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SEX DIFFERENCES IN OUTCOMES OF ADULT PATIENTS WITH TRAUMATIC BRAIN INJURY

by
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ABSTRACT

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Title: Sex Differences in Outcomes of Adult Patients with Traumatic Brain Injury

Traumatic brain injury (TBI) will become one of the major causes of death in year 2020. Medical management that is based on guidelines is not the only factor that decreases secondary brain injury. Sex difference has an effect on outcomes of TBI patients. The aim of this study was primarily to explore the effect of sex differences on admission in adult TBI patients. Mortality and length of stay were also investigated.

This was a retrospective cohort study that investigated sex difference in mild, moderate, and severe TBI patients at the American University of Beirut Medical Center (AUBMC) between 2012 and 2014. Sample size was 344, more males (68.9%) than females (31.1%).

There was no significant difference in admission, mortality from arrival to Emergency Department (ED) through hospital discharge, and hospital length of stay (LOS) in days between males and females. Females who were in the subgroup of moderate to severe TBI and <50 years old had significantly increased hospital LOS duration compared to males in the same subgroup [(39.2 $\pm$ 33.9 versus 11.54 $\pm$ 13.7) (p=0.02)]. Males in the subgroup of mild TBI $\geq$ 50 years old had longer hospital LOS in comparison to females in the same subgroup [(7.8 $\pm$ 13.1 versus 2 $\pm$ 2.8) (p<0.001)]. Admission and mortality were not significantly different between males and females in any age and severity subgroups.

In general, long-term outcomes such as, cognitive and functional performance, could be more specific in determining the effect of sex difference on TBI outcomes.

CONTENTS

TABLES

Table Page

CHAPTER I

BACKGROUND AND SIGNIFICANCE

Traumatic brain injury (TBI) is defined by the Centers for Disease Control and Prevention (CDC) as "a bump, blow or jolt to the head or a penetrating head injury that disrupts the normal function of the brain" (CDC, 2016a). The incidence, morbidity, and mortality rates of TBI vary globally; however, it has been trending upwards over the years (Roozenbeek, Maas, & Menon, 2013). The United States witnessed an increase of TBI- related mortality and admissions to Emergency Departments (EDs) and hospitals from a total of 2.5 million in 2010 to a total of 2.8 million in 2013 (Taylor, Bell, Breiding, & Xu, 2017). On the other hand, TBI in Europe was associated with 2.1 million hospital discharges and 82,000 cases of mortality in 2012 (Majdan et al., 2016). The incidence rates of TBI in Europe, however, were mostly invariable since 1980 (Brazinova et al., 2016). This lack of variability has been mainly attributed to inconsistency in the measurement of incidence rates and utilization of different methodologies for TBI case identification in epidemiological studies in Europe (Peeters et al., 2015). When comparing incidence and mortality rates between other countries, New Zealand had the highest incidence of TBI (811/100,000/year), whereas South Africa had the highest rate of TBI-related mortality (80.73/100,000/year) (Li, Zhao, Yu, & Zhang, 2016). Although TBI rates of incidence, mortality, and hospitalizations vary between countries, it is estimated that TBI will be characterized as one of the foremost causes of death and morbidity worldwide in 2020 (Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007).

Incidence and mortality rates of TBI were not adequately documented in Lebanon, even though investigators had identified TBI cases since 1975 (Abou-Abbass et al., 2016; Habre, Darwish, & Noureddine, 2012). The majority of data were collected in hospitals in Beirut and during intermittent time intervals (Abou-Abbass et al., 2016). As a result, patients who were treated for TBI in rural and remote areas and during periods that lacked data collection were not studied. Evidently, a total of 682 TBI cases in Lebanon, which was inferred from retrospective and prospective studies since 1975, is considered an underestimation (Abou-Abbass et al., 2016). Furthermore, the overall TBI-related mortality rate could not be deduced since previously conducted studies did not report it consistently (Abou-Abbass et al., 2016). Nevertheless, although TBI-related incidence and mortality rates in Lebanon are not described accurately, they are presumably high in a region inflicted with recurrent wars and bombing incidents and high rate of motor vehicle accidents, among others.

The causes of head trauma in low and high-income countries are variable. The predominant cause of injury in developed countries was falls (42.4%), particularly among the older adult population (Li et al., 2016). On the other hand, low and middle-income countries had motor vehicle accidents (MVAs) as the major cause of TBI (34.4%) (Li et al., 2016). In Lebanon, a study conducted over a period of 6 months in 2010 reported that falls constituted 42.1% of TBIs, followed by MVAs (20.7%), being struck by an object (16.5%), assaults (10.7%), and sports injuries (3.3%) (Habre et al., 2012). During periods of war and conflict in Lebanon, the highest rate of TBI was blast-related, including shrapnel, bullets, and bombing incidents (Abou-Abbass et al., 2016). In general, identifying the different patterns of TBI in nations with various income levels is particularly vital, as it leads to planning TBI-related preventive strategies.

Regardless of the cause of injury, TBI patients experience common symptoms, manifested as acute or chronic deficits in cognitive, behavioral/emotional, physical, sensory, and sleep functions (CDC, 2017a, 2017b). The cognitive symptoms following a TBI include attention and memory deficits (CDC, 2017b). Patients might not be able to focus or recall information (CDC, 2017a). Hence, they either become unemployed, shift to part-time jobs, or work in a sheltered setting (Stocchetti & Zanier, 2016; Theadom et al., 2017). They may also demonstrate emotional and behavioral problems, such as irritability, anxiety, impulsivity, depression, or hostility (CDC, 2017a, 2017b). Thereby, TBI patients isolate themselves and limit their participation in social activities (Ponsford et al., 2014; Stocchetti & Zanier, 2016). Physically, patients may complain of headache, nausea, vomiting, lassitude, disability, and loss of coordination (CDC, 2017a, 2017b; Ponsford et al., 2014; Theadom et al., 2017). Sensory impairments, such as photophobia, noise intolerance, and blurred vision might also be experienced following a TBI (CDC, 2017a, 2017b). Additionally, TBI patients may report sleeping disorders such as drowsiness and somnolence (CDC, 2017a). As a result, they could require several medical consultations and rehabilitation sessions to enhance their recovery (Ponsford et al., 2014; Theadom et al., 2017). Subsequently, loss of productivity, compounded with increased costs of TBI therapy and rehabilitation, result in a global socio-economic and public health strain (Corrigan, Selassie, & Orman, 2010; Hyder et al., 2007; Nguyen et al., 2016).

Implementing evidence-based therapeutic interventions reduces secondary brain injury and mortality following head trauma. Patients' outcomes, however, are not entirely determined by medical therapy. For instance, sex difference, characterized by distinctive gonadal chromosome and hormonal distributions, affects patients' response

to TBI treatment (Wright et al., 2014a). The female gonadal hormone, namely progesterone, was shown to have a possible neuroprotective role that promotes the recovery of the brain after neurological injury (Wright et al., 2014a). Hence, it is recommended, particularly by the National Institutes of Health, to explore the impact of sex differences on patients' neurological outcomes following a TBI (Wright et al., 2014a). Therefore, the aim of this study was to explore the effect of sex difference on admission in adult patients who have sustained mild, moderate, and severe TBI. Other secondary outcomes that were investigated were mortality and hospital length of stay (LOS).

CHAPTER 2

LITERATURE REVIEW

A. Classification of TBI

TBI is classified into three categories of severity: mild, moderate and severe (Mcginn & Povlishock, 2016). Collectively, structural imaging, loss of consciousness (LOC), post traumatic amnesia (PTA), the Glasgow Coma Scale (GCS) score, and the Abbreviated Injury Scale (AIS) score of the head are used to accurately determine the severity of TBI (CDC, 2015). Generally, any abnormality detected instantly by structural imaging indicates an increased severity of TBI (CDC, 2015). In addition, prolonged durations of PTA and LOC are associated with moderate and severe TBI (CDC, 2015). On the other hand, the GCS score, which is the most widely used tool for TBI classification, is based on the assessment of eye opening, motor behavior, and verbal response (CDC, 2015). A GCS score that is less than or equal to 8 indicates a severe injury, whereas a GCS score that ranges from 13 to 15 indicates a mild injury (CDC, 2015) and a GCS between 9 and 12 is usually considered a moderate TBI. The final criterion, the AIS head score, is used to measure patient survival on a scale that extends from mild injury (AIS head score of 1) to non-survivable injury (AIS head score of 6) (Baker, O'neill, Haddon, & Long, 1974; CDC, 2015). Table 1. represents the criteria used to classify TBI severity based on the five criteria recommended by CDC.

