The independent effect of gender on outcomes following traumatic brain injury: a preliminary investigation

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Although epidemiological studies of gender differences in outcome after brain injury are limited, studies in animals indicate higher fatality rates for females. Studies in which healthy human brain metabolism was investigated also suggest gender differences. In this paper the authors examine gender as an independent predictor of survival following brain injury. A prospective cohort of severely and moderately brain injured individuals was identified from two trauma centers over a period of 3.5 years. Patients enrolled in the cohort were followed for as long as 18 months postdischarge. The Glasgow Outcome Scale was used to measure long-term outcome. Overall, mortality was 1.28 times higher in females than males, with the greatest difference of 2.14 found in deaths postdischarge. Controlling for age, admission Glasgow Coma Score, penetrating as compared with blunt injury, and the presence of multiple trauma, females were 1.75 times more likely than males to die of their brain injury (95% confidence interval 1.09—2.82). Furthermore, females were 1.57 times more likely to experience poor outcomes (that is, severe disability or persistent vegetative state) than males. These findings suggest the need to examine similar effects in different cohorts and to identify the pathophysiological basis for the differences observed in this epidemiological study.

KEY WORDS • brain injury • epidemiology • etiology • gender • mortality

Recently, the Brain Trauma Foundation and the United States Brain Injury Association published Guidelines for the Management of Severe Head Injury.¹ One section of the guidelines dealt with prognosis and included a comprehensive evaluation of the published literature on the subject of prognostic factors in TBI. Age, GCS score, pupillary diameter and light reflex, hypotension, and CT-documented features were identified as factors related to outcome after injury. However, no single study has been performed to examine all factors simultaneously, and many of those studied are acknowledged to be confounders with one another.

Despite the large body of literature on prognostic factors for brain injury, the research rarely mentions, and even less frequently evaluates, the effect of gender in differences in TBI outcome. In many studies that have appropriate data to

examine this relationship, the investigators fail to consider it or fail to control for other confounding factors in the analysis. Nonetheless, the epidemiological evidence published thus far, albeit very limited, is intriguing.

Klauber, et al.,¹⁰ have reported in-hospital overall CFRs of 8.5 per 100 for males and 5.8 per 100 for females, but in two age groups the CFRs were significantly elevated for females as compared with males. This finding did not account for confounding factors. In a separate report, Klauber, et al.,¹¹ have reported that the CFR for females was higher than for males in all age groups except those age 60 years and older.

Excess risk of poorer outcomes after TBI for females compared with males has also been noted in the literature on mild brain injury. Rutherford, et al.,¹⁵ have reported from Great Britain that a greater number of persistent symptoms was demonstrated in females when compared with males at 1-year follow up after a medically diagnosed mild brain injury. Fenton, et al.,⁵ have shown that depression following mild TBI was more common in females, especially females older than 25 years of age. Recently, Bazarian and colleagues³ found that female gender was a

Abbreviations used in this paper: CFR = case fatality rate; CI = confidence interval; CT = computerized tomography; ED = emergency department; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; TBI = traumatic brain injury.

significant predictor of postconcussion syndrome among those assessed with a GCS score of 15 and followed to 1 month after discharge from the emergency department. It should be noted, however, that Groswasser and associates⁶ have reported that female TBI patients made better recoveries than male patients. The study outcome measure was return to work (or school), and the study groups excluded in-hospital deaths.

Analysis of published information on gender differences in the healthy normal human brain suggests baseline differences in brain metabolism. Warkentin, et al.,¹⁹ and Gur and Gur⁷ have found that higher mean regional and hemispheric cerebral blood flow was present in females as compared with males. However, gender differences have not been found for either whole brain or regional cerebral glucose metabolic rates.^{2,14} Analysis of limited evidence also suggests that basic brain physiology may differ by sex. Rabinowicz and colleagues¹⁶ have found that although mean cortical thickness of 60 loci were equal in males and females, significantly higher neuronal densities were demonstrated in males. However, the authors also concluded that females had increased neuronal processes in the same loci.

