Effects of Inpatient Rehabilitation on Long-Term Motor, Neuropsychological, and Functional Outcomes in Children with Severe Traumatic Brain Injury

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Abstract

Despite growing clinician and family recognition of the need for rehabilitation in children surviving severe traumatic brain injury (TBI), there is a paucity of evidence to inform comprehensive rehabilitation guidelines. To advance understanding of rehabilitation care after acute medical management in children with severe TBI, we characterized the use of inpatient rehabilitation services and evaluated its associations with long-term motor, neuropsychological, behavioral, functional, and quality-of-life outcomes in a multisite, multinational cohort, the Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial.

First, we observed that children receiving inpatient rehabilitation, regardless of the need for additional non-inpatient rehabilitation services, had a shorter length of acute hospitalization compared to those receiving only non-inpatient rehabilitation. Children from the US were more likely to receive inpatient rehabilitation compared with children from the UK. Among the US cohort, whites were more likely to receive inpatient rehabilitation compared with African Americans.

Next, using inverse probability weighting to adjust for confounding and selection biases, we found no differences between children receiving inpatient rehabilitation and children receiving only non-inpatient rehabilitation in tests of motor skills, intellectual functioning, verbal learning,

memory, processing speed, cognitive flexibility and parent/guardian-rated executive function and behaviors at 12 months after injury.

Then, using a similar analytical approach, we found that children receiving inpatient rehabilitation had more favorable global function at 12 months after injury among those with a Glasgow Coma Scale (GCS) < 13 at hospital discharge, though such association was not observed in children with a higher GCS. No differences between rehabilitation groups in parent/guardian-reported or child self-reported health related quality of life were found. These results likely reflect the benefits of inpatient rehabilitation for children with more severely impaired consciousness when medically stable.

Overall, these findings provided the much-needed evidence on the characteristics associated with the use of inpatient rehabilitation and the effects of different patterns of rehabilitation care on long-term outcomes in children with severe TBI. These results are of public health relevance by providing a strong foundation for the development and implementation of policies or clinical practice to optimize rehabilitation care for children with severe TBI.

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Preface

I would like to first thank my inspirational advisor, Dr. Stephen Wisniewski. It is a great honor to learn from him and work with him. I am also thankful for my supervisors Dr. Anthony Fabio and Dr. Bedda Rosario for their unwavering support and encouragement. Further, I want to thank Dr. Sue Beers, Dr. M. Kathleen Kelly, Dr. Michael Bell and Dr. Amery Treble-Barna for providing critical insights for this dissertation. Finally, this dissertation would not have been possible without the support of my family and friends.

1.0 Introduction

1.1 Background

Every year 37,200 children in the US sustain a severe traumatic brain injury (TBI), resulting in a mortality rate of 24% [1, 2]. Among acute survivors, severe TBI can lead to a range of motor, cognitive and behavioral issues, and result in impaired daily functioning and reduced quality of life [3]. The road to recovery for children may continue with medical rehabilitation after initial stabilization [2]. However, there is no systematic continuum of rehabilitation care after acute medical management for children suffering severe TBI. Children who transition from acute medical care can be admitted to inpatient rehabilitation or discharged home but referred to outpatient or community-based rehabilitation therapies. Despite the preliminary evidence in support of early initiation of inpatient rehabilitation after acute care [4, 5], only 27% of children hospitalized for severe TBI in the US were discharged to an inpatient rehabilitation facility [6]. Characteristics of children with different patterns of rehabilitation process following severe TBI were limitedly described before [7-9]. Moreover, evidence on the effectiveness of medical rehabilitation on improving motor, neuropsychological, functional and quality-of-life outcomes in children with severe TBI remains scarce. Previous studies focusing on the efficacy of multidisciplinary inpatient rehabilitation or specific non-inpatient rehabilitation therapies demonstrated that children's motor skills, neuropsychological outcomes and global function significantly improved over the course of rehabilitation following brain injury [10-12]. However, no studies to date have determined the contribution of rehabilitation process, including the use of inpatient rehabilitation and/or non-inpatient rehabilitation, to long-term outcomes in children with severe TBI.

Studies on long-term outcomes of children with TBI are usually conducted in clinical research samples, where children or parents/guardians have volunteered to be evaluated over time. There is always a concern about the systematic differences between those who volunteered to be included in a study and those who refused to participate, which may result in selection bias [13]. Further, selection bias due to loss to follow-up can influence the results of a longitudinal study [13]. Such volunteer bias and attrition bias may threaten both the internal and external validity of a study. However, limited research on rehabilitation in pediatric TBI has accounted for these selection biases. Ignoring or failing to adjust for these biases can lead to inappropriate interpretation of results and flawed conclusions [14]. Given the gaps within previous studies, there is a critical need of well-designed studies, which appropriately adjust for several selection biases, to evaluate the effectiveness of rehabilitation process on the recovery in children with severe TBI.

1.2 Specific Aims

To provide new evidence for future guidelines or recommendations on rehabilitation for children with severe TBI, this dissertation aims to delineate characteristics of children receiving inpatient rehabilitation or only non-inpatient rehabilitation after acute hospitalization for severe TBI and evaluate the relationship between rehabilitation process and motor, neuropsychological, behavioral, functional and quality-of-life outcomes. We will base our study on the Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial, which enrolled a representative pediatric cohort with severe TBI from 2014 to 2016 and followed to one year after injury. Our specific aims are:

Aim 1: To characterize sociodemographic and clinical factors associated with the use of inpatient rehabilitation and only non-inpatient rehabilitation after acute care among children with severe TBI.

Hypothesis: Among children with severe TBI, specific sociodemographic (e.g. age, race/ethnicity, family socioeconomic status), clinical (e.g. length of hospital stay) and injury related factors (e.g. injury severity, mechanism of injury) are associated with the use of inpatient rehabilitation compared to the use of only non-inpatient rehabilitation after acute hospitalization.

Aim 2: To compare the effects of receiving inpatient rehabilitation versus only non-inpatient rehabilitation after acute care on long-term motor and neuropsychological outcomes including intellectual functioning, processing speed, verbal learning, memory and executive function, as well as behavioral outcomes among children with severe TBI.

Hypothesis: Receipt of inpatient rehabilitation after acute care will be associated with better motor skills and neuropsychological outcomes including intellectual functioning, processing speed, verbal learning, memory and executive function, as well as behavioral outcomes at one year after injury as compared to receipt of only non-inpatient rehabilitation in children with severe TBI. Such associations may be attenuated when being examined in bias-adjusted heterogeneous samples of pediatric patients with severe TBI.

Aim 3: To compare the effects of receiving inpatient rehabilitation versus only non-inpatient rehabilitation after acute care on long-term functional outcome and health related quality of life among children with severe TBI.

Hypothesis: Receipt of inpatient rehabilitation after acute care will be associated with better global function, caregiver-reported and child self-reported health-related quality of life at one year after injury as compared to receipt of only non-inpatient rehabilitation in children with severe TBI. Associations of rehabilitation process with functional and quality-of-life outcomes may be attenuated when such associations are categorized among bias-adjusted heterogeneous samples of pediatric patients with severe TBI.

Public health impact: Successful completion of these aims will inform us of important factors related with the use of inpatient rehabilitation after acute hospitalization and demonstrate the associations of receiving inpatient rehabilitation versus only non-inpatient rehabilitation with motor skills, neuropsychological outcomes, behavioral outcomes, global function, and health related quality of life among pediatric patients with severe TBI. Identified disparities in the access to inpatient rehabilitation may inform policy makers of planning strategies to promote health equity for pediatric patients. A better understanding of the effectiveness of rehabilitation process will help healthcare providers to make difficult discharge decisions and optimize post-acute health care for children with severe TBI. This dissertation will provide critical evidence to inform future pediatric TBI guidelines or recommendations on rehabilitation care.

2.0 Literature Review

2.1 Epidemiology of Pediatric TBI

A traumatic brain injury (TBI) is an injury that interferes with the normal function of the brain. It can be caused by a blow, jolt or bump to the head or a penetrating head injury [15]. Pediatric TBI is a primary public health concern in both developed and developing countries. In the US, close to half a million children aged 14 years and younger visit the emergency department (ED) for a TBI each year [16]. For the same age group, there are more than 35,000 TBI-related hospitalizations annually [16]. A recent systematic review of 30 worldwide epidemiological injury studies reported that the incidence of pediatric TBI ranged from 12 to 486 persons per 100,000 with the lowest rates from northern European countries and the highest rates from Australia [17]. In the US, the annual mortality rate for TBI among children less than 14 years of age was estimated to be less than 5 persons per 100,000 [16]. Most worldwide epidemiological injury studies reported a case fatality rate below 10% for pediatric TBI [17].

Demographics

Males are more commonly affected by TBI than females [16-18]. In the US, the incidence of TBI is higher in males than in females in every pediatric age group [16]. In children under 10 years, the risk of TBI is 1.4 times higher among males than among females [18]. In older children, males are more than twice as likely as females to experience a TBI [18]. Several pediatric TBI studies described a bimodal age distribution with the most frequent injury occurrence in very young children (0-4 years) and older adolescents (15-17 years) [6, 19, 20]. According to the Centers for Disease Control and Prevention (CDC), children aged 0 to 4 years had a much higher rate of TBI-related ED visits than those in other age groups [16]. Racial differences in the incidence of pediatric TBI remain unclear due to the scarcity of related data. According to the CDC, African Americans had the highest ED visit rates in every pediatric age group [16]. Mixed results were reported for racial differences in TBI-related hospital admission rates. Based on three nationally representative data sources, Langlois et al. found that among very young children (0-4 years), the TBI-related hospitalization rate was nearly twice as high in African Americans than whites [21]. However, some studies found similar TBI-related hospitalization rates in whites and African Americans [16, 20]. Studies from the US and the UK indicated that children living in lower socioeconomic neighborhoods were more likely to sustain a TBI [22, 23].

Cause of TBI

Cause of injury ranged broadly across age groups in children with TBI. Overall, falls and motor vehicle collisions accounted for most injuries in children with TBI [17]. A recent report by the CDC showed that unintentional fall was the leading cause of TBI-related ED visits and hospitalizations among children aged 0-4 years, though the leading cause of TBI-related deaths was assault/homicide, which included abuse and other causes like firearm-related injuries [24]. Among children aged 5 to 14 years, unintentional fall remains the leading cause of TBI-related ED visits, followed by sports or recreation related injuries [18]. For the same age group, unintentional fall and motor vehicle collision account for the majority of injuries requiring admission into hospitals [18]. Motor vehicle collision is the primary cause of fatal injuries within this age range [18]. Among older adolescents aged 15 to 19 years, motor vehicle collision is the single most common cause of TBI-related ED visits, hospitalizations and deaths [16].

Severity of TBI

The clinical presentation and prognosis of children with TBI can vary dramatically depending on the severity of injury. The majority of TBI research categorized injury severity on a three-tier scale (mild, moderate, severe). The 15-point Glasgow Coma Scale (GCS) score is a main classification system of severity in TBI, with scores for mild TBI (GCS 13-15), moderate TBI (GCS 9-12), and severe TBI (GCS 3-8) fairly established in the literature [25]. Based on motor and verbal responsiveness, and eye opening to appropriate stimuli, the GCS was developed and now widely used to assess the level of impaired consciousness after brain injury [26]. The standard GCS scores cannot be used to assess preverbal children due to the need of verbal interaction, so the pediatric GCS which accommodates age-appropriate modifications has been used for preverbal children who are developmentally and verbally limited and not capable of answering questions or following commands [27]. In pediatric TBI studies incorporating all severities according to the initial GCS score, data indicate that more than 90% of children experienced mild TBI, and below 6% suffered severe TBI [19, 28, 29]. However, the GCS has limitations. Factors like alcohol or drug intoxication, medical sedation or organ system failure, which may not be necessarily related with TBI can influence the GCS score and result in the misclassification of injury severity. Therefore, some additional criteria have been applied in clinical practice and research to help determine TBI severity. These include markers of duration of impaired consciousness like time to follow commands and duration of post-traumatic amnesia. Research studies also used a 6-point Abbreviated Injury Scale (AIS) scoring system to quantify the severity of brain injury based on neuroradiologic or operative findings [6, 23, 30]. However, the definition of severe injury varied across studies using the AIS scoring system. Two nationwide studies from the US analyzed data of children hospitalized for a TBI and reported that close to 20% suffered severe TBI, defined as a head AIS ≥ 4 [6, 30]. In another study of children suffering TBI that results in hospitalization or death, authors defined a severe TBI as having a head AIS ≥ 3 and reported the occurrence of severe TBI in nearly 40% of study children [23]. Studies using AIS scoring to assess TBI severity usually demonstrated higher severities compared to those using the GCS [17].

2.2 Why Pediatric Severe TBI?

Although severe brain injuries constitute a small proportion of all traumatic brain injuries in children and adolescents, they represent a substantial public health burden. In the US, the case fatality rate of severe pediatric TBI is estimated to be 23.9% [1]. The cost of pediatric severe TBI is also considerable. Graves et al. found that the median individual-level costs over the first year after injury were more than $9,000 for severe TBI in the US, which were approximately 1.6 and 5 times higher than that for moderate and mild TBI respectively [31]. Furthermore, within the operational framework of disability endorsed by the World Health Organization [32], severe TBI can lead to unfavorable cognitive, physical, and behavioral sequelae, and result in impaired daily functioning and reduced quality of life. Over two thirds of children with severe TBI have been reported to experience disability [33].

2.2.1 Motor, Neuropsychological, and Behavioral Outcomes in Children with Severe TBI

Motor Outcomes

Children with severe TBI often develop motor impairments [34]. Based on the Bruininks-Oseretsky Test of Motor Proficiency, Chaplin et al. found that children with moderate-to-severe

TBI performed more poorly on tests of gross and fine motor skills compared to age- and sex-matched healthy children at more than one year after injury [35]. Studies focusing on balance and gait patterns also reported that children with moderate-to-severe TBI had poorer balance performance and reduced gait speed or step length compared to healthy children throughout the first few years after injury [36-39].

Verbal Learning and Memory

Children who suffer severe TBI can have significant difficulties acquiring, retaining and retrieving information [40], and such deficits in memory and learning process can persist at least one-year post-injury [41]. Impaired verbal learning and memory in children with severe TBI have been consistently reported in studies using the California Verbal Learning Test – Children's Version (CVLT-C) to examine related cognitive performance [42-46]. Salorio et al. found that the overall learning score (List A Trials 1-5) of CVLT-C in children with moderate-to-severe TBI was approximately one standard deviation below the population average at one year after injury [44]. Further, children with severe TBI were found to perform more poorly on the CVLT-C compared to those with orthopedic injuries and those without any diseases throughout the first year after injury [45-48].

Executive Function

Deficits in executive function are among the most commonly reported cognitive impairments in children suffering TBI [49, 50]. Executive function refers to an individual's capability to carry out goal-directed behaviors and includes a variety of skills like planning and sequencing multi-step actions, inhibiting emotions and behaviors, as well as preserving effort for extended period [49]. On the basis of intact frontal-striatal circuits, development of executive function emerges in the first few years of life and continues to strengthen throughout childhood and adolescence [51]. However, these frontal-striatal circuits are frequently damaged from severe brain injuries because they are dispersed networks that run through regular lesion areas like frontal and prefrontal cortex [52]. One study found that over 35% of children with severe TBI had clinically significant impairment of executive function at one-year post-injury, though only 10% had preinjury impairment [50]. Executive dysfunction in daily life can persist for several years following severe TBI in children [53, 54].

Attention and Processing Speed

Attentional sequelae following pediatric severe TBI such as slowed processing speed have been widely reported in previous studies [55-59]. Catroppa et al. recruited 70 children aged 2 to 7 years who did or did not sustain TBI and examined their processing speed 5 years later using the subtest of the Wechsler Intelligence Scale for Children – Third Edition (WISC-III) [57]. The average Processing Speed Index (PSI) score of children with severe TBI was approximately one standard deviation below the population mean. The PSI scores of children with severe TBI were found to be significantly lower than those of healthy children. The same group of researchers also found that among children aged 8 to 12 years at the time of injury, those with severe TBI had significantly lower PSI scores than those with moderate TBI and mild TBI at one-year post-injury [56]. According to a systematic review of studies on attentional deficits after pediatric TBI, children may experience deficits in multiple domains of attention for several years after severe TBI [58].

Intellectual Functioning

Previous studies suggested that children with severe TBI were at an elevated risk of long-term deficits in intellectual functioning [60-62]. Anderson et al. assessed the intellectual functioning of children aged 3 to 12 years using the age-appropriate instruments (Wechsler

Preschool and Primary Intelligence Scale-Revised for children < 6.5 years and WISC-III for children ≥ 6.5 years) within 3 months after TBI, and at 12 and 30 months post-injury [60]. Children with severe TBI scored approximately one standard deviation below the population average on the full-scale intellectual quotients (FSIQ), verbal IQ and nonverbal IQ within 3 months after injury, though significant improvements in FSIQ and nonverbal IQ scores were observed from 3 to 12 months after injury [60]. According to a meta-analytic review of studies on intellectual functioning after pediatric TBI, children with severe TBI showed greater improvement in nonverbal IQ than in verbal IQ during the first two years after injury, while recovery seemed to stabilize thereafter [47]. In one study of young children aged 2 to 7 years who experienced severe TBI, persistent intellectual deficits influencing both verbal and nonverbal domains were found even at 5 years after injury [61].

Behavior

Increased behavioral problems have been reported in children surviving severe TBI [63-65]. Anderson et al. measured the pre- and post-injury behavioral outcomes of school-age children with TBI using parent-reported Child Behavior Checklist (CBCL) scale [66]. For children with severe TBI, the post-injury CBCL total score was significantly higher than the preinjury CBCL total score (mean score, 55.9 vs. 51.2), which suggested that parents rated their child as having increased behavioral problems after brain injury. In a longitudinal study of children with TBI and orthopedic injuries, those with severe TBI scored significantly higher on CBCL affective, anxiety, and attention-deficit/hyperactivity disorder (ADHD) subscales than those with orthopedic injuries at one-year post-injury [67].

2.2.2 Global Function in Children with Severe TBI

All motor, neuropsychological, and behavioral impairments following TBI are believed to manifest as the decline in daily functioning. Recent studies examined the long-term global function in children with severe TBI using the current gold standard for assessing TBI outcome - Glasgow Outcome Scale - Extended, Pediatric Revision (GOS-E Peds) or its original form – Glasgow Outcome Scale (GOS) [68, 69]. Fulkerson et al. reviewed the medical records of 67 children who were admitted to a level I pediatric trauma center in the US and presented with a GCS score of 3 or 4 between 1988 and 2014 [70]. They found that 10 (34.5%) out of 29 children who survived up to one year after injury had a GOS score indicating severe disability or vegetative state requiring complete care [70]. At the long-term follow-up visit (median 10.5 years), only 10 (45.5%) out of 22 children were found to have normal function or minor functional limitations (GOS of 5) [70]. Another study found that 133 (77.3%) of 172 children with severe TBI, who were treated at a Level I pediatric trauma center during 2001 to 2012, had normal function or mild-to-moderate disability, defined as a GOS score of 4 or 5 or a GOS-E Peds score of 1 to 4 at 6 to 18 months after injury [71].

2.2.3 Health Related Quality of Life in Children with Severe TBI

Health related quality of life (HRQOL) is a multidimensional construct comprising an individual’s perception of how a disease or injury affects physical and psychosocial functioning [72]. Substantial reduction in HRQOL has been reported in children with severe TBI compared with population norms, preinjury status and HRQOL of those with mild or moderate TBI [73-75]. McCarthy et al. found that nearly two thirds of children with severe TBI had impaired HRQOL at one year post-injury, when they took the general population norms into account [74]. Further, the overall HRQOL for children with severe TBI were significantly worse at any follow-up time compared with baseline throughout the first two years after injury, though there were some improvement over time [74, 75]. Children with severe TBI also have poorer overall HRQOL compared to those with mild or moderate TBI at one-year post-injury [74, 75].

2.2.4 Factors Associated with Outcomes in Children with Severe TBI

Recovery from pediatric severe TBI is influenced by a variety of factors including individual child characteristics, social-environmental factors, and receipt of healthcare services after injury.

Individual Characteristics

The most extensively studied individual characteristics in relation to outcomes after pediatric severe TBI are age at injury and severity of injury. Early research suggested that younger age at injury is a protective factor for children, because those at early developmental stages were thought to have enhanced brain plasticity [76]. More recently, studies showed that TBI at younger ages is associated with worse cognitive, behavioral, and functional outcomes than an injury acquired at older childhood [41], though mixed findings on the association between age at injury and mortality in children with severe TBI were reported [77-79]. For children who survived severe brain injuries, younger age was found to be associated with unfavorable long-term global function [71]. Children who suffered moderate-to-severe TBI before the age of 7 years demonstrated worse neurobehavioral outcomes as compared to those who sustained a similar injury at older ages [41, 80-82]. Further, those who sustained severe TBI at an early age were more likely to have poor employment outcomes such as working for limited hours per week and holding low-skilled jobs with low pay in the long run [83, 84]. It appears that severe brain injuries occurring at the time that coincide with critical periods of cognitive development and brain growth can lead to remarkable life-long difficulties [85].

Severity of brain injury is a well-recognized risk factor for multiple outcomes following TBI in children. A dose-response relationship has been observed, where children with more severe brain injuries were more likely to have worse cognitive outcomes including intellectual functioning, attention, memory, and executive function [41]. Among children with severe TBI, those with GCS scores of 3-5 were at greater risks of mortality and long-term impairments in daily functioning than those with GCS scores greater than 5 [86-88]. Compared to those with unintentional injuries, children suffering abusive TBI appeared to sustain a more severe injury and have worse outcomes [89]. Possible reasons for the poor outcomes in children with abusive TBI include the young age at injury and the mechanism of injury – increased frequency of repeated offense [90].

Studies also show that preinjury functioning is related to various health outcomes of children with severe TBI. Preinjury adaptive functioning has been found to be strongly associated with long-term adaptive abilities and behavioral outcomes after TBI in children [63, 91, 92]. Preinjury behavioral problems such as aggression, anxiety and attention problems can be exacerbated by TBI [59, 93, 94]. According to the theory of cognitive reserve, children with higher preinjury cognitive ability often preserve more functional capacity, so they may use those preserved cognitive resources to gain better recovery after injury [95].

Social-Environmental Factors

Social-environmental factors including socioeconomic status and other family-level factors can influence the recovery especially with regards to behavioral, social and academic outcomes after severe TBI in children. Children with limited socioeconomic advantage, such as low household income, parental educational attainment or parental occupational status, were found to have more behavioral problems, and worse adaptive ability or academic performance following severe TBI as compared to those with more socioeconomic resources [96, 97]. Unfavorable family-level factors such as family dysfunction, parent/caregiver burden and distress also negatively impact the long-term recovery following pediatric severe TBI. Previous work indicated that impaired family function was significantly associated with worse cognitive, behavioral and social outcomes in children with TBI [83, 91, 98]. Additionally, parent/caregiver distress was suggested as a potential predictor for long-term behavioral problems in children after TBI regardless of the severity of injury [96]. Among those with severe TBI, greater parent/caregiver burden was found to be strongly related to poorer neuropsychological outcomes and adaptive function [96]. Cumulative family-level risk factors including impaired family function, low socioeconomic status and limited resources can further exacerbate poor social outcomes following pediatric TBI [99].

Receipt of Health Care Services

Unfavorable long-term outcomes of children from low socioeconomic status families may be partly due to the limited use of needed health care services [100]. Aggressive acute medical management is often needed to improve survival and resolve acute medical problems in children with severe TBI, while rehabilitation care may be important to promote long-term health outcomes. Acute medical management of children with severe TBI mainly depends on their symptoms and signs at initial presentations. Although guidelines for the acute medical management have been published [101, 102], there is still great variability of the acute medical care provided for children with severe TBI across centers [103, 104]. In a retrospective cohort study of children treated at 5 pediatric level I trauma centers for severe TBI, the overall adherence rate to guidelines was found to be 73% [103]. This study indicated that increased adherence to pediatric severe TBI guidelines was associated with better survival and more favorable functional outcomes at discharge [103]. Moreover, children treated at pediatric trauma centers demonstrated better outcomes than those treated at adult trauma centers [105]. Children who transition from acute care are often admitted to rehabilitation facilities or referred to certain rehabilitation programs. Although several sets of guidelines for adult TBI rehabilitation have been developed in recent years, there is a critical lack of evidence-based guidelines for rehabilitation evaluation, planning and implementation for children due to the limited pediatric TBI research on rehabilitation.

2.3 Overview of Rehabilitation in Children with TBI

TBI rehabilitation is a set of interventions designed to facilitate neurocognitive recovery and motor skill development, minimize complications and maximize functional independence for patients with TBI [2]. Some rehabilitation services can be provided early for pediatric patients during acute hospitalization. After being discharged from acute care facilities, children who are disabled may receive inpatient and/or outpatient or community-based rehabilitation services such as occupational therapy (OT), physical therapy (PT) and speech-language therapy (ST).

