

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

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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.^{3–5} 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”.⁶ 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.⁷ 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,¹¹ epilepsy,^{9,13,18} and functional dependence^{12,13,17} as important variables. Studies suggest that post-TBI death rates are equivalent to those of the general population for some diseases (eg, neoplasia),

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.

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 BIRP admission; severe TBI (Glasgow Coma Scale score < 9 and/or duration of post-traumatic amnesia > 1 day²¹); and discharged alive before 1 October 2007. This date was selected to coincide with introduction of the Lifetime Care and Support Scheme for adults severely injured in a motor vehicle accident in NSW. Admissions for subsequent brain injuries for any patient were excluded,

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

Variable	No. of patients	Measure	Hazard ratio (95% CI)	P
Demographic characteristics				
Mean age*† (SD)	2545	35 (14)		
16–20 years (reference group for Cox regression)		374 (15%)	1	
21–25 years		459 (18%)	0.65 (0.32–1.32)	0.24
26–35 years		591 (23%)	1.44 (0.81–2.55)	0.21
36–45 years		457 (18%)	2.82 (1.64–4.86)	< 0.001
≥ 46 years		664 (26%)	5.36 (3.23–8.88)	< 0.001
Sex*	2545			
Female (reference group for Cox regression)		485 (19%)	1	
Male		2060 (81%)	2.39 (1.57–3.64)	< 0.001
Pre-injury medical history				
Pre-injury history of traumatic brain injury*	2545	61 (2%)	1.71 (0.96–3.06)	0.07
Pre-injury history of epilepsy*	2545	77 (3%)	5.63 (3.90–8.12)	< 0.001
Pre-injury history of alcohol/drug misuse*	2169			
History not reported in medical record		1533 (71%)	1	
History verified‡ or reported in medical record		636 (29%)	3.01 (2.34–3.87)	< 0.001
Pre-injury history of psychiatric disorder*	2168			
History not reported in medical record		1848 (85%)	1	
History verified§ or reported in medical record		320 (15%)	1.36 (0.98–1.88)	0.06

* 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)²² 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 (oth-

erwise 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 tables²³ based on the age, sex and risk-exposure time for each person with TBI in the study. SMRs with 95% CIs²⁴ 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

2 Clinical, service and mortality variables of the 2545 patients with severe traumatic brain injury, and results of the univariate Cox regression analysis

Variable	No. of patients	Measure	Hazard ratio (95% CI)	P
Clinical variables				
Brain injury cause	2464			
Motor vehicle accident-related		1442 (58%)		
Fall/dive		524 (21%)		
Assault/non-accidental injury		355 (14%)		
Sport/recreation-related		63 (3%)		
Gunshot		15 (1%)		
Other traumatic brain injury		65 (3%)		
Mean functional independence measure scores (SD)*				
Admission total score	2144	69 (37)		
Independent (108–126) (reference group for Cox regression)		430 (20)	1	
Moderate assistance (55–107)		909 (42)	1.07 (0.71–1.63)	0.74
Maximal assistance (18–54)		805 (38)	1.96 (1.29–2.84)	0.001
Discharge total score	2126	104 (29)		
Independent (108–126) (reference group for Cox regression)		1447 (68)	1	
Moderate assistance (55–107)		466 (22)	1.51 (1.07–2.13)	0.02
Maximal assistance (18–54)		213 (10)	4.82 (3.49–6.66)	< 0.001
Occurrence of in-hospital aspiration pneumonia*	2199	79 (4%)	3.82 (2.54–5.74)	< 0.001
Presence of percutaneous endoscopic gastrostomy during admission	1692	311 (18%)		
Dysphagia reported/documentated at discharge	1752	204 (12%)		
Anticonvulsants prescribed at discharge	1467	465 (32%)		
Guardianship order in place	2545	171 (7%)		
Service variables				
Median days from injury to rehabilitation admission (IQR)	2534	25 (24)		
Median length of stay for rehabilitation (IQR)*	2545	37 (66)		
< 30 days (reference group for Cox regression)		1099 (43)	1	
31–60 days		546 (22)	1.26 (0.90–1.78)	0.18
≥ 61 days		900 (35)	1.79 (1.36–2.37)	< 0.001
Median days from injury to rehabilitation discharge (IQR)	2545	68 (89)		
Financial compensation for injury	1851	826 (45%)		
Discharge destination*	2332			
Private house (reference group for Cox regression)		1730 (74%)	1	
Ongoing rehabilitation/medical care		421 (18%)	1.45 (1.03–2.04)	0.035
Care facility (nursing home or hostel)		181 (8%)	5.91 (4.40–7.95)	< 0.001
Mortality variables				
Deceased	2545	258 (10%)		
Median years from discharge to death (IQR)	258	4.8 (6.6)		
Place of residence at time of death	253			
Private house		201 (79%)		
Hospital or care facility (nursing home/hostel)		52 (21%)		