Table 1: Classification of TBI (CDC, 2015)

Criteria	Mild	Moderate	Severe
Structural Imaging	Normal	Normal or Abnormal	Normal or Abnormal
LOC	<30 minutes	30 minutes to 24 hours	>24 hours
PTA	0-1 day	>1 day and <7 days	>7 days
GCS (best available score in 24 hours)	13–15	9-12	3-8
AIS (Head)	1-2	3	4-6

LOC = Loss of Consciousness; PTA = Post Traumatic Amnesia; GCS = Glasgow Coma Scale; AIS = Abbreviated Injury Severity

B. Pathophysiology

Initially, the primary injury, defined as the external mechanical insult to the brain tissue, occurs. The primary injury is followed by secondary brain injury that is characterized by decreased tissue perfusion and oxygenation. Secondary brain injury is a cascade of cellular events that follow the primary injury in the brain, such as glutamate excitotoxicity, ionic dysregulation, mitochondrial dysfunction, increased free radical generation, lipid peroxidation, depletion of energy stores, neuro-inflammation, increased permeability of the blood brain barrier (BBB), axonal injury, and cellular death (Algattas & Huang, 2014; Barkhoudarian, Hovda, & Giza, 2016; Mcginn & Povlishock, 2016; Mckee & Daneshvar, 2015; Pearn et al., 2017; Prins, Greco, Alexander, & Giza, 2013; Xiong, Mahmood, & Chopp, 2013).

Glutamate excitotoxicity (Xiong et al., 2013), or the excessive release of glutamate from pre-synaptic terminals, causes ionic dysregulation after binding to its post-synaptic receptors (Mcginn & Povlishock, 2016; Prins et al., 2013). While potassium increases in the extracellular space, the influx of sodium and marked

accumulation of intracellular calcium occurs inside the cell (Mcginn & Povlishock, 2016; Prins et al., 2013). Sequentially, the influx of calcium causes mitochondrial overload and dysfunction, leading to the formation of reactive oxygen species (ROS) (Prins et al., 2013; Xiong et al., 2013). Released ROS leads to lipid peroxidation, which is a mechanism that involves an interaction between ROS and polyunsaturated fat causing membrane disruption and neuronal death (Pearn et al., 2017; Prins et al., 2013). Concurrently, glucose becomes rapidly metabolized in an attempt to re-establish ionic stability (Mcginn & Povlishock, 2016). Hence, glucose stores become depleted, brain cells shift to anaerobic metabolism, and lactate increases (Mcginn & Povlishock, 2016).

Furthermore, the brain injury promotes a cascade of inflammatory events that stimulate cerebral and peripheral immune response (Mcginn & Povlishock, 2016). Primary brain injury activates microglia that triggers the release of anti-inflammatory substances such as interleukin-4 (IL-4), interleukin-3 (IL-3), and prostaglandins, in addition to pro-inflammatory components namely glutamate, reactive oxygen species, interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), and interferon γ (INFγ) (Pearn et al., 2017). As a consequence, inflammatory mediators cause the production of free radicals that promote cell death (Mckee & Daneshvar, 2015). Concurrently, peripheral immune cells migrate to the injury site across a compromised blood brain barrier (BBB) (Mcginn & Povlishock, 2016). Gradually, The breakdown of BBB leads to an increased permeability and leakage, edema, increased intracranial pressure (ICP), and decreased brain perfusion and oxygenation (Corps, Roth, & McGavern, 2015).

Axonal injury is another pathological mechanism that involves diffuse damage to the axonal plasma membrane following trauma to the brain (Barkhoudarian et al., 2016). Initially, disrupted axonal membranes lead to calcium influx. In sequence,

neurofilament compaction, microtubule destabilization, impaired axonal transport, aggregation of cellular organelles, and eventually swelling, stretching, and disconnection of axons occur (Barkhoudarian et al., 2016; Hill, Coleman, & Menon, 2016).

As noted above, the complex cellular events that occur during secondary brain injury indicate that TBI outcomes are determined by interrelated physiological mechanisms. Hence, it is imperative to investigate efficacious TBI therapy that targets these mechanisms simultaneously.

C. Sex Difference in TBI

The effect of sex difference on brain injury and patient outcomes remains uncertain despite several pre-clinical and clinical studies. Pre-clinical studies examined progesterone's mechanism of action in the brain that could prevent secondary injury. While these studies were able to show that progesterone improved cognitive and functional outcomes in rats, researchers failed to translate these findings consistently in phase II and III clinical trials (Stein, 2015; Wright et al., 2014a). Below is a review of pre-clinical trials, phase II and III clinical trials, in addition to observational studies that explored sex difference in TBI outcomes.

Pre-clinical Trials. Cerebral edema is one of the hallmarks of secondary brain injury. Continuous increase in cerebral edema leads to uncontrolled intracranial pressure (ICP), herniation, and death (Carney et al., 2017). The aim of few preclinical studies was to explore the effect of progesterone on cerebral edema. One of these studies assessed the extent of cerebral edema 24 hours after instigating frontal contusions to anesthetized rats (Roof, Duvdevani, & Stein, 1993). Rats were divided into males,

pseudo-pregnant females (high levels of progesterone), and females with a normal cycle who received the contusion at a pro-estrus phase (suppressed levels of progesterone) (Roof et al., 1993). The findings of this study indicated that pseudo-pregnant female rats did not have brain edema (0.3 ± 0.4%); on the other hand, female rats in the pro-estrus phase had less edema (3.5±0.6%) compared to male rats (6.4±0.9%) ($p<0.01$) (Roof et al., 1993). Another group of ovariectomized female rats were evaluated to eliminate the effect of endogenous estrogen and progesterone (Roof et al., 1993). Ovariectomized female rats were divided as follows: rats with estrogen implants and progesterone injections, rats with estrogen implants and oil injections, rats injected with progesterone only, and rats injected with oil only (Roof et al., 1993). The results revealed that rats who were injected with oil and rats who had estrogen implants and oil injections have significantly increased edema (3.38±0.68% & 4.2±0.37% ;$p <0.05$ & $p <0.01$)respectively) in comparison to rats who received estrogen implants and progesterone injections and rats who were injected with progesterone only (1.5±0.3% and 1.7±0.4 respectively) (Roof et al., 1993).

An additional pre-clinical study assessed the level of edema formation between male and female rats who received an injury to the cortex (Roof, Duvdevani, Heyburn, & Stein, 1996). Male and female rats were divided into a group who received oil injections only and another that received progesterone injections at 1 hour, 6 hours, and 24 hours, followed by one progesterone injection every 24 hours for 7 days (Roof et al., 1996). In general, the peak of edema in male rats was significantly higher than the peak of edema in female rats after 24 hours of the contusion ($p<0.05$) (Roof et al., 1996). However, progesterone injections at 1 hour post contusion reduced edema formation significantly and similarly in male and female rats in comparison to those who received

oil injections (p<0.001) (Roof et al., 1996). Moreover, the level of edema at day 3 among contused rats who received progesterone injections was equal to the level of edema at day 7 among contused rats who received oil injections only (Roof et al., 1996).

A third pre-clinical interventional study compared water content in the brain between three groups of male rats: control, TBI, and TBI followed by progesterone treatment (Si et al., 2014). Male rats in the control group (SHAM) did not receive a brain injury nor progesterone injections (Si et al., 2014). Male rats in the TBI group received an injury to the cranial dura (Si et al., 2014). The treatment group included male rats that received the same mechanism of TBI in addition to progesterone injections at 1 hour, 6 hours, and 12 hours post TBI (Si et al., 2014). As anticipated, the SHAM group had a significantly decreased water content in comparison to the TBI group (74.3±0.92 and 82.6±2.13 respectively, p<0.05) (Si et al., 2014). Likewise, the TBI group that received progesterone treatment had significantly lower brain edema in comparison to the TBI group (78.4±1.47 and 82.6±2.13, p<0.05) (Si et al., 2014).

