

**ACUTE INFLAMMATION AND INFECTION: THE EFFECTS ON RECOVERY
FOLLOWING MODERATE-TO-SEVERE TRAUMATIC BRAIN INJURY**

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ABSTRACT

Current thinking by Traumatic Brain Injury (TBI) researchers and clinicians has devolved from the idea that TBI is an event with a finite recovery period, and have shifted to considering TBI a chronic disease with long-term implications for health. Therefore, there is great interest in determining acute biological and clinical factors that influence long-term health and function after injury. This interest drives the two central themes of this dissertation, to better understand: 1) the continuum of TBI disability from acute to chronic recovery; 2) the effects of non-neurological factors on recovery from TBI. Notably, the availability of data that spans the TBI disability continuum—from early stages post-injury to death—is sparse. Aim 1 of this dissertation explains a probabilistic marching procedure used to merge two databases, the National Trauma Databank and TBI Model Systems, which creates an infrastructure to examine the long-term effects of relevant acute care variables. In aim 2, the merged dataset is leveraged to assess the negative effects of acute care hospital-acquired pneumonia (HAP) on long-term global disability and health care utilization. HAP is one example of a non-neurological factor that impacts TBI recovery. Aim 3 focuses on two systemic markers of inflammation and hormone dysfunction, tumor necrosis factor-alpha (TNF α) and estradiol (E2), and assesses their inter-relationship acutely after injury, and their temporal relationship to mortality. The public health implications of the work herein provide observational data to better understand the continuum of TBI disability, and major non-neurological contributors to recovery from injury.

TABLE OF CONTENTS

PREFACE.....	XI
1.0 INTRODUCTION.....	1
1.1 TBI EPIDEMIOLOGY	1
1.2 TBI CLINICAL CARE CONTINUUM.....	2
1.3 TBI RESEARCH CONTINUUM.....	3
1.4 TBI-RELATED DISABILITIES.....	4
1.5 TBI BIOLOGY: ACUTE TO CHRONIC PATHOPHYSIOLOGY	6
1.6 TBI BIOLOGY: A HUMORAL TRIAD.....	7
1.6.1 Neurotrophins	7
1.6.2 Endocrine System.....	8
1.6.3 Acute Inflammation	9
1.6.4 Chronic TBI Inflammation	10
1.7 UNDERSTANDING BRAIN-TO-BODY CONNECTIONS AND SYSTEMIC CONTRIBUTORS TO IMMUNITY	11
1.8 SPECIFIC AIMS	14
1.8.1 Aim 1: Applications of Probabilistic Matching.....	14
1.8.2 Aim 2: Effects of HAP	15
1.8.3 Aim 3: Effects of E2 and TNFα	16

1.9	INTEGRATIVE SUMMARY OF DISSERTATION.....	16
2.0	AIM 1: PROBABILISTIC MATCHING OF DEIDENTIFIED DATA FROM A TRAUMA REGISTRY AND A TRAUMATIC BRAIN INJURY MODEL SYSTEM CENTER: A FOLLOW-UP VALIDATION STUDY	18
2.1	ABSTRACT.....	18
2.2	INTRODUCTION	19
2.3	METHODS AND MATERIALS	21
2.3.1	Probabilistic linkage	21
2.3.2	Matching blocking	22
2.3.3	Linking variables and weight estimation.....	22
2.3.4	Clustering and cluster weight difference	24
2.4	RESULTS	26
2.5	DISCUSSION.....	29
2.5.1	Implications of the Project and Future Directions	32
3.0	AIM 2: EFFECTS OF HOSPITAL-ACQUIRED PNEUMONIA ON LONG-TERM RECOVERY AND HOSPITAL RESOURCE UTILIZATION FOLLOWING MODERATE-TO-SEVERE TRAUMATIC BRAIN INJURY	34
3.1	ABSTRACT.....	34
3.2	INTRODUCTION	35
3.3	METHODS AND MATERIALS	37
3.3.1	Statistical analysis	41
3.4	RESULTS	42
3.4.1	Demographic and Clinical Variables by HAP Status.....	42

3.4.2	Demographic and Clinical Variables by GOS-E at 1 year.....	44
3.4.3	Primary analysis: GEE Model of GOS-E at 1, 2, and 5 years after TBI using NTDB probabilistic cohort.....	45
3.4.4	Sensitivity analysis: GEE Model of GOS-E at 1, 2, and 5 years after TBI using Deterministic Cohort	46
3.4.5	Secondary analysis: Hospital utilization variables by HAP Status	47
3.5	DISCUSSION.....	47
4.0	AIM 3: RELATIONSHIP BETWEEN ACUTE SERUM ESTRADIOL AND TUMOR NECROSIS FACTOR-ALPHA AND RISK FOR MORTALITY AFTER SEVERE TRAUMATIC BRAIN INJURY	52
4.1	ABSTRACT.....	52
4.2	INTRODUCTION	53
4.3	METHODS AND MATERIALS.....	55
4.3.1	Serum Sample Processing	56
4.3.2	E2 and TNF α Classification: Early and Delayed Response.....	57
4.3.3	Aromatase genetics: rs2470152.....	57
4.3.4	Clinical and Demographic Variables	57
4.3.5	Primary Outcome: Mortality.....	58
4.3.6	Statistical Analysis	58
4.4	RESULTS.....	61
4.4.1	Demographic and Clinical Variables by E2 and TNF α	61
4.4.2	Demographic and Clinical Variables by Mortality Status.....	64
4.4.3	Cross-lagged Panel Model.....	65

4.4.4	Survival Analysis.....	66
4.5	DISCUSSION.....	69
5.0	GENERAL DISCUSSION	74
5.1	SUMMARY OF RESULTS	74
5.2	PUBLIC HEALTH IMPACT.....	77
5.3	FUTURE RESEARCH.....	81
5.3.1	TBI is a global health problem requiring worldwide research	82
5.4	CONCLUSION	83
	APPENDIX: SUPPLEMENTAL TABLES CHAPTER 1	85
	BIBLIOGRAPHY	87

LIST OF TABLES

Table 1. Descriptive characteristics of algorithm generation and validation subset.....	27
Table 2. True match status by probabilistic linkage status in training set	28
Table 3. Description of measures.....	39
Table 4. NTDB Demographics and Clinical Variables by HAP Status.....	43
Table 5. NTDB Demographic and Clinical Variables by GOS-E Status at 1 Year	44
Table 6. Probabilistic Cohort GEE Regression Model for Repeated Measures GOS-E at 1, 2, and 5 years	46
Table 7. Deterministic Cohort GEE Regression Model for Repeated Measures GOS-E at 1, 2, and 5 years	47
Table 8. Demographic and Clinical Variables by T1 and T2 E2.....	62
Table 9. Demographic and Clinical Variables by T1 and T2 TNF α	63
Table 10. Demographic and Clinical Variables by Mortality Status	64
Table 11. Cox Proportional Hazards Regression of TI Epoch (1st 72 hours post-injury).....	68
Table 12. Cox Proportional Hazards Regression of T1 Epoch (1st 72 hours post injury)	68
Supplementary Table 1. Cluster weight differences for true and false matches in the algorithm generation and validation sets.....	85
Supplementary Table 2. Distribution of selected blocking and matching fields by Tier II matching status in the algorithm generation and validation sets.....	85

LIST OF FIGURES

Figure 1. HPG Axis Dysfunction Leads to Secondary Hypogonadism after Severe TBI	9
Figure 2. Mean Lymphocyte Levels by Lymphocyte Trajectory Group	14
Figure 3. Kumar Dissertation Conceptual Model	17
Figure 4. Schematic representation of determining probabilistic linkage by using progressively stringent criteria (Tier I-III)	25
Figure 5. Frequency distribution of weights	27
Figure 6. CWD and Weight by Matching Status.	29
Figure 7. Conceptual Cross-Lab Panel	60
Figure 8. Fitted Cross-Lab Panel	66
Figure 9. TBI Disability Clinical & Research Continuum	82

PREFACE

I have so many people to thank for putting me in this position to defend my dissertation as a PhD candidate in Epidemiology specializing in Neuroepidemiology. First of all, my parents have been my foundation my entire life; without their unwavering support, I can say in no uncertain terms that I would not be in this position. I would also like to thank my support committee members. Dr. Wagner has been an incredible mentor for me for the last several years. My passion is TBI research, and she has given me endless career opportunities in this niche field, and has always put me in a position to succeed along the way. I hope to continue to collaborate with her for the rest of my career. Dr. Rosano has been an excellent academic advisor and career mentor for me in my fervent pursuit of being a Neuroepidemiologist. Dr. Brooks is quite simply one of the best instructors I have ever had. I am truly privileged to have taken her course, and later had the chance to be her teaching assistant. Dr. Fabio is a wonderful mentor and Injury Epidemiologist; I sincerely value all the meetings that we have had discussing injury-related research. I wanted to also thank all the brilliant and insightful GSPH classmates that I have had the privilege to go to school with during my doctorate. Thank you for pushing me to be the best student I could be. I consider you all not only colleagues, but dear friends, and hope to continue that friendship for years to come. Finally, I wanted to thank my girlfriend Ashlee Adams for her support. Writing this dissertation has not been easy, but your continued support has made it possible for me to get through, and for that I am so thankful.

1.0 INTRODUCTION

1.1 TBI EPIDEMIOLOGY

Each year, the Centers for Disease Control (CDC) estimates that 2.5 million Americans suffer a Traumatic Brain Injury (TBI) that results in either an emergency department (ED) visit, acute hospitalization or death.¹ These estimates, however, do not account for individuals who do not receive medical attention for their injuries, or seek care in outpatient facilities. Many individuals with TBI are evaluated and released from an ED. However, individuals that suffer more severe injuries require hospitalization for their injuries. A subset of these individuals may go on to require care in a specialized brain injury rehabilitation program. An estimated 5.3 million Americans, or 2% of the general population, live with chronic disability as a result of a TBI that required hospitalization.² Among individuals hospitalized for TBI, 43.3% experience 1-year disability, or symptoms directly related to their injuries that impair daily functioning.³

The leading cause of TBI in the United States is falls, which account for roughly 35% of TBI, followed by motor vehicle accidents (17%), and strikes or blows to the head (17%).^{1,4} The major causes of TBI-related mortality are motor vehicle accidents, falls, and suicide.⁵ TBI can occur across the lifespan, and does not discriminate by age or sex. Infants and young children aged 0-4, as well as adolescents aged 15-19, and older adults over the age of 75 have the greatest frequency of ED visits from their injuries. However, those aged 75 and older have the greatest

burden of TBI-related hospitalizations, suggesting that injuries in this population are often complicated to treat, potentially due to co-morbid burden.^{4,6} Men are more likely than women to suffer a TBI;⁴ however, evidence is equivocal with regards to sex differences in TBI outcomes.⁷⁻

10

The cost of TBI is considerable and warrants attention. The costs associated with prolonged disability is largely tied to loss of productivity; individuals with moderate-to-severe TBI often are unable to return to work or school. The per-patient lifetime cost of a moderate-to-severe TBI is estimated to be over \$100,000.¹¹ Older individuals with TBI, though likely not having loss of vocational productivity costs like their working counterparts, represent a disproportionately higher economic burden compared to younger and middle-aged adults.¹² Each year, 2 billion dollars is spent on healthcare costs for adults older than 65 with TBI.^{12,13}

1.2 TBI CLINICAL CARE CONTINUUM

The recovery for patients with moderate-to-severe TBI is different than mild TBI, or concussion, where most patients return to pre-injury functioning within 3 months.^{14,15} For moderate-to-severe TBI, recovery from injury is long, and spans numerous phases. Acutely following injury, patients most often present to an ED and require an extended acute inpatient hospitalization. During this phase, patients are treated by clinicians in several departments, including trauma, critical care medicine, and neurosurgery. The priority at this time is acute clinical management in line with the Guidelines for the Management of Severe TBI, which may include: intracranial and cerebral perfusion pressure monitoring, decompression of mass lesions, seizure prophylaxis, management of systemic illnesses, blood pressure, and temperature.¹⁶

For acute survivors of TBI, the road to recovery continues with rehabilitation. The rehabilitation team includes: occupational therapists (OT), physical therapists (PT), nurses, social workers, neuropsychologists, and psychiatrists. The inter-disciplinary rehabilitation team is focused on functional gains so patients can eventually re-assimilate into the community.¹⁷ The goal is not necessarily to make an individual exactly as they were before their injuries, but rather work with patients, and their family members, to identify their functional limitations, and find ways to adapt. Successful rehabilitation is usually measured by performance in activities of daily living, and eventually returning back to work or school and participating in community activities.¹⁸

1.3 TBI RESEARCH CONTINUUM

The long, extended care that exists clinically for patients with TBI may create a natural isolation between acute care and rehabilitation providers. In fact, in many hospitals, rehabilitation care is in an entirely different physical building than acute care. One downstream consequence of this schism is limited interaction between clinicians across the continuum. The implications are not limited to clinical care but can also trickle down to research. To date, clinical TBI research has been segmented; acute care research focuses on early factors that influence short-term survival and discharge disposition, and rehabilitation researchers pose research involving long-term disability and integration back to the community. Large databases, such as the National Trauma Databank and TBI Model Systems National Database, have moved the field in its understanding of components of the recovery course of moderate-to-severe TBI. However, there is a need to conduct more cross-cutting studies to bridge the gap between acute

and long-term factors to better understand the continuum of TBI-related disability from pre-hospital factors all the way to death.

1.4 TBI-RELATED DISABILITIES

Individuals with TBI often have disorders of mood and behavior. Post-traumatic depression (PTD) is one of the most common complications after TBI, with prevalence rates ranging between 13-53.1% in the first year after TBI, a nearly 8-fold increased rate compared to the general population.¹⁹⁻²³ Individuals with PTD more often endorse chronic functional impairment and psychosocial difficulties compared to individuals without PTD.^{24,25} In addition to PTD, individuals with TBI commonly suffer from behavioral dysfunction, which can manifest in problems of impulsivity, apathy, and personality changes. In instances of TBI with lesions to the frontal lobe,²⁶ individuals present with executive and behavioral dysfunction.²⁷ Overt behavioral changes represent the interplay between internal thoughts and feelings and the external environment, and are a component of a larger manifestation of emotional and cognitive changes that occur after severe TBI.²⁸⁻³⁰ Individuals with TBI with behavioral dysfunction have greater difficulty in assuming pre-injury life roles,³¹ and report more psychosocial difficulties.^{32,33}

Patients with moderate-to-severe TBI also manifest with chronic cognitive impairment. In fact, cognitive deficits after TBI are among the most common symptoms, with roughly 70% of severely injured patients experiencing substantial cognitive deficits across multiple domains.³⁴ One case-control study compared patients with TBI to trauma patients without brain injuries, and found that patients with TBI had greater deficits in the domains of: attention, information

processing, reaction time, memory and learning, verbal fluency, and mental flexibility.³⁵ The location of focal brain lesions are a major contributor to the specific domains of cognition that are impaired. For example, one study of penetrating TBI determined that lesions of the left hemisphere were associated with poor vocabulary performance, and lesions to the right hemisphere were associated with visuospatial deficits.³⁶ It is also well understood that focal lesions to the frontal lobe are closely linked to deficits in executive functioning, like planning and task completion.²⁷ White matter disruption, which occurs most often in the setting of axonal injury, is also associated with cognitive impairment.³⁷ Other studies have shown that dysfunction in dopamine (DA) pathways,^{38,39} and variability in DA genes, are linked with cognitive impairment across multiple domains.⁴⁰ Cognitive impairments in patients with TBI are extremely common and are important considerations for brain injury clinicians because it affects rehabilitation planning⁴¹ and are a primary indicator of the ability to return to work.³¹

Evidence from observational studies conducted in the last few decades suggests that most individuals with moderate-to-severe TBI take months to years to recover, and a majority of patients never fully return to pre-injury functioning and live with chronic disability.^{42,43} As stated above, rehabilitation clinicians focus on improving function for patients with TBI and working towards community integration, which includes: independence in activities of daily living (e.g. toileting, personal care, feeding)⁴⁴ and transportation,⁴⁵ return to work or school,⁴⁶⁻⁴⁸ and maintenance of productive social relationships.⁴⁹ The latter, maintenance of productive social relationships, has been reported by patients in focus groups as the single most important factor that they personally characterize as “successful” integration into the community.⁵⁰ Research in TBI is moving towards an integration and partnership between basic science, clinical researchers, and policy makers to improve functioning for TBI survivors.⁵¹ This research focus aligns well

with the International Classification of Functioning, Disability and Health (ICF)⁵² framework, which defines functioning and disability as more than just a biomedical construct focused on disease, but rather as a multidimensional concept, relating to dynamic interaction of “body functions and structures, activities, participation, and environmental factors.” This framework also is the cardinal basis of the Rehabilomics model of Rehabilitation research that has been pioneered by committee member, Dr. Amy Wagner.⁵³⁻⁵⁵ My charge as a TBI epidemiologist is to integrate these principles into my dissertation research, appreciating that the end goal is to understand how early biological factors interface and influence long-term health and functioning among individuals living with TBI.

1.5 TBI BIOLOGY: ACUTE TO CHRONIC PATHOPHYSIOLOGY

TBI can be broadly characterized by a primary insult and subsequent secondary injury cascade. The primary insult may be the result of focal or diffuse damage. Focal injuries are characterized by contusions, intracranial or extra-axial hemorrhages. Diffuse damage results from axonal stretch injuries, most commonly resulting from rapid acceleration/deceleration forces. Following primary injuries, there is a secondary injury biological cascade that evolves in the months to years following incident injury. Beyond the structural brain damage associated with TBI, the components of the secondary injury response to brain injury are complicated and can be broadly grouped into a **humoral triad**, which involves neurotrophic, endocrine, and immunological networks that each have independent functions, but also possess the capacity for cross-talk via multiple signaling pathways that contribute to homeostatic regulation. Acute dysfunction in components of the humoral triad may eventually lead to chronic disruption.

Chronic pathology to these humoral signaling systems is, at least in part, the biological basis of why TBI is considered a biological aging accelerator, which may lead to premature neurodegenerative disease, as well as increased risk for chronic health conditions, such as epilepsy, depression, and suicide.

1.6 TBI BIOLOGY: A HUMORAL TRIAD

There have been several clinical observational studies characterizing acute disturbances to the humoral triad after severe TBI. Existing studies also examined how variability in acute biomarkers in the brain and periphery are associated with recovery from injury across multidimensional outcomes. Fewer studies, however, have integrated multiple humoral signaling systems into their assessment to understand how these are connected.