Animal studies offer additional analyses of gender differences in outcomes. Kozniowska, et al.,¹² have found that in female rats significant depression of both oxygen use and cerebral blood flow in conditions of hyponatremia was demonstrated, and these reactions were sensitive to the estrogen cycling of the female rat. The authors of some studies have indicated further that higher mortality rates are seen in female rats following induced fluid percussion injury.^{4,8} Emerson, et al.,⁴ have reported that estrogen is protective in male rats but that it exacerbated brain injury in female rats through effects mediated by estrogen reception binding.

In summary, there are few reports of epidemiological, clinical, or animal studies in which outcomes are examined by gender in moderate or severe TBI, and the reported findings available are equivocal. The objective of this report was to examine the role of gender as an independent factor in outcomes following moderate or severe TBI in a clearly defined study cohort.

CLINICAL MATERIAL AND METHODS

Study Design and Definition

The research design was a prospective cohort consisting of moderate and severely brain injured patients consecutively admitted from December 1992 to July 1996 at two large Level I teaching medical centers in Los Angeles, California. Brain injury was defined as a traumatic insult to the brain including diffuse axonal injury, contusion, laceration, intracranial hemorrhage, and acute intracranial hematoma (epidural or subdural). Eligibility was based on a GCS score between 3 and 12 based on the best observation obtained in the ED after stabilization generally from 4 to 6 hours postinjury. Those patients with a GCS score of 13 or greater were not included in this study unless, in the ED, a subsequent examination yielded a GCS score of 12 or less, significant positive CT findings were identified, or deterioration occurred requiring neurosurgical

intervention or resulting in death due to the brain injury. Minimum age for eligibility was 16 years, and the maximum age was undefined. There were no study group restrictions because of race, ethnicity, or socioeconomic status.

Cases were excluded from the study group if injuries were limited only to the olfactory, optic, or facial nerves, or to the spinal cord at or below C2–3. Severe preexisting comorbidity, defined as terminal illness at the time of trauma, history of chronic severe neurological disturbance or severe diminished mental capacity, or nontraumatic events leading to severe brain hypoxia, was cause for exclusion from the cohort. This study was approved by the University Institutional Review Board.

All moderately and severely brain injured patients received initial evaluation and resuscitation in the EDs according to Level I Trauma Center protocols. After hemodynamic stabilization and neurological assessment, all patients underwent head CT scanning and other high-priority diagnostic studies, and surgery was performed if necessary. Subsequent management was conducted in state-of-the-art neurosurgical intensive care units. Intracranial pressure monitoring was performed in all patients with GCS scores of 8 or less, and in others when CT findings warranted it. Therapy to maintain intracranial pressure under 20 mm Hg and cerebral perfusion pressure above 70 mm Hg included head elevation, mild hyperventilation, and maintenance of normothermia, followed, if necessary, by ventricular cerebrospinal fluid drainage, a narcotic dose of pentobarbital or propofol, and a bolus injection of mannitol. When intracranial hypertension and other injuries were stabilized, the patient was transferred to the neurosurgical ward or rehabilitation facility. After hospital discharge, through both regular phone calls and scheduled clinic visits at 6, 12, and 18 months physical and mental status was assessed and a GOS score was determined.

Because age is recognized as a prognostic factor (or effect modifier) in TBI outcomes,¹ it should not be “controlled” in some data analyses. However, age can also be a potential confounding factor in studies of associations of putative exposures and outcomes. To account for the dual role of age (effect modifier and confounder) we present our findings on age in two ways: unadjusted and adjusted odds ratios. For adjustment purposes and to show the relationship of age with gender we used three age intervals: 16 to 29, 30 to 49, and 50 years of age or older. The basis for the intervals is the distribution of mortality rates by age across the studies reported in the Guidelines for the Management of Severe Brain Injury,¹ in which age intervals ranged from one to eight categories with varying age intervals. We followed the intervals most closely to those reported by Jennett, et al.⁹

Cause of injury was determined directly from the emergency medical services run sheet and grouped into five distinct classes: assault, motor vehicle, bicycle, pedestrian, fall, and other.