Other physiologic mechanisms that worsen cerebral edema, such as disruption of the blood brain barrier and release of inflammatory mediators, were also measured in the same pre-clinical trial (Si et al., 2014). These two mechanisms were compared between the three groups of male rats: SHAM, TBI, and progesterone-treated following a TBI (Si et al., 2014). The findings of this trial indicated that rats in the SHAM group had low permeability of blood brain barrier and decreased levels of prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2), nuclear factor κB (NF-κB) and tumor necrosis factor-α (TNF-α) in comparison to rats in the TBI group (p<0.05) (Si et al., 2014). Progesterone, however, was significantly effective in preserving the blood brain barrier

and lowering the level of circulating inflammatory mediators in TBI patients compared to those TBI rats that did not receive progesterone ($p<0.05$) (Si et al., 2014)

Progesterone seems to have a role in promoting anti-apoptotic proteins (Bcl-2 and Bcl-x_L) and downregulating the pro-apoptotic proteins (Bax and Bad) (Yao, Liu, Lee, Ling, & Mccabe, 2005). Male rats were divided into three groups: Rats who received progesterone injection without a TBI, rats who received a TBI only, and rats who received progesterone injections following a TBI injury (Yao et al., 2005). The results suggested that the pro- Bax and Bad were significantly elevated following a TBI (Yao et al., 2005). TBI rats that were treated with progesterone had significantly lower levels of Bax and Bad compared to TBI rats who did not receive progesterone injections ($p<0.05$) (Yao et al., 2005). On the other hand, TBI alone did not increase the levels of anti-apoptotic proteins except for Bcl-x_L on day 5 only (Yao et al., 2005). TBI patients who were treated with progesterone injections had significantly increased level of Bcl-2 on day 2 and 3 and of Bcl-x_L during the first two days of TBI in comparison to the other two groups (Yao et al., 2005).

Lipid peroxidation occurs when polyunsaturated fatty acids in the phospholipid bilayer of the cell membrane react with reactive oxygen species following a TBI (Mcginn & Povlishock, 2016; Roof, Hoffman, & Stein, 1997). Hence, it is an indirect indicator of free radical formation that causes the breakdown of the blood brain barrier (Mcginn & Povlishock, 2016). A pre-clinical study measured lipid peroxidation in male rats after applying a cortical contusion (Roof et al., 1997). Following TBI, the first group of the male rats received progesterone treatment; the other group of rats received oil injections only (Roof et al., 1997). A marker of lipid peroxidation was then measured at day 1, 2, and 3 after the injections (Roof et al., 1997). The results showed

that TBI rats who received progesterone had lower levels of lipid peroxidation marker as compared to the TBI rats who received oil injections only (Roof et al., 1997).

Decreased tissue perfusion, ischemia, and cell death are features of secondary brain injury. Progesterone plays a role in promoting angiogenesis and vascular repair by regulating endothelial progenitor cells (EPCs) (Li et al., 2012). Male rats were divided in three groups: control rats that did not receive TBI nor progesterone treatment, TBI rats that were treated with vehicle control, and TBI rats that were treated with progesterone after 1 hour, 6 hours, 1 day after injury, followed by daily administration of progesterone for two weeks (Li et al., 2012). TBI rats who were treated with progesterone had significantly increased levels of EPCs three hours following a TBI in comparison to TBI rats who received vehicle controls only ($p<0.05$) (Li et al., 2012). The levels of circulating EPCs remained high for three weeks following a TBI (Li et al., 2012).

An additional pre-clinical study examined the estrous cycle of female rats and compared them to male rats (Wagner et al., 2004). Females groups consisted of females in the proestrus phase (high levels of progesterone and estrogen) and non-proestrus phase (low levels of progesterone and estrogen) (Wagner et al., 2004). Male and female rats were further divided into a group that received a TBI and another that did not (Wagner et al., 2004). The results showed that all injured females, regardless of their estrous phase, had similar motor performances (Wagner et al., 2004). However, TBI female rats had significantly improved motor functions in comparison to TBI male rats (beam balance performance $p< 0.003$ and beam walking performance $p<0.005$) (Wagner et al., 2004). Although estrous cycle did not have an effect on motor function, it is important to note that all female rats performed better than males, probably due to

higher levels of endogenous progesterone.

In summary, the majority of pre-clinical studies showed that progesterone decreases cerebral edema, decreases pro-apoptotic proteins in cerebral cortex following TBI, preserves the blood brain barrier, decreases neuro-inflammation and lipid peroxidation, and promotes angiogenesis.

Phase II Clinical Trials. The results of the majority of pre-clinical studies encouraged researchers to examine the safety of progesterone in phase II clinical trials. The first phase II study was a randomized, double blinded, placebo-controlled clinical trial that measured the effect of progesterone on clinical outcomes of male and female TBI patients whose GCS scores ranged from 4 to 12 (Wright et al., 2007). All TBI patients received standard care that is based on the Brain Trauma Foundation guidelines Wright et al., 2007). In addition to the standard care, TBI patients allocated to the intervention group received progesterone injections, while patients in the control group received a placebo (Wright et al., 2007). The results showed that, among the patients whose GCS score is between 4 and 8, the group who received progesterone had significantly lower mortality rate after 30 days of TBI (13.2%) in comparison to the control group (40%) (RR =0.33, 95% CI 0.13 - 0.83) Wright et al., 2007). However, the treatment group of the same category remained longer in coma compared to the placebo group (10.1 days [95% CI 7.7 to 12.5 days] versus 3.9 days [95% CI 2.5 to 5.4 days]); this could be explained by the increased survival rate of the treatment group of this category in comparison to the control group (Wright et al., 2007). Despite their lower mortality rate, the progesterone-treated group in the category of patients whose GCS score is between 4 and 8 had lower "moderate to good" recovery rates (21.2%) as compared to placebo group (26.7%). On the other hand, among the category of patients

whose GCS score ranges between 9 and 12, progesterone-treated group had significantly better recovery rates (55.6%) as compared to the placebo group (0%) (p = 0.02).

Another phase II randomized, placebo controlled clinical trial was conducted in China to assess the Glasgow Outcome Scale (GOS) of patients whose GCS ≤ 8 (Xiao, Wei, Yan, Wang, & Lu, 2008). GOS is generally used by all investigators to assess disability among TBI patients (Wilson, Pettigrew, & Teasdale, 1998). It is a 5-point scale that ranges from death to good recovery (Wilson et al., 1998). In this study, GOS was measured at 3 and 6 months, then compared between TBI patients who received progesterone and others who received a placebo. At 3-months follow-up, patients who were treated with progesterone had significantly improved recovery rate compared to the placebo patients (p =0.044) (Xiao et al., 2008). GOS was then dichotomized to reflect favorable outcome (moderate disability and good recovery) and unfavorable outcome (severe disability, vegetative state, and death) (Xiao et al., 2008). The dichotomized analysis showed statistical significance at 3 and 6-months follow-up; patients who received progesterone had increased favorable outcomes in comparison to patients who received a placebo [(at 3-months: p= 0.034; at 6-months: p= 0.048)] (Xiao et al., 2008). The mortality rate, measured as a secondary outcome at 6-months follow-up, was also significantly lower in the group that received progesterone in comparison to the group who received a placebo (18% and 32 % respectively, p=0.039) (Xiao et al., 2008).

Although pre-clinical trials showed that progesterone is effective in decreasing ICP, consistent findings could not be deduced from phase II clinical trials. Wright et al. demonstrated that during the first four days following progesterone injections, the mean

ICP of patients who received progesterone was not significantly lower than the mean ICP of placebo patients (2007). Xiao et al. performed continuous ICP monitoring at one day, three days, and seven days following the injury (2008). Significant difference in mean ICP between both groups was also not detected (Xiao et al., 2008).

In general, phase II clinical trials showed that progesterone have an effect of favorable outcomes in TBI patients. Thus, researchers proceeded towards designing phase III clinical trials at multiple sites and on larger samples.

Phase III Clinical Trials. An interventional, double-blinded, parallel group trial was conducted at a multinational level to assess the effect of progesterone on outcomes of TBI patients (Skolnick et al., 2014). Participants were male and female patients who had a minimum of one reactive pupil and a GCS score ≤ 8 (Skolnick et al., 2014). Male and female patients were randomly assigned to a group that received progesterone injections and to another that received a placebo (Skolnick et al., 2014). Progesterone was administered to the treatment group at eight hours following TBI and continuously up to 120 hours (Skolnick et al., 2014). The primary outcome was the GOS score of the treatment and placebo group at six months following treatment (Skolnick et al., 2014). In contrast to previous clinical trials, both groups had comparable GOS scores after six months of follow-up (OR 0.96, CI 0.77-1.18) (Skolnick et al., 2014).

