

Long-term mortality trends in patients with traumatic brain injury

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(Received 9 December 1999; accepted 24 January 2000)

Comparison of long-term mortality rates between patients with traumatic brain injury (TBI) and the general population has not been adequately investigated. This project aimed to obtain information on the long-term mortality rate of patients with TBI. Using a rehabilitation database of a major teaching hospital, the search identified 476 patients, of whom 27 were deceased. This mortality rate (5.7%) was compared with the expected mortality rate for an equivalent population without TBI (1.5%) using Australian Life Table data. It was found that patients with TBI had a significantly higher mortality rate than the general population ($\chi^2 = 12.2$, $p < 0.001$). Possible reasons for this finding are discussed.

Introduction

Traumatic brain injury (TBI) is a significant cause of death and long term disability worldwide. While numerous investigations have looked at aspects of the human cost of TBI, there are few investigations in the international literature regarding long-term mortality trends for patients who survive the initial post-injury period. There is no published data from Australian studies. Of the limited literature available, the majority of papers have restricted their sample to military or paediatric populations, with only one paper focusing on a community-based adult population.

In a classic study of long-term mortality trends following TBI, Walker *et al.* [1] found that, in the first 15 years following head injury, the death rate amongst WWI soldiers was three to four times greater than expected. This finding was repeated when Walker *et al.* [2] increased their sample size to approximately 600 males. By constructing Life Expectancy (LE) tables, the authors estimated a reduced LE for highly functioning patients of 3-5 years.

Higher than expected mortality rates among persons with penetrating TBI were also found by Rish *et al.* [3], who investigated 1127 Vietnam Veterans over a 15-year period. Subjects were 21-35 year old males who had survived at least 1 week post-injury. Of the 90 deaths in this study, most deaths were concentrated in the first year post-injury (46), with 16 occurring in the period between 1-4 weeks of injury. Deaths were usually attributable to the effects of the injury or the sequelae of

coma. Forty-seven of the 49 patients who remained in a coma or Persistent Vegetative State (PVS) were deceased at the conclusion of the 15-year study period. The authors concluded that the mortality rate for their sample began to approach that of the general population, as determined by the actuarial levels projected for North American males of similar age after 3 years. Despite this finding, closer inspection of their published data reveals that the annual mortality rate consistently exceeded that of the general population for the first 12 years post-injury.

In a long-term investigation of mortality rates of non-military patients with TBI, Lewin *et al.* [4] followed 479 patients in England for a period of 10–24 years. All patients had experienced coma or Post Traumatic Amnesia (PTA) duration of more than 1 week. Functional status was estimated by examining mobility, with independent mobility suggesting a high level of function. The study found that there was a 4–5 year reduction in LE in high functioning patients. Amongst patients in a PVS, most died within 1 year and none survived longer than 10 years. Causes of death were also estimated and Lewin [4] reported that after the initial high-risk period, many causes of death were no more common among patients with TBI than in the general population. Exceptions included epilepsy, meningitis, accidents and suicides, and respiratory disease.

A more recent study looking at long-term mortality trends following TBI in a paediatric-adolescent population was that of Strauss *et al.* [5]. Nine hundred and forty-six subjects, aged 5–21 years and with a male:female ratio of 3:1, were assessed. Patients were identified due to the presence of long term or permanent disability. These patients were sub-divided into high and low functioning groups by their classification on the California State Department of Developmental Disabilities Service's measure, the Client Development Evaluation Report. The authors reported that high functioning patients had a reduction in LE of ~3–5 years, as compared to that of the general population. The LE for patients functioning at a low level 6 months post-injury was only 15 years. Males were found to have a significantly elevated mortality rate when compared to females, with a relative risk of 1.20 (95% confidence interval 1.03–1.39).

In light of the previous findings, this study aimed to evaluate mortality rates in a cohort of patients with severe TBI who survived the initial post-injury period to be admitted to inpatient rehabilitation. The primary aims of this study were to:

- (1) Explore the impact that differences in gender, age, injury related variables and level of functional independence have on mortality rates.
- (2) Determine mortality rates of persons who have sustained a TBI, as compared with an age and sex matched general population sample over a 10 year period.
- (3) Examine whether causes of death amongst patients with TBI differ from the general population.

