ORIGINAL ARTICLE

Protection From Traumatic Brain Injury in Hormonally Active Women vs Men of a Similar Age

A Retrospective International Study

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Background: It has been suggested that women with traumatic brain injury have more favorable outcomes than do men because of higher levels of circulating estrogen and progesterone that may reduce brain edema.

Objectives: To determine whether there is any association between sex and mortality in TBI patients and whether there is any association between sex and brain edema.

Design: Retrospective cohort study using data from 2001 to 2007 collected from a trauma registry in Hong Kong and the Victorian State Trauma Registry.

Setting: Two regional trauma centers in Hong Kong and 2 adult major trauma centers and 1 pediatric trauma center in Victoria, Australia.

Main Outcome Measures: Mortality and brain edema.

Patients: Trauma patients with an Abbreviated Injury Scale score (head) of at least 3 who were aged 12 to 45 years were included. Patients with minor head injury and undisplaced closed skull fracture were excluded.

Results: Both the Hong Kong and Victorian data showed no significant difference in sex-related mortality. Increased mortality was associated with decreased systolic blood pressure and Glasgow Coma Scale score and with increased New Injury Severity Score or Injury Severity Score. In Hong Kong, brain edema was associated with female sex ($P = .02$), and the odds of brain edema in females were greater than for males. However, this association was not found in Victorian patients.

Conclusion: This study found no significant association between sex and mortality in either Victoria or Hong Kong and does not support the concept that females have better outcomes after traumatic brain injury.

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TRAUMATIC BRAIN INJURY (TBI) is the most common life-threatening injury after trauma and a major cause of disability and mortality worldwide.[1-4] In Hong Kong, more than 50% of patients with major trauma have TBI, which is the leading cause of posttraumatic death and disability.[5,6] It has been suggested that females with brain injury after trauma have more favorable outcomes and appear to recover better than their male counterparts.[7] It is postulated that females may be protected because of higher levels of circulating estrogen and progesterone.[8-12]

See Invited Critique at end of article

Although some animal studies[8,13-18] have found that progesterone reduces cerebral edema after TBI, others[19] have not confirmed this finding. Progesterone appears to have a neuroprotective action, and it may have potential as a treatment for brain edema in patients with TBI.[20,21]

Clinical studies have been inconclusive. Some suggest that progesterone improves outcomes in patients with TBI,[22,23] whereas others[2,24-27] suggest that sex is not related to the severity of TBI and that females do not have better outcomes than males.[28-31] Some of these studies included women not of childbearing age—even women aged 80 years or more—and others did not focus on TBI. One population-based study[32] indicated that hormonally active women may have a better physiologic response than males; these researchers used serum lactate as a marker of the hemodynamic response to injury but did not report mortality or functional outcome. From this literature, it is not clear whether women with TBI have better outcomes than do men or whether there is any association between sex and brain edema.

The aims of this study were, first, to determine whether there is any association between sex and mortality in TBI patients aged 12 to 45 years and, second, to determine whether there is any association between sex and brain edema in the same group of patients.

METHODS

STUDY DESIGN

Ethical approval was obtained from the joint Chinese University of Hong Kong–New Territories East Cluster clinical research ethics committee in Hong Kong, from the Standing Committee on Ethics in Research Involving Humans at Monash University, and by all participating institutions in Australia to conduct a retrospective study of high-quality administrative trauma databases in which patients with TBI were selected for analysis.

SETTING

Data were collected from the Victorian State Trauma Registry (VSTR),[33] Victoria, Australia, and from the Prince of Wales Hospital Trauma Registry, New Territories East Cluster, and the Queen Elizabeth Hospital Trauma Registry, Kowloon East Cluster, Hong Kong. The period of study was January 1, 2001, to December 31, 2007.