Another phase III randomized clinical trial explored the difference in Extended GOS scores between patients assigned to progesterone treated and placebo groups (Wright et al., 2014b). Extended GOS is an 8-point score that divides the categories of good recovery, moderate disability, and severe disability into upper and lower classifications (Wilson et al., 1998). Eligible participants had a blunt trauma to the head and a GCS score that ranged from 4 to 12 (Wright et al., 2014b). Progesterone or

placebo was infused at four hours post injury and continued for four days (Wright et al., 2014b). Results showed that favorable outcomes between the intervention group and placebo group were similar (p=0.35) (Wright et al., 2014b). In addition, mortality rates were not significantly different between the two groups (hazard ratio 1.19, CI 0.86-1.63) (Wright et al., 2014b).

The setting of TBI clinical trials is not as controlled as the setting in the pre-clinical studies. Various factors, such as heterogeneity of TBI and failure to administer progesterone immediately may have contribute to incongruence of results between all TBI trials.

The sex hormones, including progesterone, do not seem to explain the sex difference in TBI outcome; however, the evidence regarding the effect of sex difference in outcomes of TBI patients is still evolving. Observational studies continue to investigate the effect of sex difference and other patients' characteristics on mortality and functional outcomes of male and female TBI patients

Observational Studies. A prospective non-experimental study compared the GOS score and mortality between male and female patients (n=439) six months after they have sustained moderate and severe TBI (Leitgeb et al., 2011). Mortality rate was not significantly different between males and females (32.5% versus 39.6% respectively, p=0.16) (Leitgeb et al., 2011). After adjusting for penetrating traumas, hypotension, decreased GCS, and bilateral non-reactive pupils, sex difference was not found to be significantly associated with mortality (Leitgeb et al., 2011). Moreover, GOS score was assessed six months after TBI and was dichotomized as favorable (scores = 4 or 5) and unfavorable (scores ≤ 3) (Leitgeb et al., 2011). Unfavorable outcome was not significantly different between males and females (53.4% versus

58.7% respectively, p=0.09) (Leitgeb et al., 2011). As a conclusion, the authors argued that the sample was not large enough to detect small differences in outcomes between male and female TBI patients (Leitgeb et al., 2011) .

Another prospective study examined the effect of sex and age on Extended GOS and functional status examination (FSE) after three and six months of trauma in 157 patients with moderate to severe TBI (Kirkness, Burr, Mitchell, & Newell, 2004). FSE indicates the extent of functionality of a TBI patient in his/her daily life activities (Kirkness et al., 2004). Poor outcomes of Extended GOS and FSE were significantly associated with female sex who are 30 years and older (p=0.031 & p=0.037, respectively) (Kirkness et al., 2004). This is an unanticipated outcome for women who are below the menopausal age. Therefore, a larger sample size is required to assess the effect of premenopausal age on outcomes of TBI patients.

Retrospectively, the effect of sex difference on GOS score, a functional assessment measure, and mortality was examined among age-matched male and female patients after sustaining an MVA-related TBI in Australia (Slewa-Younan, Green, Baguley, Gurka, & Marosszeky, 2004). Patients had moderate to severe TBI, characterized by GCS score below 12 or PTA duration greater than 24 hours. None of the outcomes was significantly different between male and female TBI patients (Slewa-Younan et al., 2004). The authors argued that the widely used functional assessment tools may not be suitable to detect significant differences in outcomes between males and females (Slewa-Younan et al., 2004).

An additional retrospective study explored gender differences in mortality during hospitalization among moderate and severe TBI patients (n=13,437) (Davis et al., 2006). Pre-menopausal women (<50 years of age) and post-menopausal women

(≥50 years of age) were compared to age-matched males (Davis et al., 2006). There was no significant difference in mortality rate among women who are less than 50 years old and age-matched males after sustaining TBI (21.2 % versus 20.3 % respectively) even after adjusting for age, mechanism of injury, GCS, hypotension, head AIS, and injury severity scale (OR 0.95, CI 0.84-1.07) (Davis et al., 2006). However, post-menopausal females (≥50 years of age) had significantly improved mortality outcome in comparison to age-matched males (AOR 1.25, CI 1.07-1.45) (Davis et al., 2006). The findings of this study are in contrast to the hypothesis of neuroprotective effect of progesterone in moderate to severe TBI patients.

The mortality rate was compared in another retrospective study between age and GCS matched male and female patients who sustained a TBI and were admitted to a critical care area for ICP monitoring (Czosnyk et al., 2008). Among TBI patients who were younger than 50 years of age, females had a significantly higher mortality rate at six months following TBI in comparison to males (29% versus 17%, p=0.026) (Czosnyk et al., 2008). Among TBI patients who were older than 50 years, the mortality rate after six months of TBI was similar between males and females (approximately 43% in males and females) (Czosnyk et al., 2008). The authors discussed that markedly increased ICP in females led to their increased mortality rate (60 % versus 20 % in males, p<0.05); however, in relevance to the pre-clinical studies that demonstrated the therapeutic effects of progesterone, ICP measurement is another outcome that should be modulated by progesterone.

Furthermore, the effect of sex on mortality, hospital length of stay, and ICU length of stay was assessed retrospectively in patients who sustained a severe blunt TBI (Ottochian et al., 2009). Males and females had no significant difference in their

hospital and ICU length of stay (p=0.234 and p=0.157 respectively) (Ottochian et al., 2009). In contrast, mortality rate was higher among females (41.9 % versus 29.5 % p< 0.0001) (Ottochian et al., 2009). Males and females were further stratified into age groups (<15 years, 14-44 years, 45-54 years, and ≥55 years) (Ottochian et al., 2009). After stratification, significant difference in mortality rate was demonstrated among the oldest group (≥55 years) only, in which females had an increased mortality rate in comparison to males of the same age group (AOR 1.71, 95%CI 1.11-2.62, p=0.02) (Ottochian et al., 2009). Thus, it is probable that reduced level of progesterone in older menopausal women lead to worse outcomes following a TBI (Ottochian et al., 2009).

The difference in mortality rate and functional outcomes in ICU and six months following severe TBI were explored between males and females in Spain (Herrera-Melero et al., 2015). Similar to previous results, in this retrospective investigation, sex was not found to be an independent factor that contributes to improved outcomes post TBI (Herrera-Melero et al., 2015). Functional outcome was not significantly different between males and females at ICU discharge and six months following a severe TBI (p = 0.411 and p=0.372 respectively) (Herrera-Melero et al., 2015). In addition, females had significantly higher rate of mortality in ICU (35.11% vs 23.737%; p = 0.020, OR=1.74, 95%CI=1.09-2.77) and after six months (36.8% versus 26%; p=0.039; OR=1.65; 95% CI=1.02– 2.67) compared to males. The authors explained that this finding was due to the fact that females had significantly lower hemoglobin levels, required more transfusions, and had increased rate of pre-hospital hypotension compared to males (Herrera-Melero et al., 2015).

In an additional retrospective study, the mortality rate at discharge was compared between males and females in an older sample (age was ≥ 65 years) over a

16-year period (Albrecht, McCunn, Stein, Simoni-Wastila, & Smith, 2016). The sample included patients with mild, moderate, and severe TBI. After adjusting for multiple demographic and injury characteristics such as age, race, AIS head score, GCS score, cardiac disease, blood pressure at admission, and direct transfer from the scene of trauma, mortality at discharge in an isolated TBI was not significantly associated with female sex (OR, 1.01; 95% CI, 0.66–1.54) (Albrecht et al., 2016). The authors explained that the results were congruent with their hypothesis since progesterone is minimal among older adult menopausal women (Albrecht et al., 2016).

In summary, the effect of sex difference on various TBI outcomes is still not clear. Differences in sex hormones were associated with variable outcomes and conflicting results. Progesterone was extensively studies in pre-clinical and clinical studies. The therapeutic effects of progesterone are still uncertain. Pre-clinical studies have demonstrated the therapeutic pharmacological effect of progesterone on secondary brain injury in animals who sustained a TBI. Later, phase II clinical studies determined that progesterone could be safely used in human subjects. Phase III clinical trials, which examined the effect of injected progesterone on a larger sample of TBI patients, did not demonstrate significant differences in TBI outcomes between progesterone and placebo groups. These conflicting findings lead to an inference that progesterone alone cannot explain the difference in TBI outcomes between males and females.

