with those for patients in the RAIN study. Univariable analyses were conducted to assess the relationship between risk factors and outcomes. Each risk prediction model was then validated using measures of calibration, discrimination and overall fit. A nested, inter-rater reliability study was conducted on a sample of computerised tomography (CT) scans.

For the evaluation of alternative care locations, two distinct research objectives were identified that addressed separate decision problems, to compare the relative costs, consequences and cost-effectiveness of:

1. management in a dedicated neurocritical care unit compared with a combined neuro/general critical care unit; and
2. 'early' (within 18 hours of hospital presentation) transfer to a neuroscience centre compared with 'no or late' (after 24 hours) transfer, for patients who initially present at a non-neuroscience centre and do not require neurosurgery.

The evaluation was undertaken in two phases. In the first phase, risk-adjusted costs and consequences of alternative care locations at 6 months were compared. EQ-5D-3L profiles were combined with health-state preference values from the UK general population, to give an EQ-5D-3L utility index score and quality-adjusted life-years (QALYs) at 6 months were calculated by combining survival and utility score at 6 months. Each item of resource use was combined with the appropriate unit cost to report a cost per patient for each cost category (inpatient, outpatient, community and total costs) in 2010–11 prices. For research objective 2, subgroup analyses were undertaken by age, presence of major extracranial injury, and GCS score. In the second phase, estimates from the 6-month end points and the literature were used to project lifetime cost-effectiveness. Incremental net monetary benefits (INBs) were estimated by valuing incremental QALYs at a threshold of £20,000 per QALY and subtracting from this the incremental costs. The robustness of results to alternative assumptions was tested in extensive sensitivity analyses.

Missing data were addressed with multiple imputation.

Results

Ten risk prediction models, developed and validated in three studies – Hukkelhoven *et al.* (Hukkelhoven: Hukkelhoven CW, Steyerberg EW, Habbema JD, Farace E, Marmarou A, Murray GD, *et al*. Predicting outcome after traumatic brain injury: development and validation of a prognostic score based on admission characteristics. *J Neurotrauma* 2005;**22**:1025–39), the Medical Research Council (MRC) CRASH (Corticosteroid Randomisation After Significant Head injury) trial collaborators (CRASH: MRC CRASH trial collaborators. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ* 2008;**336**:425–9) and Steyerberg *et al.* [IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI): Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, *et al*. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008;**5**:e165] were selected for external validation in the RAIN study. Four models were developed for predicting mortality at 6 months (one Hukkelhoven and three IMPACT) and six for predicting unfavourable outcome at 6 months (one Hukkelhoven, two CRASH and three IMPACT).

A total of 67 critical care units participated in the RAIN study: 31 within a neuroscience centre (13 dedicated neurocritical care units; 14 combined neurocritical/general critical units, and four additional critical care units admitting overflow patients from the neurocritical care unit); and 36 general critical care units outside a neuroscience centre.

The final RAIN study data set contained 3626 admissions; a highly representative sample of patients receiving critical care following acute TBI in the UK. After exclusions, 3210 patients remained. Of 2323 patients not reported by the Medical Research Information Service (MRIS) as having died, 1834 (79%) were successfully followed up [paper, $n = 1245$ (68%), or telephone, $n = 589$ (32%) questionnaire]. When combined with the 786 patients known to have died, this resulted in an overall follow-up rate of 82% (2620/3210).

Of 3210 patients, 101 (3.1%) had no GCS score recorded and 134 (4.2%) had a last pre-sedation GCS score of 15, which resulted in a data set of 2975 patients for analysis. The most common causes of TBI were RTA (33%), fall (47%) and assault (12%), with 3% other and 5% unknown cause. Major extracranial injury was present in 41% and intoxication confirmed/suspected in 45%. Patients were predominantly young (mean age 45 years) and male (76%).

A substantial burden of poor neurological outcomes and quality of life (QOL) 6 months after TBI was demonstrated. Mortality at discharge from acute hospital was 16% for assault, 21% for RTA and 30% for falls, rising to 17%, 22% and 32%, respectively, at 6 months. Of survivors at 6 months with a known GOSE category, 44% had severe disability, 30% had moderate disability, and only 26% had made a good recovery. When combined with the 26% mortality at 6 months, 61% of patients with known outcome had an unfavourable outcome (death or severe disability) at 6 months. Between 35% and 70% of survivors reported problems across the five domains of the EQ-5D-3L at 6 months.

Median total LOS in critical care was 7 days; this differed between survivors (median 8 days) and non-survivors (median 3 days). Median total LOS in acute hospital was 30 days for survivors compared with 5 days for non-survivors.

In terms the statistical assessment of model performance, there was very little to choose between models of similar complexity from Hukkelhoven, CRASH and IMPACT. The best discrimination overall was from the IMPACT Lab model (c-index 0.779 for mortality and 0.713 for unfavourable outcome) – the only

one of the models to include laboratory parameters – however, the improvement in performance over the models of the next level of complexity (Hukkelhoven, CRASH CT, IMPACT Extended) was very small. There was a larger difference in performance between these models and the simplest models using core data only (CRASH Basic and IMPACT Core), suggesting that there is important prognostic information within the CT scan and the presence or absence of pre-hospital hypoxia/hypotension. The Hukkelhoven and IMPACT Lab models were well calibrated for mortality at 6 months but all models substantially underpredicted the risk of unfavourable outcome at 6 months. The substudy on inter-rater reliability of CT scan reporting suggested that the CT findings included in the models could be assessed with acceptable reliability.

For subsequent analyses, we therefore selected the IMPACT Lab model as the primary model for risk adjustment in the base-case analyses, with the CRASH CT model used for sensitivity analyses (chosen over the Hukkelhoven model as it included more substantially different predictor variables from the IMPACT Lab model).

In the evaluation of alternative locations of care, baseline patient characteristics were similar between dedicated neurocritical care units and combined neuro/general critical care units. At 6 months, mortality was similar between the groups (24% vs 25%) but the dedicated neurocritical care unit group had higher mean EQ-5D-3L utility index score for survivors (0.48 vs 0.43) and higher mean QALYs (0.18 vs 0.16), although none of these differences was statistically significant after case mix adjustment. Critical care length of stay was longer for the dedicated neurocritical care unit group (mean 13 vs 11 days) resulting in higher mean total costs at 6 months (incremental cost £3694 after case mix adjustment).

There were substantial differences in case mix between patients in the 'early' and the 'no or late' transfer groups; patients in the 'early' transfer group were on average younger and with less severe case mix (median predicted risk of death at 6 months 18.3% vs 24.6%). At 6 months, patients in the 'early' transfer group had substantially lower mortality (19% vs 41%), higher mean EQ-5D-3L utility index score for survivors (0.55 vs 0.44) and higher mean QALYs (0.22 vs 0.13). These differences were reduced but remained significant after case mix adjustment. All categories of resource use in the 'early' transfer group were approximately double that of the 'no or late' transfer group, resulting in substantially higher mean total costs at 6 months (incremental cost £15,001 after case mix adjustment).

In the lifetime cost-effectiveness analysis (CEA), dedicated neurocritical care units had higher mean lifetime QALYs at small additional mean costs, with an incremental cost-effectiveness ratio (ICER) of £14,000 per QALY and INB of £1300. The cost-effectiveness acceptability curve (CEAC) suggested that the probability that dedicated compared with combined neurocritical care units are cost-effective is around 60%.

After adjusting for differences in baseline characteristics, the 'early' transfer group reported higher lifetime QALYs, at an additional cost, with an ICER of £11,000 per QALY and INB of £17,000. The CEAC suggested that the probability that 'early' transfer was cost-effective is close to 100%. The results for the subgroup analyses suggested that 'early' transfer has a very low probability of being cost-effective for patients aged >70 years, around 60% probability of being cost-effective for patients without major extracranial injury, and 60–80% probability of being cost-effective for patients with mild to moderate TBI (GCS score of 9–14). The results in the alternative subgroup were close to 100% in each case.

The results of the lifetime CEA were robust to alternative assumptions.

Conclusions

The risk prediction models evaluated in the RAIN study demonstrated sufficient statistical performance to support their use in research studies but fell below the level that would be required to recommend their use to guide individual patient decision-making.

Although the results of the RAIN study suggest that, within a neuroscience centre, management in a dedicated neurocritical care unit may be cost-effective compared with management in a combined neuro/general critical care unit, there was considerable statistical uncertainty in this finding. The results of the RAIN study support current recommendations that all patients with severe TBI (GCS score of 3–8) would benefit from transfer to a neuroscience centre, regardless of their need for neurosurgery. However, caution should be exercised with regard to the risk of residual confounding. Benefit was also found for patients with mild or moderate TBI (GCS score of 9–14) requiring critical care. The only exception was in patients aged of >70 years, for whom transfer was associated with increased risk of death, and the most cost-effective strategy was management within the hospital at which they presented.

We recommend further research to:

1. explore the potential to improve on the current risk prediction models for acute TBI
2. consider alternative approaches for handling the potential impact of unobserved confounders on the RAIN study results
3. continue to follow up the RAIN study cohort to obtain data on long-term mortality, functional outcomes and QOL
4. better understand the alternative pathways of care for patients following acute TBI and the impact of these on costs and outcomes, and
5. explore equity of access to post-critical care support for patients following acute TBI.

The RAIN study should inform future research studies in the neurocritical care of adult patients following acute TBI through provision of reliable data for sample size calculations and exploratory analyses, and informing the choice of risk adjustment methods and data set design.

Funding

Publication

Health Technology Assessment

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