Method

Sample selection

To exclude patients who died in the early high risk period, only patients admitted to the Brain Injury Rehabilitation Service (BIRS), Westmead Hospital, following severe TBI in the calendar years 1986–1996 were included in the study.

Demographic data (for example, personal contact details, age, gender) were collected for all subjects. Level of function was determined at the time of discharge from inpatient rehabilitation using the Functional Assessment Measure (FAM) [6]. Injury related details (e.g. pre-morbid psychiatric history, substance use, admission GCS, discharge FAM, etc) were available from the BIRS Database for patients admitted from August 1990. This resulted in missing data rates for the FAM of 41% and 30% and for pre-morbid psychiatric history/substance abuse of 52% and 22% for the Deceased and Alive subgroups, respectively.

The living status of patients was determined with August 1997 as the anchor point. An attempt was made to contact all patients, other than those known to be deceased, by mail, telephone or through outpatient clinic appointments. A list of patients known to be deceased or who were non-contactable during August 1997 was forwarded to the New South Wales Department of Births, Deaths and Marriages. Death certificates were obtained for deceased patients.

Statistics

The construction of a population-based control sample was achieved using the Australian Bureau of Statistic's 1997 Death data [7]. The cumulative risk of death was calculated for each subject with TBI, corresponding to the gender and age for each year they were enrolled in the study. The mortality rates of the control and TBI groups were then analysed using Fishers Exact Test (SPSS v9.0) [8].

Additional variables such as age at injury, gender, previous psychiatric morbidity, substance abuse and functional status (via discharge FAM) were also analysed across the Alive and Deceased patient sub-groups using independent samples *t*-test or Fishers Exact Test as appropriate.

Results

Four hundred and seventy-six patients were included in the study cohort and retrospectively analysed. The number of patients enrolled in the study increased each year as a result of new admissions to the BIRS. The mean duration between injury and the anchor point was 64 months, with a range of 8 months to 11 years. The median date of injury was May 1992. Injuries were almost exclusively due to closed head trauma (97%), with a small number of penetrating head injuries. Mode of injury was predominantly motor vehicle related injury (62%), followed by falls/hit by object (21%), assault (12%) and sport-related accidents (4%).

Twenty-seven of the 476 patients enrolled in the study had died by August 1997, a mortality rate of 5.7%. Table 1 describes demographic characteristics of the Alive and Deceased sub-groups. Only 8% of the Deceased sub-group were female, compared to 20% for the Alive group, however this was not statistically significant. There was some suggestion of an association between previous psychiatric morbidity and risk of death ($\chi^2 = 3.4$, $p < 0.064$), while a history of substance abuse (including alcohol) was not found to be significant between the two sub-groups. The length of time between injury and death ranged from 45 days to 9 years and 2 months post-injury, with a median interval of 17 months. It appeared that the mean age among the Deceased subgroup was slightly higher ($t(27) = -1.6$, $p < 0.055$). The Deceased sub-group displayed a significantly lower level of functional independence on discharge FAM scores compared to the Alive sub-group ($t(15) = 5$,

Table 1. Demographic characteristics of the alive and deceased sub-groups

	Alive	Deceased	<i>p</i> -value
Gender (<i>n</i>)			
Male	359	25	
Female	90	2	<i>p</i> < 0.078
Ratio	4:1	12:1	
Mean age at injury (SD)	31.7 (14)	37.6 (18)	<i>p</i> < 0.055
Mean FAM scores (SD)	174 (39)	84 (72)	<i>p</i> < 0.001
Pre-morbid psychiatric history	45	4	<i>p</i> < 0.064
Pre-morbid substance use	46	3	<i>p</i> < 0.308

p < 0.001). All subjects that had lower FAM scores (≤ 100) and were deceased at the conclusion of the study were male.