According to the CDC, TBI rehabilitation can be broadly classified as cognitive and physical rehabilitation [106]. Cognitive rehabilitation consists of therapeutic activities to address deficits in a patient's thought process and behavior. The trained cognitive skills are targeted in a hierarchical manner, from less to more sophisticated components of cognitive function [106]. Cognitive rehabilitation provided in clinical settings is administered through the disciplines of OT, ST and neuropsychology [106]. Physical rehabilitation is a collection of therapies to improve deficits in the sensory and motor system after TBI. Physical rehabilitation therapy sessions include the use of medications, orthotics, adaptive equipment and physical modalities such as massage and exercise [106]. Therapists from a variety of disciplines including physical medicine and rehabilitation, PT and OT are involved in physical rehabilitation for children with TBI [106].

Inpatient rehabilitation which involves a multidisciplinary team of physiatrists, occupational therapists, speech-language pathologists, physical therapists, pediatricians and clinical neuropsychologists is provided for individuals whose medical conditions require intensive rehabilitation care [107]. For example, many inpatient rehabilitation facilities require that patients have been screened by a therapist or a rehabilitation physician before admission to make sure they can tolerate at least 3 hours of therapy provided by at least 2 disciplines a day, 5 days per week [108]. Patients admitted to inpatient rehabilitation usually require moderate to maximum assistance and are expected to actively participate in, and benefit from different rehabilitation programs [106]. Inpatient rehabilitation services are primarily provided by inpatient rehabilitation facilities, and are also available in specific long-term care hospitals and skilled nursing facilities [106]. Children who no longer require intensive rehabilitation may participate in rehabilitation programs provided in outpatient and community-based settings or even at home [106].

Outpatient and community-based medical rehabilitation are usually less intensive and containing fewer total hours of therapy compared with inpatient rehabilitation [106]. Those non-inpatient rehabilitation therapies can be delivered by hospital facilities or non-facility private practice.

Although most medical rehabilitation services are discontinued within the first year after injury [106], cognitive and behavioral impairments after injury can persist over time. Children with significant cognitive and behavioral sequela following TBI are usually provided with behavioral therapies, transition services and special educational support after they return to school [109].

2.3.1 Rehabilitation in Children with Severe TBI

Previous studies showed that there is no systematic continuum of rehabilitation care after acute medical management for children surviving severe TBI. Although early initiation of inpatient brain injury rehabilitation has been reported to be associated with better outcomes [110, 111], many children with severe TBI are not admitted to inpatient rehabilitation after acute care [6]. In a nationwide data of US hospitals, only 6% of children with a head AIS of 4 and 27% of those with a head AIS of 5 were discharged to inpatient rehabilitation facilities after acute hospitalization [6]. Those numbers also varied widely across states. Evaluations by rehabilitation therapists during acute hospitalization are important to children with severe TBI to determine their need of rehabilitation and potential functional improvement during and after rehabilitation. Lack of sufficient therapy evaluations can result in the underuse of inpatient rehabilitation among children with severe TBI [112]. Bennett et al. reported that among children hospitalized for severe TBI, 53% with a head AIS of 4 and 15% with a head AIS of 5 did not receive any therapy evaluations before discharge [112]. As a result, some patients may only receive non-inpatient rehabilitation services or no rehabilitation at all following severe TBI. Among children insured by Medicaid who were hospitalized for a TBI, regardless of the receipt of inpatient rehabilitation, close to 40% of those with a head AIS of 4 and 60% of those with a head AIS of 5 received outpatient rehabilitation therapies within the first three years after injury [9].

2.4 Characteristics of Children Receiving Rehabilitation After Acute Care Following TBI

2.4.1 Characteristics of Children Receiving Inpatient Rehabilitation After Acute Care Following TBI

A growing body of research has established the positive association between more severe brain injury and inpatient rehabilitation admission in children [6, 7, 113, 114]. Three studies from the US consistently reported that those with higher head AIS scores were more likely to be referred to inpatient rehabilitation after acute hospitalization [6, 7, 114]. In another study of children admitted to 6 hospitals in the US, severity of injury was assessed based on the worst GCS score by 24 hours after injury. Results showed that 70% of children with moderate-to-severe TBI were discharged to inpatient rehabilitation after acute hospitalization, while only 5% of children with complicated mild TBI received inpatient rehabilitation [113]. Other characteristics of children receiving inpatient rehabilitation after acute medical management were limitedly described in previous literature. In a nationwide study of US children hospitalized for TBI, regardless of the severity of injury, Greene et al. found that age, insurance status and geographical location were associated with inpatient rehabilitation referral after acute hospitalization [6]. Specifically, compared to young children 4 years or younger, those aged 5 to 9 years, 10 to 14 years, and 15 to 19 years were approximately 1.5, 2.5 and 5.3 times more likely to be discharged to inpatient rehabilitation facilities respectively [6]. Children without insurance coverage were 68% less likely to be discharged to inpatient rehabilitation facilities compared to those with Medicaid in the adjusted analysis. The same study also found significant variation in inpatient rehabilitation admission across states [6]. The proportion of pediatric patients discharged to inpatient rehabilitation facilities varied from 2.3% in New York to 10.5% in Kentucky.

2.4.2 Characteristics of Children Receiving Non-Inpatient Rehabilitation After Acute Care Following TBI

Various demographic, clinical and injury related characteristics of those receiving any outpatient or community-based rehabilitation therapies after hospital discharge, regardless of the receipt of inpatient rehabilitation, have been delineated in previous studies of children with TBI of any severity (Table 1).

Severity of TBI

In line with the findings on inpatient rehabilitation, studies indicated that children with more severe brain injuries were more likely to receive outpatient rehabilitation after acute hospitalization for TBI [7, 9]. Jimenez et al. found that those with a head AIS of 4 and 5 were approximately 1.5 times more likely to receive any outpatient rehabilitation services over the first three years after injury compared to those with a head AIS of 1 and 2 [9]. Those with a head AIS of 3 had 20% higher rate of receiving outpatient rehabilitation than those with a head AIS of 1 and 2 in the first year after injury [9]. Another study found that more severe brain injury was positively correlated with the use of outpatient PT, OT, and ST services during the first year after injury among children [7].

Severity of Other Injuries

Previous studies have delineated injury severities of other body regions of children receiving outpatient rehabilitation following TBI. Based on Medicaid claims data, Jimenez et al. found that more severe injuries of other body regions were positively associated with the use of outpatient rehabilitation, especially within the first year after injury in children with TBI [9].

Table 1. Summary of Studies Describing the Characteristics of Children Receiving Non-Inpatient Rehabilitation After TBI

Year	Author	Sample source	Age range (y)	Sample Size	Severity of TBI	Rehabilitation variable(s)	Source of rehabilitation data	Characteristics of study population	Results
1999	Greenspan	JHH or MIEMSS	5-15	95	Head AIS: 2 (41%) 3 (25%) 4 (24%) 5 (9%)	Outpatient rehabilitation (mental health services, family counseling, cognitive therapy, PT, OT, and ST) within the 1st year after injury	Telephone interview with parents	head AIS	Children with more severe head injuries were more likely to use outpatient PT, OT, ST, mental health services and family counseling.
2006	Slomine	CHAT	5-15	302	Head AIS: 2 (30%) 3 (25%) 4 (32%) 5 (13%)	Use of non-inpatient health care services provided through the child's school or in the community within the 1st year after injury	Telephone interview with the primary caregiver	head AIS	Children with more severe head injuries were more likely to receive all types of health care services at 3 and 12 months after injury.

Table 1 (Continued)

Year	Author	Sample source	Age range (y)	Sample Size	Severity of TBI	Rehabilitation variable(s)	Source of rehabilitation data	Characteristics of study population	Results
2016	Jimenez	Medicaid Market Scan Database of 14 states	0-<21	9361	Head AIS: 1 (2%) 2 (36%) 3 (26%) 4 (33%) 5 (2%)	Outpatient rehabilitation (PT, OT, ST and follow-up by rehabilitation physicians) within the first 3 years after acute hospitalization	Provider or service claims	Age, gender, race/ethnicity, head AIS, overall injury severity excluding head injury, isolated TBI, LOS, Medicaid plan type, and receipt of rehabilitation during acute hospitalization	In bivariate analyses, older age, more severe injuries, longer LOS, insurance under a fee-for-service plan, and receipt of inpatient rehabilitation were associated with outpatient rehabilitation use. In multivariable analysis, more severe head injury and other injuries, receipt of rehabilitation in acute care settings, and insurance under a fee-for-service plan were positively related to the use of outpatient rehabilitation. Children in the other racial minority group were more likely to use PT, OT, and ST than non-Hispanic whites. Hispanics received fewer ST services than those in all other racial/ethnic groups.

Table 1 (Continued)

Year	Author	Sample source	Age range (y)	Sample Size	Severity of TBI	Rehabilitation variable(s)	Source of rehabilitation data	Characteristics of study population	Results
2018	Fuentes	6 hospitals in the US	8-18	170	Complicated mild TBI (72%): GCS 13-15 on initial exam that returned to GCS 15 by 24 hours after injury Moderate-to-severe TBI (28%): GCS at 24 hours of <15 or a worst post-resuscitation GCS of <13	Use of any rehabilitative therapies (PT, OT, ST or other) in a health care or school setting since the injury	Telephone or online interview with parents	Severity of TBI	Children with moderate-to-severe TBI were more likely to use PT, OT, ST, and physiatry services compared to those with complicated mild TBI.
2018	Haarbauer-Krupa	Community and hospital trauma registry system in a southeastern state	6-9	39 (TBI)	GCS: 13-15 (81%) 9-12 (13%) 3-8 (5%)	Outpatient rehabilitation (PT, OT, ST) since the injury (at least one year after injury)	Interview with parents	Abnormal imaging findings and LOS	Children with longer LOS were more likely to access outpatient rehabilitation services after being discharged from the hospital.

Abbreviations: AIS, abbreviated injury scale; CHAT, Children's Health After Trauma; JHH, Johns Hopkins Hospital; LOS, length of stay; MIEMSS, Maryland Institute for Emergency Medical Services System; OT, occupational therapy; PT, physical therapy; ST, speech and language therapy; TBI, traumatic brain injury.

Length of Acute Hospitalization

Children with a longer length of acute hospitalization following TBI appeared more likely to access outpatient rehabilitation after discharge [8, 9]. Jimenez et al. found that, for children enrolled in Medicaid and hospitalized for TBI, the median length of stay for those with and without any outpatient rehabilitation after discharge was 7 days and 2 days respectively. However, such difference in the length of acute hospitalization was significantly attenuated when potential confounders were taken into account in the analysis [9]. Another study found that children with TBI who stayed at acute care hospital for 5 days or more were approximately six times more likely to receive outpatient rehabilitation compared to those with a shorter length of hospitalization [8].

Age

Inconclusive associations between age and use of outpatient rehabilitation services have been reported in the existing literature. Jimenez et al. found that children of older age used outpatient rehabilitation more frequently [9]. However, this association disappeared when authors adjusted for potential confounders.

Race/Ethnicity

Racial/ethnic disparities in the use of outpatient rehabilitation following TBI among children remain unclear due to the scarcity of evidence. Jimenez et al. found no differences between non-Hispanic whites, non-Hispanic blacks and Hispanics in the use of outpatient rehabilitation services following TBI [9]. However, those of other racial/ethnic minority group were more likely to receive outpatient PT, OT and ST services compared to non-Hispanic whites [9]. Hispanics were found to use ST services less frequently than children in all other racial/ethnic groups [9]. This result aligns with previous findings that Hispanic families with limited English proficiency may have difficulties receiving needed care in their primary language because of the limited available services [115].

Socioeconomic Status

Children from families with more financial resources were shown to have better access to outpatient rehabilitation following TBI. One study found that children insured by Medicaid were less likely to receive needed rehabilitation therapies throughout the first year after injury compared to those with commercial insurance [114]. Another study found that children from households with annual incomes of at least $50,000 were more likely to receive needed PT services than those from lower-income households [113].

2.5 Rehabilitation After Acute Care and Outcomes in Children with Severe TBI

2.5.1 Rehabilitation After Acute Care and Motor and Neurobehavioral Outcomes

Inpatient Rehabilitation and Motor and Neurobehavioral Outcomes

A variety of motor, neuropsychological, and behavioral outcomes were demonstrated to improve over the course of inpatient rehabilitation in children with severe TBI [38, 39, 116-120]. Several studies found that the overall gross motor function of children with severe TBI improved significantly after the initiation of inpatient rehabilitation, which was indicated by continuously increased Gross Motor Function Measure scores [38, 39, 117, 118]. Studies focusing on gait parameters also found that inpatient rehabilitation can lead to improvements in gait velocity, cadence and stride length [38, 118]. In a study of 23 children with moderate-to-severe TBI, several gait parameters were found to recover to the age-appropriate level at 5 months after the initiation of inpatient rehabilitation [38]. The same study also showed that impaired fine motor outcomes improved significantly after rehabilitation, though fine motor outcomes recovered less than gross motor outcomes.

Several studies reported the significant improvements in cognitive and behavioral outcomes after initiation of inpatient rehabilitation in children with severe TBI [116, 119, 120]. One study found that 13 (41.9%) out of 31 children with severe TBI improved on two or more neuropsychological tests of intellectual functioning, memory, executive function, attention and processing speed after receiving inpatient rehabilitation [120]. Cognitive recovery remained significant in study participants after discharge from inpatient rehabilitation. Another study found that the mild deficits in cognitive outcomes recovered to a borderline level after a two-year inpatient rehabilitation program in 26 children with severe TBI [116]. The most severely impaired cognitive domain – attention and processing speed kept improving over the two years of rehabilitation, as indicated by steadily increasing WISC-III PSI scores. Thomas-stonell et al. assessed behavioral outcomes in 33 children admitted to inpatient rehabilitation for severe TBI and found that 48% of children had significantly reduced maladaptive behaviors from admission to discharge [119].

Non-Inpatient Rehabilitation and Motor and Neurobehavioral Outcomes

There is some preliminary evidence in support of the efficacy of rehabilitation therapies provided in non-inpatient settings to improve motor and neurobehavioral outcomes following severe TBI in children [10, 11, 121, 122]. Specifically, several home-based and outpatient physiotherapy interventions were demonstrated to improve motor outcomes [10, 123]. According to a recent systematic review, designed home-based functional strength training and virtual reality programs provided in home or outpatient clinics were effective in improving gross motor outcomes in children with acquired brain injuries [10]. Further, an emerging literature shows that cognitive and behavioral sequela following severe TBI can recover significantly after cognitive rehabilitation therapies in children [11, 121, 122]. Another systematic review identified 19 studies assessing the effects of cognitive rehabilitation therapies on neurobehavioral outcomes in children with acquired brain injuries over the past 50 years [11]. Most of the identified cognitive rehabilitation therapies were given at home, at outpatient clinics or at community-based settings when children were medically stable. It suggested that cognitive rehabilitation combining metacognition training and drill-based interventions, or external aids can result in significant improvements in a variety of neurobehavioral outcomes including memory, attention, processing speed, intellectual functioning, executive function and behavioral outcomes. However, both reviews highlighted that previous studies were limited by small sample sizes and great heterogeneity with regards to outcome measurements and characteristics of study participants such as types of acquired brain injuries [10, 11], suggesting the need of more studies to evaluate the effects of non-inpatient rehabilitation therapies on motor and neurobehavioral outcomes in children with severe TBI.

2.5.2 Rehabilitation After Acute Care and Global Function

Inpatient Rehabilitation and Global Function

Evidence is accruing in the last few decades that children with severe TBI can have significantly improved global function and daily living skills after receiving inpatient rehabilitation, and continue to make gains after discharge from an inpatient rehabilitation facility [12]. The most majority of these studies examined the change of global function from inpatient rehabilitation admission to discharge using the Pediatric Evaluation of Disability Inventory (PEDI) or the Functional Independence Measure for Children (WeeFIM) [12]. Studies consistently found that the average WeeFIM Developmental Functional Quotients (DFQs) increased from 30~45 to more than 60 over the course of inpatient rehabilitation in children with TBI [124-128]. Similar results were observed in studies using the PEDI scale. Dumas et al. conducted several studies to compare the PEDI Functional Skills scores measured at admission and discharge in children admitted to inpatient rehabilitation after acute care [129-133], and found the magnitude of improvements in PEDI scores to be clinically meaningful (change of scaled score ≥ 10). One study also included another instrument called the Vineland Adaptive Behavior Scales (VABS), which was recommended as a supplemental assessment to WeeFIM or PEDI [134], to evaluate the daily life functioning in children with severe TBI [119]. Approximately 70% of children were found to have improved scores on daily living skills, communication and socialization domains of the VABS after inpatient rehabilitation.

Moreover, studies demonstrated the long-term functional recovery following inpatient rehabilitation in children with severe TBI. Two studies examined the functional status of children with severe TBI at admission, discharge and three months after inpatient rehabilitation and found continued improvement of WeeFIM scores over time [128, 135]. Some children can even achieve age-appropriate functional status at three months after discharge [128, 135]. Another study also found that most children with moderate-to-severe TBI achieved age-appropriate functional status at one year after discharge from an inpatient rehabilitation facility [136]. However, several studies highlighted the limitations of using WeeFIM or PEDI to assess long-term global function following TBI due to their ceiling effects [119, 137]. The gold standard measure of long-term global function following pediatric TBI – GOS-E Peds and its original form – Glasgow Outcome Scale-Extended (GOSE), which have been demonstrated with better clinical responsiveness than

WeeFIM and PEDI [138], were rarely used in previous studies to examine the effects of inpatient rehabilitation.

Non-Inpatient Rehabilitation and Global Function

Previous studies revealed the improvement of global function in children receiving TBI rehabilitation services provided at outpatient, home-based, or community-based settings [139-142]. Galbiati et al. conducted a non-randomized controlled trial in 65 children with severe TBI to examine the effects of a cognitive rehabilitation program provided by therapists at an outpatient clinic [140]. The VABS was used to evaluate the daily functioning of participants before and after rehabilitation. All domain specific scores of the VABS were found to improve over time in children receiving cognitive rehabilitation, while no significant changes were found in controls. In a study of children receiving home-based and outpatient rehabilitation services that were designed to improve daily functioning following acquired brain injuries, approximately two thirds reported a significant improvement of the primary treatment goal [139]. Another study enrolled 77 individuals with acquired brain injuries (73% TBI), and 67% of study participants were 20 years or younger [142]. Study participants were provided with personalized home- or community-based interdisciplinary rehabilitation. At the end of rehabilitation, 77% of all participants were found to achieve individualized goals of functional recovery.

2.5.3 Rehabilitation After Acute Care and Quality of Life

Although the improvement in quality of life has been regarded as the distal and ultimate value of rehabilitation, effects of rehabilitation on quality-of-life outcomes in children with severe TBI were critically understudied. Very few studies focused on quality of life in those receiving inpatient or non-inpatient rehabilitation for TBI. In one study of 33 children admitted to an inpatient rehabilitation facility following severe TBI, the health-related quality of life was measured based on the Child Health Questionnaire (CHQ) during inpatient stay and later at a follow-up clinic visit (2 to 23 months later) [119]. Results showed that 64% of children scored significantly higher on the CHQ over time, which suggested that most children had improved health-related quality of life after rehabilitation. De Kloet et al. conducted a quasi-experimental study to determine the effects of a designed rehabilitation program provided at home and an outpatient clinic on health-related quality of life in patients with acquired brain injuries [139]. More than half of study participants had a TBI, and 70% were aged below 18 years at the time of study. Both participant self-reported and parent-reported health-related quality of life were measured using the Pediatric Quality of Life Inventory (PedsQL) at baseline and at the end of rehabilitation. No significant change was found for participant self-reported PedsQL scores. Significant improvement was only identified for parent-reported school functioning.

2.6 Summary of Literature Review and Gaps in Knowledge

A severe TBI can adversely impact a child's physical, cognitive, and behavioral outcomes and lead to unfavorable daily functioning and quality of life. Rehabilitation after initial stabilization and acute management is essential to favorable recovery for children with severe TBI [2]. However, there is substantial variability in the use of inpatient and non-inpatient rehabilitation services after acute hospitalization among children with TBI. Characteristics associated with the use of inpatient or non-inpatient rehabilitation services were limitedly described, though those with more severe TBI and those from higher SES families appeared more likely to receive inpatient and outpatient rehabilitation after acute care. Furthermore, despite the preliminary evidence for the efficacy of inpatient rehabilitation and specific non-inpatient rehabilitation therapies on improving motor, neurobehavioral, and functional outcomes of children with severe TBI, there remains a poor understanding of the contribution of rehabilitation process after acute care, including the use of inpatient rehabilitation and/or non-inpatient rehabilitation, to long-term outcomes in children with severe TBI.

2.6.1 Characteristics of Children Receiving Rehabilitation After Acute Care Following TBI

Hospital discharge decisions and referral to certain rehabilitation services for children with TBI are mainly dependent on their clinical conditions, while multiple other factors of patients and their families can affect and complicate these clinical decisions. Previous literature provided the important evidence that children with more severe TBI were more likely to receive both inpatient and outpatient rehabilitation after acute care. Children from households with more financial resources may have better access to medical rehabilitation after acute hospitalization.

Gaps in Knowledge

No studies to date have characterized children receiving inpatient rehabilitation, with or without the use of additional non-inpatient rehabilitation, and children receiving only non-inpatient rehabilitation after acute care for severe TBI. Children requiring rehabilitation following severe TBI may be admitted to inpatient rehabilitation facilities, skilled nursing facilities or long-term care hospitals for inpatient brain injury rehabilitation. Some children may be directly discharged home but referred to day hospital programs, or home-based or community-based rehabilitation therapies after acute hospitalization. The absence of a rehabilitation referral can also occur for some children, while they may be referred to general medical practitioners or community respite services [143]. In a broad sense, among children receiving rehabilitation after acute care for severe

TBI, some may receive inpatient rehabilitation after being medically stable, while some may only receive non-inpatient rehabilitation. However, most previous studies focused either on inpatient or outpatient rehabilitation alone, while very few included both measures. Even in the limited number of studies with measures of both inpatient and non-inpatient rehabilitation, characteristics of children with different patterns of rehabilitation process after acute medical management for severe TBI were not described [7, 9, 113, 114].

Children who received rehabilitation after severe TBI have been limitedly characterized given the lack of studies on a representative group of patients. More importantly, characteristics including preinjury conditions, acute functional status, and family functioning which may play a key role in determining the receipt of rehabilitation following TBI were largely understudied. Therefore, we will extend the current knowledge by delineating a variety of characteristics including socio-demographics, injury related and clinical factors, as well as child's functional status at acute hospital discharge among a representative pediatric population with inpatient rehabilitation or only non-inpatient rehabilitation after acute hospitalization for severe TBI.

2.6.2 Effects of Rehabilitation on Motor, Neurobehavioral, Functional, and Quality-of-Life Outcomes in Children with Severe TBI

Summarizing the results of studies on rehabilitation in children who mainly sustained severe TBI, inpatient and non-inpatient rehabilitation services appear to improve motor and neurobehavioral outcomes, as well as global function. Effects of rehabilitation on quality-of-life outcomes in children with severe TBI remain unclear due to the scarcity of related evidence. Limitations within previous studies and heterogeneity across studies in terms of characteristics of study participants and outcome measurements prevent making a definitive conclusion regarding the effectiveness of rehabilitation on long-term motor, neurobehavioral, functional, and quality-of-life outcomes in children with severe TBI.

Gaps in Knowledge

No studies to date have compared the effectiveness of different patterns of rehabilitation process following TBI for children, though a growing body of related research has been done in adults. Considering that adults with TBI may choose to use rehabilitation therapies provided in non-inpatient settings such as home or outpatient clinics instead of inpatient facilities to reduce health care expenditure or meet individual needs [144], previous studies evaluated the associations between the use of inpatient rehabilitation and health outcomes. One study of US adult patients with TBI reported that the FIM scores at one-year post-injury for those directly discharged to inpatient rehabilitation were lower than the scores for those discharged home with outpatient services, suggesting worse functional outcomes in those with inpatient rehabilitation after acute hospitalization [145]. However, important confounding factors such as severity of TBI and functional status during the acute phase were not taken into account. Recent European studies consistently demonstrated that, compared to other patterns of rehabilitation process after acute hospital discharge such as no inpatient rehabilitation at all or receipt of inpatient rehabilitation after a waiting period at another hospital, direct discharge from acute care to inpatient brain injury rehabilitation was associated with better functional outcomes as reflected by higher FIM scores at one year after injury in adults with severe TBI [4, 5, 146]. It is imperative to conduct similar studies in children and examine the effects of inpatient rehabilitation on multiple outcomes in order to optimize the continuum of health care for children with severe TBI and support challenging discharge decisions. To address the limitations such as small sample size within previous studies and provide more evidence regarding the health impacts of rehabilitation process in a real-world environment, we will apply a comparative effectiveness research approach to determine the associations of the receipt of inpatient rehabilitation after acute care with motor, neuropsychological, behavioral, functional, and quality-of-life outcomes in a representative cohort of children with severe TBI.

