The Impact of Screening for Anxious and Depressive Symptoms on the Outcome of Patients with a Mild Traumatic Brain Injury

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Abstract

An estimated 27-69 million individuals worldwide sustain a Traumatic Brain Injury (TBI) each year, establishing it as a prominent contributor to health impairment and disability. Most cases (70-90%) fall under the category of mild with an estimated annual incidence rate of 100-300 cases per 100,000 individuals treated in hospitals. This figure, however, does not encompass the numerous untreated cases, suggesting that the true population-based incidence could be considerably higher, emphasizing the significance of mild TBI (mTBI) as a critical public health concern. Many victims experience post-injury neuropsychological issues such as anxiety and depression, which are associated with more post-concussive symptoms and worse functional outcomes. These psychiatric disorders occur at a higher prevalence and for a longer duration in TBI patients compared to the general population. Therefore, we hoped to establish a systematic process to document the presence of symptoms of anxiety and depression in mTBI patients to prevent negative impacts on their recovery. This was achieved through the administration of questionnaires to determine if early identification of these symptoms may serve as an effective tool to help clinicians detect mTBI patients at risk of developing anxiety and/or depression and thus refer them to the necessary interventions to improve their outcome. The specific questions that we are interested in answering are 1) if the scores on the questionnaires can predict whether the patients will be referred to more interventions, 2) do the scores on the questionnaires predict referrals to interventions that directly target anxiety and depression or symptoms of such, and 3) do these interventions predict better patient outcomes.

We administered the Generalized Anxiety Disorder 7-Item (GAD-7) and Center for Epidemiologic Studies Depression Scale Revised (CESDR-10) questionnaires, no more than three months after injury, to screen for symptoms of anxiety and depression, respectively. A

retrospective chart review was performed for 328 patients from the Montreal General Hospital mTBI Clinic who either received these questionnaires (N=143) or did not (N=185). We used the OACIS electronic medical record system to gather data from the mTBI patients, including age, sex, education level, past medical history, pre-injury psychiatric diagnoses, whether they received referrals to specific resources (vestibular therapy, neuropsychology, outpatient rehabilitation, and psychology), and GAD-7/CESDR-10 scores. The Glasgow Outcome Scale-Extended (GOS-E) was used to quantify patient outcomes in both groups. To address our aims, we performed ordinal and binary logistic regressions to see which variables can predict either the number of interventions a patient was prescribed, referrals to each of the four specific resources, and patient outcome.

We found that higher scores on the CESDR-10 questionnaire significantly predicted an increased number of interventions, particularly referrals to psychologists, and patients who received this intervention demonstrated better outcomes. We also found that mTBI patients with a pre-injury history of depression had significantly greater odds of being referred to more interventions throughout their clinic visits, specifically to neuropsychologists, compared to those without this pre-disposition. Our model also revealed that older patients are at a significantly increased likelihood of being referred to vestibular therapy and this intervention helped improve patient outcome.

Screening for symptoms of depression post mTBI helped clinicians refer patients to the appropriate resources, in this case to a psychologist, which in turn helped improve their outcome. However, this study is exploratory and requires further investigation in larger prospective studies to help support our findings.

Résumé

On estime que 27 à 69 millions d'individus dans le monde souffrent chaque année d’un traumatisme crânio-cérébraux (TCC), ce qui en fait un facteur important d'altération de la santé et d'invalidité. La plupart des cas (70-90%) entrent dans la catégorie des traumatismes légers, avec un taux d'incidence annuel estimé à 100-300 cas pour 100 000 personnes traitées dans les hôpitaux. Ce chiffre ne tient toutefois pas compte des nombreux cas non traités, ce qui suggère que l'incidence réelle sur la population pourrait être considérablement plus élevée, soulignant ainsi l'importance des traumatismes cranio-cérébraux légers (TCCL) en tant que problème critique de santé publique. De nombreuses victimes sont confrontées à des problèmes neuropsychologiques après la blessure, tels que l'anxiété et la dépression, qui sont associés à des symptômes post-commotionnels plus importants et à des résultats fonctionnels moins bons. La prévalence et la durée de ces troubles psychiatriques sont plus élevées chez les patients victimes d'un traumatisme crânien que dans la population générale. Par conséquent, nous espérions établir un processus systématique pour documenter la présence de symptômes d'anxiété et de dépression chez les patients souffrant d'un TCCL afin de prévenir les effets négatifs sur leur rétablissement. Pour ce faire, nous avons administré des questionnaires afin de déterminer si l'identification précoce de ces symptômes peut constituer un outil efficace pour aider les cliniciens à détecter les patients souffrant d'un TCCL qui risquent de développer un trouble anxieux et/ou une dépression, et donc à les orienter vers les interventions nécessaires pour améliorer leur état de santé. Les questions spécifiques auxquelles nous souhaitons répondre sont les suivantes : 1) les scores obtenus aux questionnaires permettent-ils de prédire si les patients seront orientés vers davantage d'interventions, 2) les scores des questionnaires permettent-ils de prédire davantage d'orientations

vers des interventions qui ciblent directement l'anxiété et la dépression ou leurs symptômes, 3) ces interventions permettent-elles de prédire de meilleurs résultats pour les patients.

Nous avons administré les questionnaires Generalized Anxiety Disorder-7 (GAD-7) et Center for Epidemiologic Studies Depression Scale Revised (CESDR-10), pas plus de trois mois après la blessure, pour dépister les symptômes d'anxiété et de dépression, respectivement. Un examen rétrospectif des dossiers a été effectué pour 328 patients de la clinique de TCCL de l'Hôpital général de Montréal qui ont reçu ces questionnaires (N=143) ou ne les ont pas reçus (N=185). Nous avons utilisé le système de dossiers médicaux électroniques OACIS pour recueillir des données sur les patients victimes d'un TCCL, notamment l'âge, le sexe, le niveau d'éducation, les antécédents médicaux, les diagnostics psychiatriques antérieurs à la blessure, l'orientation ou non vers des ressources spécifiques (thérapie vestibulaire, neuropsychologie, réadaptation extérieure et psychologie), ainsi que les scores GAD-7/CESDR-10. Le Glasgow Outcome Scale-Extended (GOS-E) a été utilisé pour quantifier les résultats des patients dans les deux groupes. Pour atteindre nos objectifs, nous avons effectué des régressions logistiques ordinales et binaires afin de déterminer quelles variables peuvent prédire le nombre d'interventions prescrites à un patient, l'orientation vers chacune des quatre ressources spécifiques et les résultats pour le patient.

Nous avons trouvé que des scores plus élevés au questionnaire CESDR-10 prédisaient de manière significative un plus grand nombre d'interventions, en particulier des références à des psychologues, et les patients qui ont bénéficié de cette intervention ont montré de meilleurs résultats. Nous avons également constaté que les patients victimes d'un TCCL ayant des antécédents de dépression avant l'accident avaient beaucoup plus de chances d'être orientés vers un plus grand nombre d'interventions au cours de leurs visites à la clinique, en particulier vers des neuropsychologues, que les patients n'ayant pas cette prédisposition. Notre modèle a également révélé que les patients plus âgés sont beaucoup plus susceptibles d'être orientés vers une thérapie vestibulaire et que cette intervention a contribué à améliorer les résultats des patients.

Le dépistage des symptômes de dépression après un TCCL aidait les cliniciens à orienter les patients vers les ressources appropriées, en particulier vers un psychologue, ce qui a permis d'améliorer leur état de santé. Toutefois, cette étude est exploratoire et doit être approfondie dans le cadre d'études prospectives de plus grande envergure afin de soutenir nos conclusions.

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Contribution of Authors

Paolo Bastone (candidate): Study design, literature review, data collection and analysis, thesis preparation and revision

Dr. Judith Marcoux (supervisor): Study design, supervision, funding, assisted the candidate with data collection, thesis revision

Dr. Maude Laguë-Beauvais (co-supervisor): Study design, supervision, assisted the candidate with data analysis, thesis revision

Dr. José Correa (statistician): Statistical knowledge, assisted the candidate in analyzing the data

List of Abbreviations

5-HT: 5-HydroxyTryptamine/serotonin
5-HT1A: 5-HydroxyTryptamine 1A
5-HT2A: 5-HydroxyTryptamine 2A

ACRM: American Congress of Rehabilitation Medicine
ASI: Anxiety Sensitivity Index
ASQ: Anxiety Symptoms Questionnaire

BAI: Beck Anxiety Inventory
BBB: Blood-Brain Barrier
BDI/BDI-II: Beck Depression Inventory
BDNF: Brain-Derived Neurotrophic Factor

CBT: Cognitive Behavioural Therapy
CCI: Charlson Comorbidity Index
CDC: Centers for Disease Control and Prevention
CES-D: Center for Epidemiologic Studies-Depression Scale
CESDR-10: Center for Epidemiologic Studies Depression Scale Revised
CIRS-G: Cumulative Illness Rating Scale-Geriatrics
CNS: Central Nervous System
CSF: CerebroSpinal Fluid
CT: Computed Tomography

DAI: Diffuse Axonal Injury
DSM-IV: Diagnostic and Statistical Manual of Mental Health Disorders Fourth Edition
DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition

GABA: Gamma-AminoButyric Acid
GAD: Generalized Anxiety Disorder
GAD-7: Generalized Anxiety Disorder 7-Item
GCS: Glasgow Coma Scale
GOS-E: Glasgow Outcome Scale-Extended

HAM-A: Hamilton Anxiety Rating Scale
HAM-D: Hamilton Rating Scale for Depression
HADS: Hospital Anxiety and Depression Scale
HDRS: Hamilton Depression Rating Scale
HRQL: Health-Related Quality of Life

LMIC: Low- and Middle-Income Country
LOC: Loss of Consciousness

MAOI: MonoAmine Oxidase Inhibitor
MDD: Major Depressive Disorder

MGH: Montreal General Hospital
MRI: Magnetic Resonance Imaging
mTBI: mild Traumatic Brain Injury
MUHC: McGill University Health Centre

NMDA: N-Methyl-D-Aspartate

OCD: Obsessive-Compulsive Disorder

PCS: Post-Concussive Syndrome
PHQ-9: Patient Health Questionnaire
PPCS: Prolonged/Persistent Post-Concussion Symptoms
PTA: Post-Traumatic Amnesia
PTSD: Post-Traumatic Stress Disorder

SDAM: Serotonin-Dopamine Activity Modulator
SNRI: Serotonin-Noradrenaline Reuptake Inhibitor
SSRI: Selective Serotonin Reuptake Inhibitor

TBI: Traumatic Brain Injury
TCA: TriCyclic Antidepressant
TCC: Traumatisme Crânio-Cérébraux
TCCL: Traumatismes Cranio-Cérébraux Légers

WHO: World Health Organization

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Introduction

A traumatic brain injury (TBI) is characterized by changes in brain function caused by the transfer of mechanical energy to the head due to external physical forces (Gardner & Zafonte, 2016). More specifically, the Centers for Disease Control and Prevention (CDC) defines a TBI as resulting from a bump, blow, or jolt to the head, or from a penetrating head injury, which all disturb normal brain functioning (About Mild TBI and Concussion, 2024). Annually, 50 to 60 million individuals worldwide experience a TBI, with projections indicating that roughly half of the global population will endure one or more TBIs throughout their lifetime (Maas et al., 2017; Maas et al., 2022). It stands as the leading cause of mortality among young adults and a significant contributor to death and disability across all age groups and nations, particularly burdening low- and middle-income countries (LMICs). The economic toll of TBI on the global scale is estimated at around 400 billion US dollars per year (Maas et al., 2017). Among all cases of TBI, about 90% are categorized as mild (Gao et al., 2022), with an estimated 42 million individuals worldwide suffering from a mild TBI (mTBI) each year (Gardner & Yaffe, 2015). The incidence of hospital treated mTBI is about 100-300 cases per 100,000 individuals, but many of the cases are not treated in hospitals, so the true incidence rate may exceed 600/100,000 (Cassidy et al., 2004). Therefore, TBI is an important public health concern that must not be ignored.

The symptoms experienced by mTBI patients post-injury can fall into three different categories: somatic, cognitive, and emotional/psychological (Katz et al., 2015). The most common symptoms are headache, fatigue, dizziness, blurry vision, confusion, sleep disturbances, memory and concentration difficulties, anxiety, depression, and irritability (Bergersen et al., 2017). It is estimated that between 38% and 80% of mTBI patients will present with at least one of these symptoms in the weeks following their injury (Nelson et al., 2019). However, symptoms typically resolve within 10 to 14 days with most patients making a complete recovery and no longer being symptomatic by three months post-injury (Permenter et al., 2024; Yang et al., 2007). Despite this promising prognosis, about 48% of mTBI patients may experience post concussive symptoms that persist past this three-month period (Ruff & Weyer Jamora, 2009; Theadom et al., 2016). It has been proposed in the literature that symptoms of anxiety and depression measured shortly after sustaining an mTBI can serve as potential predictors of these persistent symptoms (Clarke et al., 2012; Dischinger et al., 2009; Meares et al., 2011; Snell et al., 2013).

Anxiety and depression are the most common psychological problems following a TBI, but it is difficult to establish the specific prevalence for each as these estimates vary widely between studies (Barker-Collo et al., 2018; Wang et al., 2021). In a large meta-analysis, researchers examined factors that affect the prevalence of anxiety and depression post-injury such as self-report measures of both disorders, TBI severity, diagnostic criteria, and time elapsed after TBI. Results showed that overall, 11% of TBI patients were diagnosed with generalized anxiety disorder (GAD) and 37% reported clinically significant levels of anxiety (Osborn et al., 2016). The participants had a mean age of 38.2 years, 69.0% were males, and 7.6% had a prior history of TBI (Osborn et al., 2016). The same group found that overall, after sustaining a TBI, 27% of patients were diagnosed with depression and 38% self-reported clinically significant levels of depression (Osborn et al., 2014). In this study, the participants had a mean age of 37.1 years, 68.6% were males, and 9.6% had a prior history of TBI (Osborn et al., 2014). Anxiety and depression also appear to exert a significant influence on the functional outcomes and recovery trajectories of individuals with mTBI. A recent study indicated that mTBI patients exhibiting anxiety four months post-injury tend to exhibit a wider array of mTBI-related symptoms (specifically fatigue, irritability, perceived stress, symptoms of depression, pain, sleep problems, and cognitive difficulties) across various categories even twelve months following the incident (Lamontagne et al., 2022). Furthermore, a study involving first-time mTBI patients revealed that individuals experiencing depressive symptoms encountered greater post concussive symptoms and faced challenges in achieving complete functional recovery within the initial six months post-injury compared to their non-depressive counterparts (Roy et al., 2022). Notably, the risk of developing persistent symptoms is heightened among those with a pre-injury history of anxiety and/or depression (Langer et al., 2021).