IQR = interquartile range.

*Variables entered into the univariate Cox regression (sufficient available data).



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 of patients (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 ($y = 11.052x^{-0.7225}$, $r^2 = 0.843$) 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

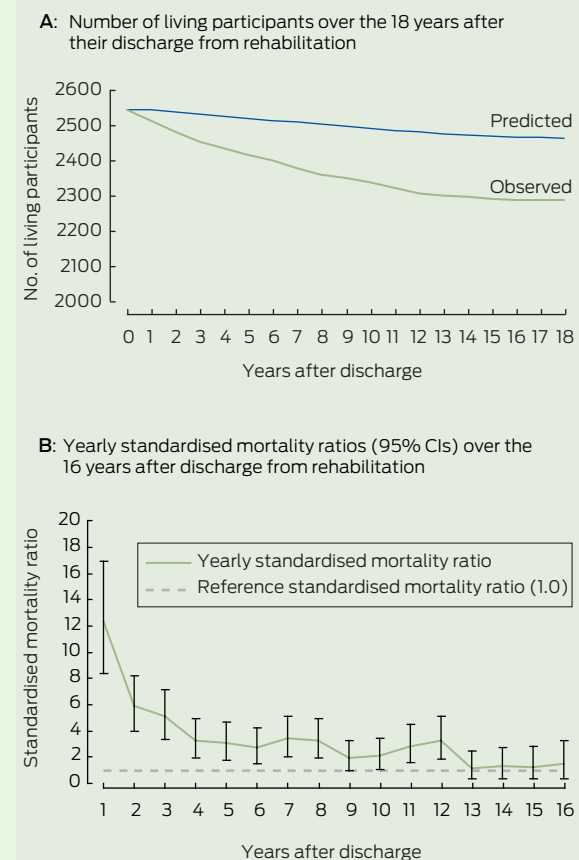
2.6 to 14.1. Deaths in the category with the highest SMR, “Symptoms, signs and abnormal clinical and laboratory findings”, were due to “natural causes” or were otherwise “not ascertainable”.

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,^{9–11,14} but consistent with those of the previous Australian study.⁷ 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.⁶

We found that functional dependence at discharge from rehabilitation

3 Predicted versus observed mortality and yearly standardised mortality ratios (95% CIs) for 2545 patients with severe traumatic brain injury



4 Significant risk factors for death after traumatic brain injury for 1635 patients, from the multivariate Cox regression analysis*