1.6.1 Neurotrophins

A family of proteins known as neurotrophins is one component of the humoral triad that promotes survival, development, maintenance and function of neurons. Following TBI, an extensively studied biomarker in the neurotrophic family is brain-derived neurotrophic factor (BDNF), the systemic levels of which are initially reduced in the periphery, but modestly increased in the brain after TBI.⁵⁶ Clinical studies demonstrate BDNF genetics and levels are associated with mortality, with nuanced effect modification observed across the lifespan of patients; the biological actions of BDNF in older adults differs compared to their younger counterparts.^{56,57} The hippocampus is a brain region that is particularly vulnerable, with focal

depression of BDNF expression, and genetic variation in the BDNF gene is associated with hippocampal volume after TBI.⁵⁸

1.6.2 Endocrine System

A second component of the humoral triad is the endocrine system. In the setting of TBI, pituitary dysfunction may result in several clinical conditions, known as neuroendocrine dysfunction.^{59–63} Signaling abnormalities may be due to direct or indirect damage to the hypothalamus or pituitary, which impacts functioning of the hypothalamus-pituitary-adrenal (HPA) or hypothalamus-pituitary-gonadal axis (HPG) axes. TBI also induces an acute stress response that increases endogenous cortisol production.⁶⁴ The beneficial and detrimental effects of cortisol elevations are an exemplar of the existence of cross-talk among the humoral triad network, as cortisol can act as a significant mediator of dysfunction in both neuroinflammation⁶⁵ and BDNF expression.⁶⁶ Also, in pre-menopausal women, chronically elevated cortisol can contribute to amenorrhea and menstrual cycle dysfunction,⁶⁷ and acute increases in cortisol are associated with long-term cognitive impairments.⁶⁸

The effects of pituitary dysfunction extend beyond elevations in cortisol and include disruptions to the HPG axis. Men experience a period of hypogonadotropic hypogonadism (low testosterone and low luteinizing hormone) that for some resolve after 8-12 weeks post-TBI, but for others, may extend for several months after injury and lead to poorer functional outcomes.⁶⁹ A series of clinical observational studies, led by committee member Dr. Amy Wagner, also show that the steroidogenesis pathway is acutely disturbed following TBI. The downstream consequence of acute dysfunction of the HPG axis is dysregulation in sex hormone products in

the gonads, known as secondary hypogonadism. As portrayed in **Figure 1**, through damage to the hypothalamus and/or pituitary, the negative feedback mechanisms are dysfunctional.

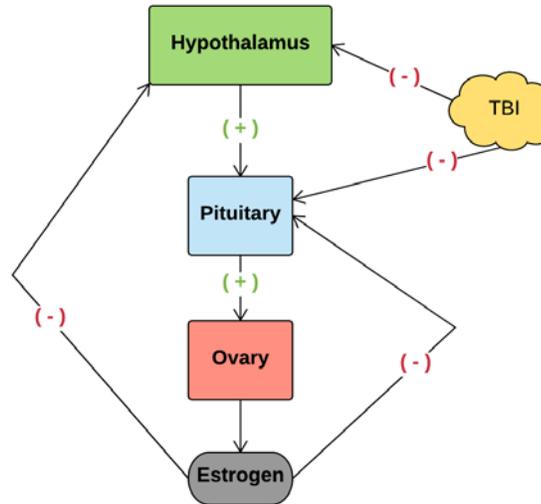


Figure 1. HPG Axis Dysfunction Leads to Secondary Hypogonadism after Severe TBI

1.6.3 Acute Inflammation

The third component of the humoral triad is the post-traumatic inflammatory response. Acute inflammation after TBI is characterized by an aggressive *innate immune response*, the body’s “first-line” defense response to injury.⁷⁰ The neuroimmune response is largely mediated by microglia, which are resident central nervous system (CNS) immune cells that rapidly change from a resting to an activated state upon surveillance and detection of CNS damage, like that seen from TBI.^{71,72} Activated microglia facilitate inflammation by recruiting pro-inflammatory cytokines, chemokines, and cell-adhesion molecules to injury sites to clear debris and dead neural tissues and cells.⁷³ There have been several recent studies characterizing acute inflammatory markers in the brain and periphery. In a previous study I co-authored,⁷⁴ “inflammatory clusters” of individuals with severe TBI were obtained from a principal

components analysis of CSF inflammatory cells. It was determined that ~30% of individuals fell into a “pro-inflammatory” cluster, which tended to include older individuals that overwhelmingly had poorer global outcomes compared to those in another cluster with an average-to-below average inflammatory load. Interestingly, in the same study we determined that individuals in the “pro-inflammatory” cluster had increased levels of CSF hormones (cortisol, progesterone, E2, testosterone) and CSF BDNF, in addition to serum cortisol and BDNF, further supporting the inter-relationship observed between biomarkers within the humoral triad.⁷⁴

The negative consequences of excessive neuroinflammation on complicating conditions and multidimensional outcomes following TBI are becoming increasingly apparent from several recent clinical studies from our group. One study found that higher CSF concentrations of interleukin-6 (IL-6), a major pro-inflammatory cytokine, in the first week are associated with poor global disability in the first year.⁷⁵ Another study found that interleukin-1 β levels and genetic variability in the interleukin-1 β gene influences IL-1 β levels and increases risk for seizures after TBI.⁷⁶ Other studies determined that acute inflammatory markers in the cerebrospinal fluid are associated with depression risk⁷⁷ and risk for suicidal ideation and impulsive behavior.⁷⁸

1.6.4 Chronic TBI Inflammation

Acute homeostatic disturbances following TBI can extend beyond the first week into a subacute and chronic period after injury. The acute innate inflammatory cascade is considered a crucial component in the healing process; however, persistent inflammation over long periods can be affect healthy tissue.⁷⁹ Generally, the beneficial effects of inflammation are derived when these processes are under tight physiological control; uninhibited levels seem to be

counterproductive to recovery from TBI.⁸⁰ This complexity is why some in the field coin post-traumatic inflammation as a “double-edged sword.”

An effective illustration of complex signaling effects associated with inflammation can be gleaned from studying the marker IL-6, which can undergo either classical signaling or trans-signaling depending on the binding patterns of IL-6 to its membrane-bound receptor (classical) or soluble receptor (trans). The former, classical signaling, leads to an anti-inflammatory cascade, and the latter, trans-signaling, can cause chronic inflammation.^{81,82} Our preliminary work suggests that higher IL-6 soluble receptor signaling during the subacute phase after TBI does have a negative effect on global outcome⁸³ and its negative effects on outcome are mediated by post-acute cortisol levels.⁸⁴

Recent observational studies have examined chronic immunological disturbances after severe TBI. A landmark study by Ramlackhansingh et al.⁸⁵ determined that individuals with TBI have microglial activation in subcortical regions of the brain present several years after injury, and activated microglia in the thalamus is associated with cognitive impairments. Another study, which I co-authored, showed that chronic inflammation in the serum was present in the first year after TBI, and increased inflammatory load in the first three months was associated with poorer global outcomes at 6 and 12 months after injury.⁸⁶

1.7 UNDERSTANDING BRAIN-TO-BODY CONNECTIONS AND SYSTEMIC CONTRIBUTORS TO IMMUNITY

Despite TBI being a primary injury to the brain, inflammatory processes are not confined to the CNS. After injury, inflammatory cells from the periphery cross a damaged blood brain

barrier (BBB) to aid in brain tissue repair.⁷⁰ Among individuals that sustain polytrauma, or concurrent traumatic injuries to multiple regions of the body, peripheral immune markers are recruited to aid in repair of bodily injuries.⁷⁵ Further, the brain and the peripheral immune system communicate via the autonomic nervous system (ANS).^{87,88} In response to acute injury, like TBI, two main “stress” pathways are activated: the SNS and the HPA axis.⁸⁷ SNS activation follows a release of sympathetic neurotransmitters, including norepinephrine (NE), which has direct effects as a neuromodulator in lymphoid organs that supports cytokine production,^{87,89} and also facilitates an acute phase hepatic response, producing pro-inflammatory cytokines like tumor necrosis factor- α (TNF α).

Peripheral contributors to immunity can be highlighted by TNF α , a pleiotropic pro-inflammatory marker, and one of the most extensively studied inflammatory proteins in the field of immunology.⁹⁰⁻⁹² The relevance of TNF α extends beyond its pro-inflammatory properties. Specifically, TNF α in the adipose is a transcription factor for the expression of the aromatase gene, located in promotor region I.4.⁹³⁻⁹⁵ The result of aromatase expression at this site is an increase in extra-gonadal production of E2, which is a known mortality marker.⁹⁶ Specifically, E2 acts as a potent vasodilator by promoting nitric oxide and hydrogen sulfide pathways.⁹⁷⁻¹⁰⁰ It is possible that a propagation of vasodilation of the vasculature, mediated by E2 and TNF α , could lead to *non-neurological* organ dysfunction. That is, individuals with TBI suffer a significant compromise to another body system besides the brain. The concept of non-neurological organ dysfunction has been proposed in the setting of neurocritical care.^{101,102} Zygun and colleagues¹⁰¹ determined that, in a cohort of severe TBI, roughly 1 in 3 patients develop some form of non-brain organ failure during their hospital stay. Respiratory failure occurred in nearly 1 in 4 patients and cardiovascular failure occurred in nearly 1 in 5 patients.¹⁰¹

In the same study, Zygun¹⁰¹ determined that individuals with the non-neurological organ failure had a 63% increase in their odds for mortality and 53% increase in odds of poor Glasgow Outcome Scale (GOS) scores during their hospitalization, compared to their counterparts without non-neurological organ dysfunction. Similarly, another study by Kemp and colleagues¹⁰² determined that approximately non-neurological organ dysfunction accounts for 2/3 of all deaths after severe TBI.

Systemic infection is another non-neurological factor, commonly co-occurring with TBI, which can propagate systemic inflammation. Patients with TBI are particularly at risk for pulmonary infections stemming from prolonged periods of mechanical ventilation and long hospital lengths of stays. Immediately following injury, some individuals also experience a trauma-induced suppression in lymphocyte production, known as lymphopenia. The result is a decreased capacity to fight new pathogens, and an increased risk for opportunistic infections. Several studies have explored the harmful effects of lymphopenia in trauma populations.^{103–107} One study found that individuals with persistent lymphopenia after the first four days of trauma had a 2.5 times increased risk of death compared to those with normal leukocyte levels.¹⁰⁶ Work that I have been actively involved with has collected preliminary data observing lymphopenia in a population of n=273 with severe TBI. In **Figure 2**, the lower lymphocyte trajectory 1 (seen in blue) has lymphocyte counts below the lower range for lymphocyte levels for an extended period in the first week after injury. In this cohort, those in the low trajectory group had an 65.9% rate of HAP versus 51.0% in the high trajectory ($\chi^2=5.0$, p=0.026).

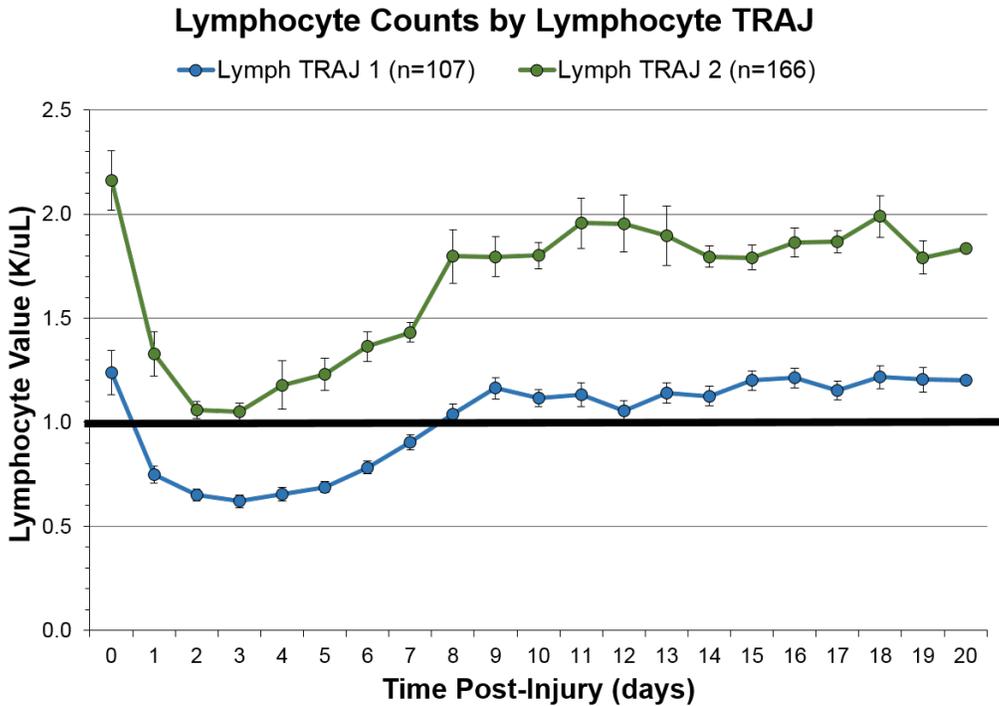


Figure 2. Mean Lymphocyte Levels by Lymphocyte Trajectory Group

1.8 SPECIFIC AIMS

The two central themes of this dissertation are to better understand: 1) the continuum of TBI disability from acute to chronic stages of recovery; 2) the effects of non-neurological factors on recovery from TBI.

1.8.1 Aim 1: Applications of Probabilistic Matching

Aim 1 details the specific statistical methodology of a probabilistic algorithm used to merge two large databases, the NTDB and the TBIMS National Database. The purpose of this merger is to address a major gap in TBI research: the lack of research across the continuum

of TBI disability, from early to late stages in the injury progression. The methodology employed is probabilistic matching, which relies on the creation of weights based on common data elements between two deidentified databases. Because patients were not co-registered in both databases, the two databases can only be merged through probabilistic techniques. To test the validity metrics of the probabilistic algorithm, we utilized a concurrent deterministic linkage that served as a gold standard. In the discussion and public health relevance sections of this dissertation, I explain the implications of creating a database infrastructure that sets the stage for future studies that can longitudinally study the effect of early factors on long-term measures of disability.

1.8.2 Aim 2: Effects of HAP

Aim 2 of this dissertation aims to examine the long-term impact of HAP on global outcomes in a large, multi-center population with moderate-to-severe TBI. The reason why patients with TBI are particularly at risk for pneumonia is multi-factorial, including prolonged ventilation, long hospital lengths of stay, exposure to nosocomial pathogens, and acute immunosuppression leading to trauma-induced lymphopenia. Much of the prior TBI literature that has examined the effects of HAP have focused on: 1) the costs of incident infection,¹⁰⁸ and 2) the effects on in-hospital outcomes (e.g. short-term survival and outcomes).¹⁰⁹⁻¹¹² Two small prior studies show preliminary evidence of the negative long-term consequences of HAP on recovery from TBI, though this remains a relatively under-studied area.^{113,114} The biological plausibility for the negative long-term effects of pneumonia post-TBI may seem elusive at first, especially if an infection is treated and cleared soon after the onset of illness. However, the rationale is grounded in the theory that early infection elicits a systemic inflammatory response,

which adds to an already considerable inflammatory response from the primary TBI, thus priming the body for a *chronic inflammatory milieu*. This hypothesis is supported by data that individuals with a greater number of acute hospital complications had a greater chronic inflammatory load 2 weeks to 3 months following severe TBI.⁸⁶

1.8.3 Aim 3: Effects of E2 and TNF α

Aim 3 of this dissertation is to examine inter-relationships between E2 and TNF α in two time epochs over the first five days after TBI, and its effects on mortality risk in the first six months after TBI. A previous study by Wagner and colleagues⁹⁶ determined that acute peripheral E2 is associated with mortality; however, the mechanism by which E2 affects mortality risk is still not clear. TNF α is a potent vasodilator and a critical molecule involved with septic shock in other ICU populations.^{90,94,115-117} Because TNF α is involved in E2 transcription,¹¹⁸⁻¹²⁰ it may explain in part the observed E2 mortality risk. Additionally, increasing E2 has a positive feedback signaling effect that contributes to exaggerated levels of inflammation.^{87,121} The potentially lethal cycle of excess E2 and TNF α has not been established to date in the TBI field; therefore, will be a focus in the third chapter of this dissertation.

1.9 INTEGRATIVE SUMMARY OF DISSERTATION

Individuals with TBI have heterogeneous pathological responses and clinical exposures immediately after their injury that has direct causal implications for long-term recovery. Considering the literature reviewed, a conceptual figure integrating the three aims of this

dissertation is presented in **Figure 2**. Complex brain-body relationships, including cross-talk between the brain and periphery from SNS activation and BBB disruption. This dissertation builds upon my previous research in the field of TBI, focusing on key elements of TBI recovery: acute infection, inflammation, and hormone dysfunction. I also discuss the procedures involved, and implications, of bridging two large databases within trauma and rehabilitation to build an infrastructure spanning the continuum of TBI disability.

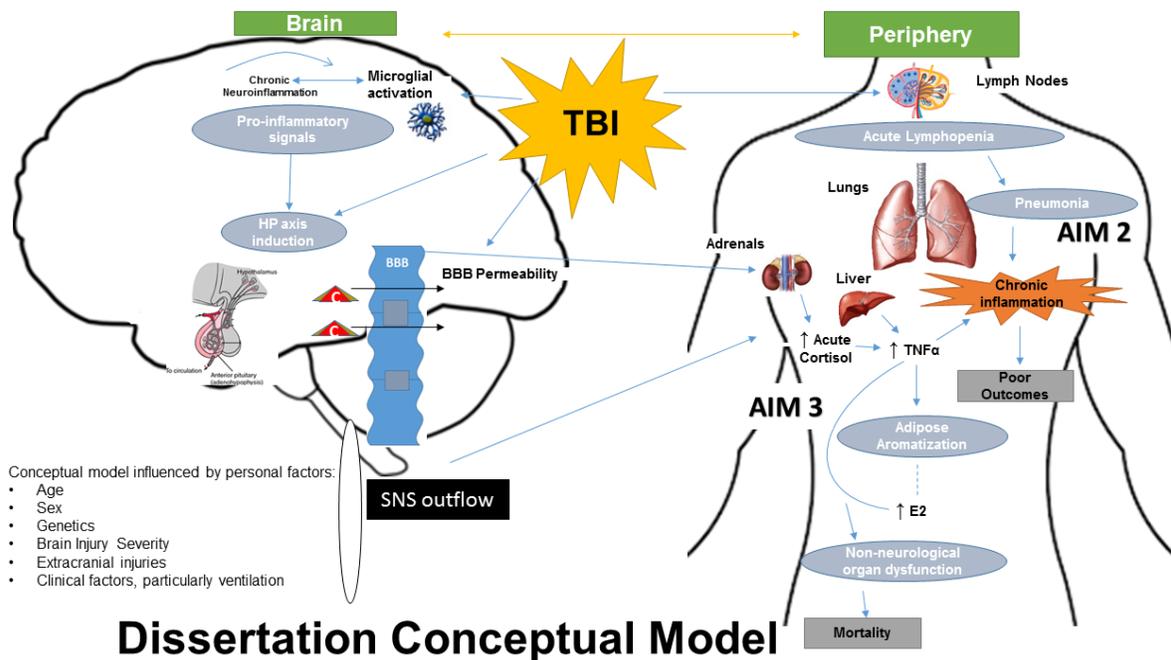


Figure 3. Kumar Dissertation Conceptual Model

The effects of TBI span the brain and periphery. Elements of brain pathology represented include an induction of the stress response, which includes the Hypothalamus-Pituitary-Adrenal (HPA) axis and sympathetic nervous system (SNS) outflow. Blood brain barrier disruption is also portrayed, which is one source of communication between the brain and periphery. **Aim 2** focuses on nosocomial pneumonia after TBI, which may be caused by prolonged mechanical ventilation on top of a trauma-induced state of lymphopenia. It is believed that acute pneumonia after TBI contributes to a chronic inflammatory state that increases risk for poor long-term outcomes. **Aim 3**, shown in the periphery, involves nuanced relations between estradiol (E2) and TNF α . Peripheral sources of TNF α include from the liver through a sympathetic nervous system-initiated acute phase response. TNF α importantly aids in extra-gonadal production of E2 in adipose tissue. The negative effects of excessive E2 and TNF α is vasodilation of systemic vasculature, which may contribute to non-neurological organ dysfunction and mortality.