2.6.3 Potential Selection Biases in Longitudinal Studies of Children with TBI

Longitudinal pediatric TBI studies are usually conducted in clinical research samples, where patients or their parents/guardians have volunteered for future outcome assessments. However, little is known about how selection biases like volunteer bias or biases due to loss to follow-up impact study results. These selection biases can harm both the internal and external validity of research when those who do and do not participate are systematically distinct with regards to characteristics of interests. One longitudinal study of children with moderate-to-severe TBI found that enrolled participants whose families provided informed consent were more likely to have health insurance and stay in acute care facilities for a shorter time compared to those unenrolled [114]. Additionally, children from families with greater socioeconomic disadvantage were found to be at increased risk of being lost to follow-up [14]. There is limited knowledge of the impacts of these selection factors on the findings regarding associations between rehabilitation and outcomes following TBI. One solution to this problem is to recruit study participants from a well-characterized population, so characteristics of those who finally do and do not participate can be compared. Further, these characteristics can be adjusted for in the analysis to understand how selection factors influence findings [147].

The Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial is a large population-based cohort study of pediatric patients with severe TBI [78, 88, 148]. Participants in the ADAPT trial were followed from acute hospital admission to one-year post-injury. Informed consent for long-term outcome assessments were obtained from children or parents/guardians at hospital discharge. Within the ADAPT trial, we are able to detect characteristics associated with potential interest in long-term outcome assessments and loss to follow-up to generate statistical weights, which then can be used to adjust results of associations between rehabilitation process and motor, neuropsychological, behavioral, functional, and quality-of-life outcomes. It will allow us to explain how selection biases such as volunteer bias and attrition bias may affect study results.

3.0 Manuscript 1: Characteristics Associated with the Use of Inpatient Rehabilitation After Acute Care in Children with Severe Traumatic Brain Injury

3.1 Abstract

To characterize inpatient rehabilitation services for children with severe traumatic brain injury (TBI), we included 254 children, whose parents/guardians reported receipt of rehabilitation within a 12-month follow-up period, from a multinational observational study. Children discharged to an inpatient rehabilitation or skilled nursing facility after acute care were classified into the “inpatient rehabilitation” group, and children discharged home after acute care were classified into the “non-inpatient rehabilitation” group. Multivariable regression analyses determined the associations of sociodemographic and clinical characteristics with rehabilitation groups. Children receiving inpatient rehabilitation had a shorter length of acute hospitalization. Children from the UK were less likely to receive inpatient rehabilitation compared to children from the US. Among the US cohort (n=190), African Americans were less likely to receive inpatient rehabilitation compared with whites. Future studies are warranted to extend current findings by identifying the reasons behind differential access to inpatient rehabilitation among children with severe TBI.

3.2 Introduction

Severe traumatic brain injury (TBI) is a leading cause of death and disability in children. In the US, the case fatality rate of pediatric severe TBI is estimated to be 24% [1]. Children who survive severe TBI often experience long-term cognitive and physical impairments, and thus disability on different functional domains [33, 37, 41, 75, 137]. One study found the incidence of disability to be more than 60% in children with moderate-to-severe TBI [33].

Rehabilitation is generally defined as a large set of medical and therapeutic services used to reduce the impact of impairments and improve daily functioning of patients [149]. However, due to the lack of comprehensive pediatric TBI rehabilitation guidelines and a limited amount of information from multicenter studies, there is great variability in the continuum of rehabilitation care after acute medical management among children with severe TBI. One of the largest nationwide studies of children in the US determined that less than one third of those hospitalized for severe TBI were discharged to an inpatient rehabilitation facility [6]. Overall, inpatient rehabilitation involves continued nursing care and multidisciplinary therapy services [150]. For many children in need of rehabilitation after acute care, therapies can only occur at home or in their community such as outpatient settings. These non-inpatient rehabilitation services are usually less intensive than inpatient rehabilitation [106].

Receipt of rehabilitation services after acute care whether inpatient or non-inpatient can be influenced by multiple factors in children with TBI. Although the child's illness severity and capacity to benefit from rehabilitation services play a primary role, family socioeconomic status (SES) and preferences, and other contextual factors may affect clinical decisions at the time of discharge from the acute care hospital and as a result impact the child's rehabilitation process [151]. Previous studies of children experiencing a TBI of any severity have suggested that less severe brain injury, younger age and lack of health insurance were associated with a reduced likelihood of receiving a referral to inpatient rehabilitation [6, 7, 113, 114]. Other studies have characterized children with and without any outpatient rehabilitation after acute hospitalization for TBI of any severity [7, 9]. Children who received outpatient rehabilitation were more likely to be older, come from higher SES families and sustain more severe brain injury and non-brain injuries compared to those without outpatient rehabilitation, regardless of whether they received inpatient rehabilitation [9, 115]. However, most children involved in previous studies suffered a complicated mild or moderate TBI and very few had a severe TBI [113]. Further, it has been reported that children with rehabilitation needs after severe TBI were unlikely to receive no rehabilitation at all within the first year after injury [114]. To date, no study has described the characteristics associated with the use of inpatient rehabilitation (with or without additional non-inpatient rehabilitation) versus non-inpatient rehabilitation only after acute care in children with severe TBI.

The current study aimed to delineate the characteristics associated with the use of inpatient rehabilitation after acute hospitalization among a pediatric population with severe TBI from the multinational Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial. Unlike clinical characteristics, sociodemographic characteristics may be more specific to country/region contexts, so we focused on the overall multinational sample and a subset of the sample who were enrolled from the US.

3.3 Methods

3.3.1 Study Participants

The ADAPT trial was a multisite, multinational observational study to evaluate the effectiveness of several acute management strategies in children with severe TBI. The detailed study design has been described elsewhere [78, 88, 148]. In brief, between 2014 and 2016, a total of 1000 children meeting the inclusion/exclusion criteria (inclusion: age < 18 years, diagnosis of severe TBI, placement of intracranial pressure [ICP] monitor at study site, and Glasgow Coma Scale [GCS] score ≤ 8 at the time of monitor placement; exclusion: pregnancy) were consecutively enrolled from 51 sites in the US, the UK, Spain, the Netherlands, India, South Africa, Australia, and New Zealand. All sites received Institutional Review Board approval (or equivalent) to perform the study and collect data regarding the acute hospitalization on eligible children. Before being discharged from the clinical site after their injury, study participants or their parents/guardians provided informed consent for the collection of data on preinjury conditions, family related factors, receipt of rehabilitation, as well as outcomes such as functional status.

For this study, children were included if there was available data on rehabilitation use at the 12-month follow-up (Figure 1). Of 399 eligible children, 101 children enrolled from Spain, the Netherlands, India and South Africa were excluded. These excluded children were not administered functional status assessments at hospital discharge due to the concerns of reliability and validity of the translated versions of the instrument. This study, therefore, focused on children from the US, the UK, Australia and New Zealand. Another 37 children without any rehabilitation therapies were excluded because over 70% of them were found to have normal or near normal functional status (Functional Status Scale [FSS] ≤ 7) at discharge and might not need additional rehabilitation. We further excluded 7 children who were discharged to other hospitals after acute care and there was not enough information to determine whether they received inpatient rehabilitation or not. This resulted in a final sample of 254 children with 190 from the US.

3.3.2 Rehabilitation Process

Rehabilitation process after acute care was defined based on child’s initial discharge destination (per the medical record) and parent/guardian-reported rehabilitation use at the 12-month follow-up. At the 12-month assessment, parents/guardians were asked whether their child received any rehabilitation including physical therapy, occupational therapy, speech and/or language therapy as a result of TBI since hospital discharge. Among those who had ever received rehabilitation, children were classified into the “inpatient rehabilitation” group if their initial discharge destination was indicated as an inpatient rehabilitation facility or skilled nursing facility in the medical records [152, 153]; “non-inpatient rehabilitation” group if they were directly discharged home after acute care and if their parents/guardians reported receipt of medical rehabilitation within the 12-month follow-up period. Children in the non-inpatient rehabilitation group may have received home health, outpatient therapies or community-based therapies. Children in the inpatient rehabilitation group may or may not have received additional non-inpatient rehabilitation services after discharge from inpatient rehabilitation. Although some children who were discharged home may be admitted to inpatient rehabilitation settings afterwards, they were considered as receiving non-inpatient rehabilitation only in this study.

3.3.3 Characteristics of Interest

We analyzed the sociodemographic and clinical characteristics including functional status at discharge from the acute care hospital. These characteristics were selected based on the existing literature suggesting their potential relationships with use of rehabilitation services [9, 108, 112-114, 154]. Demographic variables included age at injury, sex, region, race, and ethnicity (not applicable to sites outside the US). Injury related variables included cause, mechanism of injury and likelihood of abusive head trauma (AHT), which was categorized based on clinicians' certainty about related diagnosis at each clinical site. Acute injury or illness severity measures included GCS score at the time of ICP monitor insertion, Abbreviated Injury Scale (AIS) scores, Injury Severity Score (ISS), and Pediatric Risk of Mortality (PRISM) III score. Pupil response examined at the time of ICP monitor placement, pre-hospital and resuscitation events such as cardiac arrest, hypoxia and hypotension, and acute computerized tomography (CT) findings were also analyzed. Other clinical factors evaluated at hospital discharge, included length of stay, any systemic and neurological complications during acute hospitalization, as well as GCS score. All data on demographic, injury related, and clinical characteristics were collected by abstracting child's medical records.

After consenting for outcome assessments at hospital discharge, parents or guardians filled out designed questionnaires on family related factors including the highest educational level achieved by child's primary caregiver and number of employed family members. Parents/guardians were also asked to evaluate overall family functioning using the General Functioning Scale of the McMaster Family Assessment Device, which has well-documented reliability and validity [155, 156]. A score greater than 2 on this scale was used as an indicator of unhealthy family functioning [157]. Parents/guardians also reported child's preinjury conditions.

For this study, preinjury conditions were classified as neurodevelopmental disability (previous TBI, epilepsy, seizure, cerebral palsy, autism, toxic exposure, noninjury-related loss of consciousness and extremely low birth weight), attention or learning problems (attention deficit hyperactivity disorder and learning disability), and other conditions (hearing or visual impairment, muscle weakness, difficulty with balance or walking). Child's functional status at hospital discharge was evaluated by parents/guardians using the FSS with detailed instructions. FSS is a rapid and reliable measure of functional status across six domains (mental, sensory, communication, motor, feeding and respiratory) [158, 159]. The scale in each domain scores from 1 (normal) to 5 (very severe dysfunction) resulting in a total score ranging from 6 to 30 [158, 159]. The FSS has been validated against a gold-standard instrument for assessing adaptive behaviors in children during acute care [159], and increasingly used to measure in-hospital functional impairment.

3.3.4 Statistical Analysis

Characteristics of interest were described using frequencies and percentages, means and standard deviations, or medians and interquartile ranges for variables with skewed distributions. T-tests (or Wilcoxon Rank Sum tests) or Chi-square tests (or Fisher's exact tests) were used to compare these characteristics between inpatient rehabilitation and non-inpatient rehabilitation groups. Multivariable logistic regression was used to examine the independent associations between characteristics of interest and rehabilitation process after acute hospitalization. To address the missing values for some characteristics, we performed multiple imputations using the fully conditional specification method (M = 15 imputations) based on the assumption that data were missing at random. All characteristics of interest and the rehabilitation variable were included in the imputation model. Each imputed dataset was analyzed separately using a multivariable logistic regression model with all characteristics with $p < 0.2$ in the bivariate analysis. The association of the child's age and hospital length of stay (LOS) with rehabilitation variable did not appear to be linear. Therefore, age was categorized into 0 -< 5 years, 5 -<11 years and 11 -< 18 years that were consistent with categories reported earlier from the ADAPT [78]. LOS was dichotomized at the median (≤ 23 vs > 23 days). Results of regression analyses across the imputations were combined to acquire inferences. The same analytical procedure was used in the subset of analyses on children from the US. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). A two-sided $p < 0.05$ was considered statistically significant.

3.4 Results

3.4.1 Characteristics of Children in the Multinational Sample

Bivariate Analysis

Of the 254 children included in the study sample, 180 were in the inpatient rehabilitation group and had a mean age of 8.7 (SD 5.2) years at the time of injury; 74 were in the non-inpatient rehabilitation group and had a mean age of 7.5 (SD 5.5) years (Table 2). Most children in the study were male (61.4%) and white (71.3%). Children in the non-inpatient rehabilitation group were more likely to be enrolled from the UK (43.2% vs 3.3%, p<0.001) and suffer acceleration/deceleration injuries (18.9% vs 6.1%, p=0.003) compared to those in the inpatient rehabilitation group. Children in the non-inpatient rehabilitation group also appeared more likely to have AHT (21.6% vs 12.2%, p=0.056) and a lower AIS head score (4 [3, 5] vs 4 [4, 5], p=0.049).

Children receiving inpatient rehabilitation were more likely to have CT abnormalities including subarachnoid hemorrhage (52.8% vs 37.8%, p=0.030), contusion (58.3% vs 43.2%, p=0.028), midline shift (40.6% vs 24.3%, p=0.014) and cisternal compression (43.3% vs 24.3%, p=0.005).

Children in the non-inpatient rehabilitation group were more likely to have a less educated primary caregiver (30.2% vs 13.2%, p=0.003) and come from unemployed families (25.4% vs 12.0%, p=0.039) (Table 3). Although not statistically significant, children receiving inpatient rehabilitation appeared more likely to have preinjury attention or learning problems (13.2% vs 4.6%, p=0.055). Children in the non-inpatient rehabilitation group had lower FSS total scores (8.0 ± 3.8 vs 11.0 ± 5.7, p<0.001) and higher GCS scores (15 [14, 15] vs 14 [11, 15], p<0.001) at the time of discharge from acute care hospitals. They also stayed in acute care hospitals for a longer time (36.8 ± 26.1 days vs 29.0 ± 27.8 days, p=0.039). During hospital stay, children in the inpatient rehabilitation group were more likely to sustain systemic complications (45.0% vs 31.1%, p=0.040), though no differences in the occurrence of neurological complications were found between rehabilitation groups.

Multivariable Analysis

In Table 4, we show the results of modeling the receipt of inpatient rehabilitation after acute hospitalization compared with the receipt of non-inpatient rehabilitation only as a function of characteristics with p < 0.2 in the bivariate analysis. Children in the UK had 92% reduced odds of receiving inpatient rehabilitation after acute care for severe TBI compared to those in the US (p<0.001). Children who stayed in acute care hospitals for 23 days or longer had 69% decreased odds of receiving inpatient rehabilitation compared with those who stayed in acute care hospitals for less than 23 days (p=0.005). A positive association was found between the FSS total score at hospital discharge and the use of inpatient rehabilitation (OR:1.12, 95% CI 1.00-1.26), which was trending towards statistical significance. African Americans appeared to have lower odds of receiving inpatient rehabilitation compared with whites (OR:0.38, 95% CI: 0.14-1.02), though this association did not approach statistical significance.

3.4.2 Characteristics of Children in the US

Bivariate Analysis

In the subset of 190 children enrolled from the US, 154 received inpatient rehabilitation and 36 only received non-inpatient rehabilitation after acute hospitalization. Children with inpatient rehabilitation were older at the time of injury (8.7 ± 5.3 years vs 6.3 ± 5.9 years, p=0.016) and more likely to be white (76.0% vs 47.2%, p=0.004) (Table 5). Children who only received non-inpatient rehabilitation were more likely to suffer AHT (30.6% vs 13.6%, p=0.015) and acceleration/deceleration injuries (19.4% vs 5.9%, p=0.019). Although not statistically significant, children in the non-inpatient rehabilitation group appeared more likely to experience a homicide/assault related TBI (27.8% vs 13.6%, p=0.076). During the pre-hospital or resuscitation state, children in the non-inpatient rehabilitation group were more likely to sustain seizures (36.1% vs 15.6%, p=0.005), and no differences in other events were found between rehabilitation groups.

Children who only received non-inpatient rehabilitation stayed in acute care hospitals for a significantly longer time (36.9 ± 23.0 days vs 26.8 ± 15.8 days, p=0.016) when compared with those who received inpatient rehabilitation (Table 6). The average FSS total score in the inpatient rehabilitation group and the non-inpatient rehabilitation group was 11.5 (SD 5.7) and 9.6 (SD 4.9) respectively, though such difference did not reach statistical significance. Children in the inpatient rehabilitation group had lower GCS scores at hospital discharge (13 [11, 15] vs 15 [12, 15], p=0.046) compared to children in the non-inpatient rehabilitation group.

Multivariable Analysis

In the US cohort, race and length of acute hospitalization were independently associated with the rehabilitation process after acute care (Table 7). Specifically, compared to whites, African Americans and those who did not report their race had respectively 66% and 95% reduced odds of receiving inpatient rehabilitation (p=0.032). Children who stayed in acute care hospitals for at least 23 days had 73% reduced odds of receiving inpatient rehabilitation compared with those who stayed in acute care hospitals for less than 23 days (p=0.009). Children with a midline shift on CT were 3.27 times more likely to receive inpatient rehabilitation as compared to children without a midline shift, though such association did not reach statistical significance (p=0.061).

3.5 Discussion

Our study demonstrated substantial differences in the sociodemographic and clinical characteristics between children who received inpatient rehabilitation and children who only received non-inpatient rehabilitation for severe TBI. Results of the overall and subset analyses consistently indicated that children who received inpatient rehabilitation stayed in acute care hospitals for a shorter time. Children from the UK had a lower likelihood of receiving inpatient rehabilitation following acute care compared to children from the US, Australia and New Zealand. Among children with severe TBI in the US, African Americans and those who did not report their race were less likely to receive inpatient rehabilitation compared to whites. Moreover, children receiving inpatient rehabilitation after acute care appeared to be older and less likely to have sustained AHT, acceleration/deceleration injuries, and seizures during pre-hospital or resuscitation state, but more likely to have serious injury measures (AIS scores, GCS scores and CT abnormalities), systemic complications, impaired functional status at discharge, and a history of attention or learning problems. Compared to children who received inpatient rehabilitation, those who only received non-inpatient rehabilitation after acute care tended to come from families with a relatively lower SES. This study is the first to characterize inpatient rehabilitation services for children with severe TBI, independent of the need for additional non-inpatient rehabilitation services.

Longer length of acute hospitalization was found in children who only received non-inpatient rehabilitation therapies after discharge compared to those who received inpatient rehabilitation. Such disparities may be associated with differences in health care environments such as the standards for discharge planning and the availability of an on-site rehabilitation unit in acute care hospitals, as well as the availability of rehabilitation services around patient's home [143]. Clinicians have been reported to expedite patient referral from acute care to post-acute care institutions to reduce length of stay [143]. Foster et al. also showed that, due to the lack of rehabilitation resources in certain geographic areas, clinicians had to keep patients in acute care hospitals longer so that they can receive needed rehabilitation therapies as outpatients [143]. Moreover, for patients who do not meet the criteria for inpatient rehabilitation admission due to severe impairments, such as those who have not reached minimally conscious state, increased time may be spent in the acute care hospital to ensure medical stabilization and implement recommendations for assistive medical equipment before they were discharged home [160].

Our data also showed that children from the UK were less likely to receive inpatient rehabilitation after severe TBI compared with those from the US, Australia and New Zealand. This cross-regional variation in children's rehabilitation process after acute care may be partially due to the discretion of local clinicians when making referral decisions [143] and the availability of rehabilitation resources in local institutions and around patient's home [161, 162]. Future studies taking account of institutional factors and health care related environmental factors are warranted to better understand the observed regional differences in the use of inpatient rehabilitation after acute care among children with severe TBI.

Racial differences in the rehabilitation process after acute hospitalization were found in children with severe TBI in the US. Compared to whites, African Americans were less likely to receive inpatient rehabilitation. Although children who did not report race were found to have decreased likelihood of receiving inpatient rehabilitation, this may be a random finding due to small sample size. In contrast to our results, one study of children with moderate-to-severe TBI demonstrated that African Americans were more likely to be discharged to an inpatient rehabilitation facility after acute care compared to whites [163]. However, this study failed to account for child's illness severity and functional status at discharge when examining racial disparities in discharge dispositions [163]. Our results are consistent with previous adult literature showing that African Americans had significantly reduced access to inpatient rehabilitation after acute care compared with whites among those with moderate-to-severe TBI [164, 165]. However, reasons underlying these racial disparities have not been fully understood. There is increasing evidence suggesting the contribution of SES to observed racial disparities in the access to and use of needed health care services [166, 167]. When we included the primary caregiver's education and family members' employment status in the multivariable adjusted analysis among children in the US, associations between race and rehabilitation process were slightly attenuated but still significant (data not shown). It suggested that, in addition to family SES, other factors related to language, culture, stigma and discrimination may account for racial disparities in the use of inpatient rehabilitation after acute care in children with severe TBI.

We found that children in the inpatient rehabilitation group were less likely to experience AHT and acceleration/deceleration injuries compared to children in the non-inpatient rehabilitation group, though such differences were significantly attenuated in the multivariable adjusted analysis. Observed differences may be partially driven by the excess of younger children in those who only received non-inpatient rehabilitation after acute care, especially among children in the US. The AHT typically affects children under 5 years [168], and infants less than 1 year of age have much higher rates of non-fatal AHT compared to older children [169]. Younger children are also at increased risk of acceleration/deceleration injuries due to a higher water content in the brain especially when they sustain AHT [168]. Additionally, among children in the US, those who only received non-inpatient rehabilitation after acute care were found to be more likely to have seizures during pre-hospital or resuscitation state in unadjusted analysis. Again, this difference may be explained by the overrepresentation of younger children, some of whom sustained AHT, in the non-inpatient rehabilitation group. Among the US cohort in our study, children in the inpatient rehabilitation group were older than those in the non-inpatient rehabilitation group. Previous studies reported that younger children and those suffering AHT are at increased risks of seizures within the first few days after injury [170]. When we assessed seizures among children of 5 years or older, no differences were found between rehabilitation groups (data not shown).

Another related finding is that, in the overall unadjusted analysis, children receiving inpatient rehabilitation appeared more likely to have preinjury attention or learning problems. This trend of disparity may also be explained by the underrepresentation of younger children and overrepresentation of older children among those receiving inpatient rehabilitation. Attention or learning problems are usually not diagnosed until children reach the school age [171, 172]. In the ADAPT trial, none of those with preinjury attention or learning problems were younger than 5 years and none had suffered acceleration/deceleration injuries. Our findings regarding the potential age differences between rehabilitation groups are in alignment with the results of a recent nationwide study of children with a variety of diagnoses in the US. It showed that those discharged to inpatient rehabilitation or skilled nursing facilities after acute care were much older than children with home health after discharge [173]. Future studies are warranted evaluating the role of age on rehabilitation process in children with severe TBI.

Children who received inpatient rehabilitation after acute hospitalization for severe TBI appeared to have greater initial injury severity such as CT abnormalities and more unfavorable outcomes at hospital discharge including systemic complications, impaired consciousness and functional status in the overall analysis, though significant results were not found in children from the US due to limited power. These results are consistent with previous literature on pediatric TBI of mixed severity in that children with more severe brain injuries were more likely to be referred to inpatient rehabilitation after acute care [6]. Our results also highlighted that illness severity and functional status as assessed late in the acute hospitalization play an important role in the post-discharge rehabilitation process among children with severe TBI. This aligns with previous qualitative findings from acute care clinicians that referral decisions were mainly influenced by patient's functional status prior to discharge [143].

Our overall analysis suggests that children from low SES families were less likely to receive inpatient rehabilitation following severe TBI, though associations between SES characteristics and rehabilitation process were not significant in the multivariable adjusted analysis. These unadjusted findings are consistent with prior research that children from lower SES families were less likely to receive needed rehabilitation therapies for TBI [113]. Greene et al. also found that children without health insurance were less likely to be referred to inpatient rehabilitation after acute hospitalization for TBI regardless of severity in the US [6]. It was surprising that no differences in primary caregiver's education or family members' employment status were found between rehabilitation groups among the US cohort in our study. However, these SES measures may not be sufficient to represent family's monetary resources and child insurance status. Since the majority of rehabilitation therapies in the UK, Australia and New Zealand are funded by the single payer system, the underuse of inpatient rehabilitation among children from low SES families in these countries was unlikely due to financial concerns about rehabilitation, but may be associated with family's concerns about time management and caregiving, as well as other related expenses. One qualitative study showed that, during the inpatient rehabilitation period, caregivers were concerned about expenses related to traveling to be close to the patient with TBI and finding accommodations near the rehabilitation facility [174]. Additionally, children from low SES families are more likely to live in disadvantaged areas and may not receive inpatient rehabilitation due to lack of local care resources. Further investigation on the associations between other family SES characteristics and the receipt of inpatient rehabilitation in children with severe TBI is warranted.

Limitations

We note several study limitations. First, rehabilitation disposition may have been misclassified for some children as it was only based on their post-acute care discharge destination; no data was collected from an inpatient rehabilitation admission. Children who were referred to but not admitted to inpatient rehabilitation may have been misclassified in the inpatient rehabilitation group. Children who were directly discharged home after acute care and later admitted to inpatient rehabilitation may have been misclassified in the non-inpatient rehabilitation group. Misclassification of the rehabilitation process may have resulted in more similar groups.