Therefore, anxiety and depression significantly impact the functional outcomes of individuals with TBI and greatly reduce their health-related quality of life (HRQL) (Scholten et al., 2016). It has been shown that the greater the levels of anxiety and depression experienced by mTBI patients, the higher the likelihood of experiencing reduced satisfaction of needs. This is evidenced by a lower perception of autonomy, competence (interacting effectively with an individual's environment), and relatedness (feeling of having positive connections with loved ones) (Auclair-Pilote et al., 2021). This demonstrates the importance of early identification and treatment of these disorders following injury to help improve mTBI patient outcome, psychosocial functioning, and quality of life.

The common occurrence of mTBI and the subsequent onset of anxiety and depression, coupled with the suboptimal recovery observed in mTBI patients with these psychiatric conditions, has inspired us to screen for the presence of symptoms of anxiety and depression in the acute phase post mTBI (0-3 months). Thus, we administered, no more than 3 months after the injury, the GAD-7 (Spitzer et al., 2006) and the CESDR-10 (Björgvinsson et al., 2013; Miller et al., 2008; Radloff, 1977) questionnaires to identify anxious and depressive symptoms in mTBI patients, respectively. The overarching objective of the project is to assess if the identification of these symptoms through the administration of these questionnaires may serve as an effective tool to help clinicians detect mTBI patients who may be at risk of developing anxiety and/or depression and thus refer them to the necessary interventions to prevent negative impacts on their recovery and ultimately improve outcome. The specific questions that we are interested in answering are 1) if the scores on the questionnaires can predict whether the patients will be referred to more interventions, 2) do the scores on the questionnaires predict referrals to interventions that directly target anxiety and depression or symptoms of such, and 3) do these interventions predict better patient outcomes. We believe that the results from these two questionnaires will aid clinicians to properly refer patients to resources and treatments targeting anxious and/or depressive symptoms and in doing such, improve their outcome.

Chapter 1: Literature Review

1.1 What is a TBI?

A TBI can be caused in many ways such as a bump, blow, or jolt to the head, by a hit to the body that causes the brain and head to move rapidly back and forth, or by a penetrating head injury (in more moderate and severe cases) that disrupts normal brain function (Report to Congress, 2003). A sudden and quick movement of the head may lead to some bouncing or twisting of the brain within the skull, causing chemical changes, and stretching and damaging of brain cells (Report to Congress, 2003; Giza & Hovda, 2014). There are two broad types of head injuries: penetrating and non-penetrating. A penetrating TBI, or an open TBI, occurs when an object pierces the skull and enters the brain tissue, so only part of the brain is typically damaged (Traumatic Brain Injury, 2024). On the other hand, a non-penetrating TBI (closed head injury or blunt TBI), is caused by an external force that is powerful enough to move the brain (Traumatic Brain Injury, 2024). Some common causes of a blunt TBI are falls, motor vehicle collisions, sports injuries, or being hit by an object (Traumatic Brain Injury, 2024).

A TBI can cause primary and secondary brain injuries. A primary injury encompasses focal and diffuse lesions that results from mechanical injury at the time of the incident (Huffman et al., 2010). A focal injury usually results from a blow to the head that causes cerebral contusions or hematomas (Huffman et al., 2010). Contusions manifest as bruising or swelling of the brain, resulting from the leakage of small blood vessels into brain tissue (Traumatic Brain Injury, 2024). These injuries can occur either directly beneath the impact site (known as a coup injury) or more commonly, on the opposite side of the brain from the impact (referred to as a countercoup injury), where the brain bounces on the inner skull (Traumatic Brain Injury, 2024). The appearance of contusions may be delayed, becoming evident hours to a day after the traumatic event. Contusions can also potentially lead to hematomas (Hegde, 2006), which is a more significant amount of bleeding in and around the brain, triggered by the rupture of a blood vessel. The specific type of hematoma formed depends on the location where blood accumulates relative to the meninges, the protective membranes enfolding the brain and comprising three layers: dura mater (outermost), arachnoid mater (middle), and pia mater (innermost) (Traumatic Brain Injury, 2024). Epidural hematomas, which involve bleeding in the space between the skull and the dura mater, pose a significant risk as they can occur rapidly (minutes to hours) after damage to a brain vessel beneath the skull. Hematomas can also be subdural where bleeding occurs between the dura and the arachnoid mater, exerting pressure on the outside of the brain, like epidural hematomas. A subarachnoid hemorrhage refers to bleeding between the arachnoid mater and the pia mater. When there is bleeding within the brain itself, it is termed an intracerebral hematoma, which causes damage to the surrounding tissue (Traumatic Brain Injury, 2024). Lacerations are another type of focal lesion which refer to tears in brain tissue and blood vessels of the brain (Hegde, 2006). The resulting morbidity and mortality depend on the location, size, and progression of the injury (Marik et al., 2002).

A diffuse lesion, also known as diffuse axonal injury (DAI), is a prevalent form of brain injury where the external force applied to the head is significant, and it involves extensive harm to the white matter of the brain, which comprises bundles of axons connecting different regions of the brain. Indeed, DAI typically arises from injuries that involve rapid acceleration, deceleration, or rotational forces that stretch or tear these axon bundles (Lezak, 1995; Traumatic Brain Injury, 2024). Common scenarios leading to DAI include auto accidents, falls, or sports-related injuries. This type of injury disrupts and deteriorates communication among neurons in the brain, triggering the release of chemicals that can exacerbate the damage. The resulting brain damage may vary in its duration, ranging from temporary to permanent, and the recovery process can be prolonged (Traumatic Brain Injury, 2024). Those who sustain an injury that causes a DAI have high rates of morbidity and mortality (Huffman et al., 2010).

Secondary brain injury can also commonly occur because of the physiological responses to the original trauma which is believed to trigger a cascade of events, with edemas and hematomas leading to greater intracranial pressure (Huffman et al., 2010). This causes compression and deformation of the surrounding brain tissue and thus further damage. The release of neurotoxic substances also plays a role in the extent of the neuronal damage (Huffman et al., 2010). The damage from a primary injury is immediate whereas the outcomes of a TBI from a secondary injury occurs gradually over the course of many days to weeks (Traumatic Brain Injury, 2024).

To expand on the effects of the secondary brain injury, it involves a complex cascade of molecular, chemical, and inflammatory events that contribute to additional cerebral damage. This cascade includes neuronal depolarization and the release of excitatory neurotransmitters such as glutamate and aspartate, leading to elevated intracellular calcium levels. Increased intracellular calcium activates enzymes like caspases, calpases, and free radicals, resulting in the degradation of cells via apoptosis (neuronal death). This neuronal degradation triggers an inflammatory response, exacerbating neuronal damage and causing disruption of the blood-brain barrier (BBB) and subsequent cerebral edema. Following the secondary injury phase, the recovery period ensues, characterized by anatomical, molecular, and functional reorganization (Galgano et al., 2017).

After a brain trauma, an increase in intracranial volume can occur due to factors such as mass effect from blood accumulation, both cytotoxic and vasogenic edema, and venous congestion. When the volume within the skull surpasses the capacity of its normal constituents, a series of compensatory mechanisms are triggered. Since brain tissue is incompressible, it cannot accommodate this excess volume. Consequently, edematous brain tissue initially displaces cerebrospinal fluid (CSF) into the spinal compartment. Over time, blood, particularly of venous origin, is also forced away from the brain. Despite intervention efforts, sometimes even maximal, these compensatory mechanisms may fail, leading to pathological brain compression and ultimately resulting in death (Galgano et al., 2017; Greenberg, 2006).

1.2 Epidemiology of mTBI

The most common causes of mTBI are falls and motor-vehicle collisions (Cassidy et al., 2004). The peak incidence of mTBI occurs in early life, late childhood/young adulthood, and among elderly populations (Taylor et al., 2017). Other populations at risk include people with low-income, those who are not married, members of ethnic minority groups, individuals who live in inner cities, men (Cassidy et al., 2004), those with a history of substance abuse, and people who suffered a past TBI (Dawodu, 2023). Low and medium-income countries have about three times as many TBI cases proportionally than high-income countries, with the greatest overall burden in Southeast Asian and Western Pacific areas (Dewan et al., 2018). The global annual incidence rate of TBI has been variably estimated at 27 to 69 million individuals, making it a leading cause of health loss and disability worldwide (Statistics, 2022; Williamson & Rajajee, 2023). This contributes to significant socioeconomic burden with an estimated $76.5 billion in direct and indirect costs in the United States alone in 2010 (Williamson & Rajajee, 2023). The majority (70-90%) of TBI cases are mild and hospital-treated mTBI occurs at an annual incidence rate of 100-300/100,000 individuals (Cassidy et al., 2004). This, however, does not account for the many untreated cases, so the true population-based incidence rate may be much higher and has been estimated to probably be above 600/100,000, making it an important health concern (Cassidy et al., 2004). A few population-based studies have reported a true incidence rate of over 700/100,000 individuals (Lefevre-Dognin et al., 2021). For example, a study in New Zealand showed that the total incidence of mTBI was 749/100,000 individuals per year regardless of hospitalization or fatality (Feigin et al., 2013).

1.3 Clinical Classification of mTBI

The clinical diagnosis and classification of an mTBI is typically based on the length of loss of consciousness (LOC) and/or post-traumatic amnesia (PTA) (state of immediate confusion following a TBI during which the individual is disoriented and unable to recall post-injury events (Ruijs et al., 1994)) as well as the results from a physical and neurological examination (Borg et al., 2004). These clinical signs can help clinicians decide whether to employ advanced diagnostic tests which include skull radiographs, computed tomography (CT) scans, magnetic resonance imaging (MRI) of the brain or other tests (Borg et al., 2004). Regarding imaging, it is important to note that CT and MRI scans are useful for detecting structural/macroscopic defects, but an mTBI primarily involves metabolic and microscopic changes that often present normally on standard neuroimaging, so the results from the scans should not be used in isolation (Agarwal et al., 2024). With regards to the diagnostic classification of TBI, it is generally accepted that patients with an mTBI experience no more than 30 minutes of LOC and/or 24 hours of PTA (Borg et al., 2004).

The Glasgow Coma Scale (GCS) is the most common TBI severity index that objectively ranks the functional ability and consciousness of all types of acute medical and trauma patients by assessing three parameters of responsiveness: eye opening, verbal response, and motor response (Jain & Iverson, 2024; Lefevre-Dognin et al., 2021; Teasdale & Jennett, 1974). The GCS is scored across all three parameters (best eye response (E), best verbal response (V), and best motor response (M)) with scores varying from 1 (no response) to 4, 5, and 6, respectively (Jain & Iverson, 2024). The total GCS score is a sum of the scores for all three parameters and ranges from 3 (worst injury) to 15 (mildest injury) (Jain & Iverson, 2024; Lefevre-Dognin et al., 2021; Teasdale & Jennett, 1974). This helps classify the TBI into mild (GCS score of 13 to 15), moderate (GCS score of 9 to 12), or severe (GCS score of 3 to 8) (Jain & Iverson, 2024).

An mTBI can be separated into two categories, complicated (complex) and uncomplicated (simple). A complicated mTBI refers to the presence of a traumatic intracranial abnormality on acute neuroimaging and an uncomplicated mTBI is the absence of such (Karr et al., 2020; Voormolen et al., 2020). Although the "complicated" and "uncomplicated" labels have been used previously in the literature, recently, the American Congress of Rehabilitation Medicine (ACRM) diagnostic criteria suggests that when imaging such as CT or structural MRI is positive, the qualifier mTBI "with neuroimaging evidence of structural intracranial injury" may be used. Evidently, if imaging is normal, then the qualifier mTBI "without neuroimaging evidence of structural intracranial injury" can be used, but no qualifier is used if there was no neuroimaging performed (Silverberg et al., 2023). There has been a longstanding debate regarding concussion versus mTBI terminology, specifically whether concussion is a type of mTBI or if they can be used interchangeably (Silverberg et al., 2023). A concussion is typically defined as a transient brain injury that could take minutes to several months to completely heal, but symptoms typically spontaneously resolve one to four weeks after injury (McCrory et al., 2017; Traumatic Brain Injury, 2024). It may be caused by any blow to the head, face, neck, or body that results in a sudden shaking of the brain (Parachute, 2017). This question regarding the specific terminology was recently voted upon using the Delphi method, with 93.8% of expert panel members agreeing that "the diagnostic label 'concussion' may be used interchangeably with 'mild TBI' when neuroimaging is normal or not clinically indicated" (Silverberg et al., 2023). As such, these terms are often traditionally used synonymously by most medical experts (Mayer et al., 2017) and the

ACRM diagnostic criteria also considers a concussion to be an mTBI (Silverberg et al., 2023). It is important to note that the term "concussion" is usually used to describe an mTBI that occurred during sports, whereas in a different context, the preference is for the diagnostic label "mTBI" (Decq et al., 2021).

1.4 Recent Diagnostic Criteria of mTBI

The most recent diagnostic criteria for mTBI were established by the ACRM in 2023 (Silverberg et al., 2023), which is a detailed and comprehensive guide that warrants discussion. These guidelines are crucial as they provide clinicians with a standardized diagnostic tool for identifying mTBI in patients. This consistency in diagnosis helps alleviate confusion amongst clinicians who may otherwise use different criteria, ensuring more accurate and reliable assessments of mTBI cases. The ACRM states that mTBI is diagnosed when, after a biomechanically plausible mechanism of injury, one or more of the following three criteria are satisfied: the occurrence of one or more clinical signs attributable to brain injury, the manifestation of at least 2 acute symptoms and, concurrently, at least one clinical or laboratory finding attributable to brain injury, and finally neuroimaging evidence of clear trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging. It is important to note that any confounding factors such as pre-existing and co-occurring health conditions cannot explain any of the criteria necessary for the diagnosis (Silverberg et al., 2023). The injury cannot be categorized as "mild" if the patient experienced any of the following: LOC greater than 30 minutes, a GCS score less than 13, and PTA greater than 24 hours (Silverberg et al., 2023).

As TBI stems from the transmission of mechanical energy to the brain through external forces, biomechanically plausible mechanisms of injury encompass instances such as being struck in the head with an object, hitting the head on a hard object or surface, the brain undergoing acceleration/deceleration movement without direct head contact, and/or forces generated from a blast or explosion (Silverberg et al., 2023).