Victoria

Victoria is a state in southern Australia, and the VSTR[33] is a statewide, population-based trauma registry that was developed in 2001 and is based at Monash University, Melbourne. In an integrated trauma system with levels 1, 2, 3, and 4 services, 139 health service facilities contribute data to a single trauma registry in the state. The system includes 2 adult major trauma centers and 1 pediatric trauma center. The VSTR includes patients with *any* of the following: death due to injury, an Injury Severity Score (ISS) greater than 15, an intensive care unit (ICU) stay longer than 24 hours requiring mechanical ventilation, and urgent surgery. The registry enables tracking of cases across the system by collecting identifiable information.

Hong Kong

In Hong Kong, 95% of the population are Chinese. The Prince of Wales Hospital and Queen Elizabeth Hospital trauma registries are hospital-based registries. Among the inclusion criteria for Prince of Wales Hospital and Queen Elizabeth Hospital are trauma deaths, patients triaged as "critical" or "emergency" in the emergency department (triage categories 1 and 2, respectively), all ICU admissions, and major trauma patients transferred from another acute hospital.

DATA COLLECTION

Data collected included age, sex, preexisting diseases, injury mechanism, injury type, primary or secondary transfer from the hospital, trauma call activation, admission specialty, arrival to accident and emergency department discharge time, intubation time in the emergency department, arrival to first head computed tomography time, surgical operation time, ICU length of stay, and hospital length of stay. The Abbreviated Injury Scale (AIS), version 98, was used to determine the severity of injury in different body regions. The ISS and New Injury Severity Score were calculated from the AIS scores. Each patient's Glasgow Coma Scale (GCS) score, respiratory rate (RR), and systolic blood pressure (SBP) were recorded.

Because the types and severity of brain injury may affect outcome, brain injuries were grouped into different subgroups, ie, penetrating injury, brainstem injury, cerebral contusion, cerebellum injury, diffuse axonal injury, extra axial hemorrhage/epidural hemorrhage, cerebral hematoma, subdural hemorrhage, subarachnoid hemorrhage, brain edema, bases of skull or displaced skull fracture, and others. The AIS (head) score was used to indicate the severity of brain injury. Patients with an AIS (head) score of at least 3 were considered to have isolated head injury, and patients with AIS (head) score of 3 or higher and at least 1 AIS score of 2 or higher in another body region were considered to have multiple trauma.

SUBJECTS

Trauma patients aged 12 to 45 years with an AIS score of at least 3 in the head region, irrespective of the presence of other major injuries, were classified as having a TBI and were included in the study. The study focused on this age group so that only premenopausal females were included in the study. Patients with minor head injury and those with a loss of consciousness without brain hemorrhage or undisplaced closed skull fracture were excluded.

OUTCOMES

The primary outcome measure was in-hospital mortality. Mortality is a hard outcome that is the same across jurisdictions. Even in patients with isolated head injury, it is not always possible to say that death was due to the head injury. The secondary outcome measure was the presence of brain swelling or edema.

STATISTICAL ANALYSES

We used SPSS, version 17.0 (SPSS, Chicago, Illinois), for data analysis. We decided to present and analyze data from Hong Kong and Australia separately for a number of reasons. First, there are substantial differences in trauma care and adjusted mortality outcomes between the 2 regions. Second, race may affect mortality from trauma.[34] The data set from Hong Kong is predominantly ethnic Chinese, whereas that from VSTR is predominantly non-Chinese. The separate analysis of the Hong Kong and Victoria data sets may partly allow for this.

Descriptive data were expressed as mean (SD) or median (interquartile range) for continuous variables and analyzed using the *t* test or the Mann-Whitney test, depending on data distribution. Categorical data were presented as frequencies and percentages and analyzed using the χ^2 test, the Fisher exact test, or unadjusted odds ratios (ORs).

Because data for the 2 countries were analyzed separately, a separate univariate analysis was conducted on data from each country. Significant variables were selected for entry into a multiple logistic regression model, and separate models were generated for Hong Kong and Victoria. Variables showing significance ($P < .05$) in these models were entered into the final model. Sex was included in each model.