Second, we did not have information on the use of rehabilitation therapies over the course of acute hospitalization, limiting our ability to determine if children in the non-inpatient rehabilitation group did receive greater amounts of therapies before discharge. Additionally, we may have inadequate measures of family SES characteristics. We had no data on child's insurance type, family income and rural/urban residence, which hampered our ability to fully understand the associations between different SES characteristics and the rehabilitation process among children with severe TBI especially among those in the US. Lastly, we had no data on contextual factors such as the availability of rehabilitation professionals and on-site rehabilitation units within the study sites, as well as the availability of rehabilitation resources around patients' homes, limiting our ability to interpret the underlying reasons for the associations of country/region and length of acute hospitalization with rehabilitation process.

Conclusion

Among a large pediatric cohort with severe TBI, those receiving inpatient rehabilitation stayed in acute care hospitals for a shorter time and were less likely to come from the UK compared with those who only received non-inpatient rehabilitation. In the US, racial differences were observed in the use of inpatient rehabilitation after acute care among children with severe TBI. Children in the two rehabilitation groups also appeared to differ in age, injury mechanism, injury and illness severity, as well as family SES. Our findings suggest the need for further quantitative and qualitative studies to elucidate the reasons behind the observed differences in the use of inpatient rehabilitation among children with severe TBI, especially across different racial groups, so that efforts can be taken to reduce such racial disparities.

3.6 Tables and Figures

Table 2. Demographics and Injury Related Characteristics of Children with Severe TBI in the Inpatient Rehabilitation and Non-Inpatient Rehabilitation Groups

Characteristics		Rehabilitation process after acute care		
	Total (n=254)	**Non-inpatient rehabilitation (n=74)**	**Inpatient rehabilitation (n=180)**	**P**
Age at injury, mean ± std	8.4 ± 5.3	7.5 ± 5.5	8.7 ± 5.2	0.112
Age at injury, n (%)				0.264
0 -< 5 yrs	90 (35.4)	30 (40.5)	60 (33.3)	
5 -< 11 yrs	69 (27.2)	22 (29.7)	47 (26.1)	
11 -< 18 yrs	95 (37.4)	22 (29.7)	73 (40.6)	
Sex, n (%)				0.876
Female	98 (38.6)	28 (37.8)	70 (38.9)	
Male	156 (61.4)	46 (62.2)	110 (61.1)	
Race, n (%)				0.104
White	181 (71.3)	46 (62.2)	135 (75.0)	
African American	45 (17.7)	15 (20.3)	30 (16.7)	
Other	22 (8.7)	10 (13.5)	12 (6.7)	
Unknown/withheld	6 (2.4)	3 (4.1)	3 (1.7)	
Region, n (%)				<0.001
US	190 (74.8)	36 (48.6)	154 (85.6)	
UK	38 (15.0)	32 (43.2)	6 (3.3)	
Australia or New Zealand	26 (10.2)	6 (8.1)	20 (11.1)	
Likelihood of abusive head trauma (Yes), n (%)	38 (15.0)	16 (21.6)	22 (12.2)	0.056
Mechanism of injury, n (%)				0.003
Acceleration/deceleration	25 (9.9)	14 (18.9)	11 (6.1)	
Direct impact/fall	210 (83.0)	58 (78.4)	152 (84.9)	
Penetrating	18 (7.1)	2 (2.7)	16 (8.9)	
Cause of injury, n (%)				0.237
Motor vehicle	144 (56.7)	47 (63.5)	97 (53.9)	
Fall	50 (19.7)	11 (14.9)	39 (21.7)	
Homicide/assault	32 (12.6)	11 (14.9)	21 (11.7)	
Other	28 (11.0)	5 (6.8)	23 (12.8)	
GCS total score at enrollment, mean ± std	5.4 ± 1.9	5.4 ± 1.9	5.4 ± 1.8	0.938
AIS head, median (IQR)	4 (4, 5)	4 (3, 5)	4 (4, 5)	0.049
Max AIS without head, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.222
Injury Severity Score, mean ± std	26.1 ± 11.3	24.7 ± 11.3	26.7 ± 11.3	0.205
PRISM III, mean ± std	14.5 ± 7.7	14.9 ± 8.4	14.3 ± 7.5	0.580
Fixed pupil(s) at enrollment, n (%)				0.496
Both	32 (12.6)	6 (8.1)	26 (14.4)	
Either	25 (9.8)	7 (9.5)	18 (10.0)	
Neither	184 (72.4)	56 (75.7)	128 (71.1)	
Unable to assess/unknown	13 (5.1)	5 (6.8)	8 (4.4)	

Table 2 (Continued)

Characteristics		**Rehabilitation process after acute care**		
	Total (n=254)	**Non-inpatient rehabilitation (n=74)**	**Inpatient rehabilitation (n=180)**	**P**
Pre-hospital and resuscitation events, n (%)				
Apnea				0.600
No/unknown	215 (84.6)	60 (81.1)	155 (86.1)	
Suspected	14 (5.5)	5 (6.8)	9 (5.0)	
Yes	25 (9.8)	9 (12.2)	16 (8.9)	
Aspiration				0.418
No/unknown	214 (84.3)	61 (82.4)	153 (85.0)	
Suspected	32 (12.6)	9 (12.2)	23 (12.8)	
Yes	8 (3.1)	4 (5.4)	4 (2.2)	
Cardiac arrest	8 (3.1)	3 (4.1)	5 (2.8)	0.695
Hypotension	75 (29.5)	19 (25.7)	56 (31.1)	0.388
Hypoxia	23 (9.1)	5 (6.8)	18 (10.0)	0.413
Seizure	41 (16.1)	15 (20.3)	26 (14.4)	0.252
Hyperthermia	25 (9.8)	8 (10.8)	17 (9.4)	0.740
Hypothermia	55 (21.7)	17 (23.0)	38 (21.1)	0.743
Hyperventilation	47 (18.5)	11 (14.9)	36 (20.0)	0.338
Acute CT findings, n (%)				
Epidural hematoma	27 (10.6)	9 (12.2)	18 (10.0)	0.611
Subdural hematoma	167 (65.7)	46 (62.2)	121 (67.2)	0.440
Intracerebral hemorrhage	161 (63.4)	45 (60.8)	116 (64.4)	0.585
Intraventricular hemorrhage	64 (25.2)	15 (20.3)	49 (27.2)	0.246
Subarachnoid hemorrhage	123 (48.4)	28 (37.8)	95 (52.8)	0.030
Diffuse axonal injury	76 (29.9)	25 (33.8)	51 (28.3)	0.388
Contusion	137 (53.9)	32 (43.2)	105 (58.3)	0.028
Midline shift	91 (35.8)	18 (24.3)	73 (40.6)	0.014
Cisternal compression	96 (37.8)	18 (24.3)	78 (43.3)	0.005

IQR, Interquartile range; GCS, Glasgow Coma Scale; AIS, Abbreviated Injury Scale; PRISM III, Pediatric Risk of Mortality III

Table 3. Family Related and Other Clinical Characteristics of Children with Severe TBI in the Inpatient Rehabilitation and Non-Inpatient Rehabilitation Groups

Characteristics		Rehabilitation process after acute care		
	Total (n=254)	**Non-inpatient rehabilitation (n=74)**	**Inpatient rehabilitation (n=180)**	**P**
Highest education of primary caregiver, n (%)				0.003
Less than high school	39 (18.1)	19 (30.2)	20 (13.2)	
High school or higher	176 (81.9)	44 (69.8)	132 (86.8)	
Number of employed family members, n (%)				0.039
None	37 (15.8)	17 (25.4)	20 (12.0)	
One	117 (50.0)	29 (43.3)	88 (52.7)	
Two	80 (34.2)	21 (31.3)	59 (35.3)	
Unhealthy family functioning, n (%)	40 (20.0)	13 (21.7)	27 (19.3)	0.700
Preinjury conditions, n (%)				
Neurodevelopmental disability	21 (9.0)	5 (7.5)	16 (9.6)	0.608
Attention or learning problems	25 (10.7)	3 (4.6)	22 (13.2)	0.055
Other conditions	17 (7.3)	3 (4.6)	14 (8.3)	0.409
Length of hospital stay, mean ± std	31.3 ± 27.5	36.8 ± 26.1	29.0 ± 27.8	0.039
Length of hospital stay, n (%)				0.058
≤ 23 days	130 (51.2)	31 (41.9)	99 (55.0)	
> 23 days	124 (48.8)	43 (58.1)	81 (45.0)	
FSS total score at hospital discharge, mean ± std	10.1 ± 5.4	8.0 ± 3.8	11.0 ± 5.7	<0.001
GCS total score at hospital discharge, median (IQR)	15 (11, 15)	15 (14, 15)	14 (11, 15)	<0.001
Any systemic complications during acute hospitalization, n (%)	104 (40.9)	23 (31.1)	81 (45.0)	0.040
Any neurological complications during acute hospitalization, n (%)	90 (35.4)	24 (32.4)	66 (36.7)	0.522

IQR, Interquartile range; FSS, Functional Status Scale; GCS, Glasgow Coma Scale

Table 4. Independent Associations Between Characteristics and Inpatient Rehabilitation Using a Multivariable Logistic Regression Model (M=15 imputations)

Characteristics	Categories	Adjusted OR	Adjusted OR (95% CI)	P
Age at injury	0-< 5 yrs	ref		0.570
	5-<11 yrs	1.71	0.59-4.95	
	11-18 yrs	1.08	0.37-3.15	
Region	US	ref		<0.001
	Australia or New Zealand	1.44	0.41-5.04	
	UK	0.08	0.02-0.26	
Race	White	ref		0.093
	African American	0.38	0.14-1.02	
	Other	0.48	0.13-1.73	
	Unknown/withheld	0.15	0.02-1.24	
Likelihood of abusive head trauma	Yes vs No	0.49	0.15-1.63	0.245
Mechanism of injury	Direct impact/fall	ref		0.181
	Acceleration/deceleration	0.36	0.10-1.32	
	Penetrating	2.67	0.34-21.09	
Employed family members	None	ref		0.435
	One	2.10	0.69-6.38	
	Two	1.63	0.51-5.25	
Primary caregiver's highest education	High school or higher vs. Less than high school	1.50	0.51-4.36	0.458
AIS head score		1.04	0.66-1.65	0.861
FSS total score		1.12	1.00-1.26	0.058
GCS total score at discharge		0.83	0.66-1.06	0.132
Systemic complications	Yes vs No	1.25	0.54-2.87	0.606
Length of hospital stay	> 23 days vs ≤ 23 days	0.31	0.14-0.70	0.005
Preinjury attention/learning problems	Yes vs No	1.62	0.30-8.67	0.571
Subarachnoid hemorrhage	Yes vs No	1.46	0.63-3.41	0.382
Contusion	Yes vs No	1.13	0.46-2.77	0.795
Midline shift	Yes vs No	1.87	0.70-4.97	0.209
Cisternal compression	Yes vs No	1.27	0.51-3.18	0.612

OR, Odds Ratio; AIS, Abbreviated Injury Scale; FSS, Functional Status Scale; GCS, Glasgow Coma Scale

Table 5. Demographics and Injury Related Characteristics of Children with Severe TBI in the Inpatient Rehabilitation and Non-Inpatient Rehabilitation Groups (Sites in the US)

Characteristics		**Rehabilitation process after acute care**		
	Total (n=190)	**Non-inpatient rehabilitation (n=36)**	**Inpatient rehabilitation (n=154)**	**P**
Age at injury, mean ± std	8.3 ± 5.5	6.3 ± 5.9	8.7 ± 5.3	0.016
Age at injury, n (%)				0.063
0 -< 5 yrs	73 (38.4)	20 (55.6)	53 (34.4)	
5 -< 11 yrs	45 (23.7)	6 (16.7)	39 (25.3)	
11 -< 18 yrs	72 (37.9)	10 (27.8)	62 (40.3)	
Sex, n (%)				0.595
Female	77 (40.5)	16 (44.4)	61 (39.6)	
Male	113 (59.5)	20 (55.6)	93 (60.4)	
Race, n (%)				0.004
White	134 (70.5)	17 (47.2)	117 (76.0)	
African American	44 (23.2)	14 (38.9)	30 (19.5)	
Other	8 (4.2)	3 (8.3)	5 (3.2)	
Unknown/withheld	4 (2.1)	2 (5.6)	2 (1.3)	
Latino, n (%)				0.756
N/A	16 (8.5)	4 (11.4)	12 (7.8)	
Not Hispanic or Latino	141 (75.0)	26 (74.3)	115 (75.2)	
Hispanic or Latino	31 (16.5)	5 (14.3)	26 (17.0)	
Likelihood of abusive head trauma (Yes), n (%)	32 (16.8)	11 (30.6)	21 (13.6)	0.015
Mechanism of injury, n (%)				0.019
Acceleration/deceleration	16 (8.5)	7 (19.4)	9 (5.9)	
Direct impact/fall	156 (82.5)	28 (77.8)	128 (83.7)	
Penetrating	17 (9.0)	1 (2.8)	16 (10.5)	
Cause of injury, n (%)				0.076
Motor vehicle	95 (50.0)	19 (52.8)	76 (49.4)	
Fall	38 (20.0)	3 (8.3)	35 (22.7)	
Homicide/assault	31 (16.3)	10 (27.8)	21 (13.6)	
Other	26 (13.7)	4 (11.1)	22 (14.3)	
GCS total score at enrollment, mean ± std	5.5 ± 1.8	5.7 ± 1.9	5.5 ± 1.8	0.519
AIS head, median (IQR)	4 (4, 5)	4 (4, 5)	4 (4, 5)	0.673
Max AIS without head, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.497
Injury Severity Score, mean ± std	26.1 ± 11.0	24.7 ± 8.5	26.5 ± 11.4	0.302
PRISM III, mean ± std	14.6 ± 7.8	15.9 ± 9.7	14.3 ± 7.3	0.342
Fixed pupil(s) at enrollment, n (%)				0.238
Both	27 (14.2)	5 (13.9)	22 (14.3)	
Either	20 (10.5)	4 (11.1)	16 (10.4)	
Neither	131 (68.9)	22 (61.1)	109 (70.8)	
Unable to assess/unknown	12 (6.3)	5 (13.9)	7 (4.5)	

Table 5 (Continued)

Characteristics		Rehabilitation process after acute care		
	Total (n=190)	**Non-inpatient rehabilitation (n=36)**	**Inpatient rehabilitation (n=154)**	**P**
Pre-hospital and resuscitation events, n (%)				
Apnea, n (%)				0.554
No/unknown	162 (85.3)	29 (80.6)	133 (86.4)	
Suspected	9 (4.7)	2 (5.6)	7 (4.5)	
Yes	19 (10.0)	5 (13.9)	14 (9.1)	
Aspiration, n (%)				>0.999
No/unknown	164 (86.3)	32 (88.9)	132 (85.7)	
Suspected	22 (11.6)	4 (11.1)	18 (11.7)	
Yes	4 (2.1)	0 (0.0)	4 (2.6)	
Cardiac arrest	7 (3.7)	2 (5.6)	5 (3.2)	0.619
Hypotension	60 (31.6)	13 (36.1)	47 (30.5)	0.516
Hypoxia	17 (8.9)	3 (8.3)	14 (9.1)	>0.999
Seizure	37 (19.5)	13 (36.1)	24 (15.6)	0.005
Hyperthermia	23 (12.1)	7 (19.4)	16 (10.4)	0.156
Hypothermia	40 (21.1)	11 (30.6)	29 (18.8)	0.120
Hyperventilation	44 (23.2)	9 (25.0)	35 (22.7)	0.771
Acute CT findings, n (%)				
Epidural hematoma	19 (10.0)	5 (13.9)	14 (9.1)	0.366
Subdural hematoma	133 (70.0)	24 (66.7)	109 (70.8)	0.628
Intracerebral hemorrhage	122 (64.2)	23 (63.9)	99 (64.3)	0.964
Intraventricular hemorrhage	50 (26.3)	10 (27.8)	40 (26.0)	0.825
Subarachnoid hemorrhage	97 (51.1)	16 (44.4)	81 (52.6)	0.378
Diffuse axonal injury	50 (26.3)	9 (25.0)	41 (26.6)	0.842
Contusion	111 (58.4)	19 (52.8)	92 (59.7)	0.445
Midline shift	78 (41.1)	11 (30.6)	67 (43.5)	0.155
Cisternal compression	84 (44.2)	12 (33.3)	72 (46.8)	0.144

IQR, Interquartile range; GCS, Glasgow Coma Scale; AIS, Abbreviated Injury Scale; PRISM III, Pediatric Risk of Mortality III

Table 6. Family Related and Other Clinical Characteristics of Children with Severe TBI in the Inpatient Rehabilitation and Non-Inpatient Rehabilitation Groups (Sites in the US)

Characteristics		**Rehabilitation process after acute care**		
	Total (n=190)	**Non-inpatient rehabilitation (n=36)**	**Inpatient rehabilitation (n=154)**	**P**
Highest education of primary caregiver, n (%)				0.769
Less than high school	21 (13.0)	3 (9.4)	18 (13.8)	
High school or higher	141 (87.0)	29 (90.6)	112 (86.2)	
Number of employed family members, n (%)				0.661
None	23 (13.0)	6 (17.6)	17 (11.9)	
One	97 (54.8)	18 (52.9)	79 (55.2)	
Two	57 (32.2)	10 (29.4)	47 (32.9)	
Unhealthy family functioning, n (%)	29 (19.9)	6 (21.4)	23 (19.5)	0.817
Preinjury conditions, n (%)				
Neurodevelopmental disability	18 (10.2)	3 (8.8)	15 (10.5)	>0.999
Attention or learning problems	22 (12.5)	2 (6.1)	20 (14.0)	0.379
Other conditions	14 (7.9)	2 (6.1)	12 (8.3)	>0.999
Length of hospital stay, mean ± std	28.7 ± 17.8	36.9 ± 23.0	26.8 ± 15.8	0.016
Length of hospital stay, n (%)				0.091
≤ 23 days	98 (51.6)	14 (38.9)	84 (54.6)	
> 23 days	92 (48.4)	22 (61.1)	70 (45.4)	
FSS total score at hospital discharge, mean ± std	11.2 ± 5.6	9.6 ± 4.9	11.5 ± 5.7	0.105
GCS total score at hospital discharge, median (IQR)	14 (11, 15)	15 (12, 15)	13 (11, 15)	0.046
Any systemic complications during acute hospitalization, n (%)	88 (46.3)	13 (36.1)	75 (48.7)	0.173
Any neurological complications during acute hospitalization, n (%)	78 (41.1)	18 (50.0)	60 (39.0)	0.225

IQR, Interquartile range; FSS, Functional Status Scale; GCS, Glasgow Coma Scale

Table 7. Independent Associations Between Characteristics and Inpatient Rehabilitation Using a Multivariable Logistic Regression Model (Sites in the US) (M = 15 imputations)

Characteristics	Categories	Adjusted OR	Adjusted OR (95% CI)	P
Age at injury	0-<5 yrs	ref		0.189
	5-<11 yrs	2.21	0.60-8.18	
	11-18 yrs	0.60	0.17-2.12	
Race	White	ref		0.032
	African American	0.34	0.12-0.96	
	Other	0.16	0.02-1.12	
	Unknown/withheld	0.05	0.003-0.87	
Likelihood of abusive head trauma	Yes vs No	0.47	0.12-1.90	0.289
Mechanism of injury	Direct impact/fall	ref		0.101
	Acceleration/deceleration	0.20	0.04-1.00	
	Penetrating	2.30	0.23-22.48	
Seizure	Yes vs No	0.52	0.18-1.51	0.229
Hyperthermia	Yes vs No	0.50	0.15-1.64	0.252
Hypothermia	Yes vs No	0.45	0.15-1.32	0.146
Systemic complications	Yes vs No	1.89	0.68-5.24	0.224
Length of hospital stay	> 23 days vs ≤ 23 days	0.27	0.10-0.72	0.009
FSS total score		1.09	0.95-1.24	0.236
GCS total score at discharge		0.86	0.63-1.19	0.370
Midline shift	Yes vs No	3.27	0.95-11.30	0.061
Cisternal compression	Yes vs No	1.29	0.45-3.71	0.633

OR, Odds Ratio; FSS, Functional Status Scale; GCS, Glasgow Coma Scale

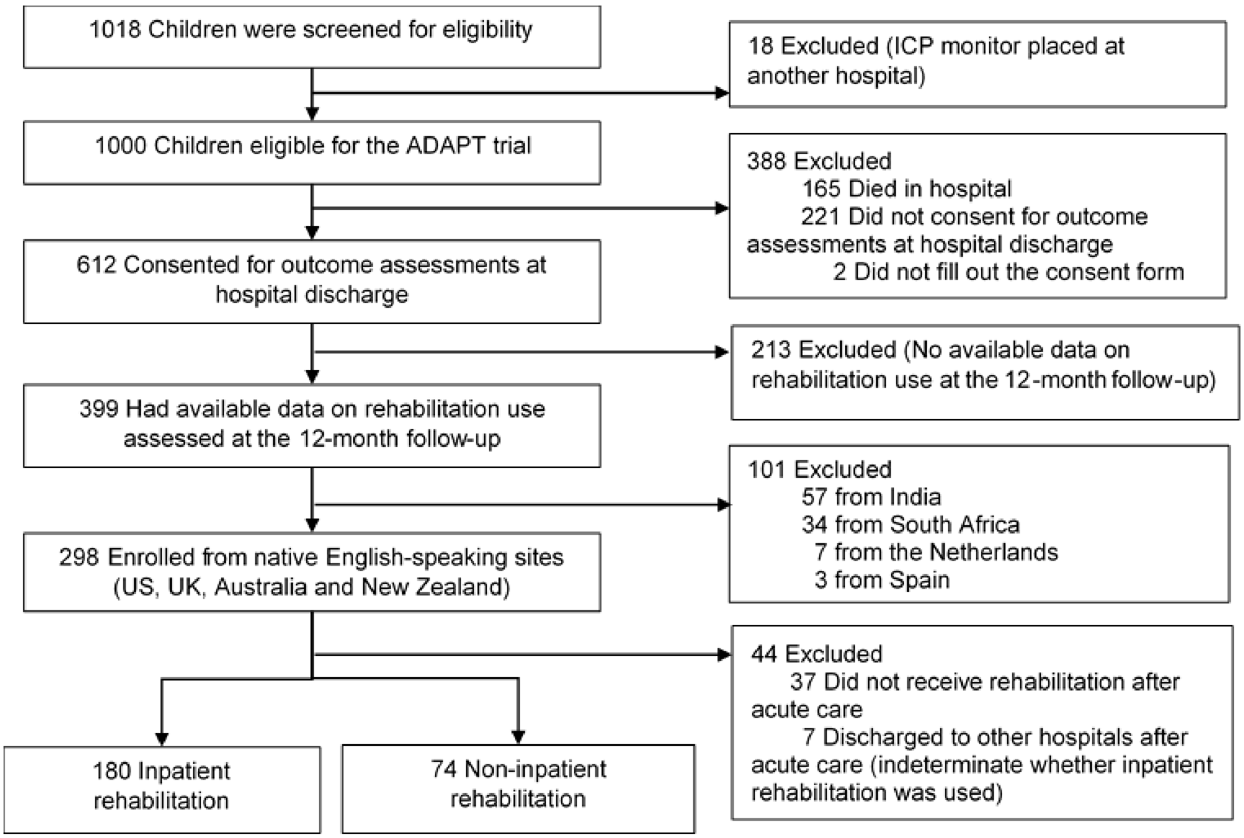

Figure 1. Flow of Children Included in the Study of Characteristics Associated with the Use of Inpatient Rehabilitation After Acute Care

4.0 Manuscript 2: Effects of Inpatient Rehabilitation After Acute Care on Motor, Neuropsychological, and Behavioral Outcomes in Children with Severe Traumatic Brain Injury

4.1 Abstract

A multisite observational study of children with severe traumatic brain injury (TBI) (Approaches and Decisions in Acute Pediatric Traumatic Brain Injury [ADAPT] Trial) demonstrated the benefits of inpatient rehabilitation on functional outcome for those with more severely impaired consciousness when medically stable. We conducted a secondary analysis of motor, neuropsychological, and behavioral outcomes to evaluate 1) whether receiving inpatient rehabilitation after acute hospitalization, regardless of the use of additional non-inpatient rehabilitation, was associated with better outcomes compared to receiving only non-inpatient rehabilitation among children with severe TBI; and 2) how selection biases influenced these findings. We included 180 children who received inpatient rehabilitation and 74 children who only received non-inpatient rehabilitation from the ADAPT trial. At 12 months after injury, children underwent tests of motor skills, intellectual functioning, verbal learning, memory, processing speed, cognitive flexibility and parents/guardians rated children's executive function and behaviors. We performed inverse probability weighting to adjust for potential confounders and selection biases to determine associations between rehabilitation process and outcomes. The confounder only-adjusted analysis revealed no significant differences in any motor, neuropsychological or behavioral measures between children receiving inpatient rehabilitation and children receiving only non-inpatient rehabilitation. Consistent results were observed when the

analysis was further adjusted for selection biases. Analysis of more granular outcomes did not provide evidence of beneficial effects of inpatient rehabilitation over non-inpatient rehabilitation on motor, neuropsychological or behavioral outcomes in children with severe TBI.