After the injury, there is an immediate disruption of brain function, evidenced by one or more clinical signs. These signs encompass loss of consciousness and/or alteration of mental status immediately following the injury. This altered mental state may manifest as reduced responsiveness, inappropriate responses to external stimuli, delayed response to questions or instructions, agitation, inability to follow two-part commands, or disorientation to time, place, or situation. Additional clinical signs may include complete or partial amnesia for events post-injury; if post-traumatic amnesia cannot be assessed, retrograde amnesia for events immediately preceding the injury can satisfy this criterion. Other possible acute neurologic signs involve motor incoordination upon standing, seizures, or tonic posturing after the injury (Silverberg et al., 2023).

Various acute symptoms emerge after an injury, presenting as either new or exacerbated. These symptoms can be classified into four distinct categories: acute subjective alteration in mental status, physical symptoms, cognitive symptoms, and emotional symptoms. An acute subjective alteration in mental status, characterized by feelings of confusion, disorientation, and/or dazedness, occurs immediately after the injury or upon regaining consciousness. The onset of physical, cognitive, and emotional symptoms may be delayed by a few hours, but they typically manifest within 72 hours after the injury (Silverberg et al., 2023).

Upon acute clinical examination, some findings that provide evidence for brain injury are cognitive, balance, and oculomotor impairment or symptom initiation following a vestibular-oculomotor challenge. For laboratory findings, increased levels of blood marker(s) suggesting an intracranial injury acts as evidence of brain injury (Silverberg et al., 2023).

1.4.1 Diagnostic Criteria of Concussion

A productive approach to examining the similarities and distinctions between mTBI and concussion involves exploring the definition and diagnostic criteria of concussions as well. A concussion is defined as a brain injury that is characterized by several key elements. Firstly, it arises from the direct or indirect transmission of kinetic energy to the head. This impact leads to an immediate and transient dysfunction of the brain, marked by at least one of the following disorders: loss of consciousness, loss of memory, altered mental status, and neurological signs. Subsequently, it may give rise to one or more functional complaints, resulting in what is known as concussion syndrome. Importantly, these signs and symptoms are distinctive and not explained by any other cause. Concussion syndrome comprises of non-specific symptoms that are traditionally divided into four categories: somatic, cognitive, emotional, and sleep related (Decq et al., 2021), which is something that is in common with mTBI.

The diagnosis of concussion is established based on specific criteria. Within the first 24 hours of the kinetic energy transmission to the head, the presence of at least one of the following signs or symptoms, observed or reported, confirms the diagnosis, provided that it cannot be attributed to another cause: loss of consciousness, convulsions, tonic posturing, ataxia, visual trouble, neurological deficit, confusion, disorientation, unusual behaviour, amnesia, headaches, dizziness, fatigue, low energy, feeling slowed down, drowsiness, nausea, sensitivity to light/noise, not feeling right, in a fog, and difficulty concentrating (Decq et al., 2021). Therefore, the definition, diagnostic criteria, and symptoms experienced after injury are almost identical to that of an mTBI.

1.5 Post-injury Symptoms

In the short period after an mTBI, an individual might experience a brief LOC (or altered consciousness), transient confusion, disorientation, amnesia at the time of injury, and other neurological and neuropsychological dysfunctions such as seizures (Dixon, 2017). The other symptoms experienced can be placed into three different categories: somatic/physical, cognitive, and psychological/emotional (Ryan & Warden, 2003; Skjeldal et al., 2022). The somatic/physical symptoms may include headache, dizziness, fatigue, photophobia (light sensitivity) and phonophobia (noise sensitivity), sleep disturbance, visual disturbances, nausea, balance problems, and tinnitus. For cognitive symptoms, patients can feel slowed down, have mental fog, experience impaired memory, attention/concentration deficits, word finding difficulty, and executive function deficits. The psychological/emotional symptoms include depression, anxiety, irritability, low mood, and affective lability (Ryan & Warden, 2003; Silverberg et al., 2020; Skjeldal et al., 2022).

While these symptoms are common in the acute stage after an mTBI in the adult population, recovery within months is the norm for most patients (Carroll et al., 2004). More specifically, the majority of mTBI patients have complete resolution of symptoms in about three months (McInnes et al., 2017). Given this timeframe, the acute phase encompasses symptoms that occur within three months after injury, while patients experiencing symptoms three months post-mTBI are considered in the chronic phase (McInnes et al., 2017).

Although mTBI patients typically have a good clinical outcome, with most patients achieving a full recovery within weeks or months, approximately 10-25% of patients will experience persistent symptoms with social and vocational repercussions that appear to be disproportionate to the severity of the TBI experienced (Caplain et al., 2017). This is known as post-concussive syndrome (PCS) where the persistence of mTBI symptoms extend beyond the expected recovery period and can have an impact on patient outcome across all aspects of life, with significant consequences on public health as well (Broshek et al., 2015; Caplain et al., 2017). The Diagnostic and Statistical Manual of Mental Health Disorders fourth edition (DSM-IV) defines PCS as neuropsychological impairments as well as symptoms that lasted more than 3 months after the injury and were not present before the injury or worsened post-injury (Langer et al., 2021). It is important to note that PCS was removed from the DSM-5 and replaced with "Major or Mild Neurocognitive Disorder due to Traumatic Brain Injury" in response to literature that brought attention to the insufficient specificity in diagnosis and the resultant limited usefulness in clinical practice (Diagnostic and statistical manual, 2013; Wortzel & Arciniegas, 2014).

There are many factors that may lead to PCS after an mTBI. In a ground-breaking paper commissioned by the World Health Organization (WHO), the authors aimed to determine which prognostic factors contributed to the prolongation of symptoms in a subset of mTBI victims. Other than the existence of a compensation/litigation which associated significantly with prolonged symptoms, no other factors were clearly associated with the remaining symptoms in the long term (Carroll et al., 2004). More recently, it has been shown that more acute symptoms, poorer premorbid mental and physical health, and a major acute life stressor could predict persistent symptoms (Cassidy, Cancelliere, et al., 2014). Similarly, a large retrospective cohort study carried out in Ontario found the main contributors of prolonged post-concussion symptoms (PPCS) to be age >61 years, bipolar disorder, high pre-injury primary care visits per year, personality disorders, anxiety, and depression (Langer et al., 2021).

It is noteworthy that anxiety and depression do seem to play a role in the subsequent emergence of these persistent symptoms in mTBI patients. One study showed that experiencing psychological distress, specifically anxiety and depression, during the initial two weeks following an injury substantially raises the likelihood of exhibiting persistent post-concussion symptoms (PPCS) at the six-month mark post-injury (Hou et al., 2012). It has also been proposed by some authors that symptoms of anxiety and depression measured in the days following an mTBI are potential predictors of persistent symptoms that extend at least three months after injury (Lamontagne et al., 2022). This shows that symptoms of anxiety and depression can present shortly after injury, hinting at the importance of early screening of these symptoms. It has also been shown that among adults, pre-existing mental health issues and post-injury psychological distress, characterized by symptoms of anxiety and depression, are strong indicators of an extended recovery period (Silverberg et al., 2020). Therefore, when evaluating individuals with persistent symptoms after mTBI, it is essential to include screenings for anxiety and depression, as these mood symptoms commonly manifest post-mTBI and are among the most influential factors associated with an extended recovery period (Silverberg et al., 2020).

1.6 What is Anxiety?

When discussing anxiety, it is important to consider its distinction with fear, which is an automatic conscious feeling of alarm that is caused by present or imminent danger. Anxiety is linked to fear, but it entails the anticipation of future threat or danger, whether it be real or imagined (Chand & Marwaha, 2024; Penninx et al., 2021). It is a normal response that is often adaptive and facilitates survival, but it becomes a problem when an individual experiences anxiety that is disproportionate to a situation, is severe and persistent, or affects their ability to function normally (Dean, 2016; Penninx et al., 2021). This is known as an anxiety disorder, which is different from the normal temporary worry or fear as an individual's anxiety does not go away, and it can get worse with time (Anxiety Disorders, 2024). Anxiety disorders are the most common group of mental disorders and affect up to 20% of adults each year (Munir & Takov, 2024; Penninx et al., 2021). There are different types of anxiety disorders such as GAD, panic disorder, specific phobias, agoraphobia, social anxiety disorder, and separation anxiety disorder (Penninx et al., 2021). We will focus on GAD since it is what we are interested in measuring in this project. GAD involves persistent and excessive feelings of worry, anxiety or dread that may be accompanied by physical symptoms such as restlessness, feeling on edge or easily tired, difficulty concentrating, muscle tension, or difficulty sleeping (Anxiety Disorders, 2024; Munir & Takov, 2024).

From a neurochemical perspective, there are many different neurotransmitters that have been shown to be involved in anxiety. An important one is gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system (CNS). The strongest piece of evidence for its involvement in the regulation of anxiety is that the GABA system, particularly the GABA receptors, is the main target of benzodiazepines and other drugs that are used to treat anxiety disorders (Lydiard, 2003; Nutt et al., 2002). It has also been shown that even the slightest reduction of the GABAergic system leads to anxiety, insomnia, exaggerated reactivity, restlessness, and arousal (Nemeroff, 2003). Glutamate is also thought to be involved as many studies demonstrated that glutamatergic neurotransmission of the limbic system plays a key role in the pathophysiology of anxiety disorders (Kaur & Singh, 2017). Being exposed to severe stress causes pathologically high levels of glutamate and thus excitotoxicity which can result in neuronal damage and/or death. A reduction in anxiety can be achieved by decreasing the level of endogenously released glutamate (Kaur & Singh, 2017). It has also been shown that the acute administration of glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonists have antianxiety and antidepressant effects (Kaur & Singh, 2017). Serotonin (5-HT) is another neurotransmitter involved in anxiety as many studies have shown that an increased concentration of 5-HT in the brain increases anxiety and a reduction of serotonin levels reduce anxiety (Jia & Pittman, 2014; Murphy et al., 2013). Patients with anxiety disorders may have genetic polymorphisms in serotonin genes such as the 5-HT transporter, the 5-HT2A receptor, and/or the 5-HT1A receptor (Kaur & Singh, 2017).

1.6.1 Treatment of Anxiety

There are effective treatments that exist for individuals with anxiety disorders, which help reduce anxiety symptoms, improve their quality of life and functioning. The first line treatments for anxiety disorders are psychotherapy and medications, which may also be used in combination (Penninx et al., 2021). A type of psychotherapy that has much evidence for its effectiveness in treating anxiety disorders is cognitive behavioural therapy (CBT), which is a short-term therapy that involves establishing objectives and acquiring skills to diminish anxiety and the perception of threat. Rather than avoiding situations that provoke fear or seeking constant reassurance, individuals will learn to confront these situations directly, manage them effectively, utilize techniques to maintain composure, and develop skills to sustain progress in the long term (Penninx et al., 2021). Physicians may choose to prescribe medications as a treatment option due to factors such as unresponsiveness to psychotherapy, chronic or complex cases, and depression comorbidity. The preferred medications are selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) because of their advantageous balance between risks and benefits across all age groups, especially in children and adolescents. Benzodiazepines are also effective since they are anxiolytic (drug that reduces anxiety), but their effectiveness is limited to acute relief and result in relapse upon termination and are linked with dependency (Penninx et al., 2021).

1.7 What is Depression?

Depression is characterized as a mood disorder that causes persistent feelings of sadness and loss of interest in things that the individual once enjoyed. The prevailing characteristics present in all depressive disorders encompass feelings of sadness, emptiness, or irritability, alongside somatic and cognitive changes that profoundly impact the individual's ability to function (Chand

& Arif, 2024). This disorder is common with an estimated worldwide prevalence of 3.8%. More specifically, 5% of adults suffer from depression, which then jumps to 5.7% when over the age of 60 (Depressive disorder, 2023). As per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), an individual must have at least five of the following symptoms to be diagnosed with depression: depressed or low mood, interest or pleasure reduction in once enjoyable activities, feelings of guilt or worthlessness, lack of energy, concentration impairments, appetite changes, psychomotor disturbances, sleep disturbances, or suicidal ideation. One of these symptoms, however, must be depressed mood or loss of interest/pleasure for the individual to be diagnosed with depression (Bains & Abdijadid, 2024; Chand & Arif, 2024).

At the neurochemical level, there has been much emphasis placed on the link between depression and neurotransmitter abnormalities, particularly the monoamines which include serotonin, dopamine, and noradrenaline (Kaltenboeck & Harmer, 2018). There are many findings involving serotonin that provide evidence for this idea of monoaminergic dysfunction in depression. For example, researchers found that depression is associated with decreased serotonin transporter binding in the midbrain and amygdala (Gryglewski et al., 2014) and decreased 5-HT1A receptor binding in frontal, temporal, and limbic regions (Sargent et al., 2000). It has also been shown that depression is associated with an increased density of monoamine oxidase A (enzyme that breaks down monoamines) (Bortolato et al., 2008; Meyer et al., 2006). It has been consistently shown that there is decreased dopaminergic signalling in major depression that may be due to dampened dopamine release from presynaptic neurons or impaired signal transduction, which is either due to alterations in receptor number or function and/or altered intracellular signal processing (Dunlop & Nemeroff, 2007). There are other neurotransmitters that are associated with depression such as GABA and glutamate (Kaltenboeck & Harmer, 2018). There is consistent evidence for lower levels of GABA in the plasma and CSF of depressed patients (Sanacora, 2010). There have also been studies that showed a decreased density of a subset of GABAergic interneurons in regions of the prefrontal and occipital cortex of depressed patients (Maciag et al., 2010; Rajkowska et al., 2007). As for glutamate, imaging studies have suggested decreased levels of glutamate in depressed patients, especially in anterior brain regions (Kaltenboeck & Harmer, 2018; Yüksel & Öngür, 2010). However, the strongest piece of evidence for the involvement of the glutamatergic system in depression is the rapid antidepressant effects of ketamine, an antagonist of the NMDA receptor (Mandal et al., 2019).

1.7.1 Treatment of Depression

The treatment options for depression are like those of anxiety with medication and psychotherapy proving useful in relieving symptoms. A combination of the two also works well and has been associated with higher rates of improvement in depressive symptoms, better quality of life, and enhanced adherence to treatment (Chand & Arif, 2024). Some examples of medications include SSRIs, SNRIs, atypical antidepressants, Serotonin-Dopamine Activity Modulators (SDAMs), Tricyclic antidepressants (TCAs), and Monoamine oxidase inhibitors (MAOIs). For psychotherapy, CBT and interpersonal therapy have been proven to be effective in treating depression (Chand & Arif, 2024). For patients who are not responding well to medications or are suicidal, electroconvulsive therapy is useful (Salik & Marwaha, 2024; Saracino & Nelson, 2019).