Predictive factors in multivariate analysis	Hazard ratio (95% CI)	P
Sex		
Female (reference group for Cox regression)	1	
Male	2.24 (1.38–3.62)	0.001
Age		
16–20 years (reference group for Cox regression)	1	
21–25 years	0.57 (0.24–1.33)	0.19
26–35 years	1.13 (0.58–2.20)	0.73
36–45 years	2.01 (1.07–3.80)	0.03
≥ 46 years	3.25 (1.80–5.87)	< 0.001
Pre-injury history of epilepsy	2.11 (1.35–3.30)	0.001
Pre-injury history of alcohol/drug misuse	2.39 (1.76–3.25)	< 0.001
Occurrence of aspiration pneumonia	1.79 (1.10–2.91)	0.02
Discharge destination		
Private house (reference group for Cox regression)	1	
Ongoing rehabilitation/medical care	0.98 (0.65–1.47)	0.91
Care facility (nursing home or hostel)	1.94 (1.28–2.94)	0.002
Discharge functional independence measure scores		
Independent (108–126) (reference group for Cox regression)	1	
Moderate assistance (55–107)	1.06 (0.72–1.57)	0.76
Maximal assistance (18–54)	3.39 (2.22–5.19)	< 0.001

* Variables removed during backward multivariate Cox regression were length of stay and admission functional independence measure score. ◆

5 Causes of death based on relevant ICD-10 chapters, number of observed and predicted deaths with cause-specific SMR

ICD-10 Chapter	Title	Observed	Predicted	SMR (95% CI)*
I	Certain infectious and parasitic diseases	4	1.4	—
II	Neoplasms	29	28.8	1.0 (0.7–1.4)
III	Diseases of blood	1	0.3	—
IV	Endocrine	2	2.2	—
V	Mental and behavioural disorders	9	1.7	5.4 (2.4–9.6)
VI	Diseases of the nervous system	14	2.2	6.4 (3.4–10.3)
IX	Diseases of the circulatory system	52	19.9	2.6 (1.9–3.4)
X	Diseases of the respiratory system	49	4.8	10.2 (7.5–13.4)
XI	Diseases of the digestive system	15	2.9	5.2 (2.9–8.3)
XIV	Diseases of genitourinary system	3	0.9	—
XVIII	Symptoms, signs and abnormal clinical and laboratory findings	8	0.6	14.1 (5.9–25.8)
XX	External causes of mortality†	54	10.3	5.2 (3.9–6.7)
	Cause of death pending	18		
	Total	258		

ICD-10 = *International statistical classification of diseases and related health problems*, 10th revision. SMR = standardised mortality ratio.

*SMR (95% CI) not calculated for causes of death for which fewer than five deaths were observed, because of the inaccuracy of the prediction. †External causes of mortality include transport accidents, falls, accidental drowning and submersion, other accidental threats to breathing, exposure to smoke, fire and flames, accidental poisoning by and exposure to noxious substances, intentional self-harm, assault and inhalation of gastric contents/food. ◆

was the strongest factor associated with an increased risk of death in adults with severe TBI, supporting findings from Australian¹⁷ and international research.^{9–13,25} 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 observed in the general, non-injured population,²³ which led to the observed normalisation of year-by-year SMR with increasing years after injury. The interaction between age-related mortality risk and longitudinal SMR warrants further study.

In the general population, males at all ages have elevated mortality rates compared with females, but the mortality rate of males in this cohort was 20% higher than would be expected. This finding confirms those of previous studies,^{1,7,10,15–17} and remains unexplained. In our study, all but one of the deaths due to external causes (eg, transport accidents, falls, assault and intentional self-harm) were in males. Similarly, deaths from circulatory disease (including ischaemic heart disease, myocardial infarction and cerebrovascular disease) were almost exclusively observed in males. This observation may go some way to

explaining the consistent over-representation of males in studies of late mortality after TBI. In particular, factors affecting external causes of death, such as altered regulation of behaviour or impaired judgement, and circulatory diseases warrant further examination.

Discharge from rehabilitation to aged care facilities doubled the risk of mortality after TBI. This risk factor remained significant even when controlling for level of functional dependency at discharge, suggesting that discharge to an aged care facility contributed a unique mortality risk independent of the level of assistance needed by the person at discharge from rehabilitation as measured by FIM. It is unclear whether this effect was the result of characteristics related to individual patients or services.

The inception cohort design, implemented across multiple rehabilitation centres, resulted in a large sample of working-age people undergoing specialty rehabilitation after TBI in NSW, thereby improving the rigour of data 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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