Observational studies, on the other hand, continue to explore the effect of sex difference on TBI outcomes. Observational studies have also failed to show that females have better outcomes than males.

It is controversial whether sex difference in TBI outcomes actually exists. Future clinical studies need to investigate the causes of contradictory findings. Current

postulations suggest that TBI is more complicated and variable in the clinical setting compared to the experimental animal model studies. For example, a standardized mechanism of injury is implemented on all animal subjects in pre-clinical studies; whereas human subjects in clinical trials are characterized by different mechanisms and intensities of injury within the same sample or even within one participant (Maas et al., 2012). Second, researchers investigate short term outcomes in animal studies in contrast to clinical studies that explore long term outcomes such as GOS and mortality three and six months after injury (Bazarian, Blyth, Mookerjee, He, & Mcdermott, 2010).

Additional factors that may have contributed to the inconsistency in the findings of clinical trials is that medical management differs across and within medical centers, contributing to the increased variability of research findings (Maas et al., 2012). Moreover, all known covariates, such as pre-existing comorbidities and history of medications taken by patients, should be included in TBI studies (Maas et al., 2012; Skolnick et al., 2014). These factors have an effect on the metabolism of therapeutic agents and increase the likelihood of having poor outcomes (Maas et al., 2012).

Furthermore, bio-behavioral factors that accurately measure patients' prognosis following a TBI are not identified yet. For example, brain biomarkers that are clinically relevant to the progression of TBI, are still under investigation. In addition, outcomes and specific response to TBI are sex dependent as suggested in an animal study that compared TBI response between male and female adolescent rats (Wright, O'Brien, Shultz, & Mychasiuk, 2017). After repeated mild traumatic brain injury, male rats exhibited deficits in short term working memory, while female rats demonstrated an increased depression (Wright et al., 2017). Hence, sex-dependent specific cognitive outcomes in humans should be identified and assessed in order to provide a better

understanding of progesterone's effect.

The objective of this study was to explore the effect of sex differences on admission rate in TBI patients. We examined mortality and hospital length of stay as secondary outcomes. Contrary to previous retrospective studies, the sample in this study included TBI patients with GCS scores ranging from 3 to 15 and patients with blunt and penetrating injuries; mainly to examine the differences between mild, moderate, and severe TBI. Past medical/surgical history and history of taking medications were considered in the analysis to assess their impact on TBI outcomes. In addition, the outcomes were compared between males and females in subgroups of age and TBI severity.

CHAPTER 3

METHODS

A. Design

This is a sub-study from an ongoing multi-site retrospective cohort study that covers a period of two years (2012-2014). The TBI registry included 697 patients who sustained a head trauma between 2012 and 2014 and were treated at the American University of Beirut Medical Center, Rafik Hariri University Hospital, Makassed General Hospital, Al Zahraa University Hospital, Bahman Hospital, Sahel General Hospital, and Mount Lebanon Hospital in Beirut. Participants' characteristics, injury related events, assessment, interventions, and outcomes were retrieved from this TBI registry. The registry is based on common data elements (CDE) of TBI that are recommended by TBI CDE Working Group and the National Institute of Neurological Diseases and Stroke.

B. Sample

Records of patients were retrieved from the TBI registry if they met the following inclusion criteria: patients who were treated at the American University of Beirut Medical Center (AUBMC) between 2012 and 2014, patients who were 18 years old and above, and patients who survived a mild, moderate, or severe TBI. The sample size of retrieved patients who met the inclusion criteria was 344.

C. Data Collection

Data of adult patients were collected from the patients' medical records at AUBMC. Patients who presented to ED with a chief complaint of head trauma, major trauma, multiple trauma, polytrauma, fall on face/head, scalp/forehead laceration, fall from height, blast injury, MVA, road traffic accidents, loss of consciousness following trauma were included in the registry and selected for this study.

The dependent variables that were collected from the registry and then used in this study were admission, mortality, and hospital LOS of patients in days. The independent variable was sex. Covariates entered in the registry were:

a. Age: Mean age was calculated and then stratified into less < 50 years old and ≥ 50 years old.
b. Past medical and surgical history: Patients were considered to have a past medical history if they had diabetes, chronic obstructive pulmonary disease, asthma, liver disease, esophageal varices, congestive heart failure, coronary artery disease, myocardial infarction, hypertension, renal failure, seizures, transient ischemic attack, stroke, cancer, or any other neurological and/or psychiatric disorder. Surgical history included cardiac surgery, brain surgery. History of hysterectomy and oophorectomy were not included since only three females in this sample who were ≥ 80 years old had this surgical history.
c. Existence of medication history, mainly antiplatelet agent, anticoagulants, and steroids, was entered as well. Hormone replacement therapy was not considered in the analysis because it was found missing in the patients' charts.
d. Severity classification of TBI was categorized based only on the GCS score (mild 13-15, moderate 9-12, and severe 3-8). The latest recommendations for

accurate TBI classification is based on structural imaging, PTA duration, LOC duration, GCS score, and AIS head score collectively (CDC, 2015). However, data pertaining to PTA were unknown or missing in 40% of the patients' records. LOC data were missing in 18.3 % of the patients in this sample. In addition, data on AIS head were neither collected nor entered on any patient in the registry. The GCS score, on the other hand, was documented on the majority of the patients, it was missing in only 5.2 % of the patients' records. Therefore, the GCS was the only criterion used to classify TBI in this study.

e. Type of TBI: blunt or penetrating.
f. Mechanism of injury: fall, violence, explosion, sports, or vehicle.
g. Presence of injuries associated with TBI such as injuries in the chest, abdomen, pelvis, spine, and extremities.
h. Presence of hypotension upon the patient's presentation to ED, defined as systolic BP less than 90 mmHg.
i. Required transfusion: Yes/No.
j. Hypoxemia upon his presentation to ED defined as SpO2 less than 90%.

D. Data Analysis

Statistical Package for the Social Sciences (SPSS) version 24 was used for statistical analysis. Descriptive analysis was conducted for the all the sample variables. All covariates were compared between male and female patients. Chi-square was used for categorical variables and independent t-test was used for continuous variables. Stratification by age and sex followed. All independent and dependent variables were compared between stratified groups of males and females as follow:

a. < 50 years old and have mild TBI only

b. < 50 years old and have moderate to severe TBI

c. ≥ 50 years old and have mild TBI only

d. ≥ 50 years old and have moderate to severe TBI

Moderate and severe TBI were combined in every subgroup since moderate TBI patients constituted only 6.9 % of the sample, whereas severe TBI patients constituted 9.8% of the sample.

Non-parametric tests such as Fisher's exact test and Mann-Whitney test were used for the analysis of small group sizes after stratification. In addition, admission, mortality, and hospital length of stay were compared between male and female patients after being stratified by age (< 50 years old, ≥ 50 years old).

Multivariate logistic regression was used to analyze the association between covariates and admission and between covariates and mortality. Multivariate linear regression was used to assess the relationship between covariates and length of stay in hospital. Sex and age were always included in the regression analysis since they are considered the main exposure. After bivariate analysis, covariates with significance level $p>0.1$ were excluded from the regression models. An alpha of 0.05 was used for statistical significance.

CHAPTER 4

RESULTS

A total of 418 patients presented to AUBMC during the study period. Of these, 344 patients met the inclusion criteria after reviewing patients' chief complaints, history of injury, and ED and hospital management. Of the 344, as expected, the number of males who sustained a TBI was greater than that of females [237 (68.9%) versus 107 (31.1%). Falls constituted the highest percentage among all other mechanisms of injury (42.9%), followed by vehicle-related TBIs (33.6%). Females had significantly higher rate of falls in comparison to males (51% versus 39.3%, *p*-value=0.049).

The mean age difference between males and females was not statistically significant: mean age of males was 46.3 ± 22.1 and of females it was 49 ± 22.6 (p=0.30), even when age was dichotomized (p=0.19). However, females had a significantly increased rate of past medical and surgical history in comparison to males (61.3% versus 44.4%, p=0.004), in addition to an increased rate of medication history compared to males (55.8% versus 36%, p=0.001). Overall, there was a statistically significant difference in TBI classification between males and females. Females had increased rate of mild and severe injury in comparison to males [mild (90.9% versus78.4%), severe (12.3% versus 6.1%) respectively] while males had and increased rate of moderate TBI compared to females (9.3% versus 3%) (p=0.023). Males had a significantly increased rate of associated injuries (47.3%) in comparison to females (31.8%), p=0.007. Admission, mortality, and length of stay were not significantly different between females and males (p=0.08*; p*=0.06; p=0.42). The demographic and clinical characteristics of TBI patients compared by sex are described in Table 2.