4.2 Introduction

Traumatic brain injury (TBI) is among the leading causes of mortality and severe disability in children. Children with severe TBI are at increased risks of motor deficits, cognitive impairments and behavioral problems [46, 67, 175]. It is important for children to receive continued care, especially rehabilitation services, after acute medical management to gain better recovery from injury related motor or neurobehavioral deficits. However, comprehensive guidelines for the rehabilitation of children surviving severe TBI do not exist, allowing for variability of rehabilitation services. Inpatient rehabilitation, which generally refers to therapy services and continued nursing care received during an inpatient hospital stay, is a common treatment option for children after they leave acute care [106]. Other options for children requiring rehabilitation include non-inpatient rehabilitation services such as those provided at home or in outpatient settings [106].

Despite the gradually growing recognition of the importance of rehabilitation after acute care, there remains limited evidence to determine the most effective rehabilitation management strategies for children with severe TBI [176, 177]. One area that is significantly understudied is the contribution of rehabilitation process, including the use of inpatient rehabilitation and/or non-inpatient rehabilitation, to children's long-term outcomes. Studies in adults with severe TBI have consistently found that patients directly transferred from acute care to inpatient rehabilitation had more favorable functional outcomes than those who did not receive inpatient rehabilitation at all or received inpatient rehabilitation after a waiting period [5, 178]. However, in pediatrics, there is not yet sufficient evidence to support the effectiveness of inpatient rehabilitation. Our recent study of children with severe TBI in the multisite, multinational Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial observed that among those with a Glasgow Coma Scale (GCS) < 13 after acute hospitalization, receiving inpatient rehabilitation was associated with more favorable Pediatric Glasgow Outcome Scale – Extended (GOS-E Peds) scores at 12 months after injury compared with receiving only non-inpatient rehabilitation [179]. These findings suggested the benefits of inpatient rehabilitation for children with more severely impaired consciousness when medically stable. However, we failed to demonstrate the beneficial effects of inpatient rehabilitation on GOS-E Peds or parent/guardian-reported or child self-reported health related quality of life among those with normal or mildly impaired consciousness after acute care. We noted that the blunt measure of functional outcome and subjective quality of life measures may not be sufficient to capture the complexity of motor, neuropsychological and behavioral outcomes after severe TBI. Studies that incorporate more granular outcome measures are needed to evaluate the effects of different patterns of rehabilitation process.

Using the data from the ADAPT trial, we aimed to determine if those receiving inpatient rehabilitation (with or without additional non-inpatient rehabilitation) have better motor, neuropsychological, and behavioral outcomes at 12 months after injury compared to those receiving only non-inpatient rehabilitation. As selection biases due to selective consent at enrollment and attrition during follow-up may threaten both the internal and external validity of a longitudinal study, we used the information of observed characteristics of children in the ADAPT trial and applied the inverse probability weighting approach to adjust for potential attrition and volunteer biases in the analysis of the associations between rehabilitation process and outcomes. We are the first to report 1) if children receiving inpatient rehabilitation had more favorable motor, neuropsychological, and behavioral outcomes at 12 months after injury compared to those that received only non-inpatient rehabilitation; and 2) how selection biases (attrition bias and volunteer bias) may have influenced findings.

4.3 Methods

4.3.1 Study Participants

The ADAPT trial was a large observational study to evaluate the effectiveness of multiple acute management strategies in children with severe TBI. The detailed study design has been described elsewhere [78, 88, 148]. In brief, 1000 children under 18 years who had an intracranial pressure (ICP) monitor placed following severe TBI (GCS ≤ 8 at the time of ICP monitor placement) were enrolled from 51 sites in the US, the UK, Australia, New Zealand, Spain, the Netherlands, India and South Africa during 2014 to 2016. Exclusion criteria were pregnancy and ICP monitor placement at another institution. All sites obtained the Institutional Review Board approval (or equivalent) to perform the study and collect data regarding children's acute hospitalization. Informed consent for the collection of data on rehabilitation use and motor, neuropsychological or behavioral outcomes at 12 months after enrollment were obtained from study participants or their parents/guardians at the time of hospital discharge. For this study, children enrolled from Spain, the Netherlands, India and South Africa were excluded, because their motor, neuropsychological or behavioral outcomes were not assessed due to concerns regarding the reliability and validity of the translated version of instruments.

4.3.2 Rehabilitation Process

Rehabilitation process after acute hospitalization was defined based on the child's initial discharge destination (per the medical record) and parent/guardian-reported use of rehabilitation within the 12-month follow-up period. At the 12-month assessment, parents/guardians were asked to recall if their child received any rehabilitation therapies such as physical therapy, occupational therapy, speech and/or language therapy as a result of TBI after hospital discharge. Of those who had ever received rehabilitation after acute hospitalization, children were classified into the "inpatient rehabilitation" group if their initial discharge destination was shown as an inpatient rehabilitation facility or skilled nursing facility in the medical records [152, 153, 180]; "non-inpatient rehabilitation" group if they were directly discharged home and if their parents/guardians reported receipt of rehabilitation within the 12 months follow-up period. Children in the inpatient rehabilitation group may or may not have received additional non-inpatient rehabilitation therapies after discharge from inpatient rehabilitation. We did not compare motor, neuropsychological or behavioral outcomes between children who received rehabilitation and children who did not receive rehabilitation at all, because many of those without rehabilitation were found to have normal or near normal functional level (Functional Status Scale (FSS) ≤ 7) at hospital discharge and might not need additional rehabilitation. Further, children who were discharged to other hospitals after acute care and reported receiving rehabilitation within the 12-month follow-up period were not included in the comparison due to the insufficient information to determine if they received inpatient rehabilitation or not.

4.3.3 Outcomes

At the 12-month assessment, a standardized neuropsychological test battery (Appendix: Table 14) was administered to each child to assess intellectual functioning (IQ), processing speed, verbal learning, memory, cognitive flexibility and motor skills. This neuropsychological battery was administered by site neuropsychologists or supervised technicians, who all had participated in a standardized web-based training and been study certified. In addition, parents/guardians completed several questionnaires to rate children's executive function and behaviors. These outcome assessments were in accordance with the National Institute of Neurological Disorders and Stroke TBI Common Data Elements [134], and occurred at the study site or via visit to the child's residential place (home or medical facility), if permitted by site IRB and parents/guardians, and within 100 miles of the study site.

IQ

Assessment of IQ depended on child's age at 12 months. The Cognitive scale of the Bayley Scales of Infant and Toddler Development – Third Edition (Bayley-III) was used for infants and toddlers of less than 3 years [181]. The Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV) and the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II) were used to assess IQ for children aged 3 years to less than 6 years and children of 6 years or older respectively [182, 183]. All these instruments have demonstrated good test-retest reliability [184-186]. Both the WPPSI-IV and WASI-II correlate favorably with other instruments measuring cognitive function in children [185, 186]. The full-scale intelligence quotient (FSIQ), which denotes a summary index of intellectual functioning, were derived from each of these measures and included in the analysis. For children who completed the WPPSI-IV or WASI-II, we also analyzed the Verbal IQ (VIQ) (that is the Verbal Comprehension Index of WPPSI-IV or

WASI-II) and Nonverbal IQ (NVIQ) (that is the Visual Spatial Index of WPPSI-IV or the Perceptual Reasoning Index of WASI-II) scores.

Verbal Learning and Memory

The California Verbal Learning Test – Child Version (CVLT-C) and Adult Version (CVLT-II) were used to evaluate verbal learning and memory for children of 5 to 16 years and those aged greater than 16 years respectively [187, 188]. Previous TBI studies have supported the construct and criterion validity of the CVLT as an assessment of verbal learning and memory [189, 190]. Although several subtest scores of CVLT were obtained, we focused on four subtests – List A Trial 1, List A Trial 5, Long-Delay Free Recall and False Positives, which represent the four-factor performance constructs (attention span, learning efficiency, delayed recall and inaccurate recall) that have been validated in children with TBI [190].

Processing Speed

Processing speed was assessed using the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV), the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) and the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) in children aged 4 to <6 years, 6 to 16 years and >16 years at 12 months respectively [183, 191, 192]. The Animal Coding subtest score of the WPPSI-IV was used to determine processing speed in the youngest age group. Processing Speed Index (PSI) scores of the WISC-IV and the WAIS-IV, which were derived from both the Coding and the Symbol Search subtests were used in the analysis to determine processing speed in the other two age groups. The PSI has shown acceptable criterion validity in the evaluation of children with TBI [193].

Cognitive Flexibility

The Verbal Fluency test from the Delis-Kaplan Executive Function Scale (D-KEFS) was used to measure cognitive flexibility of children aged 8 years or older [194]. Although several subtest scores of Verbal Fluency were obtained, we focused on the Category Switching subtest, which has been suggested to provide additional clinical utility in the assessment of cognitive flexibility compared to other subtests among patients with TBI [195]. The total correct score of the Category Switching subtest was included in the analysis.

Motor Skills

Motor skills of children were assessed using the Bruininks-Oseretsky Test of Motor Proficiency Second Edition (BOT-2) Short Form [196]. It is a short version of the BOT-2 Complete Form to measure gross and fine motor skills in children aged 4 years or older. It examines motor functions across domains of fine manual control, manual coordination, body coordination, strength and agility. The BOT-2 Short Form demonstrates good test-rest reliability and moderate to strong correlations with the BOT-2 Complete Form [197, 198]. The overall composite score of the BOT-2 Short Form was included in the analysis.

Executive Function

Parents/guardians rated children's daily executive function using the age-appropriate versions of the Behavior Rating Inventory of Executive Function (BRIEF) (for children aged 2 to <6 years and children aged 6 years or older) at 12 months [199]. Cumulative evidence suggests that the BRIEF is a valid instrument to evaluate executive function of children experiencing a TBI regardless of severity [200, 201]. The BRIEF has also shown good test-retest reliability [201]. The global executive composite (GEC) index, which is an overall summary measure of the BRIEF, was used in the analysis.

Behavior

Age-appropriate versions of the Child Behavior Checklist (CBCL) (for children aged 1.5 to <6 years and children aged 6 years or older) were used by parents/guardians to rate their child's emotional and behavioral problems at 12 months [202]. The CBCL has high test-retest reliability and criterion validity, and is sensitive to behavioral problems in children with severe TBI [97, 202, 203]. For the current study, scores for internalizing and externalizing scales were included in the analysis.

4.3.4 Covariates

We collected data on participants' sociodemographic and clinical characteristics including functional level at discharge from acute care hospitals. These covariates were chosen based on the existing literature suggesting their potential associations with rehabilitation services use and outcomes [9, 74, 75, 112, 113, 195, 204]. Children's demographic variables included age at injury, sex, country/region, race and ethnicity. Injury related variables included likelihood of abusive head trauma, mechanism and cause of injury. Injury or illness severity measures included GCS at the time of ICP monitor placement, GCS at hospital discharge, Abbreviated Injury Scale scores, Injury Severity Score, and Pediatric Risk of Mortality III score. Data were also collected on pupil response at the time of ICP monitor placement, prehospital and resuscitation events such as cardiac arrest, hypoxia and hypotension, as well as acute computed tomography findings. Other clinical data that were collected included length of hospital stay, systemic and neurological complications during acute hospitalization. Data on demographic, injury-related and clinical characteristics were collected by abstracting child's medical records. Data on social and family related factors, including the highest educational level achieved by child's primary caregiver, number of employed family members and overall family functioning, were collected from self-administered questionnaires completed by parents/guardians at hospital discharge. Parents/guardians also reported children's preinjury conditions. For this study, preinjury conditions were classified as neurodevelopmental disability (previous TBI, epilepsy, seizure, cerebral palsy, autism, toxic exposure, noninjury-related loss of consciousness and extremely low birth weight), attention or learning problems (attention deficit hyperactivity disorder and learning disability), and other conditions (hearing or visual impairment, muscle weakness, difficulty with balance or walking). Children's functional level at hospital discharge was evaluated by parents/guardians using the FSS with detailed instructions. Furthermore, hospital discharge disposition and GOS-E Peds at 3 and 6 months post-injury, which were determined by interviewing parents/guardians, were included in the bias adjustment analysis.

4.3.5 Statistical Analysis

For each motor, neuropsychological, and behavioral test, a reliability code was assigned by the examiner at the time of assessment to denote departures from standard procedure and reasons for incomplete or unreliable test data. Then, the Outcomes Center compiled all reliability codes and made necessary revisions after chart review. Test scores with final reliability codes of "standard completion" or "irregular completion, minor effect on reliability" were considered reliable and included in analyses as observed test scores. All obtained norm referenced scores for each motor, neuropsychological, and behavioral measure were transformed to T scores (mean 50; standard deviation 10). Then we combined test scores within each domain across age groups (Appendix: Table 14). Higher T scores for the CVLT False Positives, the BRIEF GEC, and the Internalizing and Externalizing CBCL indicate worse cognitive or behavioral outcomes, while lower T scores for all other tests are indicative of worse motor or neuropsychological performance. Cognitive or neuromotor deficits may prevent severely impaired children completing certain neuropsychological tests. Therefore, for children that were unable to perform a neuropsychological test due to cognitive deficits, we assigned a T score of minus 1 (or plus 1 for CVLT False Positives and BRIEF GEC) beyond the worst possible score for that test [205]. For children who were still in vegetative state at 12 months, we assigned a T score of minus 2 (or plus 2 for CVLT False Positives and BRIEF GEC) beyond the worst possible score for neuropsychological tests. These imputed values were used in all analyses. Similar analytical approaches, which imputed test values for patients failing to complete neuropsychological tests due to cognitive impairment, have been used in previous TBI studies to minimize missing data [205-207].

T scores for each outcome measure were summarized for the inpatient rehabilitation group and non-inpatient rehabilitation group and compared between groups using two-sample t tests (or Wilcoxon rank-sum tests). Propensity score methods were used to reduce the effects of potential confounders and balance children's baseline characteristics between inpatient rehabilitation and non-inpatient rehabilitation groups. We estimated the propensity scores using the Generalized Boosted Models (GBM) approach [208, 209]. All baseline characteristics described in the previous section were included in the propensity score model. After estimating the propensity scores, we assessed the balance of covariates between rehabilitation groups using the absolute standardized differences (ASD), prior to and after inverse probability of treatment weighting (IPTW). If, after IPTW, the ASD for a potential confounder exceeded 0.25, this confounder was considered not to be sufficiently balanced by IPTW and further included in the linear regression models for the outcome analysis. Propensity score weighted linear regression models with the adjustment for unbalanced covariates were used to estimate the associations between rehabilitation process and each motor, neuropsychological and behavioral outcome.

To address the missing values for outcome measures due to non-neurological reasons other than speaking a non-English language, we conducted multiple imputations using the fully conditional specification method (M = 15 imputations) based on the assumption that data were missing at random. All measured confounding variables, rehabilitation variable and certain outcome variable were included in the model to impute missing values. In each imputed dataset, a combination of PS (estimated based on the unimputed data) weighting and unbalanced covariates adjustment was performed to estimate the relationship between rehabilitation process and outcome. Estimates from 15 imputed datasets were combined using Rubin's rules.

To account for potential selection biases due to attrition during the follow-up and selective participation at enrollment, we applied the inverse probability weighting approach [209]. Two sets of propensity scores were estimated using the GBM to predict each child's probability of participation in the 12-month assessment among (1) all children who consented for long-term outcome assessments at hospital discharge and (2) all children who were alive at hospital discharge. For the propensity score model in those who provided informed consent, we included all baseline covariates, hospital discharge destination, and GOS-E Peds assessed at 3 and 6 months post-injury. Adequacy of computed propensity scores were evaluated by checking the ASD of covariates between the weighted sample who had rehabilitation data and the unweighted consented sample [209]. For the propensity score model in those alive at hospital discharge, we included baseline covariates for which data were collected before the acquisition of informed consent, as well as the variable indicative of hospital discharge destination. Adequacy of propensity scores were examined by checking the ASD of covariates between the weighted sample who had rehabilitation data and the unweighted sample who were all alive at hospital discharge.

To generalize the results from children attending the 12-month assessment to children who provided informed consent at hospital discharge, we used weighted linear regression models with the adjustment for covariates that were not fully balanced after weighting. The weight included in the weighted regression was a product of the weight denoting the inverse probability of receiving inpatient rehabilitation conditional on confounding variables and the weight denoting the inverse probability of participation in the 12-month assessment. This weight used to account for selection bias was estimated using the propensity score model described above in all consented children. Similarly, to generalize the results to all children who were alive at hospital discharge, we again used the weighted linear regression with the adjustment for unbalanced covariates after weighting. The weight included in this weighted regression was a product of the weight denoting the inverse probability of receiving inpatient rehabilitation given confounding variables and the weight denoting the inverse probability of participation in the 12-month assessment. This weight used to account for selection bias was estimated using the propensity score model mentioned above among all those alive at hospital discharge. To account for the effects of weighting on standard errors, we performed all inverse probability weighted regression analysis using the survey sampling technique.

In the sensitivity analysis, we sought to identify children with significant motor, neuropsychological or behavioral impairments. We conducted 3 parallel analyses with different impairment thresholds – more than 1, 1.5, or 2 standard deviations (i.e., T score <40, <35, and <30) below the mean of test norms (or above the mean of test norms [i.e., T score >60, >65, and >70] for the CVLT False Positives, the BRIEF GEC, and the Internalizing and Externalizing

CBCL). We performed similar analytical procedures that were used for T scores and applied weighted logistic regression models to adjust for potential confounders and selection biases when determining the associations between rehabilitation process and motor, neuropsychological or behavioral impairments. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). A two-sided $p < 0.05$ was considered statistically significant.

4.4 Results

Initially, a total of 1000 children were enrolled in the ADAPT trial. Of the 868 enrollees from English-speaking sites, 716 (82.5%) were alive at hospital discharge (Figure 2). Of these, 496 (69.3%) provided informed consent for long-term outcome assessments at discharge, while only 298 (60.1%) of those who consented returned for rehabilitation assessment at 12 months. Finally, 180 children were classified into the inpatient rehabilitation group, and 74 children were classified into the non-inpatient rehabilitation group. Sociodemographic and clinical characteristics of children in the two rehabilitation groups have been presented in our previous work submitted for publication [210].

Motor, neuropsychological and behavioral outcomes of children in the two rehabilitation groups are demonstrated in Figure 3 and summarized in Table 8 and Appendix. Table 15. The most severely impaired domains included verbal learning efficiency (CVLT-ListA5), delayed recall (CVLT-LDFR), processing speed (PS) and motor skills (BOT2-SF), and approximately one third of children scored worse than 2 standard deviations below the population norm on corresponding assessments at 12 months. Without adjusting for potential confounders or selection biases, the inpatient rehabilitation group demonstrated poorer verbal IQ (VIQ), nonverbal IQ

(NVIQ), processing speed, attention span (CVLT-ListA1), learning efficiency, delayed recall, cognitive flexibility (DKEFS-VF) and motor skills compared with the non-inpatient rehabilitation group (Table 8). No significant differences were found between rehabilitation groups in the assessments of full-scale IQ (FSIQ), inaccurate recall (CVLT-FP), executive function (BRIEF-GEC) and externalizing behaviors (CBCL-EX). However, the inpatient rehabilitation group appeared to have more favorable internalizing behaviors (CBCL-IN) than the non-inpatient rehabilitation group, though this result is only trending towards significance (p=0.063).

Table 9 summarizes unadjusted and adjusted associations of rehabilitation process after acute care with T scores for each motor, neuropsychological and behavioral measure at 12 months. In confounder only-adjusted analyses, rehabilitation process was not significantly associated with motor, neuropsychological or behavioral outcomes. Differences in T scores for verbal IQ, nonverbal IQ, processing speed, attention span, learning efficiency, delayed recall, cognitive flexibility and motor skills, as well as internalizing behaviors between inpatient rehabilitation and non-inpatient rehabilitation groups were attenuated and became nonsignificant after adjustment for potential confounders. Results were consistent when weighted for children consenting for long-term outcome assessments at hospital discharge and when weighted for children alive at hospital discharge.

Consistent with the results of primary analyses, sensitivity analyses revealed no differences between rehabilitation groups in impaired motor, neuropsychological or behavioral outcomes, as defined by domain scores worse than 1, 1.5 or 2 standard deviations from the population norm, when potential confounders and selection biases were taken into account (Appendix. Table 16).

4.5 Discussion

Our investigation is the first to examine the associations between different patterns of rehabilitation process after acute care and long-term motor, neuropsychological, and behavioral outcomes in children surviving severe TBI. In confounder only-adjusted analyses, no differences were found between inpatient rehabilitation and non-inpatient rehabilitation groups in motor, neuropsychological or behavioral measures at 12 months after injury. Further weighting to account for attrition and volunteer biases yielded similar results.

The lack of differences in motor, neuropsychological or behavioral outcomes between children who received inpatient rehabilitation and children who only received non-inpatient rehabilitation after acute hospitalization is consistent with our previous findings regarding functional and quality of life outcomes, the GOS-E Peds and parent/guardian-reported or child self-reported health related quality of life, in demonstrating no compelling evidence for a beneficial effect of inpatient rehabilitation over non-inpatient rehabilitation at 12 months after injury among children with severe TBI regardless of their consciousness level at hospital discharge [179]. We previously found that, among children with a GCS < 13 at hospital discharge, receiving inpatient rehabilitation was associated with more favorable GOS-E Peds at 12 months as compared to receiving only non-inpatient rehabilitation, though such association was not identified in those with a higher GCS [179]. We had anticipated that the inclusion of sensitive and granular motor and neuropsychological measures would demonstrate a benefit in specific motor or cognitive domains beyond the global functional measure (GOS-E Peds). However, the results do not provide support for our hypothesis. In contrast to our results, studies in adults with TBI have reported that a direct transfer from acute care to inpatient rehabilitation is associated with better functional outcomes compared with no inpatient rehabilitation at all or delayed initiation of inpatient rehabilitation [5, 146, 178]. One study in children with severe TBI also demonstrated that timely transitioning from acute care to inpatient rehabilitation was associated with more favorable functional recovery [211]. The lack of beneficial effects of inpatient rehabilitation at 12 months in the current study may be due to the gradual improvement in motor and neuropsychological outcomes over time in the non-inpatient rehabilitation group. It's also possible that residual confounding effects play a role. Although we adjusted for multiple injury severity measures and clinical characteristics including GCS and FSS total score at hospital discharge, they may not be sufficient to capture child's motor and neuropsychological status before the initiation of rehabilitation. However, we cannot rule out the possibility that results of previous adult and pediatric studies were biased due to the application of less rigorous confounding adjustment approaches, and the insufficient adjustment for all potential confounders such as patient's acute functional level and family related factors.

In our unadjusted analysis, the inpatient rehabilitation group demonstrated poorer performance on several neuropsychological tests but appeared less likely to have internalizing behavioral problems. We further found that parent/guardian-rated internalizing or externalizing behaviors did not correlate with neuropsychological test results (absolute Pearson correlation coefficient [r] ranges from 0.01 to 0.13, $p>0.10$). The absence of correlations between neuropsychological test performance and behavioral outcomes is consistent with observations from previous research [203]. One possible explanation for the lack of correlations is that parent/guardian ratings of behaviors can be significantly influenced by home environment, family functioning and psychosocial burden [50, 92, 98, 175, 212, 213], while child's neuropsychological test performance is less sensitive to these factors. Additionally, we only found moderate correlations between parent/guardian-rated executive function and neuropsychological test results

(|r| ranges from 0.20 to 0.32, $p<0.05$), which were in accordance with previous studies [214, 215]. It has been suggested that parent/guardian-rated BRIEF essentially measures the behavior component of executive function and is more sensitive to executive deficits in daily activities [214]. It's possible that children with normal neuropsychological test performance have difficulty in everyday living situations. Including both parent/guardian-rated and performance-based measures in this study allowed to capture a comprehensive array of outcomes that were impacted by TBI and critical for daily functioning and quality of life.

Several strengths of our study should be noted. Our study is the first to determine the effects of different patterns of care continuum with regards to rehabilitation process on comprehensive neuropsychological assessments in a large cohort of children with severe TBI. Furthermore, we applied the inverse probability weighting approach to generalize the findings to successively larger groups of children to account for potential attrition and volunteer biases. Results of bias adjusted analyses were consistent with those of confounder only-adjusted analyses, which suggested that our findings may be robust to selection biases. However, limitations should also be considered when interpreting the results of this study. First, rehabilitation disposition may have been misclassified for some children. We defined it only based on child's discharge destination from acute care and did not collect data from an inpatient rehabilitation admission. Children who were referred to inpatient rehabilitation but were not admitted may have been misclassified in the inpatient rehabilitation group. Children who were directly discharged home but later admitted to inpatient rehabilitation may have been misclassified in the non-inpatient rehabilitation group. Such misclassification may have led to more similar groups and biased the findings towards the null. Second, as with all observational studies, the possibility of residual confounding cannot be excluded. Although we have considered and controlled for various sociodemographic and clinical characteristics, there may still be inadequate adjustment for potential confounders such as motor and cognitive status before the start of rehabilitation, as well as the use of other health care services. We did not have data on the use of behavior therapies and mental health services, which may confound the association between rehabilitation process and behavioral outcomes. Additionally, as a limited number of children had a GCS < 13 at hospital discharge, especially among those in the non-inpatient rehabilitation, we were underpowered to assess the effect modification for GCS at hospital discharge. Potential beneficial effects of inpatient rehabilitation on motor and neuropsychological outcomes in children with impaired consciousness when medically stable should be investigated in future studies.