1.8 Anxiety and Depression after a TBI

Regardless of injury severity, a TBI is linked to an elevated risk of developing psychiatric disorders (Fann et al., 2004). TBI patients exhibit a higher prevalence (Schwarzbold et al., 2008) and longer duration (Koponen et al., 2002) of these disorders compared to the general population (Vaishnavi et al., 2009). It is important to consider the effects of psychiatric disorders following a

TBI as it increases patient disability, loss of income, costs, and medical use (Delmonico et al., 2022); making it an important issue that should not be ignored. Affective disorders like anxiety, depression, and adjustment disorders appear to be the most common psychiatric disorders after a TBI (Delmonico et al., 2022) with the prevalence of major depression and anxiety post-TBI estimated to be 25-50% and 10-70%, respectively (Vaishnavi et al., 2009). This larger variability for the prevalence of anxiety is due to limited studies on anxiety disorders following a TBI (Delmonico et al., 2022). For mTBI specifically, 17-31% of patients develop depressive symptoms making it among the most common neuropsychiatric consequence of mTBI (Roy et al., 2022). A recent study showed that 32.5% of mTBI patients presented with at least one anxiety disorder 12 months after injury and 20.5% of participants with a history of anxiety were significantly more anxious after the incident (Lamontagne et al., 2022).

The origin of post-TBI depression is complex, encompassing neurobiological mechanisms, pre-existing and concurrent individual factors, alterations in functional capability, independence and participation following the injury, as well as psychological factors linked to adaptation after the injury (Juengst et al., 2017). Several neurobiological mechanisms are implicated in post-TBI depression. Evidence suggests a connection between mood disorders following TBI and the disruption of neural circuits involved in emotional regulation, encompassing regions such as the prefrontal cortex, amygdala, hippocampus, insula, basal ganglia, and thalamus (Jolly et al., 2019; Jorge & Starkstein, 2005; Moreno-López et al., 2016). After an individual sustains a TBI, there is an increase in extracellular glutamate which results in unusually high levels of intracellular calcium (Fisher et al., 2019). It has been previously shown that the upregulation of both glutamate and calcium is associated with neuronal cell death in the hippocampus of patients with major depressive disorder (MDD) (Lee et al., 2002). This may provide a potential pathway for the development of MDD after TBI as both are associated with a reduction in hippocampal volume (Fisher et al., 2019). This observed decrease in regional brain volume could be explained by the diminished involvement of brain-derived neurotrophic factor (BDNF) which has been documented in both MDD and TBI cases (Korley et al., 2016; Lee & Kim, 2010). BDNF is primarily associated with neurogenesis, so insufficient production may be a plausible mechanism for this phenomenon (Fisher et al., 2019). In general, post-TBI depression correlates with diminished gray matter measures (volume, thickness, and/or density) and increased white matter damage. Consistently replicated findings across multiple studies demonstrated reduced gray matter in the rostral anterior cingulate cortex, prefrontal cortex, and hippocampus, as well as damage to five white matter tracts (cingulum, internal capsule, superior longitudinal fasciculi, and anterior and posterior corona radiata) (Medeiros et al., 2022).

Apart from these potential neurobiological mechanisms, the strongest predictors of post-TBI depression are associated with non-injury factors such as unemployment or a history of depression before injury (Cnossen et al., 2017). It has also been shown that individuals with a history of mTBI face over three times the risk of experiencing depression compared to those without a history of mTBI, and this risk extends for decades beyond the injury and into later life (Hellewell et al., 2020; Manley et al., 2017). Patients may also struggle to adjust to the injury and/or the changes in their personal, social, and professional lives which can cause some frustration and lower self-esteem, contributing to the development of depression (Fisher et al., 2019).

The causes of anxiety after an mTBI remain unclear, however it has been suggested that prefrontal cortex dysfunction after injury may be linked to the emergence of anxiety (Rauch et al., 2006). Alternative theories propose that the injury induces a transient psychological susceptibility to the emergence of mental health disorders. This vulnerability is thought to be influenced by various stressors encountered during the accident itself such as the transition to a hospital setting, hospitalization, or the adjustment to deficits associated with mTBI (Mooney & Speed, 2001). A prior history of mental health challenges may elevate the susceptibility to anxiety disorders following TBI (Moore et al., 2006). Individuals with a pre-existing background of psychological disorders are indeed more prone to developing anxiety and may possess fewer adaptive strategies (Ponsford et al., 2012). One study showed that individuals with a history of anxiety disorders are nine times more likely to experience post-injury anxiety disorders compared to those without a prior history (Gould et al., 2011).

Certain risk factors can contribute to the development of both anxiety and/or depression after injury including the female gender, younger age, lower education, and pre-injury unemployment (Hart et al., 2014). Similarly, common neurobiological theories can explain the emergence of anxiety and/or depression after a TBI. One such theory posits that the chronic neuroinflammation following a TBI may contribute to the development of anxiety and/or depression after injury (Bodnar et al., 2018; Rodgers et al., 2014). In cases of depression in the general population, there is an increase in cytokines and this increase is also seen following a TBI. The use of biomarkers shows that the levels of cytokines peak hours to days after injury and pro-inflammatory cytokines can still be elevated above normal levels months to years after a TBI, which aligns with the timeframe that post-TBI depression typically emerges (Bodnar et al., 2018). Similarly, the inflammatory response after TBI has been the target for treatment of anxiety after injury. Research has consistently shown that chronic neuroinflammation persists for months to years after injury and there is evidence of this inflammation in patients with GAD, post-traumatic stress disorder (PTSD), panic disorder, and obsessive-compulsive disorder (OCD) (Rodgers et al., 2014).

1.9 Relationship Between mTBI Recovery and Anxiety/Depression

Anxiety and depression seem to play a role in the functional outcome and recovery of mTBI patients. The risk of developing PCS was found to be highest in those with a pre-injury history of psychiatric disorders and a history of anxiety and/or depression (Langer et al., 2021). One study showed that about every fourth mTBI patient had a psychiatric disorder and these patients reported more post-concussion symptoms and their functional outcome was worse one month after injury (Marinkovic et al., 2020). Another study with first-time mTBI victims demonstrated that patients with depressive symptoms had more post concussive symptoms and incomplete functional recovery in the first six months after injury compared to those with no depressive symptoms (Roy et al., 2022). It has also recently been shown that mTBI patients who were anxious four months after injury had more mTBI-related symptoms in different categories 12 months after the incident compared to patients who were not anxious. This shows that anxiety may play a role in the exacerbation and prolongation of mTBI symptoms (Lamontagne et al., 2022).

Anxiety and depressive disorders significantly influence the functional outcomes of individuals with TBI and substantially diminish their HRQL (multi-dimensional concept that gathers information regarding the physical and mental health status of individuals and thus the influence of their health status on quality of life (Yin et al., 2016)) (Scholten et al., 2016). Therefore, the early identification and treatment of psychiatric disorders in TBI patients is crucial and may improve outcome, psychosocial functioning, and HRQL (Scholten et al., 2016). There are not many studies that investigated whether early treatment of anxiety and depression does indeed improve patient outcome, but one study found that post-TBI rehabilitation significantly reduced the risk of psychiatric disorders (Yeh et al., 2020). This shows the need for early identification and treatment of these disorders to improve patient recovery and outcome (Scholten et al., 2016).

1.9.1 Treatment of Anxiety and Depression after mTBI

Given this information, it is important to determine the best methods to treat these patients who develop depression and/or anxiety post mTBI. Depression symptoms following TBI are typically addressed with pharmacotherapy, although there is limited methodologically rigorous research guiding clinical practice and no universally accepted treatment standard (Juengst et al., 2017). Clinical guidelines commonly recommend SSRIs as a first-line treatment, while TCAs, stimulants, SNRIs, and tetracyclic antidepressants are also considered options (Hicks et al., 2023). Surveys of clinical practice align with these recommendations, revealing that SSRIs, particularly citalopram, escitalopram, and sertraline, are the most frequently prescribed medications for post-TBI depression. Additionally, mirtazapine, a tetracyclic antidepressant, is commonly utilized (Albrecht et al., 2015). Regardless of the treatment, a patient can develop depressive symptoms as early as one week after injury, so interventions should be promptly administered (Bay, 2009). For treatment of anxiety after TBI, it was found that patients were mostly prescribed psychotropic medication such as antidepressants (majority), intermediate-acting benzodiazepines, and anticonvulsants, with few patients receiving psychotherapy (Marks et al., 2022).

1.9.2 Screening of Anxiety and Depression after mTBI

The importance of early screening of anxiety and depression post-injury provokes some exploration on the current tools being used in the literature to do so. For anxiety, it has been shown that the GAD-7 holds diagnostic usefulness as a screening tool for identifying anxiety disorders in TBI patients. It is important to note that this questionnaire should not be used in isolation, but it must be incorporated into a broader assessment alongside thorough patient interviews and history. By integrating the GAD-7 into such assessments, clinicians can better identify and address anxiety symptoms, leading to more timely treatment interventions (Zachar-Tirado & Donders, 2021).

With regards to depression, the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) is renowned for its extensive use as a depression screening tool in both TBI patients and in general populations. Despite its robust psychometric performance in adults with TBI (Bombardier et al., 2010; Bombardier et al., 2016; Dyer et al., 2016; Fann et al., 2005), there exists some debate in the literature concerning whether screening tools for TBI patients should incorporate the assessment of somatic symptoms, as is the case for the PHQ-9 (Cohen et al., 2018). The main concern is that somatic symptoms like fatigue or sleep disturbances might be attributable to the TBI rather than depression (Gass & Russell, 1991; Gass & Wald, 1997; Kim et al., 2007; Rosenthal et al., 1998). Certainly, emotional symptoms of depression might offer greater diagnostic value post-TBI compared to vegetative symptoms (Jorge et al., 1993). Conversely, an argument posits that somatic symptoms are integral to clinical diagnosis, supported by robust evidence indicating that items assessing somatic symptoms are impartial to individuals with TBI (Cook et al., 2011; Dyer et al., 2016). Therefore, there are both sides to the argument, but it is still important to be aware of this when screening for symptoms of depression (as well as anxiety) in patients with TBI. Other tools such as the Hamilton Rating Scale for Depression (HAM-D), Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS) show a high validity and utility in screening for depression in patients with severe TBI (Schwarzbold et al., 2014). The Center for Epidemiologic Studies-Depression scale (CES-D), a questionnaire consisting of 20 items (Radloff, 1977), has shown to be a valid and reliable screening tool for symptoms of depression in TBI patients (Bush et al., 2004) and has also proven useful for measuring these symptoms in patients with mild to moderate TBI (McCauley et al., 2006).

Despite the common use of the GAD-7 and PHQ-9 as screening tools for anxiety and depression, respectively, they have been used in TBI research in different ways. In a study exploring the association of anxiety and depression with TBI, the researchers used the GAD-7 and PHQ-9 as a mental health assessment of their participants. This helped them find evidence that there is a significantly higher incidence of anxiety and depression in those with a history of mTBI compared to controls (Al-Kader et al., 2022). Another study used these questionnaires on TBI patients to investigate the frequency, concurrent presence, and alterations in scores of the GAD-7 and PHQ-9 during evaluations conducted at 3 months, 6 months, and 12 months post-TBI. This helped the authors find a high consistency in symptoms of anxiety and depression, where 49-67% of post-TBI patients experiencing both conditions reported a persistence of their symptoms over time (Teymoori et al., 2020). Therefore, the literature suggests that the GAD-7 and PHQ-9 are amongst the most widely used tools aimed at screening for symptoms of anxiety and depression, whether it be in patients with TBI or in other medical settings.

In summary, this literature review emphasizes the significant prevalence of mTBI and its consequential impact on patients, highlighting the importance of addressing this topic. It also illustrates that in addition to the typical symptoms experienced by mTBI patients, many can develop neuropsychological issues such as anxiety and/or depression, or symptoms thereof, which can adversely affect their recovery and overall outcome. It is widely acknowledged and recommended that early interventions targeting these psychiatric disorders would benefit mTBI patients. Therefore, we decided it was crucial to administer questionnaires to screen for symptoms of anxiety and depression, aiming to identify individuals at risk of developing these psychiatric disorders post-injury. This early identification should enable clinicians to refer these patients to appropriate resources before their recovery is negatively impacted, ultimately improving their outcome.

Chapter 2: Methodology

2.1 Study Design and Patients

In this retrospective study, data was collected from the medical records of 328 patients who were under the care of the mTBI Clinic at the Montreal General Hospital (MGH), a level 1 trauma center, part of the McGill University Health Centre (MUHC). The inclusion criteria are as follows: 1) patients with a confirmed diagnosis of mTBI, 2) outpatients, and 3) patients who have had a visit with an mTBI Clinic physician. This study was approved by the Research Ethics Board of the MUHC Research Institute (2023-9134).

The patients were separated into two distinct cohorts based on whether they were administered the questionnaires. The pre-questionnaire group, comprising of 185 mTBI patients, did not receive the GAD-7 and CESDR-10 questionnaires. The period studied for this group was between March 1, 2019, and March 1, 2020, so the patients had clinic visits related to their injury within this range. We chose this as the period of study as the period spanning between March 2020 and May 2022 had less in-person visits due to the COVID-19 pandemic and may introduce biases of referral. The post-questionnaire group, consisting of 143 mTBI patients, received the GAD-7 and CESDR-10 questionnaires. Although the CESDR-10 has not been used in TBI populations, our reasoning for using it was twofold: 1) the CES-D (original and longer version of the CESDR-10 consisting of 20 items (Radloff, 1977)) was validated with the TBI population (Bush et al., 2004; McCauley et al., 2006) and 2) amongst the questionnaires that assess symptoms of depression, the CESDR-10 has the least amount of items focusing on somatic symptoms (two of the items (El-Ammari et al., 2023)), which is important for its use in TBI populations as their symptoms may resemble those covered by the questionnaire, potentially leading to inaccurate scores and decreased reliability. In addition, the retest reliability and validity of the CES-D and

CESDR-10 questionnaires are almost the same (Miller et al., 2008). The distribution of these questionnaires by the mTBI Clinic physicians began in September 2022. Therefore, the study period for this group encompasses clinic visits related to their injury occurring between September 1, 2022, and September 1, 2023.

2.2 Collected Variables

All medical files were consulted using OACIS, a system that the MUHC uses as an electronic medical record database, with the goal of obtaining patient demographic information, pre-morbid status, outcome information, and GAD-7/CESDR-10 scores. The collected data are those that are only present in the MGH medical file of the patients and are systematically documented by the treating medical and professional team.