Table 1. Patient Characteristics[a]

Variable	Hong Kong (N=698) Male (n=529)	Hong Kong Female (n=169)	Hong Kong P Value	Victoria, Australia (N=2281) Male (n=1823)	Victoria Female (n=458)	Victoria P Value
Injury						
Isolated head injury	236 (44.6)	77 (45.6)	.83	391 (21.4)	79 (17.2)	.047
Multiple trauma	293 (55.4)	92 (54.4)		1432 (78.6)	379 (82.8)	
Age, mean (SD), y	29.6 (9.6)	27.9 (9.7)	.049	27.2 (8.7)	26.3 (9.3)	.04
Cause of injury						
Motor vehicle driver	60 (11.3)	1 (0.6)	<.001	414 (22.7)	134 (29.3)	<.001
Motor vehicle passenger	39 (7.4)	24 (14.2)		181 (9.9)	90 (19.7)	
Pedestrian	66 (12.5)	68 (40.2)		175 (9.6)	83 (18.1)	
Motorcycle driver or passenger	64 (12.1)	9 (5.3)		245 (13.4)	9 (2.0)	
Bicycle-related	39 (7.4)	18 (10.7)		81 (4.4)	8 (1.7)	
Cutting	14 (2.6)	3 (1.8)		14 (0.8)	0	
Fall	154 (29.1)	35 (20.7)		271 (14.9)	60 (13.1)	
Others[b]	93 (17.6)	11 (6.5)		442 (24.2)	74 (16.2)	
SBP group, mm Hg[c]						
<90	32 (6.0)	12 (7.1)	.07	78 (4.3)	33 (7.2)	<.001
90-139	340 (64.3)	124 (73.4)		797 (44.0)	287 (62.7)	
140-160	109 (20.6)	21 (12.4)		660 (36.2)	110 (24.0)	
>160	48 (9.1)	12 (7.1)		278 (15.2)	26 (5.7)	
Multiple-system injury	292 (55.2)	92 (54.4)	.86	1432 (78.6)	379 (82.8)	.047
ISS group						
<16	109 (20.6)	34 (20.1)	.79	79 (4.3)	23 (5.0)	.30
16-25	212 (40.1)	62 (36.7)		825 (45.3)	188 (41.0)	
26-40	131 (24.8)	48 (28.4)		614 (33.7)	157 (34.3)	
>40	77 (14.6)	25 (14.8)		305 (16.7)	90 (19.7)	
Time, median (IQR)						
Arrival to first CT, min	53 (37-82)	48 (34-71)	.06	64 (36-119)	73 (37-132)	.10
Arrival to intubation, min	19 (10-32)	15 (8-25)	.045	12 (4-37)	11 (2-26)	.38
LOS, d	9 (5-19)	10 (5-19)	.19	8 (4-17)	9 (4-19)	.02
ICU LOS, d	1 (0-5)	1 (0-6)	.47	2 (0-7)	2 (0-10)	.05
OT-head	164 (31.0)	56 (33.1)	.60	712 (39.1)	180 (39.3)	.92
Other operation	234 (44.2)	58 (34.3)	.02	1276 (70.0)	333 (72.7)	.26

Abbreviations: CT, computed tomography; ICU, intensive care unit; IQR, interquartile range; ISS, Injury Severity Score; LOS, length of stay; OT-head, emergency operation related to head injury; SBP, initial emergency department systolic blood pressure.

[a] Data are given as number (percentage) of patients unless otherwise indicated.

[b] Other causes of injury include fire, flames, smoke and scalds, horse- and other animal-related injuries, machinery, other transport-related circumstance, struck by or collision with object, struck by or collision with person, submersion or drowning, and unspecified external cause.

[c] Number of patients do not sum to total in column heading because some data are missing.

RESULTS

STUDY POPULATION CHARACTERISTICS

From January 2001 to December 2007, a total of 18 804 (13 376 male and 5428 female) patients were entered into the VSTR, Prince of Wales Hospital, and Queen Elizabeth Hospital trauma registries. Of these, 2979 patients, 698 in Hong Kong and 2281 in Victoria, met the inclusion criteria and were included in this study. The ratio of males to females was 3.8:1.