Table 2: Demographic data and clinical characteristics of TBI patients by sex

Variables	**Total** (N=344)	**Females**	Males	***p*-value**
Gender		107 (31.1%)	237 (68.9%)	<0.001
Age $\bar{X}$ ± SD[t]	47.1 ± 22.32	49 ± 22.6	46.3 ± 22.1	.30
Age <50 years n (%)[c]	201 (58.4%)	57 (53.3)	144 (60.8)	.19
Age ≥50 years n (%)[c]	143 (41.6%)	50 (46.7)	93 (39.2)	
Past medical/Surgical history n (%)[c]	168 (49.7%)	65 (61.3)	103 (44.4)	.004*
Medications history n (%)[c]	139 (42.2%)	58 (55.8)	81 (36)	.001*
Classification of TBI n (%)[c]				.023*
Mild	268 (82.2%)	90 (90.9)	178 (78.4)	
Moderate	24 (7.4%)	3 (3.0)	21 (9.3)	
Severe	34 (10.4%)	28 (12.3)	6 (6.1)	
Type of TBI n (%)[c]				.29
Blunt	277 (80.5%)	86 (80.4)	191 (80.6)	
Penetrating	35 (10.2%)	8 (7.5)	27 (11.4)	
Others	32 (9.3%)	13(12.1)	19(8.0)	
Mechanism of Injury n (%)				
Fall[c]	141 (42.9%)	51 (51)	90 (39.3)	.049*
Vehicle[c]	111 (33.6%)	31 (30.7)	80 (34.9)	.45
Violence[c]	32 (9.7%)	6 (5.9)	26 (11.4)	.12
Explosion[f]	14 (4.2%)	5 (5)	9 (3.9)	.76
Sports[f]	7 (2.1%)	0 (0)	7 (3.1)	.105
Others				
Associated injuries n (%)[c]	146 (42.4%)	34 (31.8)	112 (47.3)	.007*
Required Transfusion n (%)[c]	65 (19%)	22 (20.6)	43 (18.2)	.60
Hypoxemia n (%)[f]	11 (3.7%)	2 (2.3)	9 (4.3)	.51
Hypotension n (%)[f]	3(0.9%)	2 (1.9)	1(0.4)	.23
Admission n (%)[c]	231 (67.2%)	65 (60.7%)	166 (70%)	0.08
Mortality n (%)[c]	18 (5.2%)	2 (1.9%)	16 (6.8%)	0.06
LOS $\bar{X}$ ± SD[t]	8.32 ± 18.4	7.14 ± 20.3	8.85 ± (17.45)	0.42

TBI, Traumatic brain injury; $\bar{X}$, Mean; SD, Standard Deviation; * Significant; [t]Independent t-test; [c] Chi Squared test; [f] Fisher's exact test

Table 3: Multivariate Logistic Regression analysis for admission of TBI patients

Nagelkerke R square	**.423**	**Admission**		
Variables		**OR**	**95 % CI**	***p*-value**
Age		1.01	0.99 - 1.04	0.07
Sex				
	Male	Reference		
	Female	0.63	0.31-1.26	0.19
Past medical/Surgical history				
	No	Reference		
	Yes	3.72	1.23-11.2	0.01*
History of Medications				
	No	Reference		
	Yes	0.43	0.14-1.25	0.12
TBI Classification				
	Mild	Reference		
	Moderate & Severe	19.25	2.43-151.98	0.005*
Type of Injury				
	Blunt	Reference		
	Penetrating	3.34	0.90 -12.34	0.07
Mechanism of Injury				
	Fall	1.16	0.59 - 2.28	0.65
	Sports	0.22	0.02 -2.12	0.19
Associated Injuries				
	No	Reference		
	Yes	2.87	1.45-5.70	0.002*
Required Transfusion				
	No	Reference		
	Yes	10.83	1.34-87.01	0.02*

TBI, Traumatic brain injury; OR, Odds ratio; CI, Confidence Interval, * Significant

Table 4: Multivariate logistic regression analysis for mortality in TBI patients

Nagelkerke R square	**.453**	**Mortality**		
Variables		**OR**	**95 % CI**	***p*-value**
Age		1.02	0.99-1.96	.15
Sex				
Male		Reference		
Female		0.24	0.02-2.55	.24
Past medical/Surgical history				
No		Reference		
Yes		5.45	0.77-38.42	.08
TBI Classification				
Mild		Reference		
Moderate & Severe		25.65	3.64-180.33	.001*
Required Transfusion				
No		Reference		
Yes		1.89	0.38-9.18	.43
Hypoxemia				
No		Reference		
Yes		5.67	0.88-36.39	.06

TBI, Traumatic brain injury; OR, Odds ratio; CI, Confidence Interval, * Significant

Table 5: Multivariate linear regression analysis for length of stay in TBI patients

R Square	**.293**	**Length of Stay**		
Variables		**β**	**95% CI**	***p*-value**
Sex				
Male		Reference		
Female		-0.73	-4.70-3.24	.71
Age		-0.006	-0.11- 0.10	.91
Past medical/surgical history				
No		Reference		
Yes		3.94	-0.87 - 8.75	.10
TBI Classification				
Mild		Reference		
Moderate & Severe		8.87	3.56-14.18	.001*
Associated Injuries				
No		Reference		
Yes		4.31	0.49-8.13	.02*
Required Transfusion				
No		Reference		
Yes		18.54	13.30-23.77	<0.001*

TBI, Traumatic brain injury; β, Beta Coefficient; CI, Confidence Interval; *Significant

Multivariate Logistic Regression: Admission (Table 3.)

In the multivariate logistic regression where "Enter" method was used, sex was not significantly associated with odds of admission after adjusting for age, past medical and surgical history, history of medications, TBI classification, type of injury, fall,

sports, associated injuries and required transfusions (OR 0.63, 95%CI 0.31-1.26). Age was also not significantly associated with admission (OR 1.01, 95%CI 0.99-1.04). Patients with past medical and surgical history were 3.7 times more likely to be admitted in comparison to the group who had no past medical and surgical history (95% CI 1.23-11.2). Moderate to severe TBI (OR 19.25, 95%CI 2.43-151.98) were significantly associated with higher odds of admission. Moreover, patients who had associated injuries were 2.8 times more likely to be admitted compared to those who didn't (95% CI 1.51-6.03). Patients who required transfusions were 10.8 times more likely to be admitted in comparison to those who didn't (95% CI 1.34-87.01). History of taking medications, penetrating injury, falls, and sports were not significantly associated with admission. This model explained 42.3% of the variance in the admission.

Multivariate Logistic Regression: Mortality (Table 4.)

Logistic regression "Enter" method was used to assess the association between the covariates and mortality. Sex and age were forced into this model. Neither sex nor age were significantly associated with mortality rate after adjusting for past medical history, TBI classification, requiring transfusions and hypoxemia [(OR 0.24, 95% CI 0.02-2.55) and (OR 1.02., 95%CI 0.99-1.96) respectively] (Table 7.). The only variable that was significantly associated with mortality was TBI classification. The odds of mortality increased by 25.65 times in moderate to severe TBI patients compared to mild TBI patients. Hypoxemia approached significance (p=.06) with hypoxemia associated with higher risk for mortality. Required transfusion and past medical history were not significantly associated with mortality. This model explained 45.3% of the variance in the mortality.

Linear Regression: Length of Stay (Table 5.)

Linear regression "Enter" method was used to assess the association between the variables and the hospital LOS. Sex and age were both considered in the model. Neither sex nor age were significantly associated with LOS after adjusting for past medical and surgical history, TBI classification, associated injuries, and required transfusions (p=0.71 & p=0.91). Variables that were associated with LOS in the linear regression model were moderate to severe TBI (p=0.001), associated injuries (p=0.02), and required transfusions (<0.001); all of them were associated with prolonged length of stay. This model explained 29.3% of the variance in length of stay.

Sex Difference within TBI and age Strata

Mild TBI patients < 50 years (Table 6.)