Inasmuch as external cause was highly correlated with blunt or penetrating TBI status, the latter was used for purposes of controlling the potential confounding effects of this variable.

Analysis of Factors

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In-hospital death rates were examined for all members of the study group over four time periods that reflect distinct cut-off points in the UCLA Brain Injury Research Center enrollment process; these periods included death at 1) less than 1 hour after arriving at the ED; 2) between 1 and 6 hours; 3) greater than 6 hours after arriving at the ED but prior to discharge; and 4) deaths after discharge through 18 months postdischarge. Because some patients could not be followed through every time period, the measures represent a series of cross-sectional comparisons rather than an overall time trend.

Outcome was measured using the GOS at discharge from the hospital and at 6, 12, and 18 months postdischarge. The GOS has five levels of outcome, ranging from one to five: GOS score of 1 indicates death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; and 5, good recovery. A total of 795 individuals were followed through their hospital stay, and 106 were followed for at least 6 months postdischarge. Of the latter, 44 patients (41.5%) were followed for only 6 months, 29 (27.4%) for 12 months, and 33 (31.1%) for 18 months. When examining outcome postdischarge, the last available GOS score was used.

Logistic models predicting death and poor outcome were run in SAS (SAS Institute, Inc., Cary NC). The independent variables included gender, penetrating versus blunt injury, multiple or nonmultiple trauma, admission GCS score coded into the categories (scores of 3–8, 9–12, and 13 or higher), and age coded into categories (16–29, 30–49, and 50 years of age or older). In models predicting poor outcome GOS scores of 2 (vegetative state) and 3 (severe disability) were used to determine poor outcome, whereas GOS scores of 4 (moderately disabled) and 5 (good recovery) indicated good outcome.

RESULTS

Mortality Rates

Of the 795 brain-injured patients studied, 652 (82.0%) were males and 143 (18.0%) were females. Proportional survival curves according to gender showed the same general pattern of mortality over time (Fig. 1). Steeper decreases in survival curve at all points were shown for females, but this difference becomes most pronounced with death more than 6 hours postinjury but prior to discharge. By the final time period, a cumulative total of 75.8% of males and 69.0% of females survived.

Overall, whereas the CFR for males was 24.7, for females it was 31.6 per 100 brain-injured individuals (Table 1). In the 1st hour in the ED, CFRs were 2.9 per 100 for males and 3.5 per 100 for females. Case fatality rates increased with time up to discharge, and a large peak in deaths was seen during the time category of 6 hours postinjury to discharge. During this time period, the CFR among patients followed through discharge was 15.3 per 100 for males and 53.1 per 100 for females. In patients followed postdischarge, the CFR was 5.3 per 100 for males and 20.3 per 100 for females.

Case fatality rate ratios were higher for females than males at each time interval, and this disparity increased over time. The overall rate ratio of CFRs of males com-

pared with females was 1.28 (95% CI 0.98–1.69), which indicates slightly but not significantly higher CFRs in females. The lowest gender difference was found in the time period from 1 to 6 hours after arrival in the ED, with a CFR ratio of 1.06. In the period from 6 hours to discharge, which accounted for the greatest rate of deaths, the CFR ratio was 1.33 (95% CI 0.79–5.77). The greatest gender difference was found postdischarge, with a rate ratio of 2.14 (95% CI 0.90–1.97). These CFRs are not cumulative and therefore indicate independent increases in disparity between genders. Although there is a difference between genders found in the rate ratios, 95% CIs around these ratios did not reach significance for any individual time period or for the overall sample.

In males and females their patterns of other factors differed, which could influence survival (Table 2). Females were significantly older than men, with 32.9% of females over age 50 years compared with only 19.5% of males. Females were more likely to be injured in motor vehicle crashes and as pedestrians, whereas males were more likely to be injured from assaults and bicycle crashes. The proportion injured from falls was similar. Although not statistically significant, slightly higher admission GCS scores were found in females, even though their survival rate was lower. The proportion of cases with multiple trauma did not differ by gender.