Baseline characteristics for Hong Kong and Victoria are shown in **Table 1**. In Hong Kong, males were older than females ($P = .049$). The percentage of females injured as motor vehicle passengers or pedestrians was higher than the corresponding percentage of males, but the percentage of males injured as motor vehicle drivers, motorcycle drivers, and passengers and as a result of falls was higher than the corresponding percentage of females ($P < .001$). Females had shorter emergency department arrival to intubation time ($P = .045$) and fewer surgical operations ($P = .02$).

In Victoria, there were significant sex differences in age, cause of injury, blood pressure, injury count, and length of stay, with females being significantly younger ($P = .04$). The percentage of females injured as a motor vehicle driver or passenger or as a pedestrian was higher than the corresponding percentage of males, and the percentage of males injured by bicycle riding and motorcycling was higher than the corresponding percentage of females ($P < .001$). Victorian females also had a significantly lower SBP ($P < .001$), more multiple-system injuries ($P = .047$), and a longer hospital stay ($P = .02$).

Regarding the injury severity in injured body regions, males had more severe abdominal injuries in both Hong Kong ($P = .046$) and Victoria ($P < .001$). There were no significant sex differences in the AIS scores for head, neck, face, thorax, extremities, or external regions in either the Hong Kong or Australian data. The only difference

Table 2. Sex-Related Mortality Rates in Hong Kong and Victoria, Australia[a]

	Hong Kong Deaths[b]			Victoria Deaths[b]		
Variable	**Males (n=68)**	**Females (n=21)**	***P* Value**	**Males (n=185)**	**Females (n=56)**	***P* Value**
Injury count						
Isolated head injury	21 (30.9)	4 (19.0)	.41	19 (10.3)	3 (5.4)	.18
Multiple trauma	47 (69.1)	17 (81.0)		166 (89.7)	54 (96.4)	
Age group, y						
12-19	10 (14.7)	3 (14.3)	.74	37 (20.0)	23 (41.1)	.01
20-29	22 (32.4)	8 (38.1)		68 (36.8)	13 (23.2)	
30-39	15 (22.1)	6 (28.6)		51 (27.6)	12 (21.4)	
40-45	21 (30.9)	4 (19.0)		29 (15.7)	8 (14.3)	
ISS						
<16	0	0	.40	4 (2.2)	0	.03
16-25	16 (23.5)	3 (14.3)		36 (19.5)	4 (7.1)	
26-40	18 (26.5)	4 (19.0)		59 (31.9)	15 (26.8)	
>40	34 (50.0)	14 (66.7)		86 (46.5)	37 (66.1)	
GCS score at ED						
<9	50 (73.5)	21 (100)	.03	180 (97.3)	55 (98.2)	>.99
9-13	12 (17.6)	0		3 (1.6)	1 (1.8)	
>13	6 (8.8)	0		2 (1.1)	0	
RR, breaths per min, at ED						
<12	15 (22.1)	14 (66.7)	.001	108 (58.4)	40 (71.4)	.13
12-24	26 (38.2)	5 (23.8)		72 (38.9)	14 (25.0)	
>24	27 (39.7)	2 (9.5)		5 (2.7)	2 (3.6)	
SBP, mm Hg, at ED						
<90	17 (25.0)	9 (42.9)	.22	40 (21.6)	18 (32.1)	.002
90-139	31 (45.6)	10 (47.6)		72 (38.9)	30 (53.6)	
140-160	8 (11.8)	1 (4.8)		47 (25.4)	8 (14.3)	
>160	12 (17.6)	1 (4.8)		26 (14.1)	0	
Brain injury[c]						
SDH large[d]	22 (32.4)	3 (14.3)	.03	14 (7.6)	3 (5.4)	.77
Cerebral hematoma small to moderate[e]	4 (5.9)	7 (33.3)	.003	71 (38.4)	22 (39.3)	>.99
Skull fracture	38 (55.9)	14 (66.7)	.38	118 (63.8)	27 (48.2)	.04
ICU admission						
Yes	63 (92.6)	13 (61.9)	.002	156 (84.3)	47 (83.9)	.94
No	5 (7.4)	8 (38.1)		29 (15.7)	9 (16.1)	
OT-head						
Yes	33 (48.5)	9 (42.9)	.80	106 (57.3)	27 (48.2)	.23
No	35 (51.5)	12 (57.1)		79 (42.7)	29 (51.8)	