Conclusion

We demonstrate for the first time that receiving inpatient rehabilitation was not associated with better motor, neuropsychological or behavioral outcomes at 12 months after injury compared with receiving only non-inpatient rehabilitation among children with severe TBI. Adjustment for selection biases allowed the generalization of findings to the population at large. Future studies are needed to further clarify the effects of different components of rehabilitation process such as the type, intensity, duration, location and timing of rehabilitation therapies on long-term functional outcomes and granular motor or neuropsychological assessments to better inform guidelines for the rehabilitation of children with severe TBI.

4.6 Tables and Figures

Table 8. Motor, Neuropsychological and Behavioral Outcomes of Children in the Inpatient Rehabilitation and Non-Inpatient Rehabilitation Groups

Domains	Total	Non-inpatient rehabilitation	Inpatient rehabilitation	P
FSIQ	N=197	N=57	N=140	0.378
Mean (SD)	39.1 (13.5)	40.5 (14.1)	38.6 (13.3)	
Median (IQR)	41 (32, 49)	43 (33, 49)	40 (32, 49)	
VIQ	N=174	N=46	N=128	0.031
Mean (SD)	40.5 (13.4)	44.1 (11.8)	39.2 (13.8)	
Median (IQR)	43 (34, 49)	45 (38, 51)	43 (33, 49)	
NVIQ	N=172	N=46	N=126	0.017
Mean (SD)	40.0 (14.0)	44.2 (12.7)	38.5 (14.2)	
Median (IQR)	42 (31, 50)	47 (36, 53)	41 (30, 49)	
PS	N=161	N=45	N=116	<0.001
Mean (SD)	35.1 (13.4)	41.1 (11.2)	32.7 (13.4)	
Median (IQR)	37 (25, 44)	42 (35, 46)	33 (20, 41)	
Attention span (CVLT-ListA1)	N=150	N=41	N=109	0.003
Mean (SD)	37.3 (18.0)	44.3 (15.2)	34.7 (18.3)	
Median (IQR)	40 (30, 50)	45 (40, 55)	35 (30, 50)	
Learning efficiency (CVLT-ListA5)	N=150	N=41	N=109	<0.001
Mean (SD)	34.0 (20.3)	42.5 (15.5)	30.8 (21.0)	
Median (IQR)	40 (20, 50)	45 (40, 50)	35 (15, 50)	
Delayed recall (CVLT-LDFR)	N=148	N=40	N=108	0.015
Mean (SD)	34.2 (19.4)	40.6 (17.1)	31.8 (19.8)	
Median (IQR)	35 (25, 50)	45 (32.5, 52.5)	35 (20, 45)	
Inaccurate recall (CVLT-FP)	N=148	N=40	N=108	0.100
Mean (SD)	64.1 (32.0)	58.5 (27.1)	66.2 (33.5)	
Median (IQR)	50 (45, 65)	47.5 (45, 62.5)	50 (45, 70)	
Cognitive flexibility (DKEFS-VF)	N=118	N=32	N=86	0.033
Mean (SD)	40.6 (13.6)	44.9 (11.0)	38.9 (14.2)	
Median (IQR)	43 (30, 50)	45 (37, 50)	40 (27, 47)	
Motor skills (BOT2-SF)	N=159	N=44	N=115	<0.001
Mean (SD)	34.2 (13.2)	40.6 (15.0)	31.7 (11.7)	
Median (IQR)	35 (18, 42)	41 (32, 47.5)	33 (18, 41)	
Executive function (BRIEF-GEC)	N=191	N=55	N=136	0.493
Mean (SD)	60.0 (17.5)	61.6 (20.7)	59.4 (16.1)	
Median (IQR)	59 (47, 69)	60 (46, 72)	59 (47.5, 68)	
Behavior Internalizing (CBCL-IN)	N=196	N=59	N=137	0.063
Mean (SD)	53.4 (12.1)	56.1 (13.8)	52.2 (11.1)	
Median (IQR)	51 (45, 62)	55 (48, 68)	50 (45, 61)	
Behavior Externalizing (CBCL-EX)	N=196	N=59	N=137	0.522
Mean (SD)	52.6 (11.6)	53.5 (12.9)	52.3 (11.1)	
Median (IQR)	53 (44, 60.5)	56 (44, 61)	52 (44, 59)	

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; NVIQ, Nonverbal Intelligence Quotient; PS, Processing Speed; CVLT-ListA1, California Verbal Learning Test – List A Trial 1; CVLT-ListA5, California Verbal Learning Test – List A Trial 5; CVLT-LDFR, California Verbal Learning Test – Long Delay Free Recall; CVLT-FP, California Verbal Learning Test – False Positives; DKEFS-VF, Delis Kaplan Executive Function Scale - Verbal Fluency; BOT2-SF, Bruininks-Oseretsky Test of Motor Proficiency Second Edition - Short Form; BRIEF-GEC, Behavior Rating Inventory of Executive Function – Global Executive Composite; CBCL-IN, Child Behavior Checklist – Internalizing scale; CBCL-EX, Child Behavior Checklist – Externalizing scale.

Table 9. Unadjusted and Adjusted Associations of Inpatient Rehabilitation Versus Non-Inpatient Rehabilitation with Motor, Neuropsychological and Behavioral Outcomes in Children with Severe Traumatic Brain Injury (M=15 imputations)

	No selection bias adjustment				**Adjustment for selection biases**			
	Unadjusted		**Confounder-adjusted**		**Weighted for children consenting for outcome assessments**		**Weighted for children alive at hospital discharge**	
Inpatient rehabilitation vs. Non-inpatient rehabilitation (ref)	**β (95%CI)**	**P**	**β (95%CI)**	**P**	**β (95%CI)**	**P**	**β (95%CI)**	**P**
FSIQ	-1.88 (-6.07, 2.31)	0.378	1.19 (-3.45, 5.82)	0.613	1.44 (-3.21, 6.10)	0.540	1.27 (-3.38, 5.92)	0.589
VIQ	-4.99 (-9.50, -0.47)	0.031	0.34 (-5.31, 5.99)	0.906	0.11 (-5.55, 5.77)	0.969	-0.38 (-6.22, 5.47)	0.899
NVIQ	-5.73 (-10.43, -1.04)	0.017	-1.19 (-6.66, 4.29)	0.670	-1.18 (-6.63, 4.27)	0.670	-0.68 (-6.93, 5.57)	0.831
PS	-8.37 (-12.83, -3.90)	<0.001	-2.65 (-7.56, 2.25)	0.289	-2.58 (-7.41, 2.25)	0.294	-2.24 (-7.07, 2.59)	0.364
Memory and Verbal Learning								
Attention span (CVLT-ListA1)	-9.63 (-15.97, -3.28)	0.003	-4.12 (-11.33, 3.10)	0.263	-4.22 (-11.35, 2.91)	0.246	-4.21 (-11.39, 2.97)	0.251
Learning efficiency (CVLT-ListA5)	-11.65 (-18.78, -4.52)	0.002	-4.20 (-11.76, 3.35)	0.275	-4.53 (-12.23, 3.17)	0.248	-4.99 (-12.46, 2.48)	0.190
Delayed recall (CVLT-LDFR)	-8.73 (-15.72, -1.73)	0.015	-3.88 (-12.27, 4.52)	0.364	-4.35 (-12.88, 4.17)	0.315	-4.55 (-12.79, 3.69)	0.277
Inaccurate recall (CVLT-FP)	7.73 (-3.93, 19.40)	0.192	-5.11 (-16.55, 6.32)	0.380	-4.24 (-15.41, 6.94)	0.456	-5.54 (-16.72, 5.64)	0.330
Cognitive flexibility (DKEFS-VF)	-5.98 (-11.49, -0.48)	0.033	-2.30 (-9.92, 5.32)	0.554	-2.19 (-9.87, 5.50)	0.576	-2.29 (-9.79, 5.21)	0.548
Motor skills (BOT2-SF)	-8.89 (-13.33, -4.45)	<0.001	-4.67 (-10.25, 0.90)	0.100	-4.55 (-9.97, 0.89)	0.101	-4.56 (-10.12, 1.00)	0.108
Executive function (BRIEF-GEC)	-2.14 (-7.67, 3.38)	0.445	-3.97 (-13.40, 5.45)	0.408	-2.20 (-10.84, 6.45)	0.618	-2.89 (-12.34, 6.56)	0.549
Behavior								
Internalizing (CBCL-IN)	-3.84 (-7.51, -0.16)	0.041	-1.99 (-7.59, 3.60)	0.485	-1.83 (-7.32, 3.65)	0.512	-1.72 (-7.31, 3.88)	0.547
Externalizing (CBCL-EX)	-1.17 (-4.75, 2.42)	0.522	1.19 (-3.67, 6.05)	0.631	1.87 (-2.85, 6.59)	0.437	2.16 (-2.66, 6.99)	0.378

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; NVIQ, Nonverbal Intelligence Quotient; PS, Processing Speed; CVLT-ListA1, California Verbal Learning Test – List A Trial 1; CVLT-ListA5, California Verbal Learning Test – List A Trial 5; CVLT-LDFR, California Verbal Learning Test – Long Delay Free Recall; CVLT-FP, California Verbal Learning Test – False Positives; DKEFS-VF, Delis Kaplan Executive Function Scale - Verbal Fluency; BOT2-SF, Bruininks-Oseretsky Test of Motor Proficiency Second Edition - Short Form; BRIEF-GEC, Behavior Rating Inventory of Executive Function – Global Executive Composite; CBCL-IN, Child Behavior Checklist – Internalizing scale; CBCL-EX, Child Behavior Checklist – Externalizing scale.

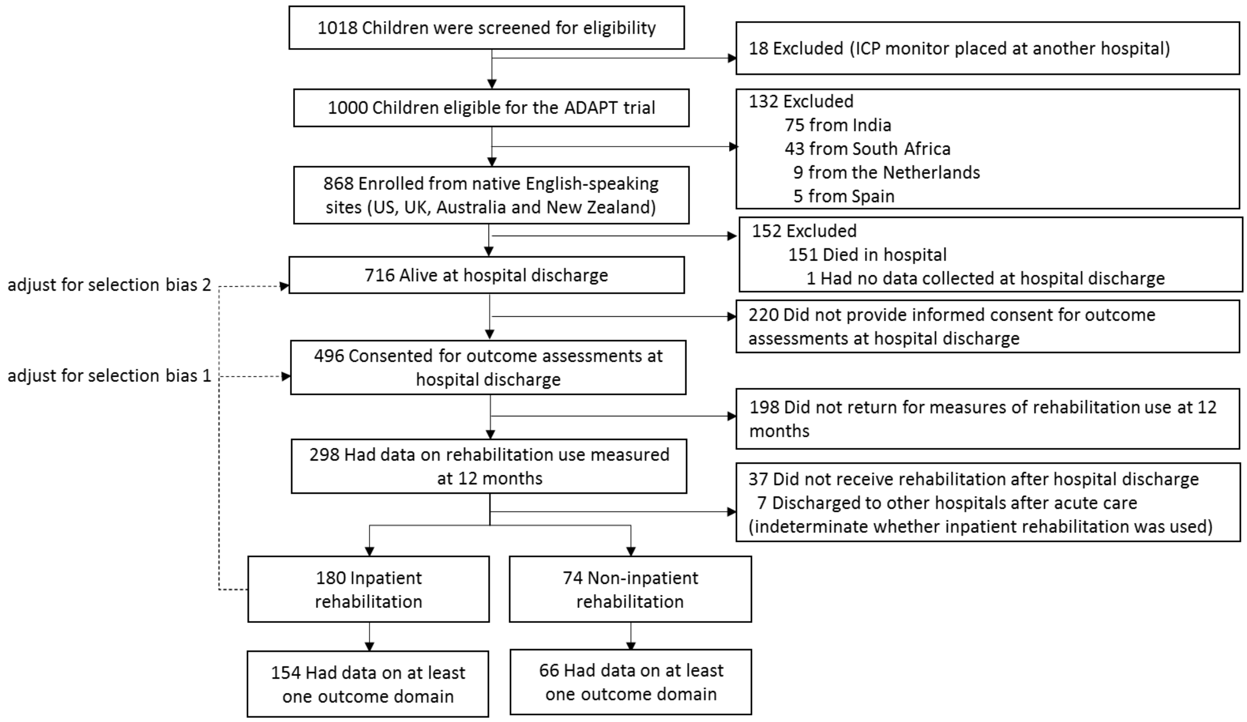

Figure 2. Flow of Children Included in the Analysis of the Associations Between Rehabilitation Process and Motor, Neuropsychological and Behavioral Outcomes

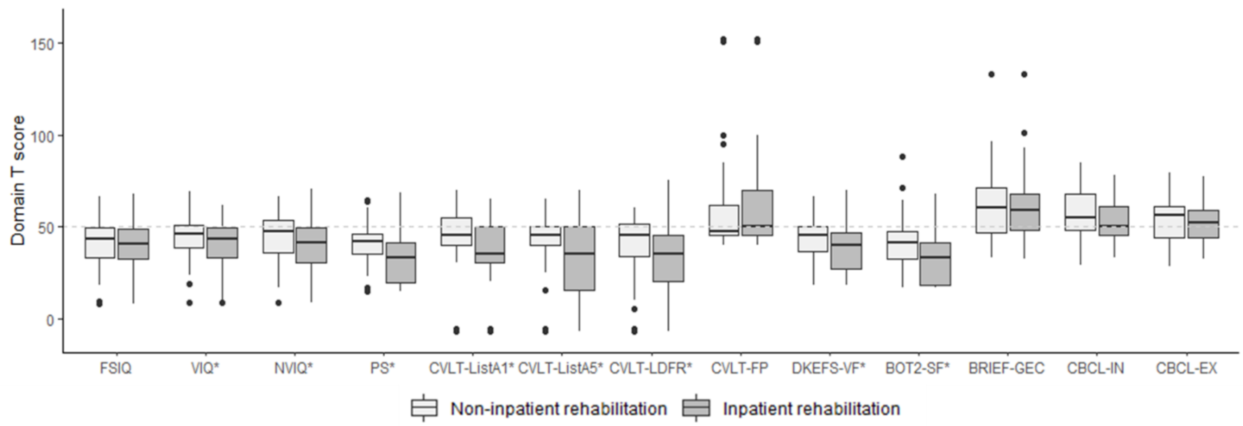

Figure 3. Boxplot of Outcome Domain T Scores

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; NVIQ, Nonverbal Intelligence Quotient; PS, Processing Speed; CVLT-ListA1, California Verbal Learning Test – List A Trial 1; CVLT-ListA5, California Verbal Learning Test – List A Trial 5; CVLT-LDFR, California Verbal Learning Test – Long Delay Free Recall; CVLT-FP, California Verbal Learning Test – False Positives; DKEFS-VF, Delis Kaplan Executive Function Scale - Verbal Fluency; BOT2-SF, Bruininks-Oseretsky Test of Motor Proficiency Second Edition - Short Form; BRIEF-GEC, Behavior Rating Inventory of Executive Function – Global Executive Composite; CBCL-IN, Child Behavior Checklist – Internalizing scale; CBCL-EX, Child Behavior Checklist – Externalizing scale; *P < 0.05.

5.0 Manuscript 3: Effects of Inpatient Rehabilitation After Acute Care on Functional and Quality-of-Life Outcomes in Children with Severe Traumatic Brain Injury

5.1 Abstract

The effectiveness of continuum of care, including the use of inpatient rehabilitation services after acute care, in children with severe traumatic brain injury (TBI) remains unclear. The objectives of this study were to 1) evaluate whether receiving inpatient rehabilitation after acute hospitalization was associated with better global function and health related quality of life (HRQOL) compared to receiving only non-inpatient rehabilitation among children with severe TBI; 2) explore an effect modification for Glasgow Coma Scale (GCS) score at hospital discharge; and 3) examine how missing data, attrition and volunteer biases impact these results. We included 254 children with severe TBI that received rehabilitation after acute hospitalization from a multinational observational study. At 12 months post-injury, global function was assessed using the Pediatric Glasgow Outcome Scale – Extended (GOS-E Peds). Parent/guardian-reported and child self-reported HRQOL were assessed using the Pediatric Quality of Life Inventory. We determined the associations between rehabilitation process and outcomes by applying inverse probability weighting to adjust for confounding and selection biases. The confounder only-adjusted analysis showed that those receiving inpatient rehabilitation have a more favorable GOS-E Peds score [OR = 0.12, p=0.045] among children with a GCS < 13 at discharge. However, no such association was observed in children with a higher GCS. We found no differences in HRQOL between rehabilitation groups. We observed similar results when the analysis was further adjusted for selection biases. Future studies are warranted to confirm our findings especially on the benefits

of inpatient rehabilitation for children with more severely impaired consciousness when medically stable to better inform pediatric TBI rehabilitation guidelines.

5.2 Introduction

Traumatic brain injury (TBI) is the leading cause of disability and mortality among children [18]. Children with severe TBI are at increased risks of injury-related physical and neurobehavioral impairments, and therefore long-term functional disabilities [33, 41, 75]. Rehabilitation services which are designed to reduce disability and improve quality of life, can be an important component of recovery [149], yet there are no comprehensive guidelines that specify optimal care, including rehabilitation services, after acute medical management for children with severe TBI [177]. Inpatient rehabilitation, which generally refers to therapy services and continued nursing care received during an inpatient hospital stay [106], is a commonly used treatment option for pediatric patients after they leave acute care. Other options for children who require rehabilitation include non-inpatient rehabilitation services such as those provided at home or in outpatient settings [106].

Despite growing clinician and family recognition of rehabilitation services, there is a paucity of evidence to determine the most effective rehabilitation management strategies for children with severe TBI [176, 177]. One area that is significantly understudied is the contribution of rehabilitation process, including the use of inpatient rehabilitation and/or non-inpatient rehabilitation after acute care, to children’s long-term outcomes after severe TBI. Studies in adults with TBI have suggested the benefits of a direct transfer from acute care to inpatient rehabilitation [4, 5, 178]. A Norwegian study demonstrated that patients who were directly transferred from acute care hospitals to inpatient rehabilitation had more favorable functional outcomes than those who received no inpatient rehabilitation at all or received inpatient rehabilitation after a waiting period at another hospital [178]. Sorbo et al. found that early initiation of inpatient rehabilitation after acute care is associated with better functional outcomes at approximately two years after injury compared to no inpatient rehabilitation at all, or late initiation of inpatient rehabilitation in patients with severe TBI [5]. Similarly, one study of children who required inpatient rehabilitation following severe TBI indicated that delayed transfer from acute care to rehabilitation adversely affected functional recovery [211]. However, no previous pediatric study has examined whether receiving inpatient rehabilitation after acute care, regardless of the need for additional non-inpatient rehabilitation, is associated with better long-term outcomes compared with receiving only non-inpatient rehabilitation services.

A better understanding of the effectiveness of the rehabilitation process on long-term outcomes will help improve the continuum of care. Given that children with rehabilitation needs after severe TBI are not likely to receive no rehabilitation at all [114], we aimed to determine if those receiving inpatient rehabilitation (with or without additional non-inpatient rehabilitation) have better global function and health related quality of life (HRQOL) compared to those receiving only non-inpatient rehabilitation in a multisite, multinational, longitudinal cohort, the Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial. Although patients with severely impaired consciousness are often denied access to inpatient rehabilitation due to uncertain prognosis, studies have suggested that they can achieve significant functional recovery during and after inpatient rehabilitation [216, 217]. Therefore, we explored the potential effect modification for Glasgow Coma Scale (GCS) score at hospital discharge on the associations between rehabilitation process and outcomes.

As indicated in previous longitudinal studies of children with TBI, potential selection biases due to selective consent at enrollment, and attrition or missing data during follow-up may harm both the internal and external validity of a study [14, 114, 218]. One study of children with moderate-to-severe TBI found that enrolled participants were more likely to have health insurance and stay in the acute care hospital for a shorter time compared to those who were eligible but refused to participate [114]. Several longitudinal studies of pediatric TBI have reported that those with lower family income and lower parental education were at increased risks of being lost to follow-up [14, 203, 212, 219]. Ignoring or failing to adjust for these selection factors may result in biased findings and flawed conclusions. To attenuate the impacts of potential selection biases (missing data bias, attrition bias, and volunteer bias) on the findings regarding the associations between rehabilitation process and outcomes among children in the ADAPT trial, we used the information of observed characteristics of study population and applied the inverse probability weighting approach to adjust for selection biases [220, 221].

We assessed 1) if children receiving inpatient rehabilitation had better global function, as measured by the Pediatric Glasgow Outcome Scale – Extended (GOS-E Peds), and HRQOL as measured by the Pediatric Quality of Life Inventory (PedsQL), at 12 months after injury compared to those that received only non-inpatient rehabilitation; 2) whether children with a lower GCS score at hospital discharge benefited more from inpatient rehabilitation; and 3) how selection biases (missing data bias, attrition bias, and volunteer bias) may have influenced study results.

5.3 Methods

5.3.1 Study Participants

The ADAPT trial was an observational study to evaluate the effectiveness of multiple acute management strategies in children with severe TBI. The study design has been described in detail elsewhere [78, 88, 148]. Briefly, 1000 children meeting the inclusion/exclusion criteria (inclusion: age < 18 years, diagnosis of severe TBI, placement of intracranial pressure [ICP] monitor at study site and GCS $\leq$ 8 at the time of monitor placement; exclusion: pregnancy) were enrolled from 51 sites in the US, the UK, Spain, the Netherlands, India, South Africa, Australia, and New Zealand during 2014 to 2016. All sites received Institutional Review Board approval (or equivalent) to conduct the study and collect data regarding the acute hospitalization. Informed consent for the collection of data on rehabilitation use and follow-up outcomes were obtained from study participants or their parents/guardians at the time of discharge from the clinical site. For this study, children from Spain, the Netherlands, India and South Africa were excluded, because their HRQOL were not assessed due to the concerns of the reliability and validity of the translated version of the instrument.

5.3.2 Rehabilitation Process

Rehabilitation process after acute hospitalization was defined based on the child's initial discharge destination (per the medical record) and parent/guardian-reported use of rehabilitation within the 12-month follow-up period. At the 12-month assessment, parents/guardians were asked to recall if their child received any physical therapy, occupational therapy and speech-language therapy as a result of the TBI since hospital discharge. Of those who had ever received any rehabilitation therapies after acute hospitalization, children were classified into the “inpatient rehabilitation” group if their initial discharge destination was indicated as an inpatient rehabilitation facility (IRF) or skilled nursing facility (SNF) in the medical records [152, 153, 180]; “non-inpatient rehabilitation” group if they were directly discharged home and if their parents/guardians reported receipt of rehabilitation within the 12-month follow-up period. Children in the inpatient rehabilitation group may or may not have received additional non-inpatient rehabilitation therapies after discharge from inpatient rehabilitation. We did not compare outcomes between children that received rehabilitation and children that did not receive any rehabilitation after acute care, because many of those without rehabilitation were found to have normal or near normal functional level (Functional Status Scale (FSS) ≤ 7) at hospital discharge and might not need additional rehabilitation. Further, children who had an initial discharge destination of another hospital were not included in the comparison due to the lack of information regarding whether they received inpatient rehabilitation or not.

5.3.3 Outcomes

GOS-E Peds scores range from 1 to 8, with higher scores indicating a poorer outcome [68]. The GOS-E Peds is a developmentally appropriate instrument to assess the impacts of TBI on function in major areas of life in children [68]. A validation study demonstrated that GOS-E Peds was highly correlated with the overall adaptive behavior in children with severe TBI [68]. For this study, trained research personnel completed the GOS-E Peds by interviewing parents/guardians and children (if age appropriate) in person or by phone at 12 months after their enrollment into the ADAPT trial.

HRQOL was measured using the PedsQL at 12 months. The PedsQL parent proxy-report forms and child self-report forms were developed for those 2 years or older and those 5 years or older, respectively. Therefore, the analyses for parent/guardian-reported and child self-reported HRQOL were limited to children aged 1 year or older at the time of injury, and those aged 4 years or older at the time of injury, respectively. The PedsQL instrument assesses physical, emotional, social and school function, and generates scores for each domain, as well as a psychosocial summary score and a total score for overall HRQOL [222]. The PedsQL scores range from 0 to 100 with higher scores indicating better HRQOL [222]. Favorable reliability and validity of the PedsQL to measure quality of life have been demonstrated in children with TBI [201]. For comparisons, minimal clinically important differences (MCIDs) in domain specific or summary PedsQL scores have been established [222]. In the ADAPT trial, parents/guardians and children aged 8 years or older self-administered the PedsQL questionnaires after instructions from site research personnel. Children aged 5 to 7 years were interviewed by site research personnel to rate their HRQOL.