2.0 AIM 1: PROBABILISTIC MATCHING OF DEIDENTIFIED DATA FROM A TRAUMA REGISTRY AND A TRAUMATIC BRAIN INJURY MODEL SYSTEM CENTER: A FOLLOW-UP VALIDATION STUDY

2.1 ABSTRACT

In a previous study, individuals from a single Traumatic Brain Injury Model Systems (TBIMS) site and trauma center were matched using a novel probabilistic matching algorithm. The TBIMS is a multicenter prospective cohort study containing >14,000 participants with TBI, following them from inpatient rehabilitation to the community over the remainder of their lifetime. The National Trauma Databank (NTDB) is the largest aggregation of trauma data in the United States, including over 6 million records. Linking these two databases offers a broad range of opportunities to explore research questions not otherwise possible. Our objective was to refine and validate the previous protocol at another independent center. An algorithm generation and validation dataset were created, and potential matches were blocked by age, sex, and year of injury; total probabilistic weight was calculated based on 12 common data fields. Validity metrics were calculated using a minimum probabilistic weight of 3. The positive predictive value was 98.2% and 97.4% and sensitivity was 74.1% and 76.3%, in the algorithm generation and validation set, respectively. These metrics were similar to the previous study. Future work will

apply the refined probabilistic matching algorithm to the TBIMS and NTDB to generate a merged dataset for clinical TBI research utilization.

2.2 INTRODUCTION

Database linkage is a powerful statistical methodology that can be leveraged to answer important questions in the field of medicine that are not possible in either dataset alone. In instances where unique identifiers (e.g. medical record numbers) are available, deterministic linkage offers a quick and efficient way to link records between databases. However, many publicly available datasets are de-identified for privacy reasons, making record linkage a more computationally challenging endeavor. Probabilistic linkage, which relies on the matching values of common data elements between databases, can be implemented in such instances without the need for unique identifiers.¹²²

Clinical care of patients with moderate to severe TBI occurs along a continuum, beginning with emergency room care and acute inpatient hospitalization at a trauma center. After discharge from the acute hospital, many patients also require comprehensive inpatient rehabilitative services prior to integration into the community. Most of the research conducted to date in TBI has been divided, either: 1) exploring the effect of acute care trauma factors on hospital-based outcomes, or 2) examining long-term recovery in the chronic stages of TBI, beginning during inpatient rehabilitation and extending months to years after TBI. Very few research studies have bridged these two avenues of research to explore the long-term effects of acute care trauma factors, largely because of a lack of available data across these two fields to address these cross-disciplinary types of research questions. Linking the NTDB and TBIMS

offers the unique opportunity of simultaneously access both the largest acute trauma care database in the world (NTDB) and the largest longitudinal TBI outcomes National Database, the TBIMS, which follows patients for the entirety of life post-injury.

In a previous report, we developed a novel probabilistic matching algorithm at a single medical center to link two databases, the Traumatic Brain Injury Model Systems (TBIMS) single site to trauma registry data records submitted to the National Trauma Databank (NTDB).¹²³ A parallel deterministic linkage was possible due to available medical record numbers, allowing for us to derive a true match status. Thus, validity metrics were calculated based on concordance/discordance between linked matches from the probabilistic matching algorithm and true match status from the deterministic linkage. Correspondingly, an increased emphasis was placed on two specific metrics in the probabilistic matching algorithm: positive predictive value (PPV) and sensitivity. In this context, PPV is defined as the proportion of individuals linked in our probabilistic algorithm between databases that, in reality, are the same individual. Sensitivity is the proportion of individuals that are true matches between the two datasets that are linked using the probabilistic algorithm. In a previous single site study applying our algorithm, we achieved a PPV of 99% in both an algorithm generation and validation subset; and a sensitivity of 88% and 83% in these algorithm generation and validation subsets, respectively.¹²³ This initial result is important in that it indicates the accuracy and validity of the proposed probabilistic matching algorithm, in which more than 80% of target cases were matched, and almost 99% of matched cases were the same individual.

As a next step of evaluating the veracity of this probabilistic matching protocol, the purpose of the present study is to apply and validate this novel probabilistic algorithm in another, independent single medical center TBIMS dataset and trauma registry records. This validation is

technically possible because of the availability of true match status between the two datasets for all patients. Therefore, in this follow-up study, we conducted a parallel deterministic linkage to allow for calculations of algorithm validity metrics. Having the algorithm validated in an independent center will add a greater level of veracity and confidence to the protocol, with a long-term goal of this project to have a refined and validated probabilistic algorithm that can be applied to the TBIMS National Database and NTDB on a national scale.

2.3 METHODS AND MATERIALS

2.3.1 Probabilistic linkage

This study was approved by the local institutional review board. Background of the mechanics of the probabilistic linkage method applied to TBIMS and trauma dataset in previous single-site study has been described in great detail elsewhere.¹²³ Briefly, for each matched pair, agreement for each linking variable was evaluated in the algorithm by assigning a weight for each corresponding variable. The total weight was summed over all matching variables. The higher the total weight, the greater the probability that the matched pair in reality belongs to the same person. When deciding whether or not cases are considered linked between the two datasets, three tiers of criteria were examined and checked for validity metrics, with each increasing tier having more stringent criteria for matching.

To estimate the matching weight, we applied two commonly used criteria: the quality of the data and the probability of random agreement. The quality of data metric is described by m , or the probability of matched pair agreement on a given linking variable within each value of the

variable in the trauma dataset, given the pair is a true match. For example, if 90% of the matched pairs agree on systolic blood pressure (SBP) when SBP is 140 in trauma, then $m=0.9$. For a matched pair in this example that does not agree on SBP at 140, then $m=0.1$. The probability of random agreement is defined by u , which estimates the probability that a matched pair will randomly have the same value for a given linking variable. U is determined by the frequency distribution of each linking variable. For instance, while the probability of a matching pair randomly matching on sex is 50%, the probability of randomly matching on same birthday will be 0.27% (1/365).¹²²

2.3.2 Matching blocking

To increase the efficiency of matching, blocking was employed using the variables: age, sex and year of injury. Only individuals in each database with exact value matches for these three variables were included in the probabilistic match. Blocking can be regarded as a filter process to remove matching pairs that are highly unlikely to be the true match.¹²⁴ This step is crucial in reducing the computational load of the matching procedure. Age, sex and injury year were applied in the previous study¹²³ and we observed a low likelihood of human data entry error, resulting in a high specificity.

2.3.3 Linking variables and weight estimation

After blocking procedures were complete, the following variables were selected in the probabilistic matching: acute care length of stay, initial Glasgow Coma Scale (GCS) motor, verbal, eye movement, total (sum of the previous three GCS sub-scores), race, respiratory rate

and initial systolic blood pressure in the emergency department, head injury pattern (fracture of base of skull or fracture of calvarium), cause of injury and acute care health insurance payer information. When compared with the probabilistic linkage algorithm we used in the previous study¹²³, we excluded four binary matching variables: intubation status, sedated status and spinal injury status (SCI) in the current study due to: 1) poor data quality ($m < 0.7$), 2) low differentiation between deterministic true and false matches, and 3) very little appreciable improvement in overall sensitivity or PPV. Of note, the binary variables with high m values (> 0.7) were included (cranial surgery and skull based fracture) as they were deemed very high quality data to use for the purposes of matching.

Since the true match status was known through medical record numbers, m was calculated from the probability of agreement for true matches. The value of u was estimated from the frequency distribution for each linking variable in the trauma registry, the larger of the two datasets. The weight for each matched pair on each linking variable (w_{ij}) was assigned if the pair **agreed** on the matching variable:

$$W_{ij} = \log (m_{ij} / u_{ij})$$

where i was the i^{th} linking variable and j was the j^{th} matching pair.

Also, the following weight was assigned if the pair **disagreed** on the matching variable by:

$$W_{ij} = \log [(1 - m_{ij}) / (1 - u_{ij})]$$

where i was the i^{th} linking variable and j was the j^{th} matching pair.

Total weight was the sum of the weight for each matching variable. In probabilistic linkage, there is a characteristic bimodal distribution of weights: one large distribution reflecting weights of comparisons that are primarily disagreeing negative weights (left distribution), and another, smaller distribution, reflecting comparisons that primarily agree and have mostly positive

weights (right distribution). Of note, it is common to have some small overlap between the left and right distributions.

2.3.4 Clustering and cluster weight difference

For each case in the TBIMS dataset, multiple cases within the trauma registry are “potential matches” contingent on sharing the same age, sex and injury year as the TBIMS case. This group of “potential matches” is called a cluster. Within each cluster, the matched pair with the highest total weight is regarded as the most probable match. Occasionally, however, the total weights between two independent potential matches can be very similar. For example, a matched pair theoretically could differ with each other by only one or two matching variables. The cluster weight difference (CWD) was introduced as a quantitative measure of this issue. CWD was computed as the difference of the highest total weight to the second highest total weight within each cluster. If CWD was less than the chosen threshold value, all matched pairs within that cluster were rejected because of the difficulty in distinguishing within a certain margin of error which pair is the true match. Similar to our previous probabilistic matching algorithm¹²³, we applied threshold values for CWD that corresponded to the 90th percentile of CWD for false matching.

For this validation study, validity metrics were calculated and assigned to one of three “tiers”, which designate from *more liberal to more stringent criteria* (hereafter refer to Tier I-III) for considering cases to be linked between datasets (see detailed schematic representation in **Figure 4**).

Tier I: the greatest weight in each cluster is considered the linked match;

Tier II: met criteria for Tier I, and the total weight value that corresponds to the right tail of the overlapping distribution of weights;

Tier III: met criteria for Tier II, and CWD greater than 90th percentile CWD for false matches

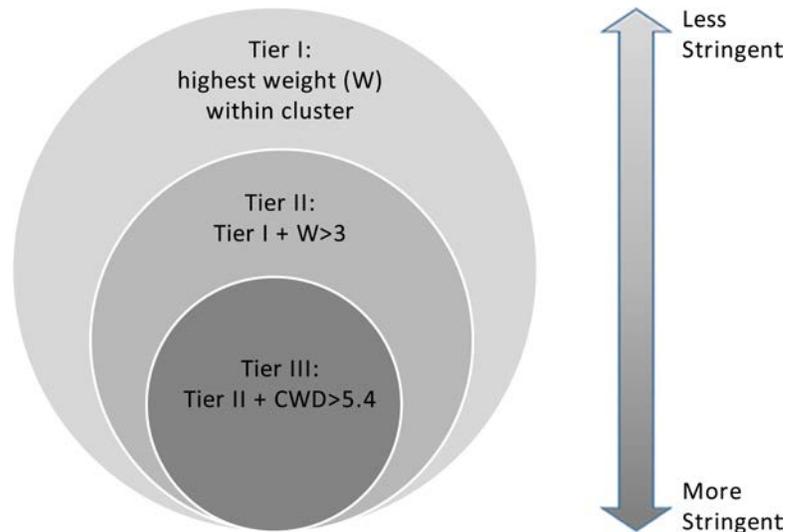


Figure 4. Schematic representation of determining probabilistic linkage by using progressively stringent criteria (Tier I-III)

We considered the Tier III criteria to be the most stringent and most conservative criteria because of the added consideration of a margin of error. It is possible that two cases in the trauma database have similarly large weights. That is, there is a strong agreement in values of several matching variables, and in such a case, the CWD is small, making it harder to correctly identify the true match. A scatter plot was generated of weight by CWD, stratified by true and false match status, with lines overlaying the Tier II and III cut points. We expected that individuals meeting both Tier II and III criteria (top right quadrant of scatterplot) will be mostly true positives.

2.4 RESULTS

To generate the probabilistic matching algorithm and validate it, a random number was generated from the uniform distribution on the interval between 0 and 1 for each subject in the TBIMS set. A threshold of 0.5 was applied to randomly divide the dataset into training and validation set. The final datasets contained 497 and 544 cases in the training and validation set, respectively. After blocking individuals in each database on age, sex and injury year, we obtained 4,428 matched pairs for the training set and 4,743 pairs for validation set.

With 440 TBIMS rehabilitation cases in the matched pair training set, a total of 4,429 comparisons were obtained from a trauma dataset that contained 12,942 trauma cases. Using Tier I criteria, the sensitivity was 82.3% (**Table 1**). Based on a visual inspection of the frequency distribution in the training set stratified by greatest weight per cluster vs. all other weights in the cluster, the weight threshold was set to 3 (**Figure 5**). Using this Tier II criteria threshold, sensitivity was at 74.1% and positive predictive value (PPV) was 98.2% if the highest weight of each cluster was considered a positive match. The 90th percentile of CWD (7.0) for false matches was used as our threshold for CWD in both the training and validation datasets (**Supplemental Table S1**). Using the added Tier III criteria of CWD of 7.0, sensitivity and PPV were 66.6% and 99.3%, respectively (**Table 2**).

For the validation set, a total of 485 TBIMS rehabilitation cases and 12,942 trauma cases were used to form a 4,744 matched pair validation set using the same blocking procedure. Using Tier I criteria, sensitivity was 84.1% (**Table 1**). Applying the same Tier II threshold cutoff for weight of 3 as the training set, sensitivity was 76.3% and PPV was 97.4%. When a further Tier III criteria of CWD greater than 7 subsequently was applied (as derived from the training set), sensitivity and PPV were 70.7% and 98.0%, respectively (**Table 2**).

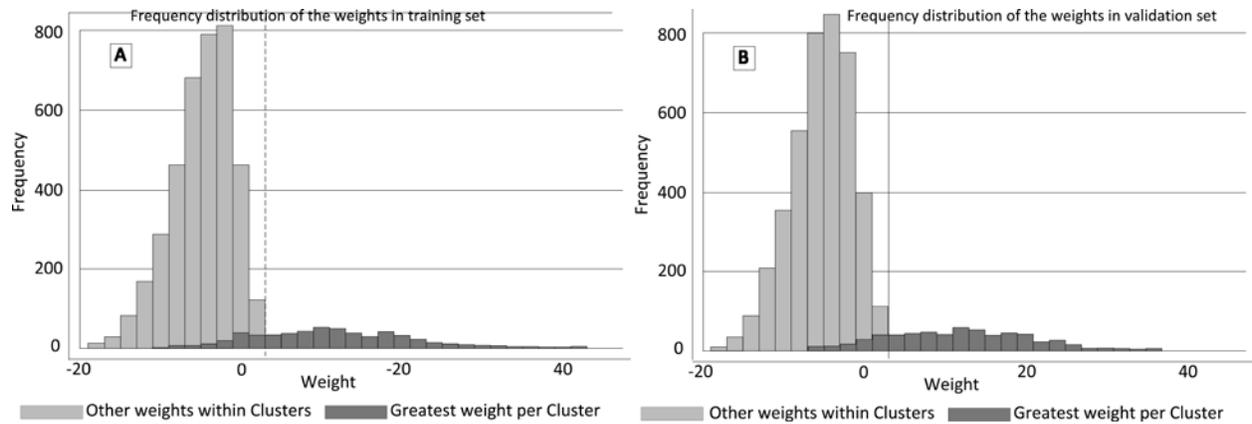


Figure 5. Frequency distribution of weights.

Panel (A) is the training set, and panel (B) represents the validation set. The frequency distribution of weights among those with the greatest weight in the cluster (dark gray), compared to other weights within cluster (light gray). A cluster is defined as all the trauma cases that are compared to a simple TBI-MS case, after blocking for age, sex, and year of injury. The vertical line represents the Tier II criteria of weights greater than 3.

Table 1. Descriptive characteristics of algorithm generation and validation subset

	Trauma	Rehab	Total comparisons	Mean cases per cluster	No. of rehab cases did not block to true match	True match with top weight in cluster (%) (TIER I criteria)
Training set	12,942	440	4,429	8.9	57	408 (82.3)
Validation set	12,942	485	4,744	8.8	59	455 (84.1)

Table 2. True match status by probabilistic linkage status in training set

Link status	Training set			Validation set		
	True match status		Total	True match status		Total
	True	False		True	False	
A						
Link	326	6	332	370	10	380
Nonlink	114	3,983	4,097	115	4,249	4,364
Total	440	3,989	4,429	485	4,259	4,744
Sensitivity		74.1%			76.3%	
PPV		98.2%			97.4%	
B						
Link	293	2	295	343	7	350
Nonlink	147	3,987	4,134	142	4,252	4,394
Total	440	3,989	4,429	485	4,259	4,744
Sensitivity		66.6%			70.7%	
PPV		99.3%			98.0%	

A. Cases with highest weight in cluster greater than 3 (TIER II criteria)

B. Adding as an exclusion criteria a CWD>7 in addition to A (TIER III criteria)

For the training and validation dataset, a scatterplot was generated of the total weight by CWD, with a vertical and horizontal line overlaid to depict the Tier II (weight=3) and Tier III (CWD=7) cut points, respectively (**Figure 6**). The true and false matching status is shown, with the top right quadrant representing individuals meeting both Tier II and III criteria. As expected, a majority of individuals in the top right quadrant are true positives in the training and validation datasets.

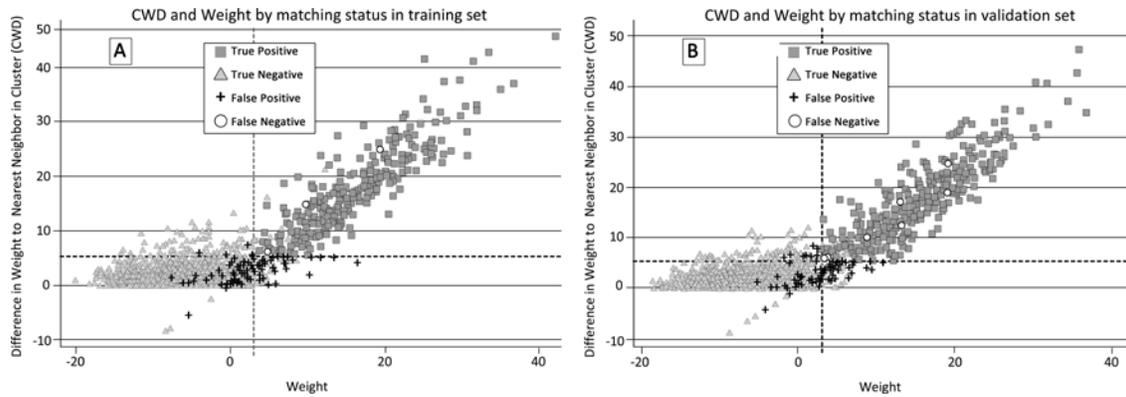


Figure 6. CWD and Weight by Matching Status.

Panel (A) is the training set, and panel (B) represents the validation set. The case weight difference (CWD) by weight. The vertical line represents the Tier II criteria of weights greater than 3. Horizontal reference line represents the chose Tier III cutoff at 5.4. The four symbols: square, triangle, plus, and circle, correspond to the true positive, true negative, false positive, and false negatives when comparing the results of the probabilistic linkage algorithm to the gold standard deterministic linkage

To assess for potential selection bias in the demographics of matched vs. unmatched individuals, selected blocking and matching fields were examined by Tier II criteria (**Supplemental Table S2**). Our data indicated that blocking and matching fields largely did not significantly differ between matched and unmatched cases except for age and LOS in the training set and SBP in the validation set, suggesting a low likelihood of selection bias.