2.2.1 Demographic Information

The demographic data collected encompasses various key attributes, including age at the time of injury, sex, and education level. Patient age was recorded as a continuous variable while their sex is a categorical variable with two levels: female and male. Notably, patient education level was determined based on the completed educational qualifications at the time of their injury, excluding any ongoing studies. This categorical variable consists of five distinct values: elementary school, high school, trade school, CEGEP, and university.

2.2.2 Pre-Morbid Status

The pre-morbid status encompasses patient medical history and pre-injury psychiatric history. In our study, we employed the Charlson Comorbidity Index (CCI) (Charlson et al., 1987) and the Cumulative Illness Rating Scale-Geriatrics (CIRS-G) (Miller et al., 1992) to quantitively assess the patients' medical history, thus making them continuous variables. The CCI serves as a predictive tool for estimating the ten-year mortality risk in patients with multiple comorbidities and assigns scores ranging from 0 (indicating no comorbidities) to 37 (indicating the highest risk of death or increased resource utilization) (Charlson et al., 1987). The CIRS-G, on the other hand, measures the overall burden of disease, including medical and psychiatric impairments, among elderly patients aged over 65. The scale ranges from 0 to 56, with higher scores indicating greater disease severity (Miller et al., 1992). Although this tool is designed for use in geriatric populations, we still decided to apply the scale to all patients in this study, regardless of age, because it is useful and detailed. We meticulously documented the medical history of each patient and the neurosurgeon on the team, using the CCI and CIRS-G scales, assigned scores to the patients based on the collected information.

Concerning the pre-injury psychiatric history of the patients, we documented whether they had been diagnosed with anxiety and/or depression before sustaining their injury, which were categorical variables coded dichotomously (yes/no). We only considered patients with an official diagnosis, even though some individuals self-reported symptoms of these psychiatric conditions that were not formally documented as part of their medical history.

2.2.3 Outcome Information

Number of Interventions Prescribed

As part of our investigation, we recognized the importance of directing patients to various supportive resources to help in their recovery from the mTBI. Consequently, we introduced a variable called "number of interventions prescribed" which serves to quantify the number of resources to which patients were referred during their clinic visits, all aimed at facilitating their recuperation and thus improving their outcome following the injury. We decided to make this variable categorical in our main analyses as the total number of interventions prescribed to patients were fixed values between zero and four. Our consideration encompassed four specific resources:

vestibular therapy, neuropsychology, outpatient rehabilitation, and psychology; each of which are categorical variables coded dichotomously (yes/no).

Glasgow Outcome Scale-Extended (GOS-E)

To evaluate the impact of the questionnaires on the recovery and outcome of the mTBI patients in our study, we sought an appropriate outcome measure. The GOS-E was selected for its widespread use in assessing global disability and recovery post-TBI as well as its usefulness in mTBI cohorts (Nelson et al., 2019; Wilson et al., 2021). This 8-point scale encompasses distinct categories, ranging from the least favourable outcome, "dead" (score of 1), to the most favourable, "upper good recovery" (score of 8) (Wilson et al., 2021). While the conventional administration involves clinician-patient interviews (Wilson et al., 2021), we used the GOS-E solely as a reference to assign an outcome score to the patients based on the data we collected from their medical files regarding the progression of their symptoms and recovery. The neurosurgeon on the team used this information in conjunction with the scale to assign a score to each patient. Given that the patients in our sample mostly had GOS-E scores of six, seven or eight, we decided to make it a categorical variable in our main analyses.

2.3 Questionnaires

The GAD-7 and CESDR-10 questionnaires were administered at the initial mTBI Clinic visit following injury and the total scores were calculated during the data collection process. Only patients in the post-questionnaire group received them and they are self-administered. The GAD-7 and CESDR-10 are two of the most utilized instruments for identifying the likelihood of experiencing anxiety and depression, within both clinical settings and research environments (Romano et al., 2022). The medical team appreciated that they are also both short questionnaires, making them easy for our cohort to complete and for the clinicians to score.

2.3.1 Generalized Anxiety Disorder 7-Item (GAD-7)

The GAD-7 is a self-report questionnaire consisting of seven items, designed to measure or assess the severity of GAD. Demonstrating validity and efficiency, the GAD-7 serves as a reliable tool for screening for GAD and assessing its severity in clinical and research settings. Moreover, its reliability and validity extend to its utility in measuring anxiety in the general population (Löwe et al., 2008; Spitzer et al., 2006). While this tool has been validated for use in TBI populations (Teymoori et al., 2020), it has not been specifically validated for use in patients with mTBI. Nevertheless, it has been employed in studies to assess anxiety in their cohort of mTBI patients (Al-Kader et al., 2022; Eagle et al., 2021). Each item prompts the patient to reflect on the frequency of experiencing specific symptoms over the past two weeks (Spitzer et al., 2006). Responses range from "not at all" to "nearly every day," with corresponding scores of 0 to 3, respectively. The cumulative score, ranging from 0 to 21, provides an indication of anxiety severity: scores of 0-4 suggest minimal anxiety, 5-9 indicate mild anxiety, 10-14 imply moderate anxiety, and 15-21 signify severe anxiety (Spitzer et al., 2006). It is important to note that while the GAD-7 offers valuable insights, it should be complemented with further evaluation by a healthcare professional for diagnostic confirmation.

2.3.2 Center for Epidemiologic Studies Depression Scale Revised (CESDR-10)

The CESDR-10, a 10-item self-report measure of depression, prompts individuals to reflect on their emotions and behaviors over the past week. Demonstrating validity, reliability, and consistency, the CESDR-10 proves effective in primary care settings and among the general population (Björgvinsson et al., 2013; Miller et al., 2008; Radloff, 1977). Although this questionnaire has not been validated in TBI patients, the longer version (CES-D) has (Bush et al., 2004) and the emphasis of the CESDR-10 on emotional rather than physical symptoms makes it a reliable tool to assess depression within our cohort. Respondents rate the frequency of each described feeling or behavior using a scale ranging from "rarely or none of the time (less than 1 day)" to "all of the time (5-7 days)," with scores of 0 to 3, respectively. Notably, the scoring reverses for items 5 and 8 and the total score is calculated by summing the scores of all items. A total score of 10 or higher suggests that the individual is depressed, while the questionnaire should not be scored if more than two items are missing (Björgvinsson et al., 2013; Miller et al., 2008; Radloff, 1977).

2.4 Data Analysis

All analyses were performed using IBM SPSS Statistics software (version 29.0) and α was set at .05. Descriptive statistics were computed for all variables and reported as means and standard deviations for continuous variables, whereas frequencies and percentages were reported for categorical variables. Initially, preliminary analyses were performed to verify the comparability of both groups concerning demographic, pre-morbid, and outcome information. Independent samples *t*-tests were conducted for continuous variables, while Chi-squared tests were employed for categorical variables. Some continuous variables (number of interventions prescribed and GOS-E score) were analyzed with *t*-tests and then transformed into categorical variables since it was more fitting for our subsequent regression analyses, and we performed Chi-squared tests on these variables to further our understanding of group differences. For the Chi-squared tests that showed significance for categorical variables with more than two groups, we performed a pairwise z-test post-hoc analysis with Bonferroni correction to determine which subgroups are different from one another. The main analysis focused on applying either ordinal or binary logistic regression models to explore the three research questions. For the binary logistic regression models with neuropsychology and psychology as the dependent variables and the ordinal logistic regression with GOS-E score as the dependent variable, we decided to remove the education level and CIRS-G score variables to promote a better fit to our data as some goodness of fit and model fitting tests were not met. As well, there was a great number of missing data for education level (*N* = 48) which decreases the power of the regressions and the CIRS-G scale is used for patients aged over 65, so we chose to include the CCI score in the model when we had to decide between the two.

Chapter 3: Results

3.1 Demographic, Clinical and Outcome Information

The characteristics of the patients, including demographic, clinical, and outcome information, along with comparisons between the pre- and post-questionnaire groups, are detailed in Table 1 for the continuous variables and Table 2 for the categorical ones. In addition to the frequencies and percentages, we decided to present the mean and standard deviation of the number of interventions prescribed and GOS-E score variables to better demonstrate the differences between groups. No significant differences were observed between the two groups across several variables, such as age, sex, education level, CCI and CIRS-G scores, as well as referrals to neuropsychology, outpatient rehabilitation, and psychology. However, significant differences between groups were found for pre-injury history of anxiety and depression variables, number of interventions prescribed, vestibular therapy, and GOS-E scores. More specifically, there were significantly more patients in the post-questionnaire group that had a pre-injury diagnosis of anxiety or depression than the pre-questionnaire group. The patients in the post-questionnaire group also received significantly more referrals to vestibular therapy. Based on the *t*-tests, there was a significantly higher number of interventions prescribed to patients in the post-questionnaire group compared to those in the pre-questionnaire group. However, post-hoc analyses for the Chi-squared test revealed that this difference is primarily in the "no interventions" subgroup. This indicates that the percentage of patients who received no interventions is significantly higher for those who did not receive the questionnaires compared to those who did (p<0.05). Additionally, the patients who received the questionnaires exhibited a significantly higher mean GOS-E score compared to those who did not. Further post-hoc analyses showed that significantly more patients in the pre-questionnaire group had a GOS-E score of seven compared to the post-questionnaire group ($p<0.05$), while there were significantly more patients in the post-questionnaire group with a GOS-E score of eight ($p<0.05$).

The average age of the sample was 40.82 (±16.047), ranging from 16 to 93 years, with the majority being female (62.2%) and possessing a university level of education (44.2%). Notably, 28.4% of patients had a pre-injury anxiety diagnosis (22.7% in pre- and 35.7% in post-questionnaire group), and 27.4% had pre-injury depression (22.7% of patients in pre- and 33.6% of patients in post-questionnaire group). The average CCI and CIRS-G scores were 0.75 (±1.367) and 1.40 (±1.801), respectively, both ranging from zero to nine. Furthermore, 29.0% of patients received no interventions, 42.7% had one, and 21.0% had two, while others had three or four interventions. Specifically, 53.0% were referred to vestibular therapy, 19.8% to a neuropsychologist, 20.4% to outpatient rehabilitation, and 12.2% to a psychologist. Most of the sample achieved GOS-E scores of seven (50.6%) and eight (41.2%), indicating a relatively positive recovery trajectory. The GAD-7 scores ranged from 0 to 21, with only one patient not completing the questionnaire. Additionally, five patients did not complete the CESDR-10 questionnaire, but for the remaining 138 who did, the scores ranged from 0 to 30. Some variables had missing values, with education level exhibiting the largest amount of missing data ($N = 48$) compared to the other measures.

Table 1. Demographic, clinical and outcome continuous variables by groups.

Variables	Total (*N*=328)	Pre-Questionnaire Group (*n*=185)	Post-Questionnaire Group (*n*=143)	*t*	*df*	*p* value	*N*
Age	40.82 (16.047)	41.17 (16.449)	40.36 (15.557)	0.449	326	0.653	328
CCI score	0.75 (1.367)	0.72 (1.288)	0.80 (1.466)	-0.514	326	0.608	328
CIRS-G score	1.40 (1.801)	1.40 (1.761)	1.41 (1.859)	-0.028	326	0.978	328
Interventions prescribed	1.07 (0.049)	0.89 (0.843)	1.30 (0.896)	-4.294	326	<0.001	328
GOS-E score	7.32 (0.036)	7.15 (0.595)	7.55 (0.636)	-5.907	294.961	<0.001	328
GAD-7 score	9.65 (5.936)	-	9.65 (5.936)	-	-	-	142
CESDR-10 score	13.95 (6.905)	-	13.95 (6.905)	-	-	-	138

The means are reported with standard deviations in parentheses and all comparisons were conducted using independent samples *t*-tests with the t-statistic (*t*) and degrees of freedom (*df*) reported as well.

Table 2. Demographic, clinical and outcome categorical variables by groups.

Variables	Total (*N*=328)	Pre-Questionnaire Group (*n*=185)	Post-Questionnaire Group (*n*=143)	χ^2	*df*	*p* value	*N*
Sex				0.059	1	0.808	328
Female	204 (62.2%)	114 (61.6%)	90 (62.9%)				
Male	124 (37.8%)	71 (38.4%)	53 (37.1%)				
Education level				2.818	4	0.589	280
Elementary	12 (3.7%)	5 (2.7%)	7 (4.9%)				
High school	48 (14.6%)	31 (16.8%)	17 (11.9%)				
Trade school	11 (3.4%)	6 (3.2%)	5 (3.5%)				
CEGEP	64 (19.5%)	37 (20.0%)	27 (18.9%)				
University	145 (44.2%)	78 (42.2%)	67 (46.9%)				
Unknown	48 (14.6%)	28 (15.1%)	20 (13.9%)				
Pre-injury anxiety				6.891	1	0.009	327
Yes	93 (28.4%)	42 (22.7%)	51 (35.7%)				
No	234 (71.3%)	143 (77.3%)	91 (63.6%)				
Pre-injury depression				4.962	1	0.026	327
Yes	90 (27.4%)	42 (22.7%)	48 (33.6%)				
No	237 (72.3%)	143 (77.3%)	94 (65.7%)				
Interventions prescribed				18.536	4	<0.001	328
None	95 (29.0%)	69 (37.3%)*	26 (18.2%)*				
1	140 (42.7%)	76 (41.1%)	64 (44.8%)				
2	69 (21.0%)	32 (17.3%)	37 (25.9%)				
3	17 (5.2%)	6 (3.2%)	11 (7.7%)				
4	7 (2.1%)	2 (1.1%)	5 (3.5%)				
Vestibular therapy				21.203	1	<0.001	328
Yes	187 (53.0%)	85 (45.9%)	102 (71.3%)				
No	141 (43.0%)	100 (54.1%)	41 (28.7%)				
Neuropsychology				0.553	1	0.457	328
Yes	65 (19.8%)	34 (18.4%)	31 (21.7%)				
No	263 (80.2%)	151 (81.6%)	112 (78.3%)				
Outpatient rehabilitation				3.516	1	0.061	328
Yes	67 (20.4%)	31 (16.8%)	36 (25.2%)				
No	261 (79.6%)	154 (83.2%)	107 (74.8%)				
Psychology				2.409	1	0.121	328
Yes	40 (12.2%)	18 (9.7%)	22 (15.4%)				
No	288 (87.8%)	167 (90.3%)	121 (84.6%)				
GOS-E score				52.606	3	<0.001	328
4	1 (0.3%)	1 (0.5%)	0				
6	26 (7.9%)	15 (8.1%)	11 (7.7%)				
7	166 (50.6%)	124 (67.0%)*	42 (29.4%)*				
8	135 (41.2%)	45 (24.3%)*	90 (62.9%)*				

The numerical values signify the raw count of patients, while the figures in parentheses denote the corresponding percentage within the sample. All comparisons were conducted using Chi-squared tests with the Chi-square statistic value (χ^2) and degrees of freedom (*df*) reported as well. *Post-hoc analyses revealed a significant difference between the subgroup ($p<0.05$).