Factors predicting overall death are summarized in Table 3. Crude odds ratios revealed that only increasing age and penetrating as compared with blunt injury were significantly predictive of death. When controlling for other study factors, females were 1.75 times more likely to die of their brain injuries as males (95% CI 1.09–2.82). Patients with penetrating brain injuries were 6.58 times more likely to die than those with blunt head injuries (95% CI 3.90–11.1). Increasing age was significantly related to death, with a 1.94-fold increase in death observed in each age increment (95% CI 1.50–2.51). Higher admission GCS scores were protective against mortality, with an adjusted odds ratio of 0.25 (95% CI 0.19–0.33). The presence of multiple trauma was not significantly related to mortality.

The lack of significance in the crude analysis as well as the statistically significant relationship of sex with other predictive factors indicates the potential for interaction. No interaction terms were significant in this data set, which is most likely due to the small sample size. Analysis of the effect of age on death, however, did show differences between genders by age strata (Table 4). In females between the ages of 16 and 29 years there was a lower proportionate mortality rate than in men but a higher mortality rate at the age of 30 years and older. The greatest difference in the proportionate mortality rate by gender was demonstrated in patients over age 50 years, in whom the proportionate mortality rate was 51.1% for females and 28.4% for males.

Patient Outcome

Of the 313 individuals followed through discharge, 263 were males (84.0%) and 50 were females (16.0%). Although analysis of GOS scores at discharge did not show a significant trend by gender, 60.0% of females but only 51.4% of males had poor outcomes (persistent vegetative

Fig. 1. Graph showing proportional survival in female compared with male patients, as demonstrated in four time points.

state or severe disability) (Table 5). Although a higher proportion of males were in a persistent vegetative state, many more females had severe disabilities. The proportion of individuals who made a good recovery was slightly higher in females (20.0%) than males (17.9%).

Of those followed through discharge, a slightly higher proportion of females were between the ages of 16 and 29 years (52% for females and 49.1% for men) and over the age of 50 years (18% for females and 12.9% for men) (Table 6). A higher proportion of very low initial GCS scores (3–8) was found in males but in females a higher proportion of moderate scores (9–12) was demonstrated. Over 90% of both females and males had sustained blunt head injuries, and just under one half of each gender group had suffered multiple trauma.

Females were 1.57 times more likely to have a poor outcome than males (95% CI 0.80–3.08), although this difference did not reach statistical significance (Table 6).

Increasing age increased the likelihood of poor outcome (odds ratio 1.69), and higher initial GCS scores and the presence of a penetrating head injury predicted lower levels of poor outcome. Initial GCS score was protective against poor outcome at hospital discharge (odds ratio 0.81; 95% CI 0.76–0.86). Although this model had a significant log likelihood, which indicates that the variables explain a significant level of variance in the outcome, the power to detect differences with the small sample size was low.

Of the 106 individuals followed beyond discharge, 17 (16.0%) were females and 89 (84.0%) were males (Table 7). Although a higher proportion of females than males were in persistent vegetative state or had severe disability (23.5% compared with 16.9%, respectively), this represents only four females and 15 males. Logistic models were not run on this sample because of the small number of cases.

TABLE 1
NUMBER OF PATIENTS, NUMBER OF DEATHS, CFRs PER 100 PATIENTS
BY TIME PHASE AND GENDER, RATE RATIOS AND 95% CIs

Time Phase	No. of Patients	No. of Deaths	CFR		Rate Ratio (95% CI)
			Women	Men	
all cases	795	206	31.6	24.7	1.28 (0.98–1.69)
death at <1 hr	795	24	3.5	2.9	1.20 (0.46–3.16)
death at >1 to <6 hrs†	771	48	6.6	6.2	1.06 (0.53–2.13)
death at >6 hrs to prior to discharge	721	117	20.3	15.3	1.33 (0.90–1.97)
death postdischarge	270*	17	11.4	5.3	2.14 (0.79–5.77)

* For enrolled patients only.