2.5 DISCUSSION

The aim of the present study was to refine and validate a probabilistic matching algorithm to link data from the TBIMS to the trauma records from a single clinical site that submits data to the NTDB. In this study, we executed a similar probabilistic procedure in an independent health system where true match status is known, allowing for the calculations of algorithm validity metrics. Importantly, any given dataset and patient population in a single site may differ from

another single site in another region, the metrics and threshold values are subject to some degree of fluctuation. Specifically, the derivation of the m and u values are a function of the data quality and frequency distribution of values in a specific dataset. Validation in an independent site thus is a crucial step to refine our novel probabilistic algorithm before full implementation in a scenario where true match status is unknown.

The probabilistic algorithm used in the original study was modified by omitting three binary variables, including intubation status, sedated status and spinal cord injury (SCI) status. In instances where the quality of the data is determined to be poor ($m < 0.7$), the probability that the value for a binary variable will match between datasets by chance alone will be increased. Therefore, we made the determination to set the u value to 0.5 to correct for uneven distributions on the likelihood of 0 or 1, and base the score of the weight of binary variables on the data quality. For binary variables with a moderate to high data quality (M value is at least greater than 0.7 for both levels), we still retained binary variables in the matching algorithm such as cranial surgery and skull base fracture. To compensate for inflation of U due to skewed distribution, we set any U above 0.5 to 0.5, and thus, made U irrelevant in the total weight computation.

Though binary variables were removed from the prior probabilistic algorithm, it is important to note that no new variables were added into the algorithm. Given the fact that we refined the algorithm, we derived a training and validation set in the present study. In the training set, using tier II criteria of a weight greater than 3, we achieved a PPV of 98.2% and sensitivity of 74.1%; and in the validation set a PPV of 97.4% and sensitivity of 76.3%. These results are roughly in line with the metrics obtained in the prior study.¹²³ In probabilistic matching having utmost confidence that cases that are claimed to be linked by the algorithm are in fact true matches, the definition of PPV, is the most important validity metric. In lay terms, since we

know it is impossible to have two trauma cases matching to the same TBIMS case, if two weights are reasonably close, then it is better to throw out that TBIMS case, then to risk incorrectly choosing the true match. Of note, when applying Tier III criteria ($CWD > 7$) in this study, we noticed a reduction in sensitivity with only small improvements in PPV, which suggests that this criterion may be too stringent, and Tier II may be sufficient for practical applications.

The data quality, m , is also another important consideration when conducting a probabilistic match. We observed that a majority of m values were comparable (within 20% percent difference) between the current study and the prior study¹²³ (data not shown). In moving forward to a national merge, we plan to use the m values derived from the current study because of its larger sample size relative to the prior study.

Our study has limitations that should be considered. First, our deterministic linkage was based on cases from a limited time period (1999-2012). Availability of validated matching variables in the algorithm can change over time. For example, systolic blood pressure and respiratory rate are no longer collected in TBIMS after 2013. Therefore, a regular reevaluation and adaptation of this algorithm likely will be needed at later points in time. Also, there could be other unmeasured or unidentified variables which may have higher data quality and lower random agreement rate than current matching fields in our matching algorithm. Based on a probabilistic algorithm developed from a single site¹²³, the present study refined and validated this algorithm to match patients in the TBIMS to the NTDB in another independent single medical center. Due to the availability of true match status for these patients, we could calculate validity metrics to assess the sensitivity and PPV of our algorithm.

2.5.1 Implications of the Project and Future Directions

Our future directions are to apply this refined protocol to the multi-site TBIMS and NTDB using only probabilistic matching. With the advent of the Federal Interagency Traumatic Brain Injury Research (FITBIR) network, there is a push by the United States federal government to share data across the entire TBI research field. The merger of the TBIMS and NTDB adds to this growing movement of data linking; combining these two datasets is of immense interest in answering a wealth of previously unexplored research questions on the relationships between acute care variables and hospital course on long-term outcomes among individuals with TBI. The NTDB contains a wealth of data on the acute hospitalization, including procedure codes, complication codes, and extensive injury information (cerebral and extracerebral injury severity). However, a major limitation of the NTDB is that there is only follow-up information until hospital discharge, which restricts the scope of research questions that can be answered. In the TBIMS National Database, there is a wealth of follow-up information years after the injury, until a patient is deceased, allowing researchers to assess chronic recovery from moderate to severe TBI. The TBIMS National Database has only limited data collection for acute variables; therefore, the long-term effects of acute factors, such as procedures and complications, immediately after TBI cannot be assessed fully without full access to trauma care data. For instance, one such application of initial single site trauma-rehab merged dataset¹¹⁴ was the examination of the long-term effects of hospital-acquired pneumonia on global outcomes after TBI. Examining hospital-acquired pneumonia effects on long-term recovery for thousands of individuals with data captured in the TBIMS national dataset may have immense implications for the field of TBI, as there is still equivocation in clinical care guidelines with respect to the administration of antibiotic prophylaxis for ventilated patients with TBI. This

initial finding serves as an exemplar for the tremendous potential of our merged database to serve as a platform to address previously unanswerable research questions that have the potential to impact clinical care and future research priorities. It is also important to consider that our methods are not confined to TBI alone, and could have a lasting impact on other rehabilitation disciplines. That is, other model systems injury databases, specifically spinal cord injury and burn injury, also may be well suited for probabilistic matching with the NTDB in future studies.

3.0 AIM 2: EFFECTS OF HOSPITAL-ACQUIRED PNEUMONIA ON LONG-TERM RECOVERY AND HOSPITAL RESOURCE UTILIZATION FOLLOWING MODERATE-TO-SEVERE TRAUMATIC BRAIN INJURY

3.1 ABSTRACT

Individuals with moderate-to-severe Traumatic Brain Injury (TBI) have extended inpatient hospital stays, often including prolonged mechanical ventilation, which increases the risk for infections, such as pneumonia. Studies have shown the negative short-term effects of hospital-acquired pneumonia (HAP) on hospital-based outcomes; however, little is known of its long-term effects. The primary objective of this study was to determine the association between HAP and long-term disability after TBI. A secondary objective was to identify associations between HAP and healthcare utilization metrics. The National Trauma Databank (NTDB) and the Traumatic Brain Injury Model Systems (TBI-MS) were merged to derive a cohort of n=3717 adults with TBI. Exposure data were gathered from the trauma database, and outcomes were gathered from the TBIMS. The primary outcome was the Glasgow Outcome Scale-Extended, which was collected at 1, 2 and 5 years post-injury. GOS-E was categorized as favorable (>5) or unfavorable (≤ 5) outcomes. A generalized estimating equation (GEE) model was fitted to estimate the effects of HAP on GOS-E over the first five years post-TBI, adjusting for age, race, ventilation status, brain injury severity, injury severity score (ISS), thoracic AIS ≥ 3 , mechanism

of injury, intraventricular hemorrhage status, and subarachnoid hemorrhage status. Individuals with HAP were at a 34% (OR=1.34, 95% CI 1.15, 1.56) increased odds for unfavorable GOS-E over the first five years post-TBI compared to individuals without HAP, after adjustment for relevant demographic and clinical covariates. Individuals with HAP, compared to no HAP, spent 10.1 days longer in acute care and 4.8 days longer in inpatient rehabilitation, and they had less efficient functional improvement during inpatient rehabilitation. Individuals with HAP during acute hospitalization have worse long-term prognosis and greater healthcare utilization post-TBI. Preventing HAP may be cost-effective and may improve long-term recovery for individuals with moderate-to-severe TBI. Future studies should compare the effectiveness of different prophylaxis methods to prevent HAP, including early extubation and early mobilization.

3.2 INTRODUCTION

An estimated 2.5 million Americans annually have an emergency department visit, are hospitalized with, or die due to traumatic brain injury (TBI).¹²⁵ Nearly half of patients hospitalized with TBI experience long-term morbidity from their injuries, contributing to a large proportion of US citizens living with chronic disability.¹²⁶ To prevent the high disability burden and associated costs, TBI researchers have focused on identifying acute predictors of long-term disability, including injury severity based on the Glasgow Coma Scale (GCS),¹²⁷⁻¹²⁹ systemic hypotension,¹³⁰ intracranial pressure,¹³¹ and post-traumatic hydrocephalus.^{132,133} Other studies demonstrate relationships between TBI-related disability and demographic factors like older age at injury,¹³⁴ female sex,^{7,135} minority race,^{2,136} and lower socioeconomic status.²

An underemphasized area of TBI research is the contribution of acute systemic infection to long-term recovery. Many patients with moderate-to-severe TBI require mechanical ventilation in the days following their injuries. A common complication of prolonged mechanical ventilation is hospital-acquired pneumonia (HAP), caused by pathogens entering the lower respiratory tract and lung parenchyma. In observational studies, HAP incidence rates range from 30-61% in TBI populations.¹¹²⁻¹¹⁴ Variation in incidence estimates arise from heterogeneous cohorts, including cohorts restricted to only ventilated patients. Ventilation is an important predictor for incident HAP after TBI, with each additional ventilator day conferring a 7% increased risk for infection.¹⁰⁹ Other variables associated with HAP incidence after TBI include thoracic Abbreviated Injury Scale (AIS) score ≥ 3 and gastric aspiration.¹¹³ Some individuals with TBI also experience a period of acute lymphocyte dysfunction following injury, known as lymphopenia.¹³⁷ The result of persistent lymphopenia is suppressed immunity and a decreased capacity to fight pathogens, which can increase the risk for opportunistic infections, like pneumonia.¹⁰³⁻¹⁰⁷

Incidence of HAP directly increases healthcare utilization and expenditures. Critically ill patients with HAP require roughly \$40,000 more in acute hospitalization costs, and they also require approximately twice the intensive care unit and hospital lengths of stay (LOS) compared to critically ill patients without HAP.^{112,138} One study evaluating acquired brain injury patients determined that individuals with ventilator-associated pneumonia (VAP) had higher hospital costs, longer LOS, and more readmissions compared to individuals without VAP.¹³⁹

Past TBI studies characterizing HAP have examined the short-term impact of HAP on cost and acute hospital outcomes.¹⁰⁹⁻¹¹² A gap exists in understanding the long-term effects of HAP in this population. Two recent small studies lend preliminary evidence that HAP negatively

impacts long-term outcomes following injury.^{114,140} To build upon these studies, a large multi-site observational study with longitudinal follow-up is necessary to more accurately and precisely estimate the long-term effects of HAP on disability and hospital resource utilization after TBI. To this end, we leveraged a large probabilistically-merged database of the National Trauma Databank (NTDB) and TBI Model Systems (TBIMS) National Database. The study objectives were to: 1) determine the long-term effects of HAP on disability after moderate-to-severe TBI; and 2) compare hospital resource utilization metrics between individuals with and without HAP.

3.3 METHODS AND MATERIALS

All TBI Model Systems centers represented in this study had approved local Institutional Review Board protocols. The present study used data from two large databases: the NTDB and the TBIMS National Database. The NTDB is the largest aggregation of trauma registry data in the United States. Participating hospitals contribute information on all trauma patients treated at their institution. Deidentified data are submitted to the NTDB and compiled for hospital benchmarking, data quality reports, and addressing trauma-related research questions. The TBIMS is a prospective cohort study funded by the National Institute on Disability Independent Living and Rehabilitation Research that includes data collected at 16 acute rehabilitation centers. Included patients received their acute care within 72 hours of injury at a designated acute care hospital, survived through acute care, and were stable medically to receive rehabilitation. Other TBIMS inclusion criteria include: a moderate-to-severe TBI (post-traumatic amnesia >24 hours, intracranial neuroimaging abnormalities, loss of consciousness exceeding 30 minutes, or GCS

less than 13) and age 16+ years at time of injury.¹⁴¹ Data are collected at enrollment and years 1, 2, and 5, as well as every 5 years afterward.

We used a probabilistic matching algorithm to combine the de-identified NTDB and TBIMS. The merger of the two databases was possible because participants in the TBIMS had a trauma record submitted to the NTDB. We developed the algorithm in two sites where exact matches on patient identifiers were available to form a deterministic dataset to quantitatively assess the veracity (e.g. sensitivity, positive predictive value) of our algorithm. We previously published detailed methods used for algorithm development¹⁴² and validation.¹⁴³ The final NTDB-TBIMS cohort contained n=4022 individuals with TBI, injured between the years 1998-2015. We further restricted our cohort to participants injured between 1998-2013 to examine five-year outcomes (n=3712). There were 21 NTDB trauma facilities across 17 TBIMS centers represented in the present dataset.

The specific variables used in this study from the NTDB and TBIMS, along with a detailed description of each variable, are provided in **Table 3**. The exposure of interest in this study is HAP, and the primary outcome is the Glasgow Outcome Scale-Extended (GOS-E) score¹⁴⁴, assessed at 1, 2, and 5 years post-injury. For the purposes of this analysis, scores were dichotomized ≤ 5 (unfavorable outcomes) vs. >5 (favorable outcomes), as this represents the distinction between severe disability and moderate disability or good recovery.¹⁴⁴ Secondary descriptive analyses were conducted to examine the association between HAP and variables related to hospital resource utilization: acute care LOS, rehabilitation LOS, and change in Functional Independence Measure (FIM) scores over time (FIM efficiency).

Table 3. Description of measures

NTDB measures	Construct	Description of Measure
HAP	Primary exposure; Pneumonia in hospital	<ul style="list-style-type: none"> ➤ Documentation for HAP was defined as one of two criteria,¹⁴⁵ either: <ol style="list-style-type: none"> 1. Rales or dullness on a physical examination of the chest and any of the following: new onset purulent sputum, organism isolated from blood culture, or isolation of pathogen from specimen obtained by transtracheal aspirate or biopsy; OR 2. positive chest radiographic exam and any of the following: new onset purulent sputum, organism from the blood, isolation of pathogen from specimen isolated from transtracheal aspirate or biopsy, isolation of virus or detection of viral antigen from respiratory secretions, diagnostic single antibody titer (IgM) or 4-fold increase in paired serum sample (IgG) for pathogen, or histopathologic evidence of pneumonia
ISS	Injury Severity-all body regions	<ul style="list-style-type: none"> ➤ An anatomic trauma severity scale derived from the AIS that quantifies overall injury severity across eight body regions¹⁴⁶ ➤ Scores range from 1-6, with 1 being minor and 6 unsurvivable ➤ ISS is the sum of squares of the 3 most severely injured body regions
Non-head ISS	Injury Severity-all non-head body regions	<ul style="list-style-type: none"> ➤ The Non-head ISS was calculated using AIS region scores ➤ The sum of squares of the 3 most severe non-head body regions
Thoracic AIS	Thoracic injury severity	<ul style="list-style-type: none"> ➤ AIS thoracic region score ➤ Scores range from 1-6, with 1 being minor and 6 unsurvivable ➤ Individuals with no thoracic injuries were assigned a score of 0 ➤ Significant thoracic injury was classified as a thoracic AIS score ≥ 3
Ventilation Status	Ventilation	<ul style="list-style-type: none"> ➤ ICD-9 Procedure code range from 96.7-96.72
Ventilation days	Number of days on a ventilator	<ul style="list-style-type: none"> ➤ Number of days on ventilator support among individuals on a ventilator

Table 3 Continued		
TBIMS measures		
Age	Age	➤ Age at injury
Race	Race	➤ Grouped as White, Black, or Other
Brain Injury Severity	Brain Injury Severity based on DoD scale	<ul style="list-style-type: none"> ➤ Calculated variable consisting of two categories, moderate or severe injuries, which is a function of the Glasgow Coma Scale (GCS), post-traumatic amnesia (PTA), and number of days it takes to follow commands ➤ Moderate injuries are defined by a GCS between 9-12, PTA between 0-7 days, or days to follow commands ≤1 day ➤ Severe injuries were defined as a GCS between 3-8, PTA >8 days, or days to follow commands >1 day
MOI	Cause of injury	➤ Grouped as Motor Vehicle, Fall, Pedestrian, or Other
CT scan findings	Nature of TBI	<ul style="list-style-type: none"> ➤ Trained abstractors review patient electronic medical records to document presence or absence of neuropathology on computed tomography images ➤ Grouped as presence/absence of: SDH, EDH, IVH, and SAH
Payor Status	Insurance	➤ Payor was dichotomized as Medicare or Medicaid vs. all other payment sources
Rehabilitation Interruption	Interruption to Rehabilitation Care	➤ Short-term interruptions during inpatient rehabilitation to acute care
Acute care LOS	Number of hospital days in acute care	➤ Hospital days in acute care
Rehabilitation LOS	Number of hospital days in rehabilitation	➤ Hospital days in rehabilitation
FIM efficiency	Rate of change in FIM over the course of Rehabilitation	➤ Calculated variable from the formula: $(FIM_{\text{discharge}} - FIM_{\text{admission}}) / (\text{Rehab LOS})$
Rehospitalization	5- year Rehospitalization	➤ All-cause rehospitalization at any point at 1, 2, or 5 years post-injury
GOS-E	Primary outcome; Global disability measure	➤ A trained research assistant conducts a 20-question structured interview that answers a variety of questions pertaining to patient's current condition, covering the following topics: 1) level of consciousness, 2) independence at home, 3) independence outside home, 4) return to work, 5) participation in social and leisure activities, 6) family and friendships, and their 7) return to normal life.

Table 3 Continued		<ul style="list-style-type: none"> ➤ The range of scores are from 1-8, with higher scores corresponding to better recovery. ➤ Scores were dichotomized ≤ 5 (unfavorable outcomes) vs. > 5 (favorable outcomes)
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Abbreviations: HAP, Hospital-acquired Pneumonia; ISS, Injury Severity Scale; AIS, Abbreviated Injury Scale; DoD, Department of Defense; MOI, Mechanism of Injury; LOS, length of stay, GCS, Glasgow Coma Scale; Post-traumatic Amnesia (PTA); Functional Independence Measure (FIM); GOS-E, Glasgow Outcome Scale-Extended Scale; CT, Computed Tomography; SDH, subdural hematoma, EDH, epidural hematoma, IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage

Though probabilistic matching is common in birth cohorts and life-course studies,¹⁴⁷ its use in merging databases in trauma, surgery, and rehabilitation is novel. To evaluate the integrity of this approach for our purposes, we developed a deterministic cohort from two TBIMS sites to conduct a post-hoc sensitivity analysis as an internal validation measure to examine the veracity of our primary findings from the probabilistically-derived cohort. This deterministic cohort included n=775 individuals with TBI injured between 2002-2013.

3.3.1 Statistical analysis

Demographic and clinical variables were compared by HAP status and GOS-E. Means and standard errors described continuous variables, and frequency and percentages described categorical variables. Chi-square tests compared categorical variables, and t-tests or Mann Whitney U test, were used to compare continuous variables by HAP status and GOS-E score.