The number of deaths expected in an equivalent sample from the general population was determined using Life Tables. This process gave 6.7 expected deaths (rounded up to 7 for further analyses) with a mortality rate of 1.5%. The number of deaths were compared using Fishers Exact Test, showing that significantly more patients with TBI had died than would be expected in the general population ($\chi^2 = 12.2$, *p* < 0.001); 95% confidence intervals (CI) were calculated for the two groups. The Poisson exact 95% CI for the mortality rate of the TBI groups is 0.037–0.083 around the point estimate of 0.057, compared to 0.006–0.030 around the point estimate of 0.015 for the expected population mortality rate. The absence of overlap in the 95% CI's corroborates the suggestion that the mortality rates between the two groups are significantly different.

Figure 1 shows survival curves for the TBI group and a statistically derived matched group from the general population plotted against time post-injury. As can be seen, the greater proportion of deaths occur in the TBI group in first 12 months post-injury.

Table 2 describes the causes and frequency of the deaths in patients with TBI. Thirty per cent of deaths were found to be due to cardiorespiratory arrests, the minority following myocardial infarction (three out of eight). Infection formed the next largest category, contributing to 22% of all deaths with bronchopneumonia being the most common (five out of six). The remaining causes of death varied in categories and frequency. No trends were found between cause of death and the variables of age, level of function and/or time from injury to death.

Discussion

This study sought to provide an analysis of long-term mortality trends in predominantly adult patients following severe TBI. An overall mortality rate of 5.7% was found, which incorporated an over-representation of low functioning patients and a trend for increased mortality amongst older patients. The mortality rate in the TBI group varied significantly from the predicted rate of 1.5%, based on an equivalent population sample. Females were relatively under-represented and subjects with pre-morbid psychiatric histories were over-represented in the deceased sub-group.

There is a degree of similarity between these results and some of the previous literature. The mortality rate was 5.7% after an average of 5 years post-injury. Rish

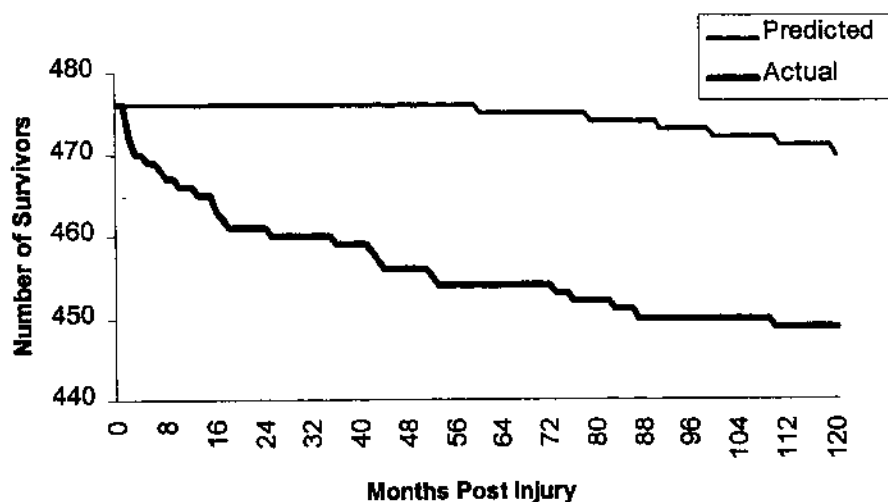


Figure 1. Comparison of actual versus predicted survival following TBI.

Table 2. Causes of death

Cause of death	Frequency
Cadiorespiratory arrest	8
Infection—bronchopneumonia/sepsis	6
Haemorrhage—intracranial/gastrointestinal/pulmonary	4
Epilepsy	1
Renal failure	1
Accidental	2
Suicide	1
Substance abuse/overdose	1
Unknown/insufficient information on death certificate	3
Total	27

et al. [3] reported a mortality rate of 8% after 15 years and, if his patients who died under 1 month were removed from the analysis, this rate falls to 6.7% (74 of 1111 subjects). Strauss *et al.* [5] had a of 4.0% rate over a 9 year 'window', whereas Lewin *et al.* [4] reported a mortality rate of 33% 10–24 years post-injury. There is a higher degree of consensus in previous literature with regards to the survival of lower functioning TBI survivors. Although definitions of what constituted a low level of function varied amongst previous studies, mortality rates for low level patients were 96% at 15 years [3], 100% at 15 years [5] and 100% at 10 years [4]. The finding of 31% deceased at 5 years is comparable with previous investigations.