5.3.4 Covariates

We collected data on children's sociodemographic, family-related, injury related and clinical characteristics including functional level at discharge from acute care hospitals. These covariates were chosen based on the existing literature suggesting their potential associations with rehabilitation services use and outcomes [9, 74, 75, 112, 113, 204]. Children's demographic variables included age at injury, sex, country/region, race and ethnicity. Injury related variables included likelihood of abusive head trauma (AHT), mechanism and cause of injury. Injury or illness severity measures included Glasgow Coma Scale (GCS) score at the time of intracranial pressure (ICP) monitor placement, GCS score at hospital discharge, Abbreviated Injury Scale (AIS) scores, Injury Severity Score (ISS), and Pediatric Risk of Mortality [PRISM] III score. Data were also collected on pupil response at the time of ICP monitor placement, pre-hospital and resuscitation events such as cardiac arrest, hypoxia and hypotension, as well as acute computed tomography (CT) findings. Other clinical information that were collected included length of hospital stay, systemic complications and neurological complications during acute hospitalization. Data on demographic, injury-related and clinical characteristics were collected by abstracting children's medical records. Data on social and family related factors, including the highest educational level achieved by primary caregiver, number of employed family members and overall family functioning, were collected from self-administered questionnaires completed by parents/guardians at hospital discharge. Parents/guardians also reported children's preinjury conditions. For this study, preinjury conditions were classified as neurodevelopmental disability, attention or learning problems and other conditions. Children's functional level at discharge was evaluated by parents/guardians using the FSS with detailed instructions. In addition, hospital discharge disposition, GOS-E Peds scores evaluated at 3- and 6- months post-injury were included in the analysis to adjust for potential selection biases.

5.3.5 Statistical Analysis

The GOS-E Peds and PedsQL scores were summarized for the inpatient rehabilitation group and non-inpatient rehabilitation group using frequencies and percentages or means and standard deviations and compared between groups using Fisher's exact test or two-sample t-tests, respectively. Unadjusted ordinal logistic and linear regression models were used to examine the associations between rehabilitation process and outcomes (i.e. GOS-E Peds and PedsQL scores).

The proportional odds assumption was assessed by plotting the rehabilitation variable against the empirical logits defined on the levels of GOS-E Peds and found to hold.

Propensity score (PS) methods were applied to reduce the effects of potential confounders. We estimated the PS using the generalized booted regression approach [208, 209]. All potential confounding variables described in the previous section were included in the PS model. From this approach, a PS indicating the probability of receiving inpatient rehabilitation after acute hospitalization given confounding variables was calculated for each child. We applied PS weighted ordinal logistic and linear regression models to assess the associations of rehabilitation process with GOS-E Peds and PedsQL scores, respectively [208, 209]. If, after weighting by the inverse probability of treatment (inpatient rehabilitation group: weight =1/PS, non-inpatient rehabilitation alone group: weight=1/(1-PS)), the absolute standardized difference (ASD) for a potential confounder exceeded 0.25 [223, 224], this confounder was regarded not to be sufficiently balanced by the inverse probability of treatment weighting (IPTW) and further included in the regression models for the outcome analysis.

To address the missing values for confounding variables, we conducted multiple imputations using the fully conditional specification method (M = 15 imputations) based on the assumption that data were missing at random. All measured confounding variables, rehabilitation variable and GOS-E Peds scores at 12 months post-injury were included in the model to impute missing covariates. In each imputed dataset, a combination of PS (estimated based on the unimputed data) weighting and unbalanced covariates adjustment was performed to estimate the associations between rehabilitation process and GOS-E Peds or PedsQL scores. Estimates from 15 imputed datasets were combined using Rubin’s rules.

The extent that GCS at discharge modified the relationships between rehabilitation process and outcomes were first tested by including an interaction term of the rehabilitation variable by GCS in adjusted outcome models. A p value < 0.10 for the interaction term was suggestive of the effect modification for GCS [225]. Then we dichotomized GCS at the mean (13.1 ± 2.5) and presented the estimated effects of inpatient rehabilitation versus non-inpatient rehabilitation on that outcome in two GCS strata (GCS 3-12 and GCS 13-15). Such GCS dichotomization has also been used to determine short-term neurological status in prior research [226].

At 12 months, all children in the inpatient rehabilitation group and non-inpatient rehabilitation group had available data on GOS-E Peds (Figure 4), while 23.0% and 25.6% of them had no measures of parent/guardian-reported (Figure 5) and child self-reported PedsQL scores (Figure 6), respectively. To address this missing data bias, we estimated the PS using generalized boosted regression to predict the probability of having available PedsQL scores using all baseline covariates, rehabilitation variable and GOS-E Peds measured at 3 and 6 months post-injury among those with available rehabilitation data [209]. We examined the adequacy of PS by calculating the ASD of covariates between the weighted final sample who had available data on both rehabilitation and PedsQL scores and the unweighted samples with complete data for rehabilitation but not for PedsQL scores [209]. To generalize the results for HRQOL from children with available data on both rehabilitation and PedsQL scores to all children who had rehabilitation data, we performed weighted linear regression. The weight used in this weighted regression model is a product of the weight mentioned above which denoted the inverse probability of receiving inpatient rehabilitation given confounding variables, and the weight denoting the inverse probability of having non-missing PedsQL scores. Covariates that remained unbalanced after weighting were also included in the linear regression model for PedsQL scores.

Close to 40% of children who consented for 12-month outcome assessments at hospital discharge were lost to follow-up (Figures 4, 5 and 6). Additionally, around 30% of children who were alive at hospital discharge refused to participate in the 12-month assessment (Figures 4, 5 and 6). To account for related attrition and volunteer biases, we again applied the inverse probability weighting approach. Two sets of PS models, using the generalized booted regression approach, were applied to estimate the probability of participation in the 12-month assessment among (1) all children who consented for long-term outcome assessments at hospital discharge and (2) all children who were alive at hospital discharge. For the PS model in those who provided informed consent at hospital discharge, we included all baseline covariates, hospital discharge destination and GOS-E Peds at 3 and 6 months post-injury. Adequacy of computed PS were evaluated by checking the ASD of covariates between the weighted sample who had available data on rehabilitation and outcomes, and the unweighted sample who provided informed consent at hospital discharge. For the PS model in those alive at hospital discharge, we included baseline covariates for which data regarding acute hospitalization were collected prior to informed consent. The ASD of covariates between the weighted sample and the unweighted sample who were alive at hospital discharge were checked to evaluate the adequacy of PS.

To generalize the results for outcomes of interest (GOS-E Peds and PedsQL scores) from complete cases who had available data on rehabilitation and outcomes measured at 12-month post-injury to those consenting for outcome assessments at hospital discharge, we used a weighted regression model (ordinal logistic or linear) with the adjustment for covariates that were not fully balanced after weighting. The weight included in this weighted regression model is a product of the weight denoting the inverse probability of receiving inpatient rehabilitation and the weight denoting the inverse probability of participation in the 12-month assessment. The weight used to account for attrition bias was estimated using the PS model described above in all consented children.

Similarly, to generalize the results for outcomes of interest (GOS-E Peds and PedsQL scores) from those with available data on rehabilitation and outcomes measured at 12-month post-injury to all children who were alive at hospital discharge, we again used the weighted regression models (ordinal logistic and linear) with the adjustment for unbalanced covariates after weighting and included the weight as a product of the weight denoting the inverse probability of receiving inpatient rehabilitation and the weight denoting the inverse probability of participation in the 12-month assessment. This weight used to account for volunteer bias was estimated using the PS model described above to predict the probability of participation in the 12-month assessment among all children alive at hospital discharge.

To account for the effects of weighting on standard errors, we performed all inverse probability weighted regression analyses using the survey sampling technique. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Except for the test of effect modification for GCS at discharge, results were considered significant at p value < 0.05.

5.4 Results

Of children who had rehabilitation data, 180 received inpatient rehabilitation and 74 received only non-inpatient rehabilitation (Figure 4). Sociodemographic and clinical characteristics of children in both rehabilitation groups have been presented in our previous work submitted for publication [210]. Table 10 summarizes the GOS-E Peds, parent/guardian-reported PedsQL scores and child self-reported PedsQL scores for children in the two rehabilitation groups.

Without adjustment for potential confounders or selection biases, the inpatient rehabilitation group had 29% (95% confidence interval [CI], 0.80-2.09) increased odds for higher GOS-E Peds scores (less favorable global function) compared with the non-inpatient rehabilitation group, though results were not statistically significant (Table 11). After adjustment for potential confounders, the inpatient rehabilitation group had 25% (95% CI, 0.37-1.53) reduced odds for higher GOS-E Peds scores compared to the non-inpatient rehabilitation group. When weighted for children who consented for follow-up outcome assessments at hospital discharge, the inpatient rehabilitation group had 27% (95% CI, 0.36-1.49) reduced odds for higher GOS-E Peds scores. When weighted for all children alive at hospital discharge, the inpatient rehabilitation group had 33% (95% CI, 0.33-1.37) reduced odds for higher GOS-E Peds scores. However, none of these adjusted associations between rehabilitation process and GOS-E Peds were statistically significant.

The effect modification for GCS score at hospital discharge on the association of rehabilitation process and GOS-E Peds was statistically significant in the adjusted analysis that controlled for only potential confounders ($P=0.049$) and marginally significant in the analysis adjusted for both confounders and selection biases ($P=0.058$ and $P=0.053$) (Table 11). In the analysis stratified by GCS < vs ≥ 13 at discharge (n=84 and n=148 respectively in the unimputed data) and adjusted for only confounders, rehabilitation process was not associated with GOS-E Peds among those with a GCS ≥ 13 (OR [95% CI]: 1.12 [0.51-2.47]). However, for children with a GCS < 13 at hospital discharge, inpatient rehabilitation was associated with reduced odds for higher GOS-E Peds scores (less favorable global function) (OR [95% CI]: 0.12 [0.02-0.95]). Moreover, the effect size persisted when weighted for children consenting for follow-up outcome assessments (OR [95% CI]: 0.12 [0.01-1.01]) and when weighted for all alive children at discharge (OR [95% CI]: 0.10 [0.01-0.96]). For children with a GCS ≥ 13 at hospital discharge, the OR for higher GOS-E Peds scores comparing the inpatient rehabilitation group to the non-inpatient rehabilitation group attenuated to 1.08 (95% CI, 0.49-2.38) when weighted for children consenting for outcome assessments and attenuated to 1.06 (95% CI, 0.50-2.28) when weighted for all alive children at hospital discharge.

Table 12 summarizes unadjusted and adjusted associations of rehabilitation process after acute care with summary and domain specific PedsQL raw scores reported by parents/guardians at 12 months. In all confounder-adjusted analyses with and without the adjustment for selection biases, differences in summary or domain specific PedsQL scores between inpatient rehabilitation group and non-inpatient rehabilitation group did not approach the MCIDs or statistical significance. We found no effect modification for GCS at hospital discharge on the association between rehabilitation process and parent/guardian-reported summary or domain specific PedsQL scores.

Table 13 displays unadjusted and adjusted associations of rehabilitation process after acute care with summary and domain specific PedsQL raw scores reported by children themselves at 12 months. In the unadjusted analysis, child self-reported physical PedsQL scores were 6.92 (95% CI, -15.40-1.55) points lower in the inpatient rehabilitation group when compared to the non-inpatient rehabilitation group, which exceeded the MCID but did not reach statistical significance. After adjustment for potential confounders, the differences in physical PedsQL scores between groups diminished to 5.81 (95% CI, -16.50-4.88). This effect size further decreased to 5.72 (95% CI, -15.84-4.40) when weighted for all children with rehabilitation data but increased to 6.53 (95% CI, -16.81-3.75) when weighted for children consenting for follow-up outcome assessments at hospital discharge and increased to 6.58 (95% CI, -17.43-4.26) when weighted for children alive at hospital discharge. These bias-adjusted differences in physical PedsQL scores between inpatient rehabilitation and non-inpatient rehabilitation groups were approaching the MCID but were not statistically significant. In the adjusted analyses for potential confounders with and without the adjustment for selection biases, no differences in other child self-reported PedsQL measures were found between groups. No significant effect modification was found for GCS at hospital discharge on the association between rehabilitation process and child self-reported summary or domain specific PedsQL scores.

5.5 Discussion

This is the first study to our knowledge to compare the effects of different patterns of care continuum with regards to rehabilitation process on long-term functional and quality-of-life outcomes in children with severe TBI. In the adjusted analysis for potential confounders in children with a GCS < 13 at hospital discharge, those who received inpatient rehabilitation showed more favorable global function at 12 months compared to children who received only non-inpatient rehabilitation. No differences were found in global function between rehabilitation groups in children with a GCS ≥ 13 at hospital discharge. No effect modification was found for GCS at hospital discharge on the associations of rehabilitation process with parent/guardian-reported or child self-reported HRQOL. Although unadjusted differences in child self-reported physical PedsQL scores between inpatient rehabilitation and non-inpatient rehabilitation groups exceeded the MCID, differences diminished and no longer exceeded the MCID after adjustment for potential confounders. None of the confounder-adjusted differences in parent/guardian-reported or child self-reported PedsQL scores between rehabilitation groups reached the MCIDs or statistical significance. When weighted for successively larger groups of children to account for missing data bias, attrition bias and volunteer bias, findings on the adjusted associations between rehabilitation process and functional or quality-of-life outcomes were consistent with those from the analyses that only controlled for potential confounders.

In our unstratified analysis of GOS-E Peds, the OR for unfavorable global function associated with inpatient rehabilitation compared with only non-inpatient rehabilitation reversed from 1.29 to 0.75 after adjustment for potential confounders, though these results were not statistically significant. Such a reversal of the effects of inpatient rehabilitation may result from strong confounding factors such as injury severity and functional level at hospital discharge, which could influence clinical decisions for rehabilitation disposition and independently associate with long-term outcomes. After controlling for potential confounders, we observed a trend towards beneficial effects of inpatient rehabilitation in the entire cohort, which may be mainly due to its effects among those with a GCS < 13 at hospital discharge, as suggested by the stratified analysis.

Previous studies have suggested a positive association between transitioning from acute care to inpatient rehabilitation and functional outcomes in adults with severe TBI. One study of 163 adults with severe TBI found that those discharged from acute care to rehabilitation facilities had greater functional improvement during the first year after injury compared to those discharged home or referred to other acute care departments [227]. Similarly, in another study of 61 adults with severe TBI, those directly transferred to IRFs when medically stable demonstrated better functional outcomes at 12 months post-injury as compared to those who did not receive inpatient rehabilitation at all or received inpatient rehabilitation after a waiting period at another hospital [178]. One pediatric study also reported that timely transitioning from acute care to inpatient rehabilitation was associated with greater functional recovery following severe TBI [211]. In agreement with these findings, we observed that receipt of inpatient rehabilitation after acute hospitalization was associated with more favorable global function in children with severe TBI who had a GCS < 13 at hospital discharge, though such association was not found in those with a higher GCS. Our findings suggested that children with more severely impaired consciousness when medically stable may benefit more from receiving inpatient rehabilitation than receiving non-inpatient rehabilitation after discharge from the acute care hospital. This is consistent with previous research in adults which showed that patients with prolonged impaired consciousness after TBI can regain consciousness and obtain at least partial functional independence during inpatient rehabilitation [217]. Patients with prolonged impaired consciousness often experience medical complications that may impede recovery [228]. It has been suggested that these patients can achieve better recovery when receiving care in a specialized setting managed by professionals who are aware of the risks related with impaired consciousness and able to initiate timely medical interventions [229]. We observed no differences in global function between inpatient rehabilitation and non-inpatient rehabilitation groups among children who had less severely impaired consciousness or normal consciousness at hospital discharge. One possible explanation for this lack of association is that among children with less severe impairment, beneficial effects of early inpatient rehabilitation failed to be maintained by 12 months due to gradual functional improvements in the non-inpatient rehabilitation group. Moreover, as the GOS-E Peds only provides one composite score to determine global function, it may not adequately represent the range of impairment [230]. Future studies are underway to incorporate multiple outcome measures including cognitive tests to detect subtle differences in outcome between children who received inpatient rehabilitation and children who received only non-inpatient rehabilitation.

The non-significant effect modification for GCS at hospital discharge on associations between rehabilitation process and HRQOL was likely due to limited power. There were fewer children with a GCS < 13 at discharge included in the analysis of parent/guardian-reported and child self-reported HRQOL (n=55 and n=41 respectively in the unimputed data) compared to the number included in the analysis of global function, especially among those who only received non-inpatient rehabilitation. Consistent with the findings on global function among children with a GCS ≥ 13 at hospital discharge, we did not observe significant associations between rehabilitation process and HRQOL. The inpatient rehabilitation group appeared to have lower scores on child self-reported physical HRQOL than the non-inpatient rehabilitation group, though these differences were only approaching the MCID and were not statistically significant. This was likely due to the inadequate control for children's physical function before the initiation of rehabilitation. Although we adjusted for multiple injury severity measures and clinical characteristics including GCS score and FSS total score at hospital discharge, they may not be sufficient to capture the entire domain of a child's physical function before rehabilitation.

Selection factors could have impacted the findings on the associations of rehabilitation process with functional and quality-of-life outcomes in several ways. First, children who did not complete HRQOL assessments may be systematically different from those with HRQOL data especially with regards to health status, which may lead to missing data bias. Second, it was possible that children who dropped out during the follow-up were systematically different from those who returned for outcome assessments at 12 months, which may result in attrition bias. Third, children who consented for 12-month outcome assessments may not represent all eligible pediatric population with severe TBI, which may result in volunteer bias. To address these potential missing data, attrition and volunteer biases, we applied the inverse probability weighting approach by calculating the weights based on measured characteristics, so that the final study sample can be weighted to be more representative of successively larger groups of children from which it was drawn. By doing so, we generalized the findings on the associations between rehabilitation process and HRQOL to all children who had available rehabilitation data to account for the effects of missing data bias. Then we generalized the findings on the associations of rehabilitation process with global function and HRQOL to children who consented for outcome assessments to additionally adjust for attrition bias, and finally generalized the findings to children who were alive at hospital discharge to further adjust for volunteer bias. We found that all bias-adjusted results were very close to the ones without the adjustment for selection biases. It suggested that our findings may be robust to selection biases.

Several limitations of this study should be noted. First, rehabilitation disposition may have been misclassified for some children as it was only based on their discharge destination from acute care; no data were collected from an inpatient rehabilitation admission. This limitation may be particularly relevant to the small number (n=4) of children discharged to SNFs, as the provision of rehabilitation services in such settings may vary. Children who were referred to but eventually failed to receive inpatient rehabilitation may have been misclassified in the inpatient rehabilitation group. Children who were directly discharged home after acute care but later admitted to IRFs may have been misclassified in the non-inpatient rehabilitation group. Such misclassification may have resulted in more similar rehabilitation groups and biased the findings towards the null. Second, we cannot rule out the possibility of residual confounding effects on results. Although we have controlled for a variety of sociodemographic and clinical characteristics which may relate to rehabilitation process and outcomes, they may not be sufficient to account for all confounding effects. For example, the FSS has been reported to be less sensitive to differences in functional level among children with mild impairment but more sensitive among those with severe impairment [231]. There may be inadequate control for children’s functional level prior to the initiation of rehabilitation. Additionally, we did not have data on parent's/guardian's psychosocial health and burden of care which may influence children's rehabilitation process and HRQOL. Nevertheless, our study is the first to evaluate the effectiveness of rehabilitation process in a large cohort of pediatric patients with severe TBI and focus on multiple outcomes including functional and both parent/guardian-perceived and child self-perceived quality-of-life outcomes.

Conclusion

The results of this study suggested that, among children with severe TBI, those with more severely impaired consciousness after acute medical stabilization benefited from receiving inpatient rehabilitation, particularly in terms of global function at 12 months after injury. Parent/guardian-reported or child self-reported HRQOL at 12 months were not different between children who received inpatient rehabilitation and children who received only non-inpatient rehabilitation after acute hospitalization. Statistical adjustment for selection biases allowed generalization of these findings to the population at large. Our findings warrant further research investigating the effects of different components of the rehabilitation process such as the types, amounts, intensity and duration of rehabilitation services, the rehabilitation settings and the timing of the initiation of rehabilitation on long-term outcomes of children sustaining severe TBI. Additionally, studies are needed to confirm the effectiveness of inpatient rehabilitation in children with prolonged impaired consciousness after severe TBI.

5.6 Tables and Figures

Table 10. Pediatric Glasgow Outcome Scale Extended (GOS-E Peds) and Pediatric Quality of Life Inventory (PedsQL) Scores at 12-Month Follow-Up of Children with Severe TBI in the Inpatient Rehabilitation and Non-Inpatient Rehabilitation Groups

	Total	Non-inpatient rehabilitation	Inpatient rehabilitation	P
GOS-E Peds, n (%)	n=254	n=74	n=180	0.325
1 - Upper good recovery	40 (15.7)	14 (18.9)	26 (14.4)	
2 - Lower good recovery	33 (13.0)	8 (10.8)	25 (13.9)	
3 - Upper moderate disability	65 (25.6)	24 (32.4)	41 (22.8)	
4 - Lower moderate disability	6 (2.4)	2 (2.7)	4 (2.2)	
5 - Upper severe disability	33 (13.0)	6 (8.1)	27 (15.0)	
6 - Lower severe disability	73 (28.7)	18 (24.3)	55 (30.6)	
7 - Vegetative status	4 (1.6)	2 (2.7)	2 (1.1)	
Parent/Guardian-reported PedsQL scores	n=181	n=54	n=127	
Total, mean ± std	67.2 ± 18.8	67.2 ± 20.2	67.2 ± 18.2	0.988
median (IQR)	67 (52, 82)	73 (49.5, 84)	67 (54, 80)	
Physical function, mean ± std	67.6 ± 27.3	71.6 ± 25.0	65.9 ± 28.1	0.201
median (IQR)	72 (53, 91)	75 (63, 91)	66 (47, 91)	
Emotional function, mean ± std	70.8 ± 21.0	68.7 ± 24.5	71.7 ± 19.3	0.432
median (IQR)	70 (57.5, 90)	75 (50, 90)	70 (60, 90)	
Social function, mean ± std	71.2 ± 21.1	72.9 ± 22.1	70.5 ± 20.7	0.486
median (IQR)	70 (55, 90)	80 (55, 90)	70 (55, 90)	
School function, mean ± std	58.7 ± 22.3	59.7 ± 25.6	58.3 ± 20.8	0.707
median (IQR)	60 (45, 75)	60 (42.5, 80)	58 (45, 70)	
Psychosocial function, mean ± std	66.7 ± 17.7	65.9 ± 20.1	67.0 ± 16.6	0.731
median (IQR)	67 (53, 80)	68 (54, 85)	67 (53, 77)	

Table 10 (Continued)

	Total	Non-inpatient rehabilitation	Inpatient rehabilitation	P
Child self-reported PedsQL scores	n=134	n=39	n=95	
Total, mean ± std	69.3 ± 17.8	69.6 ± 17.4	69.2 ± 18.1	0.904
median (IQR)	72 (58, 82)	71 (59, 83)	72 (57, 80)	
Physical function, mean ± std	69.4 ± 22.7	74.3 ± 19.1	67.4 ± 23.8	0.109
median (IQR)	75 (53, 88)	78 (59, 91)	69 (50, 88)	
Emotional function, mean ± std	70.4 ± 22.8	67.8 ± 22.8	71.4 ± 22.9	0.409
median (IQR)	75 (55, 90)	70 (55, 90)	75 (55, 90)	
Social function, mean ± std	75.4 ± 20.3	77.8 ± 20.6	74.4 ± 20.2	0.372
median (IQR)	80 (65, 90)	85 (65, 90)	75 (65, 90)	
School function, mean ± std	61.6 ± 22.8	58.3 ± 25.4	63.0 ± 21.6	0.292
median (IQR)	60 (45, 80)	57.5 (45, 70)	60 (45, 80)	
Psychosocial function, mean ± std	69.1 ± 18.4	67.6 ± 19.0	69.7 ± 18.2	0.567
median (IQR)	72 (58, 82)	69 (57, 82)	73 (60, 82)	

IQR, Interquartile range; GOS-E Peds, Pediatric Glasgow Outcome Scale Extended; PedsQL, Pediatric Quality of Life Inventory

For parent/guardian-reported PedsQL scores, Psychosocial function and Total scores were not available for 6 children in the non-inpatient rehabilitation group and 16 children in the inpatient rehabilitation group. School function scores were not available for 6 children in the non-inpatient rehabilitation group and 15 children in the inpatient rehabilitation group. Emotional function score was not available for 1 child in the inpatient rehabilitation group.

For child self-reported PedsQL scores, School function, Psychosocial function and Total scores were not available for 1 child in the non-inpatient rehabilitation group and 6 children in the inpatient rehabilitation group. Social function score was not available for 1 child in the inpatient rehabilitation group.