† Number of patients minus previous deaths and transfers.

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TABLE 2
NUMBER AND PERCENT OF RISK FACTORS BY GENDER

Risk Factors	No. (%)		Chi Square	p Value
	Men	Women		
age (yrs)				
16–29	285 (43.7)	49 (34.3)	13.1	<0.001
30–49	240 (36.8)	47 (32.9)		
≥50	127 (19.5)	47 (32.9)		
admission GCS score				
3–8	320 (49.1)	65 (45.5)	2.32	0.31
9–12	108 (16.6)	19 (13.3)		
>12	224 (34.4)	59 (41.3)		
external cause				
assault	183 (28.1)	17 (11.9)	49.7	<0.001
motor vehicle	185 (28.4)	66 (46.2)		
bicycle	31 (4.8)	4 (2.8)		
pedestrian	104 (16)	30 (21)		
fall	110 (16.9)	22 (15.4)		
other/unknown	39 (6)	4 (2.8)		
type of injury				
blunt	556 (85.3)	129 (90.2)	0.92	0.34
penetrating	96 (14.7)	14 (9.8)		
multiple trauma				
yes	262 (40.2)	65 (45.5)		
no	390 (59.8)	78 (54.5)		

DISCUSSION

Although gender in TBI has been incorporated as a variable in many clinical and epidemiological reports, findings have been equivocal, and often gender has not been specifically examined. Studies in which gender differences in myocardial infarction are examined have found that, although females sustain fewer events, they have higher mortality rates than males.^{13,17,18} The findings presented in this study similarly suggest that, although females are less prevalent in a hospital sample of severe brain injuries, higher mortality rates at several distinct periods following brain injury are revealed in females. Furthermore, after controlling for age, admission GCS, blunt or penetrating injury, and multiple trauma, increased mortality rates and poorer outcomes are found in females as compared with males.

The effect of age may be multifaceted, and the interaction between age and gender requires a much larger sample size to address thoroughly. The effect of age may be apparent as both a risk factor for injury and a prognostic factor for survival and recovery, given a similar brain

insult. Age may affect the types of injuries experienced by females and men, with a higher number of older females being injured in falls and a higher number of younger males being injured by gunshot wounds. These risk factors may affect the severity of the injury to the brain. However, when age is controlled through biologically appropriate strata, both the effects of gender and age persist. This indicates that age may act as an interactive confounder of the biological gender effect on mortality and outcome; however, it could also be an effect modifier that creates unequal age strata in the types and severities of injuries experienced by females and males.

When approaching this problem from a biomechanical perspective, gender would not be an expected predictive factor. Assuming that damage to the human brain is reliant on the specific energy transfer, it would be expected that immediate outcomes would be the same for the same level of high-energy transfer regardless of gender. For example, the probability of death at the scene in a high-speed pedestrian impact injury would be the same regardless of gender. Thus, controlling for this energy impact would ac-

TABLE 3
CRUDE AND COVARIATE ADJUSTED ODDS RATIOS PREDICTING MORTALITY AND 95% CONFIDENCE INTERVALS

Risk Factor	Crude Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
female gender	1.39	0.93–2.07	1.75	1.09–2.82
increasing age	1.21	1.00–1.49	1.94	1.50–2.51
increasing initial GCS score	0.28	0.22–0.36	0.25	0.19–0.33
penetrating injury (compared w/ blunt)	4.59	3.02–6.97	6.58	3.90–11.1
multiple trauma	1.15	0.83–1.60	0.82	0.56–1.20

TABLE 4
PROPORTIONATE MORTALITY BY AGE AND GENDER*

Age	Women		Men	
	No.	PMR (%)	No.	PMR (%)
16–29	49	18.4	285	26.0
30–49	47	23.4	240	20.0
≥50	47	51.1	127	28.4
total	143	30.8	652	24.2

*PMR = proportionate mortality rate.

count for all gender differences. However, findings from studies⁸ in animals and healthy human brains suggest inherent gender differences in brain metabolism that might affect survival following hospitalization for a brain injury. Although our findings do not suggest a possible hypothesis, they do support the notion that there may be pathophysiological reasons to explain the differences observed.