3.2 Do the Scores on the Questionnaires Predict the Number of Interventions Prescribed?

To address this question, we conducted an ordinal logistic regression analysis on the data obtained from the post-questionnaire group with the number of interventions prescribed as the dependent variable and age, sex, education level, pre-injury history of anxiety/depression, CCI/CIRS-G scores, and GAD-7/CESDR-10 scores as independent variables. To better fit the model to our data, we merged trade school with high school due to the small number of patients in the former category and excluded all patients with an elementary school level of education, as there were too few in this category and may be considered atypical when compared to the general population. A few patients were referred to all four interventions throughout their clinic visits, so we combined this category with those who received a total of three referrals, thus making "number of interventions prescribed" an ordinal variable with four levels: zero, one, two, and three. Therefore, the final sample size included in this analysis was 113 patients, which considers missing data as well. The test of parallel lines ($\chi^2(20) = 18.694$, $p = 0.542$) indicated that the proportional odds assumption was met (main assumption of the ordinal regression) and the Deviance Goodness-of-Fit Test indicated that the model fits the data well ($\chi^2(326) = 240.866$, $p = 1.000$), as demonstrated by the *p* values exceeding 0.05.

The results from the ordinal logistic regression (Table 3) showed that pre-injury depression was statistically significant at a 5% level of significance. The estimated odds ratio (OR = 2.658, 95% CI, 1.117-6.326) showed that those who had a diagnosis of depression before their mTBI were 2.658 times more likely to have more interventions prescribed to them throughout their clinic visits as compared to patients without a history of depression, holding all other variables constant. This suggests that pre-injury depression plays a crucial role in the number of resources patients obtained after sustaining an mTBI. The results also showed that CESDR-10 scores were significantly related to the number of interventions prescribed (OR = 1.107, 95% CI, 1.017-1.205). The odds of having a greater number of interventions prescribed are 1.107 times greater for mTBI patients with higher scores on this questionnaire compared to those with lower scores. In other words, if we increase the CESDR-10 score by one unit, we can expect to see about an 11% increase in the odds of the patient having more interventions prescribed to them.

Table 3. Parameter estimates of ordinal logistic regression using number of interventions prescribed as the dependent variable with four-ordered categories.

Variable	Estimate	S. E	*p* value	OR	95% CI for OR	
Age	0.029	0.0171	0.090	1.029	0.995	1.064
Sex						
Male	0			1		
Female	0.186	0.3912	0.634	1.205	0.560	2.594
Education level						
University	0			1		
Cegep	-0.075	0.4861	0.878	0.928	0.358	2.406
High school	-0.108	0.5076	0.831	0.897	0.332	2.426
Pre-injury anxiety						
No	0			1		
Yes	-0.105	0.4301	0.808	0.901	0.388	2.092
Pre-injury depression						
No	0			1		
Yes	0.978	0.4423	0.027	2.658	1.117	6.326
CCI score	-0.328	0.2170	0.131	0.721	0.471	1.103
CIRS-G score	0.101	0.1549	0.513	1.107	0.817	1.499
GAD-7 score	0.044	0.0496	0.370	1.045	0.949	1.152
CESDR-10 score	0.102	0.0433	0.019	1.107	1.017	1.205
Threshold						
None	1.397	0.7694	0.069	4.044	0.895	18.269
One intervention	4.192	0.8713	<0.001	66.154	11.992	364.941
Two interventions	5.995	0.9511	<0.001	401.502	62.241	2590.000

Parallel line test: 0.542, goodness-of-fit test of overall model: deviance, p value = 1.00, Nagelkerke's R^2 = 0.316, S.E: standard error, OR: odds ratio, CI: 95% confidence interval for coefficients
Final sample size for analysis: N = 113

3.3 Do the Scores on the Questionnaires Predict Referrals to Specific Interventions?

In our endeavor to extend the depth of our analysis, we sought to investigate whether the scores on the questionnaires could serve as predictors for clinician referrals to targeted interventions, including vestibular therapy, outpatient rehabilitation, neuropsychology, and psychology. Utilizing the same independent variables as in our previous analysis, we designated vestibular therapy as the dependent variable. Given that this variable is dichotomous, we performed a binary logistic regression and assigned the "no" value as the reference category, which will be consistent for all subsequent analyses in this section. This means that the odds ratios reported represent the likelihood of being in the "yes" category of the dependent variable, so receiving a referral to the specific intervention of interest. The Hosmer and Lemeshow test showed that the model fits the data ($\chi^2(8) = 2.610$, $p = 0.956$) and the Deviance Goodness-of-Fit Test indicated that the model is a good fit to the data ($\chi^2(102) = 108.228$, $p = 0.318$), as demonstrated by the p values exceeding 0.05. Our analysis, as presented in Table 4, revealed that age emerged as a statistically significant factor at a 5% level of significance. The estimated odds ratio (OR = 1.050, 95% CI, 1.004-1.098) indicates that with each one unit increase in age, the likelihood of a patient being referred to vestibular therapy increases by 1.050 times, signifying a 5% rise in the odds of receiving this referral.

Table 4. Parameter estimates of binary logistic regression using vestibular therapy as the dependent variable with two categories.

Variable	Estimate	S. E	*p* value	OR	95% CI for OR	
Age	0.048	0.023	0.034	1.050	1.004	1.098
Sex						
Male	0			1		
Female	0.824	0.502	0.100	2.280	0.853	6.095
Education level						
University	0			1		
Cegep	0.454	0.695	0.513	1.575	0.404	6.146
High school	-0.833	0.659	0.207	0.435	0.119	1.584
Pre-injury anxiety						
No	0			1		
Yes	0.651	0.612	0.287	1.918	0.578	6.359
Pre-injury depression						
No	0			1		
Yes	0.062	0.603	0.918	1.064	0.326	3.467
CCI score	-0.408	0.253	0.106	0.665	0.405	1.091
CIRS-G score	0.345	0.243	0.155	1.412	0.877	2.273
GAD-7 score	0.035	0.064	0.579	1.036	0.914	1.174
CESDR-10 score	0.038	0.057	0.503	1.039	0.930	1.160
Intercept	-2.451	1.059	0.021			

Omnibus test of model coefficients: p value = 0.002, Hosmer and Lemeshow test: p value = 0.956, goodness-of-fit test of overall model: deviance, p value = 0.318, Nagelkerke's $R^2 = 0.316$
Final sample size for analysis: $N = 113$

Subsequently, we conducted a similar analysis to ascertain whether questionnaire scores could predict referrals to outpatient rehabilitation. The Hosmer and Lemeshow test showed that the model fits the data ($\chi^2(8) = 4.490$, $p = 0.810$) and the Deviance Goodness-of-Fit Test indicated that this is a good fit ($\chi^2(102) = 101.320$, $p = 0.500$). Our findings, detailed in Table 5, revealed that none of the variables emerged as significant predictors of referrals to this specific intervention, as denoted by the non-significant *p* value from the Omnibus Test of Model Coefficients ($\chi^2(10) = 15.545$, $p = 0.113$).

Table 5. Parameter estimates of binary logistic regression using outpatient rehabilitation as the dependent variable with two categories.

Variable	Estimate	S. E	*p* value	OR	95% CI for OR	
Age	0.046	0.030	0.123	1.047	0.988	1.110
Sex						
Male	0			1		
Female	-0.251	0.537	0.641	0.778	0.272	2.229
Education level						
University	0			1		
Cegep	-0.127	0.752	0.866	0.881	0.202	3.843
High school	1.165	0.677	0.085	3.207	0.850	12.096
Pre-injury anxiety						
No	0			1		
Yes	-0.027	0.614	0.965	0.973	0.292	3.243
Pre-injury depression						
No	0			1		
Yes	0.668	0.576	0.246	1.951	0.631	6.032
CCI score	-0.865	0.470	0.066	0.421	0.167	1.059
CIRS-G score	-0.114	0.250	0.647	0.892	0.547	1.455
GAD-7 score	0.004	0.068	0.959	1.004	0.878	1.148
CESDR-10 score	0.103	0.060	0.088	1.109	0.985	1.248
Intercept	-4.411	1.370	0.001			

Omnibus test of model coefficients: *p* value = 0.113, Hosmer and Lemeshow test: *p* value = 0.810, goodness-of-fit test of overall model: deviance, *p* value = 0.500, Nagelkerke's $R^2 = 0.199$
Final sample size for analysis: $N = 113$

Moving forward, we performed our analysis with neuropsychology as the dependent variable. To enhance the model's fit with the data, we omitted the CIRS-G and education level independent variables as their inclusion led to a failure of the Pearson goodness of fit test ($p<0.05$). This resulted in an increased final sample size of 137 patients for the analysis. The Hosmer and Lemeshow test showed that the model fits the data ($\chi^2(8) = 11.425$, $p = 0.179$) and the Deviance Goodness-of-Fit Test indicated a good fit of the model to the data ($\chi^2(129) = 125.204$, $p = 0.578$). The results of our binary logistic regression, presented in Table 6, revealed the statistical significance of pre-injury depression. The estimated odds ratio (OR = 2.614, 95% CI, 1.013-6.746) indicated that individuals with a pre-existing diagnosis of depression before their mTBI were 2.614 times more likely to be referred to a neuropsychologist compared to patients without a pre-injury history of depression.

Table 6. Parameter estimates of binary logistic regression using neuropsychology as the dependent variable with two categories.

Variable	Estimate	S. E	*p* value	OR	95% CI for OR	
Age	-0.14	0.022	0.520	0.986	0.944	1.030
Sex						
Male	0			1		
Female	-0.179	0.479	0.708	0.836	0.327	2.137
Pre-injury anxiety						
No	0			1		
Yes	-0.340	0.504	0.500	0.712	0.265	1.910
Pre-injury depression						
No	0			1		
Yes	0.961	0.484	0.047	2.614	1.013	6.746
CCI score	-0.076	0.261	0.773	0.927	0.555	1.548
GAD-7 score	0.066	0.059	0.259	1.069	0.952	1.199
CESDR-10 score	0.057	0.050	0.254	1.058	0.960	1.166
Intercept	-2.412	0.935	0.010			

Omnibus test of model coefficients: p value = 0.023, Hosmer and Lemeshow test: p value = 0.179, goodness-of-fit test of overall model: deviance, p value = 0.578, Nagelkerke's R^2 = 0.173
Final sample size for analysis: N = 137

Next, employing the same independent variables as the previous analysis, we examined psychology as the dependent variable to identify potential predictors for referrals to this intervention. The Hosmer and Lemeshow test showed that the model fits the data ($\chi^2(8) = 7.555$, $p = 0.478$) and the Deviance Goodness-of-Fit Test indicated that this is a good fit ($\chi^2(129) = 96.396$, $p = 0.986$). Our findings, detailed in Table 7, demonstrated a significant relationship between CESDR-10 scores and psychology referrals (OR = 1.200, 95% CI, 1.061-1.358). This signifies that with each one unit increase in the score on this questionnaire, the odds of a patient getting referred to a psychologist increases by 1.200 times, reflecting a 20% increase in the odds of receiving this referral.

Table 7. Parameter estimates of binary logistic regression using psychology as the dependent variable with two categories.

Variable	Estimate	S. E	*p* value	OR	95% CI for OR	
Age	-0.024	0.028	0.391	0.976	0.925	1.031
Sex						
Male	0			1		
Female	0.495	0.619	0.424	1.640	0.487	5.520
Pre-injury anxiety						
No	0			1		
Yes	-0.635	0.617	0.303	0.530	0.158	1.773
Pre-injury depression						
No	0			1		
Yes	0.218	0.583	0.709	1.243	0.396	3.901
CCI score	0.021	0.308	0.945	1.022	0.558	1.869
GAD-7 score	-0.051	0.067	0.450	0.951	0.834	1.084
CESDR-10 score	0.182	0.063	0.004	1.200	1.061	1.358
Intercept	-3.476	1.137	0.002			

Omnibus test of model coefficients: p value = 0.014, Hosmer and Lemeshow test: p value = 0.478, goodness-of-fit test of overall model: deviance, p value = 0.986, Nagelkerke's R^2 = 0.212
Final sample size for analysis: N = 137

3.4 Do the Specific Interventions Prescribed Predict Better Outcome?

To address this question, we conducted an ordinal logistic regression analysis on the data obtained from both groups with the GOS-E score as the dependent variable and age, CCI scores, sex, pre-injury history of anxiety/depression, number of interventions prescribed, vestibular therapy, neuropsychology, outpatient rehabilitation, and psychology as independent variables. Only one patient had a GOS-E score of four while all other patients had scores between six and eight, so this patient was an outlier and we excluded them from the model to better fit our data. As a result, the "GOS-E score" became an ordinal variable with three levels: six, seven, and eight; and the final sample size included in this analysis was 326 patients. The test of parallel lines ($\chi^2(12)$ = 10.144, p = 0.603) indicated that the proportional odds assumption was met, and the Deviance Goodness-of-Fit Test indicated that the model fits the data well ($\chi^2(594)$ = 504.483, p = 0.997).

The results from the ordinal logistic regression (Table 8) showed that the number of interventions prescribed was a significant factor that influences patient outcome. Those who have no referrals to any interventions (OR = 288.327, 95% CI, 1.141-72864.172) were 288.327 times more likely to have a GOS-E score of 8 as compared to those who received three or four interventions throughout their clinic visits. Furthermore, patients who have one intervention prescribed (OR = 54.144, 95% CI, 1.135-2582.735) were 54.144 times more likely to have a GOS-E score of 8 compared to those with more total referrals (three or four). Vestibular therapy was another significant factor that influences patient outcome. The estimated odds ratio (OR = 7.490, 95% CI, 1.244-45.084) indicated that those who were referred to vestibular therapy were 7.490 times more likely to have the best outcome score as compared to those who did not receive this referral. The results also showed that psychology was significantly related to patient outcome (OR = 8.249, 95% CI, 1.415-48.073). Patients that were referred to a psychologist were 8.249 times more likely to have the highest GOS-E score compared to those who were not referred to this intervention.

Table 8. Parameter estimates of ordinal logistic regression using GOS-E score as the dependent variable with three-ordered categories.