Abbreviations: ED, emergency department; GCS, Glasgow Coma Scale; ICU, intensive care unit; ISS, Injury Severity Score; OT-head, emergency operation related to head injury; RR, respiratory rate; SBP, systolic blood pressure; SDH, subdural hemorrhage.

[a] Data are given as number (percentage) of patients, unless otherwise indicated.

[b] In Hong Kong, 68 of 529 males (12.8%) and 21 of 169 females (12.4%) died. In Victoria, 185 of 1823 males (10.1%) and 56 of 458 females (12.2%) died.

[c] Some patients had more than 1 brain injury.

[d] SDH Abbreviated Injury Scale score ≥5, >50 mL, >1-cm thick, bilateral, massive, extensive.

[e] Cerebral hematoma Abbreviated Injury Scale score <5, <30 mL, <4 cm diameter.

was that Hong Kong male patients had a higher frequency of serious abdominal injury, whereas females had a higher frequency of moderate abdominal injuries ($P = .046$). Abdominal injuries of Australian females were also more minor than those of males ($P < .001$).

SEX AND MORTALITY

Table 2 shows the sex-related mortality rates in Hong Kong and Victoria. In Hong Kong, females were less commonly admitted to the ICU despite more commonly having a lower SBP. No female who died had a GCS score greater than 9 on arrival at the emergency department. The percentage of females who died with an RR less than 12 breaths per minute was higher than the corresponding percentage of males, whereas the percentage of males who died with an RR greater than 24 breaths per minute was higher than the corresponding percentage of females ($P < .001$). Females had higher mortality rates than males when they presented with a small to moderate hematoma ($P = .003$), but males with a large subdural hemorrhage had a higher mortality rate than corresponding females ($P = .03$). In Victoria, females aged 12 to 19 years had the highest mortality rate of all male and female age groups.

In Hong Kong, the all-cause mortality rate of patients with isolated head injury was 8.0% (25 of 313), in which the female mortality rate was 5.2% (4 of 77) and the male mortality rate was 8.9% (21 of 236). The OR for male to female mortality was 1.784 (95% confidence interval [CI], 0.592-5.364; $P = .30$). In Victoria, the all-cause mortality rate of patients with isolated head injury was 4.7% (22 of 470), in which the female mortality rate was 3.8% (3 of 79) and the male mortality rate

Table 3. Adjusted and Unadjusted Odds Ratios of Sex-Related Mortality

Variable	Hong Kong		Victoria, Australia	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Unadjusted				
Male	1.04 (0.62-1.75)	.88	0.81 (0.59-1.11)	.20
Female	1.00 [Reference]	. . .	1.00 [Reference]	. . .
Adjusted[a]				
Male	2.07 (0.67-6.39)	.20	0.72 (0.35-1.45)	.36
Female	1.00 [Reference]	. . .	1.00 [Reference]	. . .

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]The Hong Kong model was adjusted for isolated head injury and multiple trauma, causes of injury, comorbidity status, transferred patients, trauma call, length of stay, systolic blood pressure, respiratory rate, Glasgow Coma Scale score, intensive care unit admission, head injury–related operation, and Injury Severity Score. The Victoria model did not include New Injury Severity Score, subdural hemorrhage, epidural hemorrhage, subarachnoid hemorrhage, hematoma, contusion, brainstem injury, cerebellum injury, skull-displaced fracture, or brain edema because the Injury Severity Score already incorporated the brain injury.