This subgroup represented the majority of the sample (N=153). Females represented 32.02% of this subgroup in comparison to males 67.98 % (p<0.001). In the group of patients who were younger than 50 years old and sustained a mild TBI, females had a significantly higher rate of past medical/surgical history and taking medications history in comparison to males [past medical history (30.6% versus 15.5%, p=0.03) medication history (30.6% vs 8%, p<0.001) respectively]. As expected, patients in this category did not have mortality, or hypotension. However, there was one female who had an oxygen saturation reading below 90% (non- documented reasons). Admission and length of stay were not significantly different between males and females (p=0.34 & p=0.58 respectively).

Moderate to severe TBI patients <50 years (Table 7.)

The total number of TBI patients in this sample was (N=41). Females represented only (n=4) 9.7 % of this group. Males in this group (n=37, 90.2%) were significantly older than females (males: 29.6 ± 8.7 versus females: 22 ± 1.8, <0.001). Three females of the four (75%) had a history of taking medications, whereas only 9.1 % of males had a medication history (p=0.01). Sports did not cause any moderate to severe injury in this group of patients. Admission rate was almost identical; all female patients were admitted in comparison to 89.2 % of males. Of interest, among the 4 females in this group, there was zero mortality compared to males (24 %). This difference did not reach statistical significance (p=0.55), possibly due to the small sample of females. As for length of stay, females had a significantly higher length of stay in comparison to males [females: (39.2 ± 33.9), males: (11.54 ± 13.7), p=.02)].

Table 6: Demographic data and clinical characteristics of Mild TBI patients aged < 50 years old by sex

Variables	Mild (N= 153)		
	Females (N=49)	**Males (N=104)**	***p*-value**
Age $\bar{X}$ ± SD[t]	29.8 ± 7.7	31.05 ± 9.4	.38
Past medical/Surgical history n (%)[c]	15 (30.6)	16 (15.5)	.03*
Medications history n (%)[c]	15 (30.6)	8 (8.0%)	<0.001*
Type of TBI[f]			
Blunt n (%)	42 (85.7)	86 (82.7)	0.77
Penetrating n (%)	3 (6.1)	11 (10.6)	
Others	4 (8.2)	7(6.7)	
Mechanism of Injury			
Fall n (%)[c]	15 (32.6)	26 (26.3)	.43
Violence n (%)[c]	4 (8.7)	14 (14.1)	.35
Explosions n (%)[f]	1 (2.2)	4 (4.0)	1
Sports n (%)[f]	0	7 (7.1)	0.09
Vehicle n (%)[c]	21 (45.7)	40 (40.4)	.55
Others			
Associates Injuries n (%)[c]	14 (28.6)	43 (41.3)	.12
Hypotension n (%)[c]	0	0	—
Required Transfusions n (%)[f]	8 (16.3)	6 (5.8)	.067
Hypoxemia n (%)[f]	1 (2.5)	0	.30
Admission n (%)[c]	21 (42.9)	53 (51)	.34
Mortality (n%)[c]	0	0	—
LOS Hospital $\bar{X}$ ± SD[t]	5.96 ± 15.8	4.65 ± 12.6	.58

TBI, Traumatic brain injury; $\bar{X}$, Mean; SD, Standard Deviation; LOS, Length of stay, * Significant; [t] Independent t-test; [c] Chi squared test; [f] Fisher's exact test

Table 7: Demographic data and clinical characteristics of Moderate to Severe TBI patients aged < 50 years old by sex

Variables	Moderate & Severe (N=41)		
	Females (N=4)	**Males (N=37)**	***P*-value**
Age $\bar{X}$ ± SD[t]	22 ± 1.8	29.6 ± 8.7	<0.001*
Past medical/Surgical history n (%)[f]	2(50.0)	8 (24.2)	.29
Medications history n (%)[f]	3(75.0)	3(9.1)	.01*
Type of TBI[f]			.31
Blunt n (%)	2(50.0)	25(67.6)	
Penetrating n (%)	1(25.0)	10(27.0)	
Others	1 (25.0)	2(5.4)	
Mechanism of Injury			
Fall n (%)[f]	1(25.0)	9(24.3)	1
Violence n (%)[f]	0	8(21.6)	.56
Explosions n (%)[f]	1 (25.0)	2 (5.4)	.27
Sports n (%)[f]	0	0	
Vehicle n (%)[f]	2 (50.0)	16 (43.2)	1
Others			
Associated Injuries n (%)[f]	4 (100.0)	23(62.2)	.28
Hypotension n (%)[f]	1 (33.3)	0	.08
Required Transfusions n (%)[f]	3 (75.0)	16 (43.2)	.32
Hypoxemia n (%)[f]	0	6 (19.4)	1
Admission n (%)[f]	4(100.0)	33(89.2)	1
Mortality (n%)[f]	0	9 (24.3)	.55
LOS Hospital $\bar{X}$ ± SD[t]	39.2 ± 33.9	11.54 ± 13.7	.02*

TBI, Traumatic brain injury; $\bar{X}$, Mean; SD, Standard Deviation; LOS, Length of stay; * Significant; [t] Independent t-test; [f] Fisher's exact test

Mild TBI patients > 50 years (Table 8.)

In this subgroup (n=115), females are less than males (35.6% vs. 64.3%, p =0.002). There was a trend for more associated injuries in males than females, although this difference did not reach statistical significance (p=0.061). Admission was not significantly different between females and males [(65.9% versus 78.4%) respectively, p=0.14]. Mortality was not common in this subgroup despite increased age. LOS, on the other hand, was the only significantly different outcome. Females spent fewer days during their admission in the hospital in comparison to males (2 ± 2.8 versus 7.8 ± 13.1 (p<0.001)) despite their similar number of medical/surgical and taking medications history.

Moderate to severe TBI patients > 50 years (Table 9.)

This group included only 17 patients of which 5 were females and 12 were males. There were no statistically significant differences in any variable or outcome between males and females who sustained moderate to severe TBI and were older than 50 years. As expected, patients in this category were all admitted. Mortality was not significantly different between females and males [(20% versus 41.7%), p=0.6]. The mean LOS was also similar between females and males (≅ 38.5 days).

Table 8: Demographic data and clinical characteristics of Mild TBI patients aged ≥ 50 years old by sex

Variables	**Mild (N=115)**		
	Females (N=41)	**Males (N=74)**	***P*-value**
Age $\bar{X}$ ± SD[t]	70.6 ± 11.1	70.9 ± 12.5	.9
Past medical/Surgical history n (%)[c]	38 (92.7)	61 (82.4)	.12
Medication n (%)[c]	32 (82.1)	55 (78.6)	.66
Type of TBI[c]			.9
Blunt n (%)	34 (82.9)	63 (85.1)	
Penetrating n (%)	2 (4.9)	4 (5.4)	
Others n (%)	7 (9.5)	5 (12.2)	
Mechanism of Injury			
Fall n (%)[c]	28 (71.8)	43 (59.7)	.2
Violence n (%)[f]	0	4 (5.6)	.29
Explosions n (%)[f]	2 (5.1)	1 (1.4)	.28
Sports n (%)[c]	0	0	
Vehicle n (%)[c]	7 (17.9)	17 (23.6)	.48
Others			
Associated Injuries n (%)[c]	10 (24.4)	31 (41.9)	.061
Hypotension n (%)[f]	0	1 (1.4)	1
Required Transfusions n (%)[c]	4 (9.8)	12 (16.2)	.33
Hypoxemia n (%)[f]	0	1 (1.5)	1
Admission n (%)	27 (65.9)	58 (78.4)	.14
Mortality (n%)[f]	1 (2.4)	2 (2.7)	1
LOS Hospital $\bar{X}$ ± SD[t]	2 ± 2.8	7.8 ± 13.1	<0.001*

TBI, Traumatic brain injury; $\bar{X}$, Mean; SD, Standard Deviation; LOS, Length of stay; * Significant; [t] Independent t-test; [c] Chi squared test, [f] Fisher's exact test

Table 9: Demographic data and clinical characteristics of Moderate to Severe TBI patients aged ≥ 50 years old by sex