A generalized estimating equation (GEE) model was used for the primary analysis assessing the relationship between HAP and 1, 2 and 5-year GOS-E. Models were fit using an unstructured correlation structure. Covariates included: age, race, ventilation status, brain injury severity, injury severity score (ISS), thoracic AIS ≥ 3 , mechanism of injury, intraventricular hemorrhage status, and subarachnoid hemorrhage status. To observe the effects of the covariates

on the effect of HAP on GOS-E, a series of four models are presented: Model 1 (unadjusted), Model 2 (adjusts for age effects), Model 3 (adjusts for age and race only), and Model 4 (fully adjusted for all chosen demographic and clinical variables). We chose covariates that were associated with HAP and 1-year GOS-E at an $\alpha=0.20$ level. Chosen covariates were not in the pathway between HAP and GOS-E. The same covariates were included in the primary, secondary, and sensitivity analyses.

In order to determine the effects of HAP on hospital resource utilization, analysis of covariance (ANCOVA) models were used to compute covariate-adjusted mean scores for acute LOS, rehab LOS, and FIM efficiency by HAP status. FIM efficiency is the change in FIM score during rehabilitation divided by the rehabilitation LOS. SAS 9.4 was used for all statistical analysis (Cary, NC).¹⁴⁸

3.4 RESULTS

3.4.1 Demographic and Clinical Variables by HAP Status

The cohort included n=1212 (32.7%) individuals with HAP and n=2500 (67.3%) individuals without HAP. The demographic and clinical variables by HAP status are presented in **Table 4**. Individuals with HAP were more likely to be younger and male than individuals without HAP ($p<0.001$ both comparisons). Injury Severity Scale (ISS) score and non-head ISS were significantly higher among individuals with HAP versus no HAP ($p<0.001$ both comparisons). A greater proportion of individuals with HAP had a thoracic AIS score ≥ 3 , were more frequently on a ventilator, spent more days on a ventilator, and had longer acute and

rehabilitation LOS compared to individuals without HAP ($p < 0.001$ all comparisons). A greater proportion of individuals with HAP had a rehabilitation interruption compared to no HAP ($p = 0.027$). A greater proportion of individuals with HAP had an intraventricular hemorrhage (IVH) and subarachnoid hemorrhage (SAH) compared to no HAP ($p < 0.01$ both comparisons). The mechanism of injury also varied by HAP status ($p < 0.001$), with a greater proportion of patients with HAP suffering MVA.

Table 4. NTDB Demographics and Clinical Variables by HAP Status

Variable	HAP (n=1212)	No HAP (n=2500)	p-value
Age (mean, SE)	38.36 (0.48)	43.45 (0.41)	<0.001*
Sex (men, % [‡])	970 (80.03)	1756 (70.27)	<0.001*
Race (n, % [‡])			0.170
White	851 (70.21)	1678 (67.15)	
Black	209 (17.24)	473 (18.93)	
Other	152 (12.54)	348 (13.93)	
Brain Injury Severity (n, %)			<0.001*
Moderate	77 (6.49)	696 (28.22)	
Severe	1110 (93.51)	1770 (71.78)	
ISS (mean, SE)	28.18 (0.36)	23.22 (0.23)	<0.001*
ISS Non-Head (mean, SE)	11.28 (0.31)	8.49 (0.20)	<0.001*
Thoracic AIS ≥ 3 (n,%)	477 (44.3)	603 (26.93)	<0.001*
Ventilation status (n, % [‡])	795 (65.59)	972 (38.88)	<0.001*
Ventilation days (mean, SE)	10.32 (0.33)	3.21 (0.15)	<0.001*
Cranial surgery status (n, % [‡])	279 (27.30)	551 (25.94)	0.418
Payor status (n, % [‡])			0.517
Government assistance	420 (37.80)	896 (38.96)	
Private pay	691 (62.20)	1404 (61.04)	
Acute care length of stay (mean, SE)	30.27 (0.49)	16.96 (0.27)	<0.001*
Rehabilitation length of stay (mean, SE)	30.44 (0.72)	23.68 (0.47)	<0.001*
Rehabilitation Interruptions (n, % [‡])	77 (6.63)	115 (4.84)	0.027*
CT Injury Type (n, % [‡])			
SDH	663 (55.02)	1296 (52.26)	0.115
EDH	139 (11.54)	311 (12.54)	0.382
IVH	405 (33.61)	651 (26.25)	<0.001*
SAH	860 (71.37)	1661 (66.98)	0.007*
Mechanism of Injury (n, % [‡])			<0.001*
MVA	802 (66.23)	1240 (49.98)	
Assault/Violence	90 (7.43)	270 (10.88)	
Fall	211 (17.42)	697 (28.09)	
Pedestrian	80 (6.61)	172 (6.93)	
Other	28 (2.31)	102 (4.11)	

Abbreviations: GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SDH, Subdural hematoma; EDH, Epidural hematoma; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage

3.4.2 Demographic and Clinical Variables by GOS-E at 1 year

Demographic and clinical variables by unfavorable/favorable 1-year GOS-E status are presented in **Table 5**. There were n=1491 (47.5%) individuals with unfavorable GOS-E scores and n=1651 (52.5%) individuals with favorable GOS-E scores. There were significant differences in GOS-E by race (p<0.001) and payor status (p<0.001). Mechanism of injury was significantly different by GOS-E status (p<0.001). Individuals with unfavorable GOS-E scores were older, more often on a ventilator, had more ventilator days, longer acute care and rehabilitation LOS, and a greater proportion of rehabilitation interruptions compared to individuals with favorable GOS-E scores (p<0.001 all comparisons). Individuals with unfavorable outcomes more often experienced SDH, IVH, and SAH injuries (p<0.01 all comparisons).

Table 5. NTDB Demographic and Clinical Variables by GOS-E Status at 1 Year

Variable	Unfavorable GOS-E (n=1491)	Favorable GOS-E (n=1651)	p-value
Age (mean, SE)	44.10 (0.50)	39.74 (0.48)	<0.001*
Sex (men, % [¥])	1099 (73.71)	1213 (73.47)	0.880
Race (n, % [¥])			<0.001*
White	953 (63.92)	1232 (74.62)	
Black	344 (23.07)	221 (13.39)	
Other	194 (13.01)	198 (11.99)	
Brain Injury Severity (n, %)			<0.001*
Moderate	245 (16.91)	392 (23.80)	
Severe	1204 (83.09)	1255 (76.20)	
ISS (mean, SE)	25.37 (0.32)	24.75 (0.29)	0.182
ISS Non-Head (mean, SE)	9.51 (0.27)	9.62 (0.26)	0.675
Thoracic AIS ≥ 3 (n,%)	422 (31.24)	498 (33.56)	0.187
Ventilation status (n, % [¥])	773 (51.84)	744 (45.06)	<0.001*
Ventilation days (mean, SE)	7.04 (0.27)	4.30 (0.21)	<0.001*
Cranial surgery status (n, % [¥])	411 (32.01)	334 (22.58)	<0.001*
Payor status (n, % [¥])			<0.001*
Government assistance	662 (48.53)	437 (28.41)	
Private pay	702 (51.47)	1101 (71.59)	
Acute care length of stay (mean, SE)	25.76 (0.46)	17.48 (0.30)	<0.001*

Rehabilitation length of stay (mean, SE)	32.12 (0.77)	20.40 (0.37)	<0.001*
Rehabilitation Interruptions (n, % [‡])	117 (8.36)	48 (3.02)	<0.001*
CT Injury Type (n, % [‡])			
SDH	858 (58.13)	834 (50.73)	<0.001*
EDH	180 (12.20)	208 (12.65)	0.699
IVH	504 (34.15)	434 (26.40)	<0.001*
SAH	1057 (71.61)	1104 (67.15)	0.007*
Mechanism of Injury (n, % [‡])			<0.001*
MVA	790 (53.27)	953 (58.00)	
Assault/Violence	176 (6.76)	111 (6.76)	
Fall	389 (26.23)	398 (24.22)	
Pedestrian	94 (5.72)	94 (5.72)	
Other	87 (5.30)	87 (5.30)	

Abbreviations: GCS, Glasgow Coma Scale; ISS, Injury Severity Score; CT, Computed Tomography; SDH, Subdural hematoma; EDH, Epidural hematoma; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage

3.4.3 Primary analysis: GEE Model of GOS-E at 1, 2, and 5 years after TBI using NTDB probabilistic cohort

The GEE models for the GOS-E primary analysis are provided in **Table 6**. In the unadjusted model, individuals with HAP had a 28% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.28, 95% CI (1.14, 1.45), $p<0.001$). After adjustment for age only, individuals with HAP had a 48% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.48, 95% CI (1.29, 1.69), $p<0.001$). After adding race, individuals with HAP had a 51% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.51, 95% CI (1.32, 1.73), $p<0.001$). In the fully adjusted model, individuals with HAP had a 34% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.34, 95% CI (1.15, 1.56), $p<0.001$).

Table 6. Probabilistic Cohort GEE Regression Model for Repeated Measures GOS-E at 1, 2, and 5 years

	Model 1 [£]		Model 2 [§]		Model 3 [¥]		Model 4 [€]	
	Odds ratio (95% CI)	p-value						
HAP		<0.001*		<0.001*		<0.001*		<0.001*
No (reference)	(reference)		(reference)		(reference)		(reference)	
Yes	1.28 (1.14, 1.45)		1.48 (1.29, 1.69)		1.51 (1.32, 1.73)		1.34 (1.15, 1.56)	

*: statistically significant at p<0.05

£: Model 1: Unadjusted

§: Model 2: Adjusted for Age only

¥: Model 3: Adjusted for Demographic Variables: Age and Race

€ Model 4: Adjusted Demographic and Clinical Variables: Age, Race, ventilation status, brain injury severity, ISS, Thoracic AIS ≥ 3 , mechanism of injury, intraventricular hemorrhage status, subarachnoid hemorrhage status

3.4.4 Sensitivity analysis: GEE Model of GOS-E at 1, 2, and 5 years after TBI using

Deterministic Cohort

Using only the deterministic cohort, the unadjusted analysis showed individuals with HAP were at a 44% increased odds for unfavorable GOS-E scores compared to individuals without HAP (OR=1.44, 95% CI (1.05, 1.98), p=0.022) (**Table 7**). After adjusting for only age, individuals with HAP had a 69% increased odds for unfavorable GOS-E compared to individuals without HAP (OR=1.69, 95% CI (1.22, 1.34), p=0.002). After adding race, individuals with HAP had a 72% increased odds for unfavorable GOS-E compared to no HAP (OR=1.72, 95% CI (1.23, 2.39), p=0.001). In the full adjusted model, individuals with HAP had a 63% increased odds for unfavorable GOS-E compared with individuals without HAP (OR=1.63, 95% CI (1.16, 2.30), p=0.005).

Table 7. Deterministic Cohort GEE Regression Model for Repeated Measures GOS-E at 1, 2, and 5 years

	Model 1[£]		Model 2[§]		Model 3[¥]		Model 4[€]	
	Odds ratio (95% CI)	p-value						
HAP		0.022*		0.002*		0.001*		0.005*
No (reference)	(reference)		(reference)		(reference)		(reference)	
Yes	1.44 (1.05, 1.98)		1.69 (1.22, 1.34)		1.72 (1.23, 2.39)		1.63 (1.16, 2.30)	

*: statistically significant at p<0.05

£: Model 1: Unadjusted

§: Model 2: Adjusted for Age only

¥: Model 3: Adjusted for Demographic Variables: Age and Race

€ Model 4: Adjusted Demographic and Clinical Variables: Age, Race, ventilation status, brain injury severity, ISS, Thoracic AIS ≥ 3 , mechanism of injury, intraventricular hemorrhage status, subarachnoid hemorrhage status

3.4.5 Secondary analysis: Hospital utilization variables by HAP Status

After covariate adjustment, individuals with HAP, compared to no HAP, had on average 10.1 more days in acute care LOS and 4.8 more days in rehabilitation LOS (p<0.001 both comparisons). The unadjusted FIM efficiency for individuals with HAP was 2.02 compared to 2.31 for individuals without HAP. After adjustment for covariates, individuals with HAP had 0.29 reduced FIM efficiency during rehabilitation compared to no HAP (p<0.001).

3.5 DISCUSSION

Our findings highlight HAP as a meaningful early modifiable risk factor that impacts TBI recovery and hospital resource utilization. We observed a HAP incidence rate of 32.7%, which is similar to past estimates.¹¹⁴ The present study provides evidence that the effects of acute HAP extend beyond the infection period itself and may persist for years after injury, perhaps through

the propagation of chronic inflammatory milieu⁸⁶ and decreased or delayed rehabilitation participation. In addition to poorer long-term prognosis, individuals with HAP also had longer average hospital stays and tended to have decreased efficiency in attaining functional rehabilitation gains compared to their counterparts without HAP. Focused and concerted efforts should be made to prevent HAP in this susceptible population.

In this study, we examined the effects of HAP on long-term outcomes among patients with TBI who survived initial injury and received inpatient rehabilitation. Recent work by Esnault and colleagues¹¹³ examined the effects of early-onset VAP among 175 individuals with severe TBI and observed an elevated odds (OR=2.71, 95% CI: 1.01-7.25) for more unfavorable GOS scores at 1-year. Similarly, a small pilot study (n=141) led by our research group¹¹⁴ used a similar design as the present study. To avoid any duplicity in reporting, no individuals in our prior study were included in our present analysis. We previously showed HAP carried a 4.6 times (95% CI: 1.80-11.60) increased odds for unfavorable outcomes in a longitudinal model.¹¹⁴ The small sample size and single-site design by Esnault et al.¹¹³ and Kesinger et al.¹¹⁴ likely account for the inflated effect sizes and wide confidence intervals compared to the present larger study where we observed a 34% increased odds of unfavorable GOS-E from HAP in the fully adjusted model.

In another previous descriptive epidemiological study, Zygun and colleagues¹¹² showed an incidence rate of VAP of 45% among 134 individuals with severe TBI, which the authors report is nearly three times the rate reported for all general trauma patients, according to the National Nosocomial Infections Surveillance program report.¹⁴⁹ This observation provides evidence that individuals with severe TBI are particularly vulnerable to hospital infections. Some individuals with TBI experience a period of lymphopenia beginning early after injury.¹³⁷

Persistent lymphopenia reflects suppressed adaptive immunity and a decreased capacity to fight pathogen exposure. Lymphopenia has been documented in trauma populations,¹⁰³⁻¹⁰⁷ in addition to preliminary observations of lymphopenia in TBI.¹³⁷ Clinical and injury factors, such as prolonged mechanical ventilation and concurrent thoracic injuries, are also risk factors for HAP. More severely injured patients are at a greater risk for developing HAP and poorer outcomes; however, our results show the harmful effects of HAP are independent of injury severity.

In our present cohort, we observed a modest negative confounding of the effect of HAP on outcome driven by age. We observed younger age is associated with a greater incidence of HAP, but is protective against unfavorable outcomes after TBI. Though this association may seem counterintuitive, it has been previously documented in the TBIMS National Database⁶ and makes sense given the mechanism of injuries experienced by older vs. younger individuals. Older individuals more often sustain less severe isolated brain injuries from falls; whereas, younger individuals are more likely to suffer more severe injuries and polytrauma. These findings highlight that HAP prevention efforts should be directed across the age span, particularly among younger ages, as HAP is both more common at younger ages and a large proportion of individuals with unfavorable outcomes had HAP.

Incidence of HAP after TBI also has significant implications for hospital resource utilization. Our results showed that individuals with HAP had longer acute and rehabilitation lengths of stay compared to individuals without HAP. We also determined that individuals with HAP were more likely to have rehabilitation interruption and had decreased FIM efficiency by 0.29. In other words, patients with HAP required roughly 30% additional days in rehabilitation to achieve similar functional gains as patients without HAP. Preventing HAP in TBI populations may yield substantial cost-related benefits.¹⁰⁸

This study highlights the importance of infection prophylaxis in TBI populations; HAP is both extremely common and often preventable. Given the high morbidity and mortality associated with TBI across the lifespan, the importance of modifiable factors that can result in improved outcomes cannot be underemphasized. The recent 2016 4th edition Guidelines for the Management of Severe Traumatic Brain Injury¹⁶ recommends Level IIA evidence for early tracheostomy as a method for infection prophylaxis. Others have also suggested early extubation is important.¹⁵⁰ A potentially cost-effective intervention is early mobility protocols during acute care, for those who are able, which has been shown to be efficacious in reducing incidence of HAP in neurointensive care unit patients.¹⁵¹ Another study in an acute stroke population found that early screening and treatment of dysphagia was associated with a decreased rate of HAP.¹⁵² A systematic review of 28 trials of intensive care and nursing home patients also found chlorhexidine oral disinfectants were effective for HAP prophylaxis.¹⁵³ Future studies in TBI would benefit from conducting trials for HAP prevention.

There are limitations of this work that warrant consideration. We assessed HAP instead of VAP because there was no clear information on time until infection in the NTDB. Despite this, our results indicate that the deleterious effects of HAP exist independent of ventilation status. Furthermore, NTDB complication codes are subject to underreporting,¹⁵⁴ which could result in an underestimation of HAP incidence and bias the effect towards the null. It is a reasonable assumption that misclassification of HAP in the NTDB is non-differential to the outcome, as the outcome was gathered from the TBIMS National Database. The primary analysis was conducted using a probabilistically-matched cohort; therefore, it is possible that a small percentage of the pairs were incorrectly matched. However, based on our previous algorithm development¹⁴² and validation¹⁴³ studies, we have empirical evidence to suggest that mismatched

pairs were likely very rare (<2%). Also, the converging results in our sensitivity analysis from a deterministic dataset support the observation of the harmful effects of HAP on outcomes after TBI found in the primary analysis. In our secondary analysis, the data we present is a proxy for hospital resource utilization; however, we do not have available claims or cost data that may be a truer measure of utilization.

We demonstrate that HAP increases odds for unfavorable outcomes by 34% up to five years after TBI. This study provides a meaningful contribution to the field by highlighting the deleterious long-term effects of acute care HAP in a large sample of individuals with TBI. The work supports the need for future studies to expand research on infection prophylaxis during acute hospitalization. TBI populations are particularly vulnerable to incident HAP, and concerted efforts are needed to prevent primary infections to improve long-term recovery.

4.0 AIM 3: RELATIONSHIP BETWEEN ACUTE SERUM ESTRADIOL AND TUMOR NECROSIS FACTOR-ALPHA AND RISK FOR MORTALITY AFTER SEVERE TRAUMATIC BRAIN INJURY

4.1 ABSTRACT

Individuals with severe Traumatic Brain Injury (TBI) are at risk for systemic compromise and acute mortality. Tumor necrosis factor-alpha (TNF α) is a major mediator of systemic shock and is an extra-gonadal transcription factor for estradiol (E2) production, a documented prognostic marker of mortality in TBI populations. Our study objectives are to test the hypotheses: 1) of a positive feedback relationship over time between acute serum TNF α and E2; and 2) acute concentrations of E2 and TNF α are prognostic indicators of mortality after severe TBI. This prospective cohort study included N=157 adults with severe TBI. Serum samples were collected from participants for the first five days post-injury. TNF α and E2 levels were averaged into two time epochs: first 72 hours (T1) and second 72 hours post-injury (T2). A cross-lag panel analysis conducted between T1 and T2 TNF α and E2 levels showed significant cross-lag effects: T1 TNF α was related to T2 E2, and T1 E2 was related to T2 TNF α , independent of confounders and autoregressive effects. Cox proportional hazards regression models determined that increases in T1 E2 (HR=1.82, 95% CI: 1.14, 2.89), but not T2 E2 (HR=0.91, 95% CI: 0.56, 1.47), were associated with increased risk for mortality. Increases in T2 TNF α (HR=2.55, 95% CI: 1.40,

4.64), and T1 TNF α (HR=1.46, 95% CI: 0.99, 2.17) to a lesser degree, were associated with increased mortality risk. E2 and TNF α are two systemic biomarkers that are interrelated and may be indicative of systemic compromise and increased mortality risk after severe TBI.