Although in-hospital mortality data reflect the experience of the entire cohort minus a few patients who were transferred to other treatment institutions, findings strongly suggest the existence of gender differences, although they are somewhat limited by a small sample size. The sample size was not sufficient statistically to control with great accuracy the overall injury severity or the brain-injury severity. However, the variables of multiple trauma, admission GCS score, and penetrating or blunt head injury were introduced into models to control for injury severity. The authors of future studies with larger samples should examine the issue further. Larger sample sizes would also assist by allowing for the examination of interaction terms.

TABLE 5
GLASGOW OUTCOME SCALE SCORE IN PATIENTS
CLASSIFIED ACCORDING TO GENDER*

GOS Score	No. of Men (%)	No. of Women (%)
2	52 (19.8)	7 (14.0)
3	83 (31.6)	23 (46.0)
4	81 (30.8)	10 (20.0)
5	47 (17.9)	10 (20.0)
total	263 (84.0)	50 (16.0)

* Chi-square = 5.1, p = 0.16.

The data in this report have limitations beyond that of sample size. The GCS and GOS are general measures that may not capture important differences in brain-injury severity or disability. There could be misclassification between those patients with moderate and severe disability. However, use of the GOS is widely uniform in many countries and does provide a gross estimation of the effect. We chose to illustrate differences at several phases in the clinical course of treatment and follow up in patients with moderate or severe TBI. We did not differentiate between patients with moderate or severe TBI because of sample size, and this question should also be addressed in future research.

Currently, many countries and investigators have collected cohort data on brain-injured individuals, each of which suffers from sample size limitations. To address more complex statistical questions with a larger sample, we have begun an international pooling project to assem-

TABLE 6
NUMBER, PERCENTAGE, AND ADJUSTED ODDS RATIOS FOR RISK FACTORS PREDICTING
POOR OUTCOME AT HOSPITAL DISCHARGE

Risk Factor	No. of Men (%)	No. of Women (%)	Total (%)	Adjusted Odds Ratio	95% CI
gender					
male			263 (84)	1.57	0.80–3.08
female			50 (16)		
age (yrs)					
16–29*	129 (49.1)	26 (52)	155 (49.5)	1.69	1.17–2.43
30–49	100 (38)	15 (30)	115 (36.7)		
≥50	34 (12.9)	9 (18)	43 (13.7)		
admission GCS score					
3–8*	126 (47.9)	21 (42)	147 (47)	0.81	0.76–0.86
9–12	53 (20.2)	12 (24)	65 (20.8)		
≥13	84 (31.9)	17 (34)	101 (32.3)		
type of injury					
blunt	240 (91.3)	47 (94)	287 (91.7)	0.86	0.34–2.16
penetrating	23 (8.8)	3 (6)	26 (8.3)		
multiple trauma					
yes = 1*	112 (42.6)	24 (48)	177 (56.6)	1.02	0.62–1.67
no = 0	151 (57.4)	26 (52)	136 (43.5)		

* The reference category used in the analysis.

TABLE 7
GLASGOW OUTCOME SCALE SCORE IN PATIENTS
AFTER HOSPITAL DISCHARGE

GOS Score	No. of Men (%)	No. of Women (%)
2	4 (4.5)	1 (5.9)
3	11 (12.4)	3 (17.7)
4	26 (29.2)	8 (47.1)
5	48 (53.9)	5 (29.4)
total	89 (84)	17 (16)

ble a large group of moderately and severely head injured adults. This pooled data set will have enough information on each patient to allow for an in-depth analysis while controlling for confounding factors.

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