Variables	Moderate & Severe (N=17)		
	Females (N=5)	**Males (N= 12)**	***P*-value**
Age $\bar{X}^{M}$	72.6	66.5	.29
Past medical/Surgical history n (%)[f]	4(100.0)	10(83.3)	1
Medications history n (%)[f]	4(100.0)	9 (75.0)	.52
Type of TBI[f]			
Blunt n (%)	4(80.0)	10(83.3)	.35
Penetrating n (%)	1(20.0)	0	
Others n(%)	0	2 (16.7)	
Mechanism of Injury			
Fall n (%)[f]	3(75.0)	6(54.5)	.6
Violence n (%)[f]	1 (20.0)	0	.31
Explosions n (%)[f]	0	0	
Sports n (%)[f]	0	0	
Vehicle n (%)[f]	0	5 (45.5)	.11
Others			
Associated Injuries n (%)[f]	3(60.0)	8(66.7)	1
Hypotension n (%)[f]	0	0	
Required Transfusions n (%)[f]	4(80.0)	8(66.7)	1
Hypoxemia n (%)[f]	0	2(18.2)	1
Admission n (%)[f]	5(100.0)	12(100.0)	
Mortality (n%)[f]	1(20.0)	5(41.7)	.6
LOS Hospital $\bar{X}^{M}$	38.6	38.5	1

TBI, Traumatic brain injury; $\bar{X}$, Mean; LOS, Length of stay; [M] Mann-Whitney test, [f] Fisher's exact test

The history of taking hormonal replacement and phase of menstrual cycle were not consistently documented in the charts of female patients. Likewise, the history of hysterectomy and oophorectomy could not be collected properly because of inadequate documentation. Three patients out of 107 females had records of hysterectomy and oophorectomy. Those patients were also in their 80s; history of surgery date wasn't documented either. Pregnancy status was also missing in the TBI registry. The registry included one pregnant patient out of 107 females, which prevented the possibility of assessing the difference between pregnant and non-pregnant females.

CHAPTER 5

DISCUSSION

To our knowledge this is the first study that examined the effect of sex difference on outcomes such as admission, mortality and hospital LOS in TBI patients in Lebanon. Our findings indicate no sex difference in admission, mortality, and LOS when all males and females in this sample were compared. However, sex differences in hospital LOS was present in the subgroup of mild TBI older than 50 years and moderate to severe TBI and age less than 50 years old.

In this study, the percentage of males who sustained a TBI was greater than that of females. This finding is concurrent with previous epidemiological studies, which have consistently demonstrated that the overall global rate of TBI is more prevalent among males (Nguyen et al., 2016). (Nguyen et al., 2016). In line with the global findings the majory of the TBI were of mild severity. Falls constituted the most frequent mechanism of injury at the American University of Beirut Medical Center. This is similar to earlier findings by Habre et al.'s (2012) and consistent with data from developed countries (Li et al., 2016). This could be due to the fact that AUBMC is a tertiary hospital, most MVAs and more severe injuries are diverted to other more proximal hospitals. Females had significantly more falls in comparison to males. This could be correlated with significantly increased past medical/surgical and medications history in females. In general, increased falls are associated with presence of past medical history since it indicates increased physical weakness and frailty (Pereira, Baptista, & Infante, 2013). The increased rate of past medical history in females in this study could be related to females' tendency to inquire more about their health, seek

more medical attention, and report more medical problems than males do (Ek, 2015).

In the multivariate analyses, sex was not associated with admission, mortality, or hospital LOS. After adjusting for multiple independent variables, as expected severity of TBI was significantly associated with admission, mortality, and increased hospital LOS. Other factors that significantly increased the odds of admission were increased presence of past medical/surgical history, associated injuries, and transfusions. An increase in associated injuries and requiring transfusions were associated with increased duration of hospital LOS.

The CDC reported that males have increased rate of TBI-related admissions in comparison to females between 2001 and 2010 (CDC, 2016a). However, other studies that assessed sex differences in outcomes following a TBI did not choose admission as their major outcome. Instead, mortality and functional outcomes were more commonly investigated in patients who were already admitted for the management of moderate and severe TBI (Davis et al., 2006; Ottochian et al., 2009).

Mortality rates were not different between males and females. Previous retrospective studies, which only investigated mortality in moderate to severe TBI patients, had conflicting findings in mortality outcomes. Ottochian et al. (2009) showed that females in the postmenopausal age had significantly higher mortality rates than males. Similarly, Herrera-Melero et al. (2015) showed that females had an increased rate of mortality possibly because they were older and had increased rate of hypoxia and anemia. On the other hand, Davis et al. (2006) showed that premenopausal females had no significant difference in mortality rates in comparison to males. In the multivariate analysis, moderate to severe TBI was the only covariate that is significantly associated with mortality. This is corroborated by the results of the mild TBI group who were older

than 50 years old. These patients have a very low mortality rate despite increased age. As for patients in moderate to severe subgroups, the lack of significance in mortality may be due to small group size, especially in the less than 50 years old subgroup.

Hospital LOS was not significantly different between males and females in this sample. However, in the subgroup of mild TBI and older than 50 years old, hospital LOS was significantly lower in females in comparison to males. On the other hand, females who had moderate to severe TBI and younger than 50 years old had significantly increased mortality compared to males in the same subgroup. Previously, Guise et al. (2014), who measured duration of LOS in mild, moderate, and severe TBI, did not show any difference in LOS between males and females. However, LOS was not measured in age-subgroups of patients in their study. Ottochian et al. (2009) also compared LOS between males and females who sustained severe TBI and did not find any significant difference. This study too did not compare LOS within groups. In other studies, hospital LOS was not measured; instead, ICU length of stay was examined or considered as a covariate for mortality outcome because patients who were included in the studies had moderate to severe TBI.

Overall, the findings in this study did not support the hypothesis that females have less admission, mortality, and shorter length of stay in comparison to males. The investigated outcomes in this study may not be the most sensitive. Long-term outcomes, such as cognitive and functional performance of TBI patients, could be more sensitive outcomes to the nature of sustained injury.

CHAPTER 6

STRENGTH AND LIMITATIONS

This study examined the difference of outcomes in male and female patients with mild, moderate, and severe TBI to enhance the understanding of TBI complexity and significant difference in outcome between mild and moderate to severe TBI patients. Moreover, this study included pre-existing conditions of patients in the analysis and was significantly associated with increased admission after adjusting for other variables. This finding complements previous recommendations of TBI common data elements that past medical/surgical history should be collected and accounted for when examining TBI outcomes.

Besides being a retrospective study, there are several other limitations in this study that are related to missing data. Exploring other outcomes of TBI such as neurologic and cognitive deficits in addition to functional status at discharge and long term was not possible in this study due to poor documentation. It was not clear in medical record whether those patients were independent, partially dependent, or completely dependent on others in their daily life activities upon discharge. Therefore, we limited our outcomes to available findings.

Moreover, assessment of hormonal replacement therapy and phases of menstrual cycle in females that may affect patients' outcomes was challenging since these data were also not documented in the charts. The TBI severity was also classified according to GCS score only due to missing values of PTA and LOC duration in many charts. Although GCS is a widely-used tool, however, it is subjective and not completely accurate on its own. Factors that could modify the GCS score, such as

alcohol consumption and use of drugs, were also not recorded in the patients' charts. Other missing data were related to patients' functional status at discharge. Other important missing data were pregnancy status and history of hysterectomy and oophorectomy. All of the latter variables may affect the level of sex steroids in females. Another limitation was inconsistency between healthcare professionals in documenting the criteria for TBI classification. This variable documentation could have led to underestimation or overestimation of patients' TBI severity. Finally, assessment of outcomes on patient who left against medical advice was not possible. The percentage of patients who left against medical advice was also not know due to poor documentation in medical records.

CHAPTER 7

FUTURE RECOMMENDATIONS

Prospective longitudinal studies are necessary to assess the functional status of TBI patients after discharge. A larger sample size is also recommended to detect subtle differences between males and females within the same age and TBI severity subgroups. Moreover, it is recommended to include more detailed neurological and cognitive assessments, in addition past medical/surgical history of patients in the analysis of TBI outcomes. Other factors that may affect TBI assessment or outcomes, namely alcohol and drug consumption, history of hormonal replacement, pregnancy, phase of menstrual cycle, accurate age of menopause, history of hysterectomy and oophorectomy should to be considered as covariates. These covariates need to be present in patients' charts; hence, it is recommended to document patients' assessment and management based on TBI common data element. Advanced practice nurses' role here is to advocate for standardized documentation based on TBI common data elements to improve the quality of future research studies.

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