4.2 INTRODUCTION

Severe Traumatic Brain Injury (TBI) constitutes a major public health and economic burden in the world. Individuals with severe TBI have an increased risk for premature mortality¹⁵⁵⁻¹⁵⁷ and survivors often live with chronic injury-related disabilities.¹²⁶ The financial burden of TBI in the United States is estimated at over \$60 billion per year.¹⁵⁸ There have been tremendous efforts over the last several decades to identify acute treatments for TBI populations. Despite some progress in clinical care, mortality rates for severe TBI are largely unchanged over the last decade.^{159,160} There are also still no treatments that received a Level I recommendation for efficacy in the recent 4th edition TBI Guidelines,¹⁶ and no treatments have been approved by the Food and Drug Administration following Phase III trials.

Several large clinical trials in TBI populations have examined the efficacy of pharmacological dosing of agents including corticosteroids and progesterone, which target inflammation^{161,162} and hormone physiology,^{163,164} respectively. However, these trials¹⁶¹⁻¹⁶⁴ largely were ineffective or were halted prematurely because of observed harm in the treatment arm. Unsuccessful findings from clinical trials come despite pre-clinical TBI studies that have shown the efficacy of exogenous progesterone^{165,166} and anti-inflammatory therapies as neuroprotective agents.¹⁶⁷⁻¹⁶⁹ Data from observational cohort studies, however, have revealed the deleterious effects of excessive peripheral hormones⁹⁶ and acute inflammation.^{74,75,170}

Interestingly, observational studies have suggested that immune and endocrine networks are highly interconnected in the brain, and the regulatory connection between the two systems is associated with recovery following severe TBI.⁶⁵ Though less is understood about endocrine-immune cross-talk in the context of the systemic response to TBI and its associated trauma complex. The failure of prior TBI clinical trials now invites further study within an intriguing line of research regarding hormone and inflammatory physiology after TBI; studies are warranted to understand the inter-connectedness between peripheral immune and endocrine networks.

Tumor necrosis factor-alpha (TNF α) and Estradiol (E2) are inflammatory and endocrine markers, respectively, that are elevated acutely in serum after severe TBI¹⁷¹⁻¹⁷³ and associated with morbidity⁷⁸ and mortality.^{96,174} These markers are important in the context of post-TBI homeostatic disturbance. After TBI, the hypothalamic-pituitary-gonadotrophic (HPG) axis is often dysfunctional, which leads to abnormal sex hormone products, including E2. The autonomic nervous system (ANS) is triggered in the trauma response, which drives the sympathetic nervous system (SNS) to initiate an acute phase response that leads to peripheral TNF α production.¹⁷⁵⁻¹⁷⁷ TNF α is the body's major mediator of septic shock and secondary systemic inflammatory response syndrome.¹⁷⁸ In the context of injury or critical illness, regulated release of TNF α is physiologically normal for healing; however, uncontrolled TNF α production may mediate a progression of systemic shock, organ dysfunction and death.⁹⁰

Observed elevations in TNF α and E2 in the setting of TBI are likely not independent. E2 is produced by the conversion of androgens via the aromatase gene,¹⁷⁹ and TNF α serves as a tissue-specific transcription factor for E2 synthesis in adipose tissue.^{93,118-120,180,181} Increasing E2 production acutely has a positive feedback that contributes to exaggerated levels of inflammation

through reuptake inhibition of norepinephrine in lymphoid tissues.^{87,121} This theoretical positive-feedback relationship is suggestive that excessive E2 in the periphery are both a cause and byproduct of excessive peripheral TNF α ; though, this hypothesis has not been tested.

A positive feedback loop between the TNF α and E2 could account in some part for the observed increased risk for mortality seen among individuals with elevations in concentrations of these markers. The concept of immune-endocrine associations of these two peripheral markers has not been empirically tested in clinical TBI studies to date. The primary objective of the present study is to test the hypothesis of a positive feedback relationship between serum TNF α and E2 over time in the acute period following severe TBI using a cross-lag panel model. The secondary objective tests the prognostic effects of acute serum TNF α and E2 levels on mortality risk in the first six months after severe TBI. Understanding the evolving relationships between acute serum TNF α and E2 will provide evidence of connections between inflammatory and endocrine markers that are relevant to survival after severe TBI. Identifying the prognostic capacity of these biomarkers for mortality risk has important implications to identify at-risk persons with TBI.

4.3 METHODS AND MATERIALS

This study was approved by the Institutional Review Board for the University of Pittsburgh. The present report is a prospective observational cohort study that includes n=157 adults with severe TBI. Eligible participants were between 16-70 years old, had an initial Glasgow Coma Scale (GCS) score of 8 or less, and had pathology present on a computed tomography (CT) scan. Patients with TBI were excluded if they had a history of cancer or

untreated thyroid disease. Next of kin were approached for consent in instances where the patient was unable to self-consent. Patients with TBI received care aligned with the TBI Guidelines for the Management of Severe Head Injury,¹⁶ which included placement of an extra-ventricular device for intracranial pressure monitoring, central venous catheter, arterial catheter, and neurosurgical intervention for the decompression of mass lesions.

4.3.1 Serum Sample Processing

Eligible and consented participants received a blood draw daily for the first six days following injury. Blood draws were obtained at 7:00 AM on most mornings, unless there was a direct conflict with clinical care. In instances where it was not possible to gather a morning blood draw, a sample was gathered at 7:00 PM. For some participants, it was not possible to receive a blood sample each day. After collection of the serum, samples were centrifuged and aliquoted, and stored at -80°C until the assaying. The serum samples were assayed for E2 using radioimmunoassay with Coat-A-Count® In-vitro Diagnostic Test Kit. E2 was measured using a ¹²⁵I radioimmunoassay using 100µL sample aliquots. Serum sample measurements for TNFα were completed using a Luminex™ bead array assay (Millipore, Billerica, Massachusetts; catalog number was HSCYTO-60SK). The minimum detectable limit for TNFα was 0.05 pg/mL. TNFα were scaled utilizing concentration standards and quality controls prior to the analysis due to observed variability across plates. The inter-assay and intra-assay coefficients of variation (CV) was <10% for both the hormone and inflammatory assays.

4.3.2 E2 and TNF α Classification: Early and Delayed Response

E2 and TNF α were grouped into two epochs: time 1 (T1) and time 2 (T2). T1 consisted of data averaged over the first 72-hours after injury, and T2 consisted of data averaged over the second 72-hours after injury. Because individuals had missing values at various time points in the first week due to conflicts with regular clinical care it was not possible to do analysis by daily levels.

4.3.3 Aromatase genetics: rs2470152

DNA was extracted from participants' whole-blood samples before transfusion. Blood samples were drawn into ethylenediamine tetra acetic acid vacutainer tubes, and immediately centrifuged to retrieve the buffy coat. The DNA was extracted using a salting out procedure.¹⁸² The single nucleotide polymorphism (SNP) rs2470152 was genotyped as part of a larger genomic analysis of the aromatase gene (CYP19A1) that included four functional SNPs and 18 tagging SNPs. A primary article examining the effects of aromatase genetics on TBI outcomes was previously published, and determined significant association between genetics and levels and global TBI outcomes.¹⁸³

4.3.4 Clinical and Demographic Variables

Clinical and demographic variables collected in this study included: age, sex, race, best in 24-hour Glasgow Coma Scale (GCS) score, injury severity scale (ISS) score, non-head ISS score, mechanism of injury, and injury type on a computed tomography (CT) scan. The GCS is a

physiological measure of TBI injury severity, made up of the following three components: motor responsiveness, verbal performance, and eye opening.¹²⁷ The scores range from 3-15, with lower scores corresponding to more severe injuries. The best GCS score in the first 24 hours was utilized for analysis purposes to adjust in part for issues with an initial GCS value being confounded by paralytics and sedatives. The ISS is an anatomical trauma scoring scale that is a function of the three most severely injured body systems from the Abbreviated Injury Scale (AIS).¹⁸⁴ A non-head ISS was re-calculated after removing the head body region. Presence of abdominal and thoracic injuries were derived from AIS region scores ≥ 1 for the respective regions. Presence of splenic injury was derived using International Classification of Disease Injury codes version 9 (ICD-9) code “865.” CT injury types included the subdural hematoma (SDH), subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), epidural hematoma (EDH), diffuse axonal injury (DAI), contusion, or other.

4.3.5 Primary Outcome: Mortality

The primary outcome for this study was time until death. When applicable, this data was extracted from the Social Security Death Index (SSDI). The date of incident TBI was subtracted from the death date to calculate the time until death in days. The data was right censored at 6 months post-injury.

4.3.6 Statistical Analysis

Demographic and clinical variables were examined by E2 and TNF α at T1 and T2, divided at the median, as well as by 6-month mortality status. Categorical variables were

examined using a chi-square test, and continuous variables were examined using a two-sample t-test or a Mann Whitney-U test, where appropriate. Biomarkers were treated continuously for the primary analysis but were divided at the median only for the purposes of grouped comparisons by demographic and clinical variables. Distributions were monitored for E2 and TNF α , and natural log transformations were made, if deemed appropriate.

The primary objective of this study is to assess evidence of a cross-lag effect between TNF α and E2. The purpose of a cross-lagged panel analysis is to determine the relationship between n repeatedly measured variables over time.¹⁸⁵ The cross-lagged panel model in this study assessed the inter-relationships between E2 and TNF α at T1 and T2 in the first week after TBI. The cross-lagged panel models for E2 and TNF α at T2 can be described using two equations:

$$E2_2 = \beta_1 * E2_1 + \beta_2 * TNF\alpha_1 + \beta_n C_n$$

$$TNF\alpha_2 = \beta_3 * TNF\alpha_1 + \beta_4 * E2_1 + \beta_n C_n$$

In these models, the subscripts 1 and 2 represent two time intervals, and C represents a matrix of relevant confounders. The corresponding beta coefficients ($\beta_1 - \beta_4$) represent the different paths in the cross-lag panel, as shown conceptually in **Figure 7**.

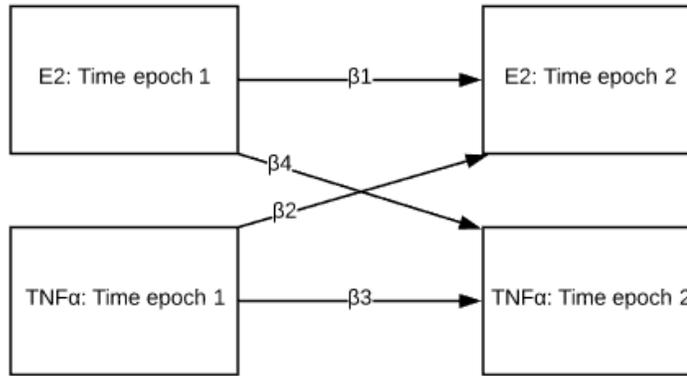


Figure 7. Conceptual Cross-Lab Panel

In this panel, β_1 and β_3 represent the effect of a variable on itself at a later time epoch, known as autoregressive effects. The autoregressive effects represent the stability of individual differences in a variable over time.¹⁸⁶ The coefficients β_2 and β_4 represent the cross-lag effects, or the relationship between a single variable at one time epoch on another variable at a later time.¹⁸⁶ Crucially, cross-lag effects are estimated adjusting for the prior level of the variable itself. That is, the association between TNF α at T1 on E2 at T2, is independent of the effects of E2 at T1. The cross-lag also adjusts for the residual covariance of E2 and TNF α at the same cross-sectional time point.

Our secondary objective was to determine the association between T1 and T2 E2 and TNF α on mortality risk in the first six months post-TBI. Time until death was right censored at six months post-TBI. Cox proportional hazards regression models were fitted for T1 and T2 biomarkers. Variables associated at a $p < 0.20$ threshold with E2 or TNF, and 6-month mortality were included as covariates in the cross-lag panel and Cox Proportional Hazards Regression Model. The list of covariates included: age, GCS, contusion, DAI, SDH, and rs2470152. To observe the effects of the covariates on the effect size of E2 and TNF α , a series of four models are presented: Model 1 (unadjusted), Model 2 (adjusts for age only), Model 3 (adjusts for age, GCS, CT abnormalities: contusion, SDH, and DAI), and Model 4 (adjusts for age, GCS, CT

abnormalities: contusion, SDH, and DAI, and rs2470152). A sex interaction with E2 at T1 and T2 was also forced in the full adjusted model in order to test whether there are differences in the relationship between E2 and mortality by sex. The Harrell's Concordance Statistic, a measure for model fit for Cox Regression,¹⁸⁷ was reported for all models. Statistical analyses were performed using Stata 15¹⁸⁸ and SAS 9.4.¹⁴⁸

4.4 RESULTS

4.4.1 Demographic and Clinical Variables by E2 and TNF α

Clinical and demographic variables were compared by T1 and T2 E2 (**Table 8**) and T1 and T2 TNF α (**Table 9**) divided at the median. Median E2 at T1 was 60.0 pg/mL and 35.6 pg/mL at T2. Median TNF α at T1 was 7.7 pg/mL and 8.5 pg/mL at T2. Older age was significantly associated with a higher T2 E2 ($p=0.023$). Individuals with higher TNF α at T1 tended to have greater ISS ($p=0.069$) and non-head ISS scores ($p=0.006$). Individuals with thoracic injuries had significantly higher E2 at both time points ($p<0.05$). Individuals with splenic injuries tended to have higher E2 at T1 ($p=0.060$), and individuals with abdominal injuries had significant higher TNF α at T1 ($p=0.035$). Participants with a contusion were more likely to have higher E2 at both time points ($p<0.05$). Finally, rs2470152 was associated with higher E2 at T1 ($p=0.028$) and T2 ($p=0.053$). Specially, participants with a TC genotype were more often in the high E2 category, compared to TT or CC homozygotes.

Table 8. Demographic and Clinical Variables by T1 and T2 E2

Variables	T1		p-value	T2		p-value
	E2 Above Median (n=75)	E2 Below Median (n=74)		E2 Above Median (n=61)	E2 Below Median (n=62)	
Age (Mean, SE)	41.71 (2.06)	36.40 (1.69)	0.119	41.54 (2.16)	34.95 (1.99)	0.023*
Sex (men, %)	57 (79.17)	58 (81.69)	0.704	47 (77.05)	50 (80.65)	0.625
Race, (n, %)			0.982			0.299
White	68 (93.15)	69 (93.24)		58 (95.08)	55 (90.16)	
Black	5 (6.85)	5 (6.76)		3 (4.92)	6 (9.84)	
Best in 24 hour GCS (Median, IQR)	7 (6-7)	7 (6-8)	0.105	7 (5-8)	7 (6-8)	0.438
ISS (Mean, SE)	34.81 (1.23)	32.55 (1.18)	0.255	35.39 (1.31)	33.02 (1.35)	0.184
Non-head ISS (Mean, SE)	13.98 (1.35)	12.29 (1.29)	0.266	14.62 (1.45)	11.73 (1.30)	0.134
Length of Hospital Stay (Mean, SE)	18.79 (1.53)	21.77 (1.48)	0.106	19.62 (1.57)	24.42 (1.72)	0.069
Mechanism of Injury, (n, %)			0.827			0.443
MVA						
Motorcycle	32 (46.38)	37 (50.00)		26 (44.07)	31 (52.54)	
Fall	15 (21.74)	14 (18.92)		16 (27.12)	9 (15.25)	
Other	15 (21.74)	13 (17.57)		11 (18.64)	11 (18.64)	
	7 (10.14)	10 (13.51)		6 (10.17)	8 (13.56)	
CT injury type, (n, %)						
SDH	48 (64.86)	49 (66.22)	0.863	39 (62.90)	38 (62.30)	0.944
SAH	54 (72.97)	46 (62.16)	0.160	48 (78.69)	39 (62.90)	0.054
IVH	17 (22.97)	24 (32.43)	0.199	15 (24.59)	21 (33.87)	0.258
EDH	11 (14.86)	8 (10.81)	0.461	8 (13.11)	7 (11.29)	0.757
DAI	17 (22.97)	26 (35.14)	0.103	15 (24.59)	23 (37.10)	0.133
Contusion	35 (47.30)	23 (31.08)	0.043*	32 (52.46)	20 (32.26)	0.023*
Splenic injury, (n, %)	11 (14.67)	4 (5.41)	0.060	9 (14.75)	5 (8.06)	0.243
Abdominal injury, (n, %)	22 (34.92)	28 (40.00)	0.546	23 (41.82)	20 (35.71)	0.509
Thoracic injury, (n, %)	25 (39.68)	13 (18.57)	0.007*	25 (45.45)	10 (17.86)	0.002*
RS2470152 genotype, (n, %)			0.028*			0.053
CC	11 (18.33)	22 (37.29)		13 (25.00)	12 (25.00)	
TC	36 (60.00)	22 (37.29)		30 (57.69)	18 (37.50)	
TT	13 (21.67)	15 (25.42)		9 (17.31)	18 (37.50)	

Table 9. Demographic and Clinical Variables by T1 and T2 TNF α

Variables	T1		p-value	T2		p-value
	TNF α Above Median (n=72)	TNF α Below Median (n=71)		TNF α Above Median (n=62)	TNF α Below Median (n=62)	
Age (Mean, SE)	41.92 (2.08)	36.77 (1.81)	0.099	38.23 (2.00)	36.98 (2.05)	0.631
Sex (men, %)	57 (79.17)	58 (81.69)	0.704	50 (80.65)	50 (80.65)	0.999
Race, (n, %)			0.074			0.079
White	70 (97.22)	63 (90.00)		60 (96.77)	54 (88.52)	
Black	2 (2.78)	7 (10.00)		2 (3.23)	7 (11.48)	
Best in 24 hour GCS (Median, IQR)	7 (5-8)	7 (6-8)	0.149	7 (6-8)	7 (6-8)	0.483
ISS (Mean, SE)	35.42 (1.18)	31.65 (1.27)	0.069	34.73 (1.43)	33.25 (1.25)	0.639
Non-head ISS (Mean, SE)	15.48 (1.39)	10.60 (1.26)	0.006*	14.16 (1.50)	11.27 (1.30)	0.181
Length of Hospital Stay (Mean, SE)	19.36 (1.52)	20.71 (1.55)	0.460	21.55 (1.74)	21.42 (1.58)	0.828
Mechanism of Injury, (n, %)			0.878			0.827
MVA	29 (42.65)	34 (48.57)		29 (49.15)	28 (27.46)	
Motorcycle	16 (23.53)	13 (18.57)		13 (22.03)	13 (22.03)	
Fall	15 (22.06)	15 (21.43)		12 (20.34)	10 (16.95)	
Other	8 (11.76)	8 (11.43)		5 (8.47)	8 (13.56)	
CT injury type, (n, %)						
SDH	45 (63.38)	50 (70.42)	0.373	43 (69.35)	34 (54.84)	0.096
SAH	53 (74.65)	45 (63.38)	0.147	49 (79.03)	38 (61.29)	0.031
IVH	18 (25.35)	21 (29.58)	0.573	21 (33.87)	15 (24.19)	0.235
EDH	11 (15.49)	7 (9.86)	0.313	6 (9.68)	8 (12.90)	0.570
DAI	20 (28.17)	19 (26.76)	0.851	15 (24.19)	25 (40.32)	0.055
Contusion	31 (43.66)	27 (38.03)	0.495	30 (48.39)	21 (33.87)	0.100
Splenic injury, (n, %)	8 (11.11)	5 (7.04)	0.397	8 (12.90)	4 (6.45)	0.224
Abdominal injury, (n, %)	28 (45.16)	18 (27.27)	0.035*	24 (42.11)	18 (33.96)	0.380
Thoracic injury, (n, %)	22 (35.48)	15 (22.73)	0.112	22 (38.60)	11 (20.75)	0.041*

4.4.2 Demographic and Clinical Variables by Mortality Status

The clinical and demographic variables by 6-month mortality status are provided in **Table 10**. The average age for non-survivors was significantly higher than survivors ($p < 0.001$). Non-survivors had lower GCS scores compared to survivors ($p = 0.028$). There also was a significant difference between survivors and non-survivors with respect to mechanism of injury ($p < 0.001$). Individuals with contusion ($p = 0.007$) and SDH ($p = 0.092$) were more likely non-survivors, and individuals with DAI were more likely survivors ($p = 0.004$). There was a trend between rs2470152 genotype and mortality status ($p = 0.099$), with individuals with TC genotype more often non-survivors.