Table 4. Adjusted and Unadjusted Odds Ratios of Sex-Related Brain Edema

Variable	Hong Kong		Victoria, Australia	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Unadjusted				
Male	0.63 (0.43-0.92)	.02	0.77 (0.56-1.05)	.10
Female	1.00 [Reference]	. . .	1.00 [Reference]	. . .
Adjusted[a]				
Male	0.62 (0.39-0.99)	.04	0.85 (0.61-1.18)	.33
Female	1.00 [Reference]	. . .	1.00 [Reference]	. . .

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adjusted for causes of injury, systolic blood pressure, respiratory rate, comorbidity, trauma call, length of stay, intensive care unit length of stay, intensive care unit admission, emergency operation–related head injury, Glasgow Coma Scale score, and Injury Severity Score.

was 4.9% (19 of 391). The OR for male to female mortality was 1.29 (95% CI, 0.37-4.48; $P = .68$).

In Hong Kong, the all-cause mortality rate of patients with multiple trauma was 16.6% (64 of 385), in which the female mortality rate was 18.5% (17 of 92) and the male mortality rate was 16.0% (47 of 293). The OR for male to female mortality was 0.84 (95% CI, 0.46-1.55; $P = .58$). In Victoria, the all-cause mortality rate of patients with multiple trauma was 12.1% (220 of 1811), in which the female mortality rate was 14.2% (54 of 379) and the male mortality rate was 11.6% (166 of 1432). The OR for male to female mortality was 0.79 (95% CI, 0.57-1.10; $P = .16$).

Table 3 shows the adjusted and unadjusted ORs for sex-related mortality. Univariate analysis showed no significant differences in the mortality rate between males and females in both registries (Hong Kong registries: $P = .88$; VSTR: $P = .20$). Both Hong Kong and Victorian data showed that the OR of mortality increased with decreased SBP and GCS score and with increased New Injury Severity Score and ISS. The Hong Kong data showed that an RR of less than 12 or more than 24 breaths per minute was also an independent predictor of hospital mortality in trauma.

SEX AND BRAIN EDEMA

Overall, 167 Hong Kong patients (115 male and 52 female) and 254 VSTR patients (193 male and 61 female) had a diagnosis of brain edema.

Comparisons of trauma-related variables and brain edema rates between males and females were performed. For Hong Kong, the only sex difference was that female pedestrians were more likely than male pedestrians to have brain edema ($P < .001$). For Victoria, brain edema was more likely to be associated with females aged 12 to 19 years and males aged 20 to 29 years ($P = .03$), female motor vehicle drivers or passengers ($P < .001$), and those females with a low RR ($P = .03$) or a low SBP ($P = .006$).

In Hong Kong, brain edema was associated with female sex ($P = .02$); trauma call activation, longer ICU length of stay, more surgical procedures for the head injury, higher ISS and New Injury Severity Score, and lower GCS, RR, and Revised Trauma Score (all $P < .001$); and SBP less than 90 or greater than 160 mm Hg ($P = .03$). Brain edema was also related to subdural hemorrhage ($P < .001$), cerebral contusion ($P = .01$), and brainstem injury ($P = .007$).

In Victoria, brain edema was associated with shorter length of stay; longer ICU length of stay; more surgical procedures for the head injury; higher ISS and New Injury Severity Score; lower GCS score, RR, SBP, and Revised Trauma Score; and the presence of other injuries to the brain (including subdural hemorrhage, subarachnoid hemorrhage, hematoma, contusion, brainstem injury, cerebellum injury, diffuse axonal injury, and skull fracture) (all $P \leq .001$).

Table 4 shows the adjusted and unadjusted ORs for sex-related brain edema. The odds of brain edema in females were greater than for males. However, this association was not found in Victorian patients. Victorian indicators for brain edema were GCS score, New Injury Severity Score or ISS, brainstem injury, and cerebral contusion.