Table 11. Unadjusted and Adjusted Associations of Inpatient Rehabilitation Versus Non-Inpatient Rehabilitation with Pediatric Glasgow Outcome Scale Extended Scores (GOS-E Peds) in Children with Severe TBI (M=15 imputations)

Inpatient rehabilitation vs. Non-inpatient rehabilitation (ref)	No selection bias adjustment (n=254)						Adjustment for selection biases (n=254)					
	Children attending the 12-month assessment						Weighted for children consenting for outcome assessments			Weighted for children alive at hospital discharge		
	Unadjusted OR	95% CI	P	Adjusted OR	95% CI	P	Adjusted OR	95% CI	P	Adjusted OR	95% CI	P
Overall	1.29	0.80-2.09	0.293	0.75	0.37-1.53	0.434	0.73	0.36-1.49	0.390	0.67	0.33-1.37	0.269
GCS ≥ 13 at discharge	1.16	0.65-2.10	0.614	1.12	0.51-2.47	0.773	1.08	0.49-2.38	0.844	1.06	0.50-2.28	0.870
GCS < 13 at discharge	0.09	0.02-0.49	0.006	0.12	0.02-0.95	0.045	0.12	0.01-1.01	0.051	0.10	0.01-0.96	0.046

GCS, Glasgow Coma Scale
P for interaction = 0.006 in unadjusted analysis (bivariate analysis)
P for interaction = 0.049 in adjusted analysis which controlled for confounding variables but not selection biases
P for interaction = 0.058 in adjusted analysis which controlled for confounding variables and selection biases to generalize results to all children who consented for outcome assessments at hospital discharge
P for interaction = 0.053 in adjusted analysis which controlled for confounding variables and selection biases to generalize results to all children who were alive at hospital discharge

Table 12. Unadjusted and Adjusted Associations of Inpatient Rehabilitation Versus Non-Inpatient Rehabilitation with Parent/Guardian Reported Pediatric Quality of Life Inventory (PedsQL) Scores in Children with Severe TBI (M=15 imputations)

Inpatient rehabilitation vs. Non-inpatient rehabilitation (ref)	No selection bias adjustment (n=181)					
	Children with available data on rehabilitation and PedsQL at the 12-month assessment					
	Unadjusted β	95% CI	P	Adjusted β	95% CI	P
Total	-0.05	-6.47-6.37	0.988	-0.60	-10.02-8.82	0.900
Physical function	-5.68	-14.41-3.04	0.200	-4.21	-17.46-9.04	0.533
Emotional function	2.96	-3.78-9.71	0.387	-4.91	-14.62-4.79	0.321
Social function	-2.40	-9.17-4.38	0.486	-0.09	-8.57-8.39	0.984
School function	-1.45	-9.07-6.17	0.708	3.02	-9.65-15.70	0.640
Psychosocial function	1.05	-5.00-7.10	0.731	0.21	-8.09-8.51	0.961

Inpatient rehabilitation vs. Non-inpatient rehabilitation (ref)	Adjustment for selection biases (n=181)								
	Weighted for children with rehabilitation data			Weighted for children consenting for outcome assessments			Weighted for children alive at hospital discharge		
	Adjusted β	95% CI	P	Adjusted β	95% CI	P	Adjusted β	95% CI	P
Total	-0.28	-8.92-8.36	0.950	-0.99	-10.21-8.23	0.830	-0.92	-9.60-7.75	0.835
Physical function	-4.70	-17.54-8.15	0.474	-4.23	-17.34-8.88	0.527	-5.10	-18.17-7.97	0.445
Emotional function	-5.03	-14.28-4.21	0.286	-4.98	-14.26-4.30	0.293	-4.73	-13.67-4.21	0.300
Social function	-0.46	-8.31-7.40	0.909	-0.34	-8.49-7.80	0.934	-1.35	-9.54-6.84	0.747
School function	2.50	-10.11-15.11	0.697	2.75	-9.64-15.14	0.663	2.83	-9.77-15.44	0.659
Psychosocial function	0.40	-7.50-8.30	0.920	-0.10	-8.21-8.01	0.981	-0.02	-8.01-7.98	0.997

Scores indicate a minimal clinically important difference: Total, 4.50; Physical function, 6.92; Emotional function, 7.79; Social function, 8.98; School function, 9.67; and Psychosocial function, 5.49.

Table 13. Unadjusted and Adjusted Associations of Inpatient Rehabilitation Versus Non-Inpatient Rehabilitation with Child Self-Reported Pediatric Quality of Life Inventory (PedsQL) Scores in Children with Severe TBI (M=15 imputations)

Inpatient rehabilitation vs. Non-inpatient rehabilitation (ref)	No selection bias adjustment (n=134)					
	Children with available data on rehabilitation and PedsQL at the 12-month assessment					
	Unadjusted β	95% CI	P	Adjusted β	95% CI	P
Total	-0.42	-7.29-6.45	0.904	-1.31	-10.73-8.10	0.784
Physical function	-6.92*	-15.40-1.55	0.109	-5.81	-16.50-4.88	0.287
Emotional function	3.60	-4.99-12.19	0.409	2.53	-10.54-15.60	0.704
Social function	-3.46	-11.10-4.18	0.372	-0.94	-10.76-8.88	0.851
School function	4.67	-4.06-13.39	0.292	-0.16	-11.90-11.59	0.979
Psychosocial function	2.05	-5.03-9.14	0.567	0.63	-9.38-10.64	0.902

Inpatient rehabilitation vs. Non-inpatient rehabilitation (ref)	Adjustment for selection biases (n=134)								
	Weighted for children with rehabilitation data			Weighted for children consenting for outcome assessments			Weighted for children alive at hospital discharge		
	Adjusted β	95% CI	P	Adjusted β	95% CI	P	Adjusted β	95% CI	P
Total	-2.10	-11.20-6.99	0.651	-3.12	-12.64-6.40	0.520	-1.49	-10.84-7.87	0.756
Physical function	-5.72	-15.84-4.40	0.268	-6.53	-16.81-3.75	0.213	-6.58	-17.43-4.26	0.234
Emotional function	1.53	-11.03-14.09	0.811	0.52	-12.33-13.38	0.936	2.87	-10.17-15.91	0.666
Social function	-2.30	-11.84-7.24	0.636	-3.22	-13.10-6.67	0.524	-0.02	-10.37-10.34	0.997
School function	-1.20	-13.07-10.67	0.843	-2.34	-15.18-10.50	0.721	-0.32	-11.04-10.41	0.954
Psychosocial function	-0.56	-10.37-9.25	0.911	-1.66	-12.04-8.72	0.754	0.86	-9.10-10.82	0.866

*Scores indicate a minimal clinically important difference: Total, 4.36; Physical function, 6.66; Emotional function, 8.94; Social function, 8.36; School function, 9.12; and Psychosocial function, 5.30.

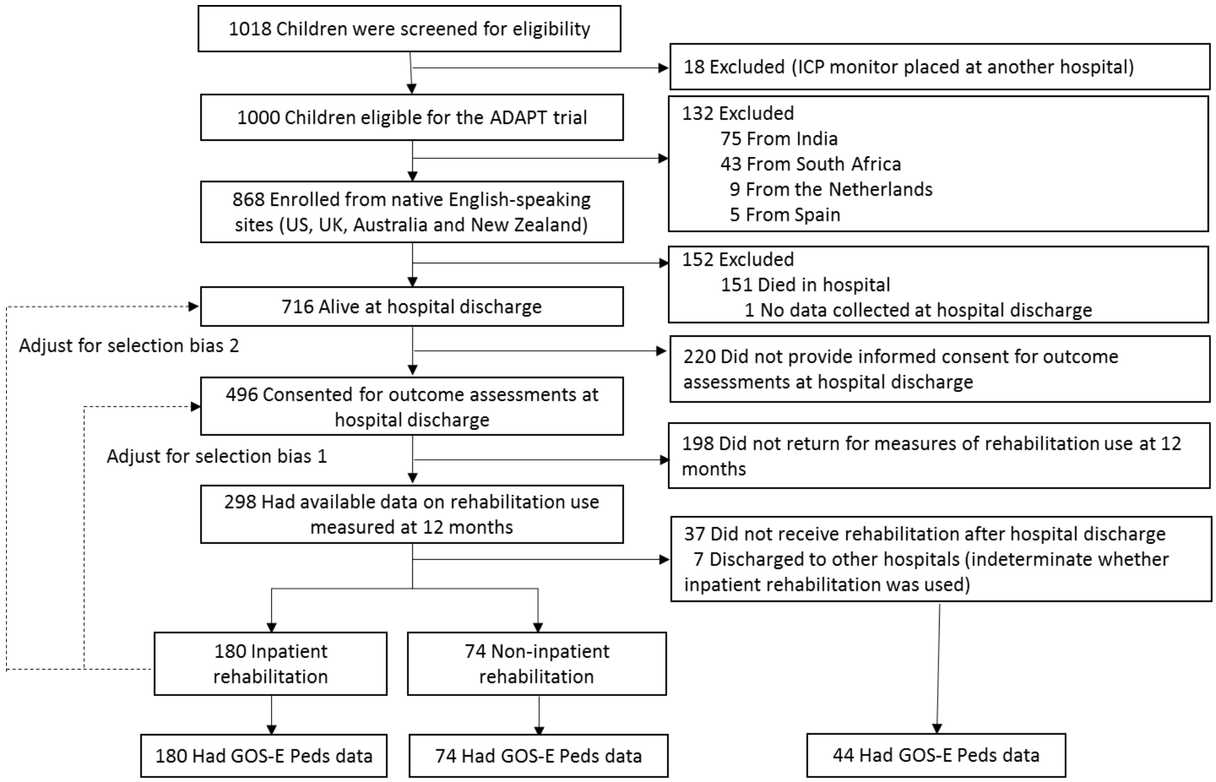

Figure 4. Flow of Children Included in the Analysis of the Association Between Rehabilitation Process and Pediatric Glasgow Outcome Scale Extended (GOS-E Peds)

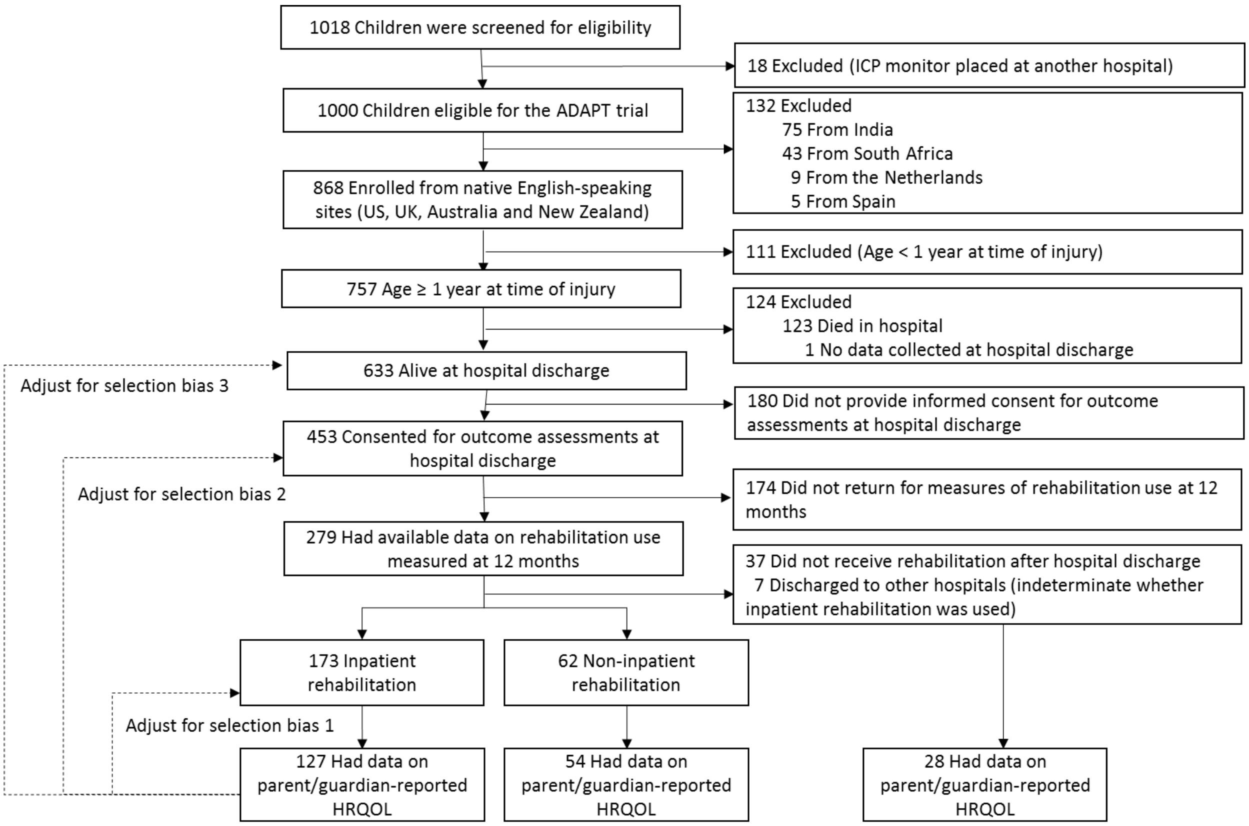

Figure 5. Flow of Children Included in the Analysis of the Association Between Rehabilitation Process and Parent/Guardian Reported Health Related Quality of Life (HRQOL)

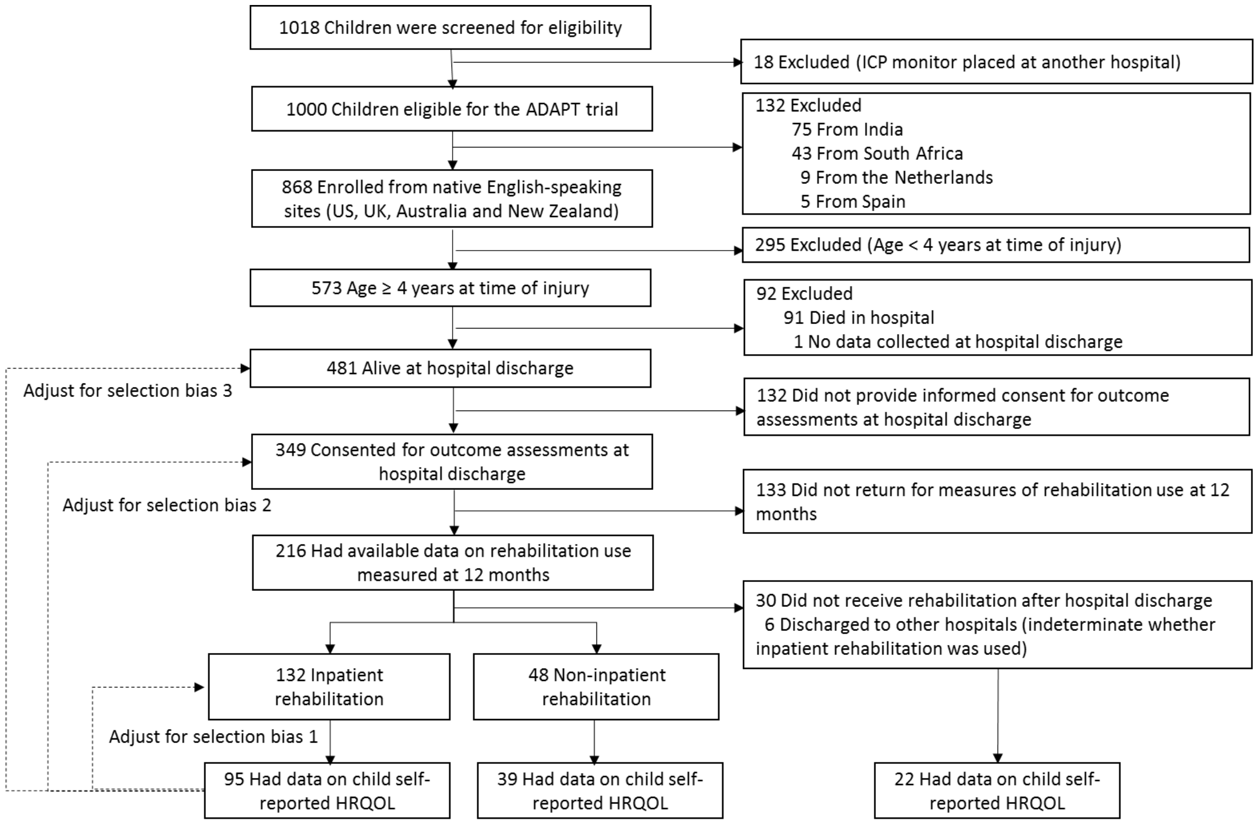

Figure 6. Flow of Children Included in the Analysis of the Association Between Rehabilitation Process and Child Self-Reported Health Related Quality of Life (HRQOL)

6.0 Synthesis

6.1 Overview of Findings

A severe TBI can adversely impact a child's quality of life in numerous ways, including physical, cognitive, and behavioral/emotional effects that affect daily functioning. According to the CDC, TBI rehabilitation is generally defined as a broad set of medical and therapeutic services designed to promote sensorimotor, cognitive and psychosocial functioning for patients with TBI [106]. Despite growing clinician and family awareness about the importance of rehabilitation, there is a paucity of evidence to inform comprehensive rehabilitation guidelines for children surviving severe TBI. The lack of guidelines allowed for variability of rehabilitation care after acute medical management. Inpatient rehabilitation, which generally refers to therapy services and continued nursing care received during an inpatient hospital stay, is a commonly used treatment option for patients after they leave acute care [106]. Other treatment options for those requiring rehabilitation include non-inpatient rehabilitation services such as therapies provided at home or in outpatient settings [106].

The global purpose of this dissertation was to provide evidence for future TBI rehabilitation guidelines by characterizing inpatient rehabilitation services for children with severe TBI, independent of the need for additional non-inpatient rehabilitation, and determining the associations of inpatient rehabilitation versus only non-inpatient rehabilitation with motor, neuropsychological, behavioral, functional and quality-of-life outcomes. We included a representative pediatric cohort with severe TBI, who were enrolled in a multisite, multinational longitudinal study - the Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial. We found that children receiving inpatient rehabilitation had a shorter length of acute hospitalization than children receiving only non-inpatient rehabilitation. Children from the UK were less likely to receive inpatient rehabilitation compared with children from the US. Among those from the US, African Americans were less likely to receive inpatient rehabilitation compared with whites. These findings highlighted the disparities in the use of inpatient rehabilitation following acute care, especially across different racial groups, among children with severe TBI.

By implementing linear regression model with inverse probability weighting to account for confounding and selection biases, we compared motor, cognitive and behavioral outcomes at 12 months after injury between children receiving inpatient rehabilitation and children receiving only non-inpatient rehabilitation. We found, contrary to our hypothesis, receiving inpatient rehabilitation was not associated with more favorable motor skills, intellectual functioning, verbal learning, memory, processing speed, cognitive flexibility, executive function or behaviors compared to receiving only non-inpatient rehabilitation. By applying ordinal logistic regression and linear regression models with inverse probability weighting to account for confounding and selection biases, we assessed the associations of inpatient rehabilitation versus only non-inpatient rehabilitation with global function and health related quality of life at 12 months after injury, respectively. We further explored the effect modification for consciousness level at hospital discharge, as measured by GCS. Those receiving inpatient rehabilitation were found to have better global function at 12 months among children with a GCS < 13 at discharge, though such association was not observed among children with a higher GCS. There were no differences in parent/guardian-reported or child self-reported health related quality of life between children receiving inpatient rehabilitation and children receiving only non-inpatient rehabilitation. Further investigation is warranted to confirm our findings on the benefits of inpatient rehabilitation for children with more severely impaired consciousness after acute medical stabilization.

6.2 Strengths

No previous study, to our knowledge, has characterized the use of inpatient rehabilitation after acute care in children with severe TBI. Our studies are also the first to examine the contribution of inpatient rehabilitation and/or non-inpatient rehabilitation to long-term outcomes of children with severe TBI. Findings from this dissertation provided the critical evidence of the benefits of inpatient rehabilitation for children with prolonged impaired consciousness and had important implications of promoting access to inpatient rehabilitation after acute care.

This dissertation was conducted using existing data from the ADAPT trial, which enrolled a large well-characterized cohort with good representation of pediatric population with severe TBI. Comprehensive data of demographics, family related factors, injury details, severity of illness and other clinical characteristics collected in the ADAPT trial allowed us to describe children with different patterns of rehabilitation process in detail. Moreover, the ADAPT cohort has been an extremely valuable source of research on outcomes following severe TBI. In the long-term follow-up, a standardized comprehensive neuropsychological test battery was used to assess motor, cognitive and behavioral outcomes, and gold-standard measurements were used to evaluate the global function and health related quality of life. Including all these measurements allowed us to capture all important aspects of recovery and compare the effects of different patterns of rehabilitation process in children with severe TBI.

Propensity score weighting was implemented in the analyses of rehabilitation process and outcomes to account for potential confounders and selection biases. Using this approach allows the study to achieve some features of randomized controlled trials by balancing measured characteristics between inpatient rehabilitation and non-inpatient rehabilitation groups. Selection biases resulted from selective participation at enrollment and other forms of attrition were also addressed when children comprising the final analytical sample were weighted to represent the population at large.

6.3 Limitations

Our conclusions should be considered in light of some limitations. Rehabilitation disposition was determined based on the child's discharge destination from acute care. We had no data collected from an inpatient rehabilitation admission. It is therefore possible that we misclassified the rehabilitation disposition for some children. Children who were referred to but eventually not admitted to inpatient rehabilitation may have been misclassified into the inpatient rehabilitation group. Children who were directly discharged home after acute care but later admitted to an inpatient rehabilitation facility or skilled nursing facility may have been misclassified into the non-inpatient group. Such misclassification tends to make the groups more similar with regards to sociodemographic and clinical characteristics, as well as outcomes, and may bias the associations of inpatient rehabilitation versus only non-inpatient rehabilitation with outcome measures in Manuscripts 2 and 3 towards the null.

Although we adjusted for multiple sociodemographic and clinical characteristics, unmeasured confounding appears to remain in the analyses of Manuscripts 2 and 3. Identifying and ascertaining all potential confounders is difficult due to the limited evidence characterizing rehabilitation services use in children with severe TBI and delineating factors predictive of long-term motor, cognitive, behavioral and functional outcomes. The presence of unmeasured confounding is a limitation that we share with most other observational studies.

Because of sample size, some of the analyses (i.e., adjusted analysis of child self-reported HRQOL) were likely to be underpowered and produced wide confidence intervals. Therefore, these analyses were interpreted with caution and will require replication in larger samples. Further, we had limited power to examine the potential effect modification for consciousness level at hospital discharge in the analyses of the associations between different patterns of rehabilitation process and motor skills, cognitive function, behavioral outcomes, and HRQOL.

6.4 Public Health and Clinical Implications

Rehabilitation services are typically pursued when a child with severe TBI is past the critical phase. However, there is a paucity of evidence to inform systematic guidelines for the allocation of rehabilitation services. In the US, only less than one third of children hospitalized for severe TBI are discharged to an inpatient rehabilitation facility [6]. We extended previous research and demonstrated racial disparities in the access to inpatient rehabilitation after acute care among children with severe TBI. These findings suggested that developing and implementing strategies to improve access to needed inpatient rehabilitation for children with limited resources, especially among racial minority groups, may be a focus for health systems to promote equity of health care access. In addition, length of acute hospitalization and regional context were found to be associated with the use of inpatient rehabilitation, which implied that contextual factors played an important role in shaping rehabilitation disposition. Further research taking account of different organizational contexts and health care environment contexts is warranted to better understand gaps in rehabilitation care and inform future policies and practice related to health care access.

Our findings further suggested that children with more severely impaired consciousness when medically stable benefited from receiving inpatient rehabilitation after acute care, particularly in terms of global function at 12 months after injury, though similar results were not observed in those with normal or less severely impaired consciousness. Without the stratification by child's consciousness level after acute care, we failed to illustrate the effectiveness of inpatient rehabilitation versus only non-inpatient rehabilitation on either granular motor and neurobehavioral measures or functional and quality of life outcomes. Although these analyses need replications in larger samples, we provided preliminary evidence in support of inpatient rehabilitation for children with prolonged impaired consciousness, which may inform future clinical practice and pediatric TBI rehabilitation guidelines. Importantly, our work provided the foundation for future pediatric studies examining the impacts of various components of rehabilitation process such as the types, intensity, location, duration and timing of rehabilitation services on outcomes following TBI. Overall, this dissertation revealed the utility of epidemiologic methods in the study of rehabilitation care in children with severe TBI and had essential implications for guiding clinical practice and public health policies aimed at improving child outcomes.

6.5 Future Research

In the continuum of care for children surviving severe TBI, acute medical management occurs in a relatively short time frame compared with the long-term care managed in inpatient rehabilitation settings, outpatient rehabilitation clinics, primary care offices, community environment and the educational system. As a substantial portion of children with moderate-to-severe TBI are reported having unmet (~20%) or unrecognized (~10%) health care needs after acute medical management [113], more research is needed to better understand inequalities in the access to outpatient rehabilitation services, home health, school services and other types of follow-up care. Subsequent health policy studies examining the effect of expanded access to certain follow-up care are also warranted.

To better inform clinical practice guidelines for rehabilitation of children surviving TBI, both real-world effectiveness studies and rigