Late mortality after severe traumatic brain injury in New South Wales: a multicentre study

Severe traumatic brain injury (TBI), a leading cause of death and disability worldwide,1 is a particularly important societal issue because of its high economic and personal cost.2 Australian studies have found acute mortality rates of 30%–35% during the first 6 months after severe TBI.3,4 Recent Australian estimates on the lifelong economic cost of moderate-to-severe TBI assumed that “patients surviving year 1 [post-injury] reverted to the mortality risk for the general population”.5 However, further data are required to determine the accuracy of this assumption and to improve the robustness of future modelling.

The only Australian investigation examining late (ie, greater than 1 year) all-cause mortality for people with severe TBI involved a single-centre cohort study of 476 patients undergoing rehabilitation in New South Wales.6 The standardised mortality ratio (SMR) — the ratio of observed mortality in the study group compared with that expected of an age- and sex-matched population — after discharge indicated a fourfold increase in mortality; this ratio is higher than international long-term mortality estimates, which range from 1.1 to 3.1.3,8-14

An increased understanding of risk factors associated with long-term mortality is important for informing clinical management. Current knowledge, predominantly from overseas studies, has identified increasing age,1,7,10,15-17 male sex,10,17 a history of psychiatric illness,7,8,11 alcohol and drug misuse,13 epilepsy,9,13,18 and functional dependence12,13,17 as important variables. Studies suggest that post-TBI death rates are equivalent to those of the general population for some diseases (eg, neoplasia), while mortality rates from other causes (eg, respiratory illnesses, aspiration pneumonia) are significantly elevated.

Here we further investigate these issues in an Australian data linkage study of people with severe TBI who were discharged from the three adult inpatient units of the NSW Brain Injury Rehabilitation Program (BIRP) in metropolitan Sydney. The study aimed to: (i) determine the long-term all-cause mortality pattern for this inception cohort; (ii) identify associated risk factors; and (iii) examine mortality rates for specific causes of death.

Methods

After obtaining approval from the appropriate local institutional ethics committees, we searched databases and medical records to identify consecutive rehabilitation admissions of patients with TBI since the NSW BIRP commenced on 1 January 1990.19,20 The resultant inception cohort was derived from this integrated, statewide, specialist inpatient and community-based rehabilitation program for people who had sustained a severe TBI. Admissions were screened against the following inclusion criteria: age 16–70 years at time of injury; primary inpatient units of the NSW Brain Injury Rehabilitation Program (BIRP) in metropolitan Sydney. The study included all-cause mortality for any patient admitted to one of the three metropolitan centres in New South Wales, even if the admission was prior to the commencement date of the study. After data linkage and cleaning, the final cohort consisted of 2545 adults consecutively discharged from one of the three metropolitan tertiary, post-acute inpatient rehabilitation services of the New South Wales Brain Injury Rehabilitation Program from 1 January 1990 to 1 October 2007 after inpatient rehabilitation for primary TBI.

Main outcome measure: Survival status at 1 October 2009.

Results: 258 deaths were recorded in this sample, yielding a standardised mortality ratio of 3.19 (95% CI 2.80–3.60). Risk of death remained elevated above societal norms for at least 8 years after discharge from rehabilitation. Mortality risk was increased by: functional dependence at discharge; age at injury; pre-injury drug and alcohol misuse; pre-injury epilepsy; and discharge to an aged care facility. The risk of death from external causes, and respiratory system and nervous system disorders was six to seven times higher, and the risk of death from disorders of the digestive system, and mental and behavioural disorders was five times higher in adults with severe TBI than in the general population.

Conclusions: People who survive to discharge from inpatient rehabilitation following a severe TBI were found to have a sustained increase in risk of death for eight years post discharge. Various demographic and injury-related variables selectively increase mortality risk and may be modifiable in order to reduce the observed increase in mortality.

Abstract

Objectives: To determine the long-term mortality pattern of adults with severe traumatic brain injury (TBI), and to identify the risk factors associated with death in this group.

Design, patients and setting: Inception cohort study of 2545 adults consecutively discharged from one of three metropolitan tertiary, post-acute inpatient rehabilitation services of the New South Wales Brain Injury Rehabilitation Program from 1 January 1990 to 1 October 2007 after inpatient rehabilitation for primary TBI.

Main outcome measure: Survival status at 1 October 2009.

Results: 258 deaths were recorded in this sample, yielding a standardised mortality ratio of 3.19 (95% CI 2.80–3.60). Risk of death remained elevated above societal norms for at least 8 years after discharge from rehabilitation. Mortality risk was increased by: functional dependence at discharge; age at injury; pre-injury drug and alcohol misuse; pre-injury epilepsy; and discharge to an aged care facility. The risk of death from external causes, and respiratory system and nervous system disorders was six to seven times higher, and the risk of death from disorders of the digestive system, and mental and behavioural disorders was five times higher in adults with severe TBI than in the general population.

Conclusions: People who survive to discharge from inpatient rehabilitation following a severe TBI were found to have a sustained increase in risk of death for eight years post discharge. Various demographic and injury-related variables selectively increase mortality risk and may be modifiable in order to reduce the observed increase in mortality.

[Additional text may be included here, including methodology, results, and discussion.]

References

### 1 Age distribution, sex and pre-injury medical history of the 2545 patients with severe traumatic brain injury, and results of the univariate Cox regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>Measure</th>
<th>Hazard ratio (95% CI)</th>
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<tr>
<td><strong>Demographic characteristics</strong></td>
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<td>Mean age ± (SD)</td>
<td>2545</td>
<td>35 (14)</td>
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<tr>
<td>16–20 years (reference group for Cox regression)</td>
<td>374 (15%)</td>
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<td>21–25 years</td>
<td>459 (18%)</td>
<td>0.65 (0.32–1.32)</td>
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<td>26–35 years</td>
<td>591 (23%)</td>
<td>1.44 (0.81–2.55)</td>
<td>0.21</td>
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<tr>
<td>36–45 years</td>
<td>457 (18%)</td>
<td>2.82 (1.64–4.86)</td>
<td>&lt; 0.001</td>
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<tr>
<td>≥ 46 years</td>
<td>664 (26%)</td>
<td>5.36 (3.23–8.88)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Sex*</td>
<td>2545</td>
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<td></td>
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<tr>
<td>Female (reference group for Cox regression)</td>
<td>485 (19%)</td>
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<td>Male</td>
<td>2060 (81%)</td>
<td>2.39 (1.57–3.64)</td>
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<td><strong>Pre-injury medical history</strong></td>
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<tr>
<td>Pre-injury history of traumatic brain injury*</td>
<td>2545</td>
<td>61 (2%)</td>
<td>1.71 (0.96–3.06)</td>
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<tr>
<td>Pre-injury history of epilepsy*</td>
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<td>77 (3%)</td>
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<td>History not reported in medical record</td>
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<td>636 (29%)</td>
<td>3.01 (2.34–3.87)</td>
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<td><strong>Pre-injury history of psychiatric disorder</strong></td>
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<tr>
<td>History not reported in medical record</td>
<td>1848 (85%)</td>
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<tr>
<td>History verified or reported in medical record</td>
<td>320 (15%)</td>
<td>1.36 (0.98–1.88)</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

* Variables entered into the univariate Cox regression (sufficient available data). † Age at injury categorised using visual binning of equal percentiles on scanned cases. ‡ Verified by drug/alcohol referral or a record of units per day. § Verified by recorded psychiatric admission, medications or referral to psychologist/psychiatrist.

as were secondary admissions for reviews and reassessments.

Data were collected on demographic, pre-injury, clinical, service-related and mortality variables (Box 1, Box 2). Where available, the functional independence measure (FIM) was used to assess each patient’s functional independence across 18 domains, with scores ranging from complete dependence (FIM score, 18) to complete independence (FIM score, 126). Patients’ survival status was censored on 1 October 2009, providing a minimum 24-month interval between patient enrolment and the census date. The cohort list was provided to two national data registries — the National Death Index (NDI) and the National Coroners Information System (NCIS) — for matching, which yielded the date, cause of death and place of residence at time of death for deceased patients.

The NDI collates Australian death data from 1980, utilising Births, Deaths and Marriages information from each Australian state and territory and from the Australian Bureau of Statistics. The NDI records International classification of diseases (ICD) codes for cause of death extracted from death certificates, identifying primary and secondary causes of death. A probabilistic method matched our sample against NDI data using date of birth, family name, first name, and all derivatives of these. Guidelines for probabilistic matching and minimum thresholds for data acceptance recommended by the NDI were followed.

The NCIS collates Australian coronial information for people with external (eg, accidental or violent) causes of death from 1 July 2000. NCIS information assisted in determining intentionality for deaths from external causes after this date.

The primary cause of death stated on death certificates was coded using International classification of diseases, injuries and causes of death, 9th revision (ICD-9) for deaths from 1980 to 1996 and International statistical classification of diseases and related health problems, 10th revision (ICD-10) for deaths from 1997 onwards. Secondary causes of death or events associated with death were recorded as factors involved in the chain of events leading to the deaths of patients with TBI.

### Statistical analysis

Descriptive statistics were calculated for all variables. Follow-up years (otherwise termed risk-exposure time) were calculated from date of discharge from rehabilitation to the census date or the date of death for those who had died. A population reference sample was constructed from Australian life-expectancy tables based on the age, sex and risk-exposure time for each person with TBI in the study. SMRs with 95% CIs were calculated for all-cause deaths across the entire study period, for individual years after discharge and for individual causes of death. An SMR greater than 1.0 indicates an increased mortality risk compared with that of the matched reference population.

Cox proportional hazards regression analysis evaluated the effect of each potential risk factor on survival. Variables for which we had data completeness of 85% or greater were used in the univariate and multivariate analyses. Univariate results with P values < 0.05 were entered into the final multivariate regression. Hazard ratios with 95% CIs were calculated. A backwards stepwise method of regression was used to sequentially eliminate factors that did not independently contribute to risk of death.

Linear variables were grouped into ordinal categories for the purpose of
Cox regression analysis. Discharge FIM scores were coded into three categories: maximal assistance (score 18–54, indicating a mean FIM item score of 3 or less); moderate assistance (score 55–107, indicating a mean FIM item score of 4 or 5); and independent (108–126, indicating a mean FIM item score of 6 or more).

Age at injury was categorised by visual binning of equal percentiles on scanned cases (20% of cases in each category): 16–20 years, 21–25 years, 26–35 years, 36–45 years, and ≥ 46 years.

## Results

The study sample of 2545 adults with severe TBI is characterised in Box 1 and Box 2. Patient admissions were evenly spread across the three BIRP units. Most injuries resulted from motor vehicle accidents; 81% of patients were male and the mean age at time of injury for the entire sample was 35 years. The median length of admission for rehabilitation was 37 days, and the mean discharge FIM score was 104. Three-quarters (74%) were discharged home, and a third (32%) required moderate or maximal assistance. The median risk-exposure time was 9.3 years (interquartile range [IQR], 7.4; range, 2.0–19.5).
Long-term all-cause mortality pattern

There were 258 deaths recorded at the census date, representing a mortality rate of 10.2%. Death certificates were available from the NSW Registry of Births, Deaths and Marriages or the NDI for 243 deceased patients (94%). The expected number of deaths in the matched reference population was 81 (3.2%), yielding an SMR of 3.19 (95% CI, 2.80–3.60). There was a 21% over-representation of male deaths (observed male to female ratio, 9.75:1 compared with a predicted ratio of 8.07:1). The median time from discharge from rehabilitation to death was 4.8 years (range, 1 month to 17.4 years). The difference between the observed discharge after rehabilitation and population-predicted deaths is shown in Box 3A.

The year-by-year SMR for the inception cohort ranged from 12.3 in the first year after discharge (95% CI, 3.9–29.3) to 1.25 in the 15th year after discharge (Box 3B). Yearly SMRs were not calculated beyond the 16th year after discharge because there were too few deaths for accurate calculation. Across this interval, the SMR decreased over time with a power law function (y = 11.052x −0.7225, r² = 0.843) potentially enabling prediction of yearly SMR. From the 9th year after discharge, the 95% CI lower bound intermittently included 1.0, suggesting an elevated mortality for patients after TBI above the general population for at least 8 years after discharge.

Univariate and multivariate risk factors

The univariate Cox regression analysis identified several risk factors contributing to risk of death (Box 1, Box 2). When entered together into the multivariate Cox regression analysis (Box 4), functional dependence produced the highest hazard ratio, more than triple the mortality risk of an independent subject.

Mortality patterns for specific causes of death

Cause of death by ICD-10 chapter is provided in Box 5. Excluding neoplasia, the number of deaths in the TBI cohort exceeded those in the statistically derived reference group, with cause-specific SMRs ranging from 2.6 to 14.1. Deaths in the category with the highest SMR, “Symptoms, signs and abnormal clinical and laboratory findings”, were due to “natural causes” or were otherwise “not ascertainable”.

Discussion

This multicentre Australian data linkage study followed an inception cohort of 2545 adults with severe TBI over a mean risk-exposure time of 10 years to determine incidence of mortality and associated risks. Mortality among this patient group was 3.2 times greater than that of the general population, a rate at the higher end of the findings of North American studies, but consistent with those of the previous Australian study. Examined year by year after discharge from rehabilitation, the mortality rate was 12 times that predicted for the general population during the first year after discharge and remained higher than the general population for each of the following seven years. This finding provides valuable new information for reviewing assumptions underlying Australian health modelling.

We found that functional dependence at discharge from rehabilitation...
was the strongest factor associated with an increased risk of death in adults with severe TBI, supporting findings from Australian research. The next greatest risk factor associated with increased mortality in the cohort with TBI was older age at injury. Adults aged 36 years and older were two to three times more likely to die during the study period than young adults. These age-related relativities are also evident in some international settings. Other Australian states, admissions in the NSW BIRP occur systematically beyond those of the single Australian study conducted to date. In contrast to other Australian states, admissions in the NSW BIRP occur systematically and without the funding constraints evident in some international settings. However, our study was limited to primarily working-age adults with severe TBI, and further research is required into patterns of mortality in people with mild TBI, and children, the elderly and indigenous Australians with severe TBI. Findings about cause of death reported in our study may underestimate true rates, because data on cause of death was undetermined for 18 deaths. Finally, further research will be required to determine whether systematic rehabilitation programs offer any advantage in terms of the late mortality of survivors of severe TBI.

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