COMMENT

To our knowledge, this is the first study to specifically investigate any sex differences in survival and brain edema in patients with TBI in hormonally active age groups. There was no apparent difference in sex-related mortality or brain edema after head injury in either Victoria or Hong Kong. Sex did not play a role in post-TBI mortality, and the assumption that female patients had better neuroprotection, possibly because of elevated circulating estrogens and progesterone, was not supported by our study.

Other studies have focused on TBI and sex differences but have investigated the whole spectrum of adult ages; they have not focused on those ages for which hormonal differences are likely to be large.[30] Some studies have investigated hormonally active differences in patients with posttraumatic shock but have not focused on brain injury.[32]

The present study found that, compared with males of a similar age, premenopausal females in Hong Kong had a higher chance of having brain edema. The findings are supported by those of other researchers[35] who concluded that females showed significantly higher frequencies of brain edema and intracranial hypertension compared with males, and the highest rates were found in female patients younger than 51 years. Females aged 30 years or older had significantly poorer outcomes, as measured by the Extended Glasgow Outcome Scale and Functional Status Examination.[36] However, the Australian data in the present study did not confirm this observation, suggesting no relationship between sex and the risk of brain edema.

A recent international cohort study[2] that included 10 008 TBI patients indicated that TBI outcome predictors were age, GCS score, pupil reactivity, and the presence of major extracranial injury. Sex was not one of the predictors. Even though Wright et al[22] concluded that progesterone caused no discernible harm and showed possible signs of benefit, further studies are required to identify the role of sex hormones in head injury outcomes.

In this study, we used a sex-age combination as a surrogate for hormonal status. Clearly there are monthly hormonal changes, and so this study can evaluate only an overall sex difference and not the effects of high or low levels of estrogen and progesterone. Second, the treatments and protocols from these health care facilities are bound to vary, and such confounding cannot be ruled out. Third, race may affect mortality from trauma and, as a consequence, may be a confounder. We do not collect specific data on race in our registries. The most that we can allow for such possible racial differences is the fact that one data set is predominantly ethnic Chinese and the other is predominantly non-Chinese. The separate analysis of the Hong Kong and Victorian data sets may partly allow for this. Other than this, it was not possible to analyze the effects of race on mortality in this study. Some variables in our study have many missing values (eg, comorbidity). Finally, the number of patients is lower in the Hong Kong group than in the Victorian group, thus reducing the power of this part of the study. Despite these limitations, our study is based on large data sets.

In conclusion, this study, which investigated posttraumatic brain outcomes in males and females in age groups associated with female fertility, found no significant association between sex and mortality in either Victoria or Hong Kong and does not support the concept that females have better outcomes than males after TBI.

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INVITED CRITIQUE

Sex Differences for Traumatic Brain Injury Outcomes

Answers or More Questions?

Yeung et al have reported the results of a multicenter, retrospective cohort study of TBI outcomes between males and females. The authors analyzed 2 separate data sets (from Australia and Hong Kong) and found no sex differences in mortality. However, females in the Hong Kong cohort were found to have a higher risk of brain edema than males.

The stimulus for this study was likely the unresolved question of the effect of sex hormones on injury outcomes. In experimental models, progesterone administration has been linked to better TBI outcomes.[1-4] However, clinical research has generated conflicting results. In several retrospective clinical studies ranging from 1800 to 72 000 patients, results varied widely, from either men or women having a mortality advantage to no differences found.[5-8]

Given the conflicts in the existing literature, it is unsurprising that these investigators were unable to find a mortality difference in these small cohorts. One of the strengths of this work is in the description of a relatively homogeneous Asian population, which is otherwise underrepresented in the literature. However, generalizability is uncertain, given study limitations. In particular, socioeconomic status and race have been shown to affect outcomes after TBI, but the authors were unable to control for these factors. This is particularly important because sex differences in brain edema were seen only in the largely Asian cohort. In addition, the reliability of coding for the complication of brain edema is unclear; this is relevant because the data set is derived from many different hospitals, which may predispose to a type II error.