Variable	Estimate	S. E	*p* value	OR	95% CI for OR	
Age	-0.001	0.0103	0.923	0.999	0.979	1.019
CCI score	0.014	0.1236	0.911	1.014	0.796	1.292
Sex						
Male	0			1		
Female	-0.305	0.2353	0.195	0.737	0.465	1.169
Pre-injury anxiety						
No	0			1		
Yes	0.164	0.2566	0.522	1.179	0.713	1.949
Pre-injury depression						
No	0			1		
Yes	-0.073	0.2583	0.777	0.929	0.560	1.542
Interventions prescribed						
3	0			1		
2	1.608	1.1778	0.172	4.992	0.496	50.214
1	3.992	1.9720	0.043	54.144	1.135	2582.735
None	5.664	2.8226	0.045	288.327	1.141	72864.172
Vestibular therapy						
No	0			1		
Yes	2.014	0.9158	0.028	7.490	1.244	45.084
Neuropsychology						
No	0			1		
Yes	1.424	0.8782	0.105	4.152	0.743	23.219
Outpatient rehab						
No	0			1		
Yes	-0.049	0.8837	0.956	0.952	0.169	5.383
Psychology						
No	0			1		
Yes	2.110	0.8994	0.019	8.249	1.415	48.073
Threshold						
GOS-E score 6	2.367	2.8031	0.398	10.666	0.044	2593.951
GOS-E score 7	5.627	2.8266	0.047	277.858	1.091	70772.538

Parallel line test: 0.603, goodness-of-fit test of overall model: deviance, p value = 0.997, Nagelkerke's R^2 = 0.177, Final sample size for analysis: N = 326

Chapter 4: Discussion, Conclusion, and Future Directions

4.1 Discussion

In this study, our primary aim was to assess whether screening for symptoms of anxiety and depression following mTBI could assist clinicians in identifying patients who may be at risk of developing these psychiatric disorders and thus administer referrals to appropriate resources to enhance the overall recovery and well-being of these patients. To address all three of our research questions, we developed models based on the premise that individuals experiencing persistent symptoms are likely to face a more challenging path to recovery, necessitating a greater number of interventions to support their rehabilitation post-injury. This increased number of referrals reflects heightened clinical complexity, signifying a potentially less favorable outcome for the patient. As such, we conducted ordinal and binary logistic regression analyses for our models, depending on the dependent variable, along with established predictors as our independent variables that have been shown in the literature to impact recovery (Cassidy, Cancelliere, et al., 2014; Langer et al., 2021; Mikolić et al., 2021; Starkey et al., 2022) and thus the potential need for more interventions.

Before exploring the findings from our regression analyses, we performed *t*-tests and Chi-squared tests to assess the comparability of the variables in our models across the two groups. Our analyses revealed a significant association between the group receiving the questionnaires and pre-injury diagnoses of anxiety or depression among the patients. Notably, the post-questionnaire group exhibited a higher rate of these diagnoses compared to the pre-questionnaire group. This observation may be attributed to the fact that the patients in the post-questionnaire group sustained an mTBI after the onset of the COVID-19 pandemic. Considering the data from the WHO indicating a 25% global increase in the prevalence of anxiety and depression since the start of the pandemic (COVAX, 2022), this disparity in diagnoses between the two groups could be linked to the timing of their injuries relative to the pandemic. It is important to note how this difference between groups may affect the interpretation of the study results. As previously mentioned, it is well known in the literature that mTBI patients with a pre-injury history of anxiety and/or depression are more likely to experience persistent symptoms and have a complicated recovery (Langer et al., 2021; Rabinowitz et al., 2015). Therefore, knowing this information, the clinicians may be referring patients to more interventions due to their history of anxiety and/or depression before their injury rather than their scores on the questionnaires. Since more patients in the post-questionnaire group had a pre-injury history of anxiety or depression compared to the patients in the pre-questionnaire group, this may be why they received more referrals to different interventions on average.

Additionally, our analysis revealed that patients who received the questionnaires were referred to a significantly greater number of resources compared to those who did not. The large impact that a pre-injury diagnosis of depression had on the number of interventions prescribed, as per the ordinal logistic regression, shows that it is driving this between group difference. Specifically, among the four interventions assessed, vestibular therapy showed a notably higher number of referrals in the post-questionnaire group compared to the pre-questionnaire group. Surprisingly, we anticipated a greater number of referrals to interventions such as psychology and neuropsychology, which directly address symptoms of anxiety and depression, as measured by the questionnaires. However, it is plausible that the physical symptoms experienced, such as dizziness and imbalance, could also exert a negative impact on the patients' mental well-being by impeding their daily activities, such as exercising and socializing. Consequently, vestibular therapy may play a crucial role in managing these physical symptoms, thereby alleviating some of the associated mental health challenges.

This preliminary indication of the potential utility of the questionnaires is insightful. However, it is important to note that while the *t*-tests and Chi-squared tests provide information regarding the relationship between variables, they do not ascertain the actual efficacy of the questionnaires in facilitating improved outcomes through timely referrals to suitable resources. To investigate this matter deeper and address our specific research inquiries, we extended our analysis by employing ordinal and binary logistic regressions. These advanced statistical techniques provide a more comprehensive understanding of the impact and effectiveness of the questionnaires in our study.

For our first question regarding whether the scores on the questionnaires can predict the number of interventions a patient receives, we found that both a pre-injury history of depression and higher CESDR-10 scores independently predicted a greater number of interventions prescribed to the patient. These findings align with existing literature, as numerous studies have demonstrated an association between these variables and impaired recovery (Langer et al., 2021; Liu et al., 2019; Mooney et al., 2005), thereby indicating a greater need for more treatment. We initially anticipated similar results with the pre-injury anxiety and GAD-7 score variables, given the recognized influence of anxiety on recovery trajectories (Lamontagne et al., 2022; Langer et al., 2021). However, our findings diverged from this expectation, presenting an unexpected outcome. Importantly, based on the results from this ordinal logistic regression, it seems like a premorbid anxiety/depression diagnosis is driving the number of interventions prescribed, which greatly undermines what we can infer from the administration of questionnaires given the significant baseline difference in pre-injury anxiety/depression diagnoses that we observed across groups.

We then decided to explore whether the scores on the questionnaires could be used to predict referrals to the four interventions we focussed on, rather than just the total number of referrals. Our results revealed that age significantly predicted referrals to vestibular therapy, so the older a patient, the more likely they are to get referred to this intervention. This finding is supported by the literature as it has been shown that following a TBI, older adults have an increased likelihood of experiencing physical symptoms including fatigue, as well as challenges related to balance and coordination (Thompson et al., 2020). These balance and coordination problems can be best addressed by a vestibular therapist, hence supporting our finding. This underscores the importance of tailored interventions for older adults, prompts awareness among healthcare providers about assessing vestibular function in this demographic, and informs resource allocation to ensure adequate support for their rehabilitation needs. When we performed the same analysis, but with outpatient rehabilitation as our dichotomous dependent variable, we found no significant predictors. Considering that most patients in our sample were directed to outpatient rehabilitation if they still exhibited symptoms at least three months post-injury, this may suggest a more complicated clinical profile and a thorough comprehensive evaluation may be necessary to facilitate such referrals. As a result, it might be challenging for the factors in our model to independently predict referrals to this intervention as an interaction between numerous variables could be in effect, so this may explain the lack of significance across all variables.

Interestingly, we found that a pre-injury history of depression was a significant predictor of referrals to a neuropsychologist. It has been shown that individuals who had depression before sustaining an mTBI are at a higher risk of developing persistent symptoms after injury (Langer et al., 2021) and that this association might simply be a result of ongoing pre-existing symptoms rather than a worsening of mTBI symptoms (Vikane et al., 2019). Consequently, undergoing a neuropsychological assessment can aid in distinguishing whether the patient's symptoms stem from a pre-existing diagnosis of depression or from the mTBI itself. This information is invaluable as it provides the treating clinician with a more comprehensive understanding of the patient's clinical condition based on the insights from the neuropsychologist. Subsequently, this enables them to deliver the most effective treatment in a timely manner. Finally, we found that the scores on the CESDR-10 questionnaire significantly predicted referrals to a psychologist, so the higher the score, the greater the odds that the patient receives this referral. This agrees with our hypothesis as we expected higher scores on the questionnaires to cause clinicians to refer patients to interventions directly targeting symptoms of anxiety and/or depression, such as a psychologist. Therefore, based on these results, we can theorize that patients with a pre-injury diagnosis of depression are more likely to be referred to a neuropsychologist to better understand if this acts as the source of their symptoms while patients who are depressed in the moment (reflected in higher scores on the CESDR-10 questionnaire) are referred to a psychologist to provide the appropriate treatment.

We did also expect the GAD-7 scores to be a significant predictor in this model and thus demonstrate that higher scores on this questionnaire increases the likelihood that the clinician will refer patients to a psychologist, but we found that these scores did not predict referrals to the different interventions, so this was an unexpected result. This finding may suggest that the physicians are not utilizing the questionnaire scores to guide their decisions on patient referrals to these interventions. Moving forward, it is essential to ensure that physicians administering the questionnaires are aware of the potential value in using the scores to identify patients who may benefit from additional care. This awareness among physicians can significantly enhance the reliability of conclusions drawn from future studies evaluating the effectiveness of these screening tools.

Our findings indicated that higher CESDR-10 scores were significantly associated with a greater number of prescribed interventions, particularly psychology, as we anticipated. Subsequently, our final regression analysis yielded promising findings, demonstrating that both the absence of any prescribed interventions and the referral to a single intervention significantly predicted a higher GOS-E score for the patients. The results highlighted that patients who did not receive referrals to any resources exhibited a notably stronger effect in predicting a better recovery (higher score on the GOS-E), in comparison to patients who received a single intervention. This observation aligns with the notion that the absence of referrals indicates favorable recovery progress. Conversely, the prescription of a single intervention still exhibited significant predictive power for achieving a GOS-E score of 8, although with a smaller odds ratio in comparison to the scenario with no interventions. This is in line with expectations, as an increase in the number of prescribed interventions corresponds to a more complex clinical profile for the patient, consequently signifying a poorer outcome and the need for this extra treatment. In other words, the data showed that more interventions were prescribed to those who scored lower on the GOS-E, which is expected. Our findings also revealed that patients referred to either vestibular therapy or psychology had an increased likelihood of achieving higher outcome scores than those who were not referred to these interventions. This supports our hypothesis that the delivery of appropriate resources and treatment contributes to improved patient outcomes. Considering our findings that higher scores on the CESDR-10 questionnaire predict referrals to psychology and the beneficial effects of this intervention on patient outcomes, we can appreciate the potential impact of these questionnaires on shaping positive recovery paths for mTBI patients.

Additionally, it's important to note that the lack of significance of neuropsychology referrals in predicting outcome may be attributed to its nature as an assessment rather than a direct intervention for rehabilitation. As for outpatient rehabilitation, we may not have observed it as a significant predictor of improved outcomes because, after receiving this referral, patients were discharged from the mTBI Clinic. Consequently, most patients did not have any follow-ups after this referral, and thus, we had to assign the GOS-E score without giving them the opportunity to undergo this intervention. This lack of follow-up makes it impossible to track whether they have gone to this resource and if it is helping them in their recovery, so the potential positive effects of outpatient rehabilitation on patient outcome is not reflected in the assigned GOS-E score of many of these patients.

It is also important to address why we did not observe significant effects of certain co-variables that we included in our models, as anticipated. This may be largely due to the limited representation in our sample of individuals who typically experience poorer outcomes following mTBI, as supported in existing literature. For example, although lower education has been associated with worse post-injury outcomes and delayed recovery (Cassidy, Boyle, et al., 2014; Starkey et al., 2022), our sample predominantly comprised individuals with higher education levels. Similarly, the average age of our sample was close to 41, whereas older age (>50) has been associated with delayed recovery and persistent post-concussive symptoms (Cassidy, Boyle, et al., 2014; Langer et al., 2021). Additionally, it has been documented that poorer premorbid physical health could predict persistent symptoms (Cassidy, Cancelliere, et al., 2014) and thus a poorer recovery, but the average CCI and CIRS-G scores of the patients in our sample were low (<1.50), which indicates less health problems and a relatively benign past medical history. We were surprised to find no effect of sex on patient outcomes despite the known higher risk of poorer functional outcomes for women after injury (Mikolić et al., 2021) and the significant female representation in our study. Moving forward, it is essential to achieve greater variability in the sample by ensuring a balanced representation of patients or increasing the sample size. Furthermore, the lack of significance in most variables may also be attributed to missing data and the presence of variables with multiple categories, leading to a reduced sample size included in our analyses and diminished model power of the regressions. We recommend transforming variables such as education level into linear measures by quantifying the total number of years in school, and emphasize the importance of mitigating missing data, which was hard to control given the retrospective nature of this study.

4.2 Critical Analysis of the Questionnaires and their Alternatives

To investigate whether the early identification of anxiety and depression, or symptoms of such, can help mTBI patients get the appropriate resources and subsequently improve their outcome, we used questionnaires as the screening tools for these psychiatric disorders. The GAD-7 and CESDR-10 questionnaires are self-report tools that are widely acknowledged for their validity, reliability, and consistency (Björgvinsson et al., 2013; Miller et al., 2008; Radloff, 1977; Spitzer et al., 2006), but there are inherent limitations to this method of assessing anxiety and depression. As typical of self-report tools, these questionnaires rely on patients' subjective reporting of their anxiety and depression symptoms, leading to potential self-report bias. Factors such as social desirability bias, misinterpretation of questions, or a lack of emotional insight might cause individuals to either under-report or over-report their symptoms. An alternative, more objective screening approach involving questionnaires administered by clinicians could alleviate these limitations, ensuring more accurate responses through the clinician's expertise and judgement. For these self-report measures, it is important to add the reliable change index (RCI)

(Jacobson & Truax, 1991), which is a statistical measure that identifies the amount of change score required on a specific self-report tool to be deemed statistically reliable (Ferguson et al., 2002). The RCI helps assess whether a change in score from pre- to post-treatment is attributable to genuine change or merely random variation, in other words, is this difference meaningful or due to random error (Ferguson et al., 2002).