Table 10. Demographic and Clinical Variables by Mortality Status

Variable	Non-Survivors (n=48)	Survivors (n=109)	p-value
Age (Mean, SE)	51.08 (2.29)	33.54 (1.35)	<0.001
Sex (men, %)	35 (72.92)	92 (84.40)	0.092
Race, (n, %)			0.607
White	45 (95.74)	99 (91.67)	
Black	2 (4.26)	8 (7.41)	
Other	0 (0)	1 (0.93)	
Best in 24 hour GCS (Median, IQR)	6 (5-7)	7 (6-8)	0.028
ISS (Mean, SE)	33.90 (1.48)	33.78 (1.00)	0.655
Non-head ISS (Mean, SE)	14.30 (1.79)	12.89 (1.06)	0.558
Length of Hospital Stay (Mean, SE)	12.53 (1.34)	23.89 (1.23)	<0.001
Mechanism of Injury, (n, %)			<0.001
MVA	16 (35.56)	56 (53.33)	
Motorcycle	8 (17.78)	23 (21.90)	
Fall	18 (40.00)	12 (11.43)	
Other	3 (6.67)	14 (13.33)	
CT injury type, (n, %)			
SDH	36 (75.00)	66 (61.11)	0.092
SAH	35 (72.92)	71 (65.71)	0.375
IVH	12 (25.00)	30 (27.78)	0.718
EDH	9 (18.75)	13 (12.04)	0.266
DAI	6 (12.50)	38 (35.19)	0.004
Contusion	27 (56.25)	36 (33.33)	0.007
Other	4 (8.33)	5 (4.63)	0.360
Splenic injury, (n, %)	4 (8.33)	11 (10.09)	0.730
Abdominal injury, (n, %)	15 (36.59)	38 (39.18)	0.775

Table 10 Continued			
Thoracic injury, (n, %)	10 (24.39)	30 (30.93)	0.439
RS2470152 genotype, (n, %)			0.099
CC	5 (13.89)	25 (28.74)	
TC	22 (61.11)	36 (41.38)	
TT	9 (25.00)	26 (29.89)	

4.4.3 Cross-lagged Panel Model

E2 and TNF α were log transformed at T1 and T2 to account for right skewedness. The cross-lagged panel is provided in **Figure 8**, focusing on primary paths between E2 and TNF α at T1 to T2. Paths between fixed effects confounders and E2 and TNF α (not shown in **Figure 8**) at T1 were as follows: older age was not associated with higher E2 at T1 ($p=0.598$), but was significantly associated with higher E2 at T2 ($\beta=0.010$, $p=0.046$). Though not meeting a statistical threshold, age tended to be associated TNF α at T1 ($\beta=0.009$, $p=0.078$), but not TNF α at T2 ($p=0.936$). GCS was significantly associated with E2 at T1 ($\beta=-0.093$, $p=0.036$), but not at T2 ($p=0.304$). GCS was marginally associated, but not statistically significant, with TNF α at T1 ($\beta=-0.064$, $p=0.090$), but not at T2 ($p=0.255$). RS2470152 genotype was not associated with E2 at T1 or T2 or TNF α at T1 or T2 (all comparisons $p>0.10$).

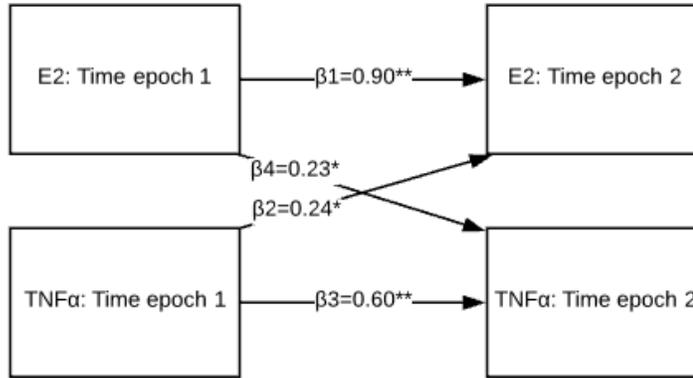


Figure 8. Fitted Cross-Lab Panel

****:**p-value <0.01;
*****: p-value <0.05

The autoregressive path between E2 at T1 and E2 at T2 was statistically significant ($\beta=0.901$, $p<0.001$), after adjustment for covariates. Likewise, the autoregressive path between TNF α at T1 and TNF α at T2 was significant ($\beta=0.602$, $p<0.001$), after adjustment for covariates. The significance of the autoregressive paths indicate stability in E2 and TNF α with time. The cross-lag path between E2 at T1 and TNF α at T2 was statistically significant ($\beta=0.227$, $p=0.002$), as was the path between TNF α at T1 and E2 at T2 ($\beta=0.236$, $p=0.018$). The significance of both cross-lag paths indicate an independent relationship between the two variables over time.

4.4.4 Survival Analysis

The unadjusted and covariate-adjusted Cox proportional hazards model for E2 and TNF α at T1 and T2 is provided in **Tables 4a and 4b**, respectively. At T1, E2 was significantly associated with risk for mortality, such that each unit increase in ln(E2) was associated with an 82% increased risk for mortality, after adjustment for covariates (aHR=1.816, 95% CI: 1.143, 2.885). However, E2 at T2 was not significantly associated with risk for mortality (aHR=0.905,

95% CI: 0.558, 1.470; $p=0.012$). TNF α at T1 was associated, though not statistically significant, with risk for mortality; a unit increase in $\ln(\text{TNF}\alpha)$ was associated with a 46% increased risk for mortality (aHR=1.464, 95% CI: 0.987, 2.171; $p=0.058$). TNF α at T2 was significantly associated with mortality risk, such that one unit increase in $\ln(\text{TNF}\alpha)$ was associated with a 2.5 times increased risk for mortality (aHR=2.545, 95% CI: 1.396, 4.639; $p=0.002$). There was no significant interaction in the effects of E2 by sex at either T1 ($p=0.475$) or T2 ($p=0.870$) (data not shown).

The Harrell's Concordance Statistic for the unadjusted T1 and T2 E2 and TNF α models were 0.707 and 0.696, respectively. Adjusting for age improved model fit to 0.790 and 0.756, respectively. Adding in clinical variables (GCS and CT abnormalities) increased the model fit to 0.836 and 0.801, respectively. The fully adjusted model, adding rs2470152 genotype, had a model fit at T1 and T2 of 0.836, and 0.820, respectively, indicating strong model fit overall.

Table 11. Cox Proportional Hazards Regression of T1 Epoch (1st 72 hours post-injury)

	Model 1[£]		Model 2[§]		Model 3[¥]		Model 4[€]	
	Hazard ratio (95% CI)	p-value						
ln(E2)	1.839 (1.305, 2.590)	<0.001*	1.743 (1.218, 2.495)	0.002*	1.800 (1.152, 2.814)	0.010*	1.816 (1.143, 2.885)	0.012*
ln(TNF α)	1.556 (1.067, 2.270)	0.022*	1.545 (1.033, 2.310)	0.034*	1.438 (0.997, 2.073)	0.052	1.464 (0.987, 2.171)	0.058
Harrell's Concordance Statistic	0.707		0.790		0.836		0.836	

*: statistically significant at p<0.05

£: Model 1: Unadjusted

§: Model 2: Adjusted for Age only

¥: Model 3: Adjusted for Age and Clinical Variables (Glasgow Coma Scale and CT abnormalities: Contusion, Subdural hematoma, Diffuse Axonal Injury)

€: Model 4: Adjusted for Age, Clinical Variables, and rs2470152 genotype

Table 12. Cox Proportional Hazards Regression of T1 Epoch (1st 72 hours post injury)

	Model 1[£]		Model 2[§]		Model 3[¥]		Model 4[€]	
	Hazard ratio (95% CI)	p-value						
ln(E2)	1.356 (0.912, 2.016)	0.133	1.238 (0.836, 1.832)	0.287	1.111 (0.703, 1.756)	0.651	0.905 (0.558, 1.470)	0.687
ln(TNF α)	1.693 (1.026, 2.793)	0.039*	1.705 (1.053, 2.760)	0.030*	2.167 (1.239, 3.789)	0.007*	2.545 (1.396, 4.639)	0.002*
Harrell's Concordance Statistic	0.696		0.756		0.801		0.820	

*: statistically significant at p<0.05

£: Model 1: Unadjusted

§: Model 2: Adjusted for Age only

¥: Model 3: Adjusted for Age and Clinical Variables (Glasgow Coma Scale and CT abnormalities: Contusion, Subdural hematoma, Diffuse Axonal Injury)

€: Model 4: Adjusted for Age, Clinical Variables, and rs2470152 genotype

4.5 DISCUSSION

The physiological response to TBI is widespread and spans neurological and non-neurological systems. Following severe trauma, two of the body's stress regulators, the HPA axis and SNS, are triggered to drive the systemic response to injury. An overactive systemic response to TBI increases the risk for acute mortality, as a majority of deaths from TBI are non-neurological in etiology.^{101,102} Yet, past studies in TBI populations have primarily focused on brain-specific biomarkers. The present study provides evidence that peripheral biomarkers, TNF α and E2, are inter-related and relevant to survival after severe TBI.

It is well-documented that TNF α in the brain is produced from activated microglia, and acts as a mediator of the neuroinflammatory response to TBI.^{79,91,189,190} However, the systemic role of TNF α is more multi-faceted in the context of TBI. In response to trauma, the SNS facilitates an acute phase hepatic response that contributes to an increase in peripheral inflammation.^{176,177,191} Serum E2 is a systemic biomarker that we have previously documented to increase in both sexes after severe TBI.⁹⁶ TNF α in the periphery directly impacts the extragonadal production of E2 by serving as a transcription factor in adipose tissue.^{93,118–120,180,181} Also, peripheral E2 propagates systemic inflammation, including TNF α , by acting as a reuptake inhibitor of norepinephrine in lymphoid tissue that directly causes the SNS response to injury to amplify.^{87,121}

Our findings from this study support our hypothesis that E2 and TNF α are significantly related over time in the first six days following TBI. This finding suggests that peripheral inflammatory and hormone networks are biologically inter-related in the acute phases following

TBI, which likely represents a pathological cascade that is relevant to survival after severe TBI. Our results show that both E2 and TNF α are significant mortality markers in different time epochs in the first five days after severe TBI. In the first 72 hours, E2 is associated with mortality risk, but its levels are not independently associated with mortality risk in second 72 hours after TBI. TNF α , in contrast, is a highly significant mortality marker in the second 72 hours after TBI, and modestly associated with mortality in the first 72 hours.

The results from this study add to the existing body of clinical evidence of the lethal consequences of excessive systemic E2 and TNF α . Two independent studies in populations of intensive care unit patients, observed that elevations in serum TNF α were associated with incident sepsis/septic shock and in-hospital mortality.^{115,192} In a clinical study in a general trauma population, Zolin and colleagues¹²¹ determined that elevations in systemic E2 at 24 hours post-injury were associated with an increased odds for multiple organ failure. Two other studies in populations of surgical and trauma patients, determined that systemic E2 is a strong predictor of mortality from trauma.^{193,194} In TBI, previous studies by Wagner and colleagues have shown that peripheral E2,⁹⁶ along with its precursors E1¹⁹⁵ and Androstenedione,¹⁹⁶ are potent mortality markers. A potential mechanism for observed harmful effects of systemic E2 after trauma could be through its vasodilatory actions, promoting harmful nitric oxide and hydrogen sulfide pathways.⁹⁷⁻¹⁰⁰ Converging evidence from clinical studies across patients with varied etiologies, suggests that the E2 and TNF α response represents broadly the pathophysiological response to severe trauma or critical illness, and correspondingly, elevations in systemic E2 and TNF α concentrations are lethal.

The results of this study are particularly timely in the field considering the recent findings of two large phase III trials for progesterone treatment for TBI population.^{163,164} Crucially,

progesterone is the biological precursor of E2 in the steroidogenesis pathway. Our findings from this study indicate that individuals with higher endogenous E2, and concurrently its extragonadal transcription factor TNF α , are at great risk for mortality after severe TBI. High baseline levels of these two systemic biomarkers may explain, in part, the null findings observed in the progesterone trials; however, this hypothesis needs to be formally tested.^{165,166}

It is important to discuss the tremendous initial promise of Progesterone as a neuroprotectant. It demonstrated appreciable neuroprotective benefits in several experimental TBI studies conducted over multiple decades.^{165,166,197–200} Though, the results did not translate to human TBI. One reason could be that experimental TBI in animals does not exactly mirror what is observed clinically with hospitalized patients with severe TBI. For instance, animals are not comatose, do not require intubation, and are not as prone as humans to systemic or critical illness. Clinical observational studies have documented the high rates of non-neurological deaths in severe TBI populations.^{101,102} It is possible that (for some) the contribution of the acute systemic response to severe trauma is a larger driver of survival than pathophysiological changes in the CNS. We propose that a baseline assessment of an individual's E2 and TNF α , along with clinical and demographic variables like age and GCS, are important to contextualize baseline risk for mortality after severe TBI. This may have specific utility to inform participant inclusion into clinical trials. Individuals with a high baseline risk may not be strong candidates for neuroprotective clinical trials, as they are at high risk for mortality independent of any treatment received. For these individuals, concerted efforts should be focused on preventing or controlling major systemic compromise to prevent mortality. In contrast, individuals with low or moderate baseline risk for mortality due to major systemic compromise would be more appropriate candidates for inclusion into neuroprotective clinical trials.

In this study, we observed extracerebral trauma is a particularly strong risk factor for systemic increases in E2 and TNF α . Individuals with concurrent thoracic, abdominal, and splenic injuries had higher levels on average of E2 and TNF α . It is likely that extracerebral trauma exacerbates the secondary systemic inflammatory response. We also observed that rs2470152 genotype and older age were associated with elevated E2; however, interestingly, we did not see differences in E2 by sex, suggesting the elevations E2 concentrations post-TBI are primarily derived from extra-gonadal sources.

A cross-lag panel analysis was utilized in this manuscript to characterize E2 and TNF α relationships over the first week. Through the simultaneous modeling of autoregressive and cross-lags paths, this statistical methodology allows for the examination of longitudinal relationships of multiple variables. Historically, this method has been principally applied in the developmental and social science literature,^{185,186} however, we argue it has tremendous utility in TBI biomarkers research to aid in the study of relationships between markers across time. Such type of statistical modeling can be used, in conjunction with hypothesized theories and empirical results from experimental studies, to better understand longitudinal patterns and feedback relationships between biomarkers of interest after TBI.

There are study limitations that should be discussed. Our primary analysis consisted of biomarkers averaged over the first 72 hours (T1) and second 72 hours (T2). Because of missing data with conflicts with clinical care, we were unable to have more granularity in our data (e.g. daily levels). In addition, though the cross-lag approach nicely shows the inter-relatedness between E2 and TNF α across T1 and T2, even after the adjustment for confounders, the study design is still a human observational study in an acute hospital setting; so we cannot conclude that the observed relationships are causal. Further, this study focuses on TNF α as the primary

systemic inflammatory marker and extra-gonadal transcription factor; however, there is evidence to suggest that cortisol²⁰¹ and interleukin-6²⁰² are also known transcription factors for E2, and may also contribute to propagation of the systemic pathophysiological response to injury. Also, we adjusted for the confounders of age, GCS, CT abnormalities (contusion, SDH, DAI), and rs2470152); however, it is possible other unmeasured confounding could alter the observed effect estimates for the cross-lag and survival analysis models. Finally, this study was performed in a cohort with severe TBI, and thus the utility of E2 and TNF α as prognostic indicators of mortality are not necessarily generalizable to those with less severe injuries; however recent studies have noted differences in neurologic and quality-of-life outcomes by sex hormones in mild TBI populations.²⁰³

In conclusion, the results from this study provide intriguing evidence to support the hypotheses that the peripheral inflammatory and hormone markers, E2 and TNF α , have a positive feedback relationship in the first week following severe TBI, and both biomarkers have prognostic value as indicators of mortality risk after injury. These biomarkers may be TBI relevant for both research and clinical purposes to gauge baseline risk for systemic compromise and mortality. Future experimental TBI studies should consider ways to simultaneously model systemic compromise or septic shock²⁰⁴ in addition to TBI-alone to more appropriately mirror severe TBI clinical conditions. Additionally, future experimental studies should examine the potential benefits of aromatase- and TNF α -inhibitors, as well as adrenergic blockage therapies. Future clinical studies would benefit from prospectively monitoring E2 and TNF α daily and the subsequent risk for major systemic compromise and NNOD.

5.0 GENERAL DISCUSSION

5.1 SUMMARY OF RESULTS

Clinicians across the care continuum that treat patients with serious brain injuries have two overarching goals: 1) avoid acute mortality; and 2) assuming acute survival, avoid long-term disability. My dissertation addresses these two topics by studying the effect of acute factors on survival and long-term recovery following moderate-to-severe TBI. I focused on two factors, which are not primarily brain-related, but rather secondary systemic components: pneumonia and peripheral inflammation and hormone levels. In the first aim of my dissertation, I describe the methods we used to create a novel dataset spanning early to chronic phases after TBI. The second and third aims are original prospective cohort studies examining acute factors associated with long-term disability and survival. The results indicated that the identified non-neurological factors are highly relevant for survival and long-term disability.

Aim 1 describes the probabilistic matching methodology used to merge two large databases, the NTDB and TBIMS. These two datasets uniquely contain variables that are largely non-overlapping across the time course of TBI; the NTDB contains extensive data on acute care hospitalizations; however, has little information after a patient is discharged. In contrast, the TBIMS is a rehabilitation database that has detailed information collected from when a patient is admitted to rehab, and it also has subsequent long-term follow-up until death. Individuals

eligible to be enrolled in the TBIMS were admitted to a Level I trauma center for their acute care, meaning they were also represented in the NTDB. However, due to the lack of co-registration of participants between the NTDB and TBIMS, there are not common identifiers between databases, requiring probabilistic matching to match participants between datasets using a series of common data elements. We first developed¹⁴² and validated¹⁴³ the algorithm using data collected at two sites where we also simultaneously identified deterministic pairs. Aim 1 of the dissertation provides detailed information on the validation of this algorithm in a single clinical site. The developed algorithm was applied to the entire NTDB and TBIMS to arrive at a matched cohort of n=4022.