While reassuring, the similarity in these results is also somewhat surprising, as the results span the greater part of a century and concern dramatically different modes of injury. The pathophysiology of penetrating and closed head injury are markedly different and it is conceivable that mortality rates would differ between the two mechanisms. Again, the experiences of survivors of TBI on the battlefield are likely to differ from those in civilian life. However, mortality rates appear approximately

equivalent in closed and penetrating head injury. Improvements in medical technology from World War I, through the Vietnam War, to current practice have increased the survival rate for patients with severe TBI. While modern medicine may be contributing to increased survival immediately following TBI, there is little to suggest any improvement in life expectancy.

The over representation of lower functioning patients with TBI in the current and previous literature [3–5] may be attributable to a number of factors. While most deaths did not appear causally linked to direct complications of the TBI, indirect links may be postulated. As suggested previously [5], inactivity in lower functioning TBI survivors may play a role in late mortality. Research looking at late mortality in patients with spinal cord injury and cerebral palsy have identified a high correlation between mobility and mortality [5, 9–11]. Indeed, immobility may be the common factor that explains similar findings in lower functioning patients with TBI despite differences in the nature of the injury and variable definitions of what constitutes low level function in previous research.

However, inactivity related morbidity may not be the whole story. Recent literature has suggested that outcome following severe TBI may be related to an individual's apolipoprotein E (APOE) status [12]. In particular, the presence of the APOE 4 allele has been linked to an increased risk of death or severe disability following severe TBI [13, 14]. This genotype has also been linked to increased risk of developing ischaemic heart disease (IHD) [15]. In patients with a low level of function post-TBI, the combined risk of reduced mobility and the presence of APOE 4 may help explain the increased mortality attributed to IHD in the group, although this would need to be investigated further. It is the increased mortality rate in higher functioning patients that is more difficult to explain. Given the poorer outcome for patients with APOE 4, one would expect that high functioning patients with TBI should be less likely to carry this allele and develop associated disorders. In large populations, this factor would imply a reduced mortality risk from IHD in this group. An alternative hypothesis to explain an increased late mortality may be a combination of lifestyle and psychological factors in this sub-group. Factors such as social isolation, relationship breakdowns, unemployment, substance abuse and psychological disorders, often reported in outcome studies of patients with TBI [16–19], may account for some of this difference. Finally, the higher mortality rate of high functioning patients might be explained from another perspective. Some studies have found that TBI is more prevalent in groups with lower socio-economic status (SES). It may prove that the use of the Australian Life Tables data, based on nation-wide death data irrespective of SES, may under-estimate the mortality rate in that portion of the population most at-risk of TBI. It is possible that the observed increase in late mortality of higher functioning patients may mirror that of people from lower SES without a TBI.

The limitations of this study are primarily attributable to the relatively short follow-up-period (mean 5 years post-injury). Information on deaths in this study came from the regulatory authorities within one state of Australia and not from a country-wide database. For this reason, the 27 recorded deaths may underestimate the actual number of deaths within the sample. The construction of life expectancy tables was not possible due to the small number of subjects in the deceased sub-group. In general, however, the similarities between this study and previous investigations implies that the current findings are robust.

Future investigations will need to address a number of issues. The finding that males appear to be over-represented in the deceased group, and particularly in the lower functioning group where all deceased subjects were male, raises the question of gender differences in late mortality following TBI. This gender difference may be quite broad-ranging, as there is some limited evidence that females may have an advantage in some aspects of recovery following TBI [20]. This question could be explored further with a longer follow-up period and larger numbers in the deceased sub-group. Another issue requiring further study is the interplay of socioeconomic status and possible sample bias in using the Australian Life Tables data.

In conclusion, this study corroborates previous research that patients with severe TBI have a significantly higher long-term mortality rate than the general population. Mortality rates are highest for those with the greatest restrictions following TBI. Males, patients who are older at the time of injury and those with a pre-morbid psychiatric history appear to be at greater risk of late mortality. While some of the reasons for these findings are yet to be adequately explained, in Australia, where the greatest cause of TBI is motor vehicle accidents, these findings have important medico-legal implications.

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