Furthermore, both the GAD-7 and CESDR-10 focus on short-term assessments: the GAD-7 evaluates anxiety symptoms over the preceding two weeks (Spitzer et al., 2006), while the CESDR-10 captures depressive symptoms experienced in the past week (Björgvinsson et al., 2013; Miller et al., 2008; Radloff, 1977). This design affects the ability to capture longer-term or cyclical variations in depressive symptoms, as well as extended anxiety symptoms and other anxiety disorders. Additionally, this temporal restriction makes the questionnaires less sensitive to minor fluctuations in symptoms over short durations, potentially influencing their utility in tracking patient outcomes. Given that both questionnaires assess the patient's more immediate emotional state, they are unable to capture variations at different time points and the progression of symptoms. Consequently, the questionnaires may yield different scores at distinct time points. It is a possibility that many patients who do not initially present with symptoms of anxiety and depression can still develop it later in their recovery process (Al-Kader et al., 2022; Barker-Collo et al., 2018), so future studies could benefit from administering the questionnaires multiple times over an extended period to obtain a more representative average score and more accurately monitor the evolution of a patient's anxious and depressive symptoms. This will ensure that the patients can get timely and appropriate interventions. While some may critique these questionnaires for screening rather than diagnostic purposes, the primary aim of our study is not diagnosis. Instead, we strive to assess the efficacy of these tools in early screening for anxiety and depression symptoms, enabling appropriate patient referrals. This proactive approach aims to mitigate a poorer mTBI recovery, ultimately enhancing patient outcomes.

It is important to explain the rationale behind our selection of the GAD-7 and CESDR-10 questionnaires over alternative instruments that are just as effective when it comes to assessing symptoms of anxiety and depression. As previously discussed, the GAD-7 and PHQ-9 questionnaires are commonly utilized tools for the screening of these symptoms in TBI patients, respectively (Cohen et al., 2018; Zachar-Tirado & Donders, 2021). In our study, we opted to adhere to the established literature by employing the GAD-7 while diverging from convention with the CESDR-10. Therefore, it is worthwhile to explore the alternatives that exist and why we made this decision.

Several widely used options for assessing anxiety include the Anxiety Sensitivity Index (ASI), Beck Anxiety Inventory (BAI), and Hamilton Anxiety Rating Scale (HAM-A). The ASI, a 16-item self-report questionnaire, focuses on anxiety sensitivity, assessing the inclination to fear somatic and cognitive symptoms of anxiety due to the belief in their potential danger and harm (Reiss et al., 1986; Rodriguez et al., 2004). It has well-established psychometric properties and predictive validity (Rodriguez et al., 2004), but focuses on how individuals interpret and react to physical symptoms (Reiss et al., 1986). The BAI, a 21-item self-report measure of anxiety, is reliable and validated for assessing anxiety severity in psychiatric populations (Beck et al., 1988). However, it predominately captures physical symptoms, neglecting a comprehensive evaluation of anxiety (Cox et al., 1996). The HAM-A, a 14-item clinician-administered scale, assesses anxiety symptom severity but demands extensive training and is time-consuming to deliver (Baker et al., 2019; Hamilton, 1959). While the HAM-A demonstrates reliability and validity (Baker et al., 2019), criticisms include an overemphasis on somatic symptoms and inadequacy in measuring

GAD symptoms according to DSM-IV and DSM-5 criteria (Koerner et al., 2010; Montgomery, 2002). Each of these instruments presents distinct advantages, yet their emphasis on somatic symptoms poses a challenge, potentially leading to confounding scores due to symptoms attributable to the TBI rather than anxiety. This could result in deviations from true scores and an overestimation of anxiety levels in patients. The GAD-7, with its emphasis on emotional rather than physical symptoms, aligns better with our study objectives. Additionally, it offers several advantages, including ease of completion, reliability, validity, and effectiveness across diverse settings (Spitzer et al., 2006). Despite its proficiency in screening for the presence or absence of anxiety symptoms, the GAD-7 only measures symptom frequency, lacking an assessment of intensity (Baker et al., 2019). A promising alternative, the Anxiety Symptoms Questionnaire (ASQ), measures both frequency and intensity of anxiety symptoms and has demonstrated validity, reliability, and effectiveness (Baker et al., 2019). Exploring the ASQ's potential as a more sensitive screening tool for anxiety symptoms within an mTBI cohort in future studies could provide valuable insights into its accuracy and efficiency compared to the GAD-7.

When considering depression questionnaires, alternative tools, including the PHQ-9, the Hamilton Depression Rating Scale (HDRS), and Beck Depression Inventory (BDI-II), warrant discussion. The PHQ-9, a 9-item self-report instrument, serves as a screening tool for MDD, with its items aligning with the diagnostic criteria of MDD in the DSM (Amtmann et al., 2014). Widely employed in medical settings, the PHQ-9 quantifies depression symptoms and aids clinicians in diagnosing depression (Amtmann et al., 2014). Notably, a score equal to or exceeding 10 on the PHQ-9 exhibits a sensitivity and specificity of 88% for major depression (Kroenke et al., 2001). While demonstrating strong psychometric properties in adults with TBI (Bombardier et al., 2010; Bombardier et al., 2016; Dyer et al., 2016; Fann et al., 2005), there is ongoing debate within the literature regarding the inclusion of somatic symptoms in screening tools for TBI patients, as observed in the PHQ-9 (Cohen et al., 2018). In contrast, the HDRS is a clinician-rated scale employed to evaluate the severity and changes in depressive symptoms. Its administration typically takes 20-30 minutes (Hamilton, 1960), which may not be conducive for our mTBI patients who may struggle with prolonged concentration. The BDI-II is a 21-item self-report questionnaire that has become a widely used tool to help assess symptoms of depression and their severity in both adolescent and adult populations (Beck et al., 1996; García-Batista et al., 2018). It is important to note that some of the items in the questionnaire target physical symptoms, so patients with co-morbid medical diseases may over-report physical complaints, such as fatigue and sleep changes, which can increase the score on the BDI even in the absence of depressive symptoms (Wang & Gorenstein, 2021). Our cohort has many patients with co-morbid medical conditions, so this questionnaire may not be the best fit for our study. Based on the literature reviewed for this study, the CESDR-10 has not been used in TBI patients to assess their symptoms of depression, so this is an interesting and novel approach. Nevertheless, both the CESDR-10 and PHQ-9 share the common purpose of assessing depressive symptoms (Andresen et al., 1994) and they are concise and user-friendly. Future studies could gain valuable insights by incorporating the PHQ-9 to evaluate its performance in comparison to the CESDR-10 within the specific context of this study.

4.3 Limitations

It is important to begin by discussing the limitations of the GOS-E, the tool we used to quantify patient outcome. While traditionally administered by clinicians through interviews (Wilson et al., 2021), we employed the scale solely as a reference. This involved assigning each patient an outcome score based on the data we collected from their medical files. However, a limitation arises as some patients had extensive information regarding their recovery progress, while others had minimal data, which makes it difficult to be confident in the GOS-E scores that we assigned to them. The lack of blindness can also have an impact on the GOS-E scores assigned as we know which group each patient is part of, so it is possible to subconsciously assign higher scores to the patients who received the questionnaires compared to those who did not since we expect them to have a better outcome. Also, the data that we collected to help us assign a GOS-E score is reported at different points in each patient's recovery, some patients were further along in their recovery than others, so this can confound the data and the score we give may not be accurate and capture the true nature of the patient's recovery. Therefore, the scoring will be less accurate for patients with less information and less clinic visits than those with more because the story of the evolution of their symptoms and recovery is less complete. To enhance validity and reliability of the scores in future studies, it is recommended that clinicians administer the GOS-E at the same timepoint during recovery for all patients (ideally a couple of months after their injury so that there is enough time for the referred resources to help them). This approach will ensure consistency across patients and give a more accurate measure of their outcome and whether the interventions are truly contributing to improving patient outcome or not. It is also worth noting that it is not too clear what we can infer from a difference between a GOS-E score of 7 and 8, so that is an important limitation to data interpretability. In future prospective studies, it would be useful to employ more sophisticated tools than the GOS-E to measure outcome in mTBI patients such as quality of life scales, life satisfaction scales, measures of activities of daily living (ADL), sleep quality, neuropsychological assessment, and psychological adjustment scales.

As for the questionnaires, an important problem that we ran into while conducting this study is the inconsistent times of questionnaire administration between patients. While our criteria specified administering the GAD-7 and CESDR-10 questionnaires within three months post-injury, the study would have benefited from a more uniform administration style. Currently, the questionnaires were distributed during the patients' initial clinic visit, which occurred at varying times for each individual and potentially introduces discrepancies in the results. For instance, certain patients may have completed the questionnaires shortly after their injury, while others may have done so weeks or even months later, placing them at different stages in their recovery. Consequently, the questionnaires could either overestimate or underestimate the patients' actual levels of anxiety and depression, affecting the overall outcome. If the questionnaires are administered when patients have minimal or no symptoms of anxiety and/or depression, it could potentially skew the outcome in favor of a more positive assessment at that specific timepoint. In future studies, adopting a standardized approach such as administering the questionnaires one-month post-injury for all patients, is recommended. The chosen time point should be a balance between being long enough after injury for anxiety and/or depression symptoms to manifest (or not) and early enough to facilitate timely resource referrals before recovery is negatively impacted. Overall, establishing a standardized timepoint contributes to enhanced data consistency, ensuring more valid and reliable results. It is also valuable to administer the questionnaires on multiple occasions to capture the fluctuations in these symptoms, which can provide a more comprehensive understanding of the patients' psychiatric condition, as supported in the literature (Barker-Collo et al., 2018).

There are various factors that can affect how well the prescribed interventions contribute to improving patient outcome. For instance, some patients may not have had adequate time to seek the necessary help, potentially resulting in the assignment of GOS-E scores before they had the opportunity to undergo the prescribed interventions. Delays in receiving referrals, spanning weeks or even months, were observed for certain patients, with reasons including financial or personal challenges, difficulty in finding a suitable professional, and waiting for appointment availability. Additionally, the lack of follow-up information for patients referred to specific resources and subsequently discharged posed challenges in confidently assigning accurate GOS-E scores. This situation is exemplified by the limited predictability of patient outcome based on referrals for outpatient rehabilitation. Patients were mostly referred to this intervention after experiencing persistent symptoms beyond three months post-injury, yet were subsequently discharged without follow-up, which led to a lack of assessment of the effectiveness of this intervention. These complexities support the necessity for standardized assessment of patient outcomes using the GOS-E scale and emphasize the importance of allowing sufficient time for interventions to positively impact patient recovery. Furthermore, considering that many patients with mTBI experience complete recovery without requiring interventions, the limited number of patients receiving interventions may impede our ability to draw definitive conclusions regarding the efficacy of interventions on patient outcomes and recovery. In future studies, it would be valuable to monitor the number of sessions each patient requires for every intervention they are referred to, to quantify the intensity of the interventions as a reflection of patient need.

Our study was a retrospective chart review where we went back into the medical files of the mTBI patients to gather the data we needed to help explore our research questions. The retrospective nature of this study presents inherent limitations by design. A primary concern is the selection of participants based on existing data, potentially resulting in a non-representative sample and limited generalizability. This also compromises data quality due to possible missing or incomplete information, thereby impacting the depth of analysis. There were many instances where information was not recorded by the physician and so we had to record it as missing data. For example, missing data for education was common in our study. In future studies, careful participant selection should involve recent mTBI cases and thorough question preparation to avoid gaps in the data. This limited data availability prevents us from commenting on improvements in patient recovery as we could not quantify changes from baseline symptoms. Thus, it is important to consider this limitation when interpreting the results.

Additionally, conducting a retrospective chart review complicates control for confounding variables and establishing event sequences, affecting the ability to determine cause-and-effect relationships. For example, it is hard to determine if the clinicians are referring patients to certain resources based on their score on the CESDR-10 questionnaire or because they are truly depressed. Lack of control over variables and uncertainty about participant adherence to referrals are important challenges in our study. For instance, while we can track patient referrals, adherence to these referrals remains uncertain, which can potentially influence the accuracy of concluding whether certain forms of rehabilitation are indeed improving mTBI patient outcome. The medical files that we extracted the data from did not always confirm whether the patients have been getting the therapy they were referred to, but there were certain instances where the physician took note of the reason for lack of adherence. Some reasons included personal issues, financial troubles, patient disagreeing with the referral, or difficulty getting an appointment. In future studies, we can make sure that the patients are going to their referrals through periodic check-ins, whether it is in person or on the phone. This can also help us control for the issues that cause non-treatment adherence and thus ensure that the patients get the help they need. Ultimately, these check-ins can make us more confident in concluding whether the referrals are helping improve patient outcomes. As mentioned previously, it would be helpful to document the number of sessions that a patient received for each intervention type as it may better highlight their need for treatment rather than just recording the number of medical referrals (which can also vary between clinicians).

Despite these limitations, retrospective studies offer valuable insights. They aid in hypothesis generation and identifying associations or patterns that can be tested in prospective studies to then establish causation. Retrospective studies provide preliminary insights into the potential impact of certain factors or interventions, inform the design of future research, identify crucial variables, and serve as feasibility assessments for larger prospective studies. Acknowledging these limitations is crucial when interpreting results, but the benefits of retrospective studies contribute significantly to the research continuum. Therefore, our study is supported by a strong rationale, and we identified many key methodological changes that can be made to further enhance the investigation of this topic and produce more reliable results. The implementation of screening tools such as these questionnaires in screening for symptoms of anxiety and depression post mTBI can help patients get the treatment they need early on, as suggested by almost all researchers studying this topic. Additionally, these tools can be applied to a range of trauma injuries and does not need to be limited to TBI.

4.4 Conclusion and Future Directions

While the detrimental effects of anxiety and depression on the recovery of mTBI patients are well-documented, there is a lack of research examining whether early identification of these symptoms and appropriate interventions can positively influence patient outcomes. In addressing this gap, we chose to administer the GAD-7 and CESDR-10 questionnaires during the acute phase of mTBI, a novel approach compared to existing literature. Our findings revealed that higher CESDR-10 scores significantly predicted an increased number of interventions, particularly referrals to psychologists, and patients who received this intervention demonstrated improved outcomes, aligning with our expectations. Although the use of the GAD-7 questionnaire did not result in increased referrals to different interventions nor affected patient outcome, this remains an exploratory study, and we acknowledge the limitations discussed earlier, which may affect our ability to draw definitive conclusions. However, the results we obtained support the value of early screening tools, such as questionnaires, in detecting anxiety and depression after injury before it exacerbates and negatively impacts patient recovery. The implications may also extend beyond mTBI patients to all individuals who experience traumatic injuries, as early detection of anxiety and depression could prove beneficial in their path to recovery as well.

It is widely known and suggested to administer early screening and interventions for anxiety and depression after an mTBI, so our work is promising, we just need to refine our approach. Therefore, this project not only emphasizes the significance of this topic, but it provides a foundation and roadmap for larger prospective studies to support our expectations and findings. Further investigation in these larger studies can validate the feasibility of these questionnaires, facilitating their adoption in real clinical settings. This will equip clinicians with a means to monitor the potential onset of these psychiatric disorders or related symptoms post-injury, allowing for preventive measures to support positive patient recovery.

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