Aim 2 of this dissertation leverages the merged NTDB-TBIMS database created in Aim 1 to test the hypothesis that HAP is associated with long-term disability after moderate-to-severe TBI. The merged cohort was restricted to n=3712 adults with moderate-to-severe TBI injured between 1998-2013. The primary outcome was the GOS-E, a measure of global disability commonly used in TBI clinical trials and observational studies. The secondary outcomes included metrics of hospital resource utilization, such as length of stay, efficiency during rehabilitation, and rehospitalization. We observed a HAP incidence rate of 32.7%. Clinical factors associated with HAP included greater brain injury severity, extra-cerebral injury severity, mechanism of injury, significant thoracic injuries, being on a ventilator, an intraventricular hemorrhage, and subarachnoid hemorrhage. We observed that individuals with HAP had a 34% increased risk for prolonged global disability compared to individuals without HAP. For the secondary objective, we observed that individuals with HAP had over a two-week longer acute and rehabilitation LOS (combined) compared to individuals without HAP, independent of confounders like age and brain injury severity.

The results gathered from this study provide compelling evidence that the effects of HAP extend beyond the infection period itself and are an independent risk factor for prolonged chronic disability. The biological rationale of this relationship is potentially explained through an inflammatory hypothesis: individuals with TBI that suffer systemic infections during their acute hospitalization prime their system to devolve into a chronic inflammatory state. In a previous study I was involved in,⁸⁶ among a cohort of n=87 adults with severe TBI, we determined that individuals with a greater number of hospital complications had significantly greater chronic inflammatory load in the first 3 months following injury, even after patients were presumably treated for their infections. Individuals with HAP more often have fever, hypotension and hypoxemia, all of which aggravate the biological response to TBI.²⁰⁵ It is likely that individuals with HAP were more likely to continue to have prolonged pathological effects from their injury that explain long-term disability.

Aim 3 of my dissertation focused on systemic pathophysiology after injury. Even though TBI is a primary injury to the brain, this study shows the biological effects are not confined to neurological processes. In response to a traumatic injury, two main “stress” pathways are triggered in the brain, the SNS and HPA axis, which exert effects throughout the body. The output of the HPA-axis is the adrenals, which releases the stress hormone cortisol upon activation, which has known anti-inflammatory properties under certain conditions. Activating the SNS results in a downstream trigger of the acute phase hepatic response, producing pro-inflammatory cytokines like TNF α . Increases in TNF α promote the synthesis of the sex hormone, E2, at extra-gonadal sites.⁹³⁻⁹⁵ E2 has potent pro-inflammatory effects that contribute to increases in peripheral cytokines. Elevations in E2 and TNF α could be the product of a

reciprocal biochemical pathway that represents increased risk for non-neurological organ dysfunction.

In Aim 3, we studied n=157 adults with severe TBI and collected serum samples of TNF α and E2 in the first five days after injury. To test the hypothesis that a positive feedback loop exists between peripheral TNF α and E2 production acutely after severe TBI, we conducted a cross-lag analysis. Our results showed that TNF α and E2 were significantly related over time across early and delayed time periods acutely following TBI. We also observed that TNF α and E2 were significant prognostic indicators of risk for mortality in early phase after TBI, and TNF α 's effects on mortality were sustained into the delayed period in the second 72 hours after injury. One potential biological explanation of the relationship is that these biomarkers represent an increased likelihood for death from systemic complications and non-neurological organ dysfunction.^{102,121} The findings from this study are important to understand baseline risk for mortality after severe TBI, and may be applied, for example, to stratify patients for inclusion in clinical trials by baseline risk.

5.2 PUBLIC HEALTH IMPACT

Each year, 2.5 million Americans suffer a TBI.¹²⁵ Moderate-to-severe TBI is a major cause of death, especially among young adults,^{126,159} and a majority of those that survive their initial injuries, live with lifelong disabilities. This accounts for an estimated 5 million Americans living with chronic TBI disability.^{2,42,206} The economic burden of chronic disability is considerable both from direct medical costs and indirect cost from lack of productivity. Previous studies have estimated that an acute TBI hospitalization is over \$4,000 per day.²⁰⁷

Brain injury is different from orthopedic injury to other parts of the body where individuals have an expected recovery timeline, and most return to pre-injury function after some structured period of rehabilitation. In contrast, individuals with moderate-to-severe TBI have an extended recovery period, which for some individuals results in a lifetime of disability. This striking difference in recovery between brain and orthopedic injuries is the consequence of great individual differences in the response of the brain. TBI researchers in the basic and clinical sciences are thus charged with characterizing this heterogeneity to inform personalized treatment regimens.

TBI Research is interdisciplinary and spans neuroscience (e.g. animal models of TBI), to many clinical disciplines (e.g. emergency medicine, critical care medicine, neurosurgery, trauma surgery, and rehabilitation), to public health (e.g. injury prevention, neuroepidemiology). In my doctoral training, I have had some exposure to these different disciplines within TBI research; my degree focus is in neuroepidemiology, and I also work closely with TBI physicians from multiple specialties. One striking conclusion I made is there is a great deal of silo'd research within medical fields in TBI. For instance, trauma researchers have not historically examined outcomes after acute inpatient hospitalization. From a rehabilitation perspective, research largely begins when a patient enters rehab and they are followed for months and years to track integration back into the community. Historically, rehabilitation researchers have seldom considered the effect of acute hospital factors on long-term recovery. Silo'd research may be caused by many factors; trauma and rehabilitation researchers often do not attend the same scientific conferences and meetings, and as a result, few collaborations have existed between the fields. The result is a dearth of available large studies that span from early to late time phases of injury. The identification of this "gap" by my mentor Dr. Wagner and myself, prompted Aim 1

of my dissertation to merge two large databases: the NTDB and TBIMS. By doing so, we created an infrastructure to study the long-term effects of acute care variables, like hospital complications, admissions vital signs, extracerebral trauma, and surgical procedures. The bridging of these field offers the opportunity to ask new questions that more completely consider the TBI life-course.

The downstream consequences of poor integration between disciplines is not restricted to research, but has profound implications for the clinical care of patients with TBI. There are data to suggest that a significant proportion of individuals with a TBI requiring a hospitalization do not receive rehabilitation care and services, with racial minorities²⁰⁸ and uninsured populations²⁰⁹ disproportionately not receiving rehab services. Disparities in the receipt of rehabilitation is likely greater than the receipt of acute care services, like neurosurgery and critical care medicine, where the acuity and urgency of injuries necessitate immediate care for survival. In contrast, payors must balance the potential benefits gained from rehabilitation to the high costs of care, when patient survival is primarily not in the balance. One low hanging solution to address this disparity is to emphasize early rehabilitation consultation and intervention during acute care itself, which has begun being implemented in many leading academic health centers. Needham and Korupolu²¹⁰ proposed a Rehabilitation Quality Improvement Model in which Rehabilitation clinicians (e.g. Psychiatrists, Physical Therapists, Occupational Therapists, Speech-Language Therapists) work with critically ill patients while they are still in the critical care unit. This program showed benefits by decreasing in the average hospital length of stay and increasing early mobility. Another study in a TBI population conducted by Wagner and colleagues²¹¹ showed that Rehabilitation consultation in acute care resulted in better functional recovery and shorter length of stay. Clinically, here in the University of Pittsburgh Medical Center, Dr.

Wagner leads a brain injury medicine consult service where she facilitates successful transition of care for acutely injured severe TBI patients. Rehabilitation services include: early neurostimulant use, restorative sleep, agitation management, and control over SNS overactivity.

The goal of building bridges between acute care and rehabilitation has gained traction in recent years. The American College of Surgeons (ACS) and American Congress of Rehabilitation Medicine (ACRM), two of the largest acute care and rehabilitation organizations respectively, are in active discussions to blend clinical and research efforts between acute care trauma surgeons and rehabilitation for TBI, including through database activities that would allow for shared data collection. Clinically, there are discussions within these groups of how to modify existing frameworks, such as the Needham's model,²¹⁰ to fit the needs of TBI populations. The ultimate long-range plans of such clinical initiatives are to increase access to rehabilitation for all patients with TBI.

From a research perspective, the leadership within these organizations specifically identified the NTDB-TBIMS merged database as an exemplar of research successes in bridging the trauma and rehabilitation fields. In fact, our expertise is being sought to develop a path forward to prospectively collect linked data between the NTDB-TBIMS through deterministic means. Specifically, Dr. Wagner and I plan to hold meetings with key stakeholders in the trauma and rehabilitation community nationally to develop and implement this plan. One tangible "boots on the ground" step could be to identify trauma and rehabilitation partners at each TBIMS clinical site, and determine ways to integrate trauma registry data into prospective data collection. The system of prospective data collection in concert between trauma and rehabilitation centers may forge opportunities to not only increase the quality of the merged

database, but also to develop new research and clinical care partnerships between trauma and rehabilitation colleagues for years to come.

5.3 FUTURE RESEARCH

My vision cast for the future direction for the field of TBI research and clinical care is to conduct more cross-cutting studies across the TBI disability continuum, from early to long term periods after injury. The merged NTDB-TBIMS dataset is one exemplar of the integration of acute and rehabilitation factors, though, it remains only one component. In **Figure 9**, I illustrate how I conceptualize the TBI disability clinical and research continuum. Prior to incident injury, individuals with TBI may have an existing physical or mental health disease burden that could complicate recovery. In a previous study I co-authored,⁶ we determined that there are three main clusters of comorbidities present among middle aged-to-older adults with TBI: 1) hospital complications, 2) chronic diseases, and 3) substance abuse disorders. From data in a follow-up study in review, we find that greater comorbidity burden is a risk factor for poorer recovery during the first year after TBI. Additionally, work from my Master's degree thesis found that presence of pre-injury depression is associated with poorer affective/behavioral symptoms, cognition, and quality of life in the first three months after TBI.²¹² These studies together suggest that an individual's pre-injury characteristics are important for post-injury recovery. In my postdoctoral training plan, I will continue to delve into the concept of a TBI disability continuum by examining late-life and post-mortem analyses of brain health. As a long-term career goal, I hope to design and conduct studies across the continuum, working alongside clinicians and

researchers spanning trauma and rehabilitation fields, to identify risk factors to target for improving long-term recovery.

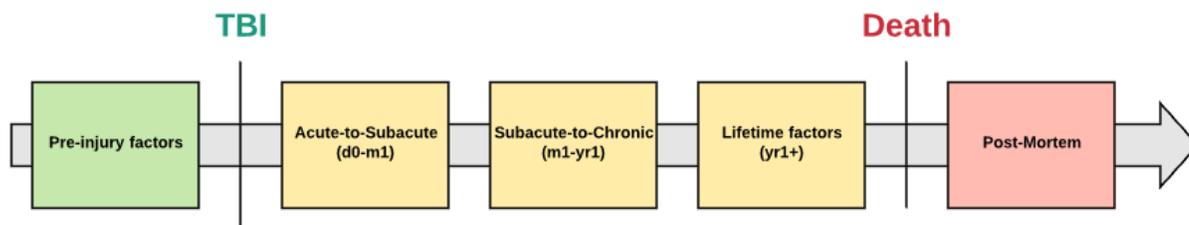


Figure 9. TBI Disability Clinical & Research Continuum

Spanning from left to right over time, the **TBI Disability Clinical & Research Continuum** spans five distinctive but interconnected phases, which are as follows: **1) Pre-injury factors:** Comorbid disease burden, which could include chronic conditions, substance abuse disorders, or mood and behavioral illnesses; **2) Acute-to-Subacute factors:** The early pathophysiological response to TBI, results in perturbations to brain-based biomarkers, peripheral biomarkers. Acutely, clinical factors may also complicate the recovery course, such as hospital infections, including pneumonia. Clinical interventions, including craniotomy and craniectomy, directly impact acute survival; **3) Subacute-to-Chronic factors:** Patients begin to depart from a state of post-traumatic amnesia; TBI-related impairments exist, including: seizures, cognitive impairment, mood/behavioral dysfunction, headache, fatigue, sleep disturbance, and pain; **4) Lifetime factors:** A subset of patients live with prolonged TBI impairments and disability. Data show evidence for an increased risk for neurodegeneration and premature death after TBI compared to individuals without TBI; **5) Post-Mortem:** Neurodegeneration in post-mortem brain of patients with TBI.

5.3.1 TBI is a global health problem requiring worldwide research

Importantly, TBI is not only a problem here in the United States, but a significant worldwide public health concern that is among the top 15 causes of death in all age groups less than 60 years old. It is also the single leading cause of disability in people under 40 years of age in the world.²¹³ The World Health Organization (WHO) estimates that motor vehicle accidents, which account for 60% of TBI in all parts of world, will be the third leading cause of disability and death for all ages worldwide by 2020.²¹⁴ The greatest burden of TBI is in low- and middle-income countries, which account for 90% of injury-related deaths in these populations. However, research is immensely lacking in developing populations.²¹⁵ An important future direction for the TBI field is testing the external validity of clinical trials conducted in the United States and other developed countries in lower- and middle-income countries to ensure interventions work in a

variety of clinical settings worldwide. It is imperative to find effective treatments to lower the mortality and morbidity burden of TBI around the world.

5.4 CONCLUSION

Though TBI is now considered by most experts in the field as a chronic disease,²¹⁶ the etiology of TBI, and associated complications, make it more heterogenous compared to many chronic diseases. That is, TBI can occur among individuals of any age, sex, race, health status, socioeconomic status, or genetic makeup, which makes it one of the most wide-ranging chronic diseases facing society today worldwide. The tremendous heterogeneity of TBI makes it difficult to study. For example, the most recent large RCT in TBI, the Progesterone for Traumatic Brain Injury Experimental Clinical Treatment trial, had an age range from 17 to 94.¹⁶³ The unfortunate reality is that over 30 large clinical trials for TBI have failed to show neuroprotective benefits.¹⁶⁰ In the extensive effort to find a single drug that works for all patients with TBI, the field is currently without a single effective neuroprotective drug for anyone.

This dissertation has several implications that add to the field. The merged database generated from methods outlined in Aim 1 is an important infrastructure from which to conduct novel research that spans trauma and rehabilitation. The results from Aim 2 indicate that every effort should be made by clinicians to prevent HAP after TBI, as it represents a known modifiable risk factor that can impact the long-term prognosis for patients with moderate-to-severe TBI. From Aim 3, the identification of objective biomarkers in the initial days following TBI to predict risk for mortality have important implications, as biomarkers are a means to promote a more personalized medicine approach to TBI clinical practice and research. There is a

movement away from clinical injury severity measures, such the GCS, as prognostic markers to identify at-risk patients. Since many patients with moderate-to-severe TBI have prolonged periods of unconsciousness and post-traumatic amnesia, having early objective molecular measures that do not rely on patient report are critical to identify patients at-risk for mortality. Clinically, this has the potential to alter the way clinicians prioritize certain treatments, such as the usage of life-saving procedures. From a research perspective, because of their elevated baseline risk for mortality, patients with high concentrations of E2 and TNF α early after TBI may not be the best candidates for enrollment future trials focused on neuroprotective strategies. Future clinical trials may also benefit from investigation of ways to directly modify E2 and TNF α through the use of aromatase and TNF-inhibitors, respectively.

APPENDIX: SUPPLEMENTAL TABLES CHAPTER 1

Supplementary Table 1. Cluster weight differences for true and false matches in the algorithm generation and validation sets

	False Match	True Match
Training set		
Mean (SD)	2.8 (3.9)	14.5 (8.5)
Median (IQR)	1.4 (0.6, 3.4)	13.8 (7.9, 19.7)
5 th percentile	0	2.4
90 th percentile	7.0	26.0
Validation set		
Mean (SD)	4.2 (4.8)	16.0 (9.3)
Median (IQR)	2.3 (1.0, 6.1)	15.5 (8.6, 22.2)
5 th percentile	0	2.2
90 th percentile	9.4	33.0

Supplementary Table 2. Distribution of selected blocking and matching fields by Tier II matching status in the algorithm generation and validation sets

	Total	Tier II matched	Tier II non-matched	<i>P</i> -value ¹
Training set				
N	497	332	165	
Age, mean (SD)	38.6 (17.6)	40.0 (18.0)	36.0 (16.7)	0.016
GCS eye, mean (SD)	2.4 (1.4)	2.3 (1.4)	2.5 (1.4)	0.345
GCS motor, mean (SD)	3.7 (2.1)	3.7 (2.1)	3.8 (2.2)	0.346
GCS verbal, mean (SD)	3.2 (1.6)	3.2 (1.6)	3.4 (1.7)	0.302
GCS total, mean (SD)	10.8 (4.3)	10.7 (4.2)	11.0 (4.7)	0.282
SBP, mean (SD)	134.8 (29.1)	134.9 (30.6)	134.5 (25.3)	0.834
Reparatory rate, mean (SD)	20.2 (6.4)	20.0 (6.7)	20.7 (5.6)	0.306
LOS, mean (SD)	20.1 (12.5)	20.8 (12.6)	18.7 (12.2)	0.048
Female, %	30.6	33.1	25.5	0.080
Race, % ²				0.483
White	78.5	77.7	80.0	
Black	17.9	19.3	15.2	
Asian/Pacific islander	0	0	0	

Supplemental Table 2 Continued

Hispanic	2.8	2.4	3.6	
Other	0.8	0.6	1.2	
Skull base fracture, %	33.2	31.9	35.8	0.393
Cranial surgery, %	20.2	20.8	19.2	0.733
Validation set				
N	544	380	164	
Age, mean (SD)	38.9 (18.3)	39.7 (19.1)	37.1 (16.3)	0.294
GCS eye, mean (SD)	2.4 (1.4)	2.3 (1.4)	2.5 (1.4)	0.309
GCS motor, mean (SD)	3.8 (2.2)	3.8 (2.1)	3.7 (2.2)	0.852
GCS verbal, mean (SD)	3.2 (1.6)	3.1 (1.6)	3.3 (1.5)	0.620
GCS total, mean (SD)	10.7 (4.3)	10.6 (4.2)	11.0 (4.3)	0.618
SBP, mean (SD)	136.0 (31.6)	138.4 (31.3)	129.3 (31.4)	0.015
Reparatory rate, mean (SD)	20.6 (9.8)	20.2 (7.2)	22 (16.1)	0.712
LOS, mean (SD)	21.4 (14.1)	22.0 (14.8)	19.9 (12.2)	0.191
Female, %	28.1	26.6	31.7	0.222
Race, % ²				0.881
White	71.7	71.3	72.6	
Black	22.1	21.8	22.6	
Asian/Pacific islander	1.6	1.6	1.8	
Hispanic	3.9	4.5	2.4	
Other	0.7	0.8	0.6	
Skull base fracture, %	29.4	29.0	30.5	0.718
Cranial surgery, %	20.4	21.4	18.2	0.470

¹ Kruskal-Wallis test for continuous variables and chi-square test unless otherwise specified for categorical variables for comparison between matched and non-matched cases

² Fisher exact test applied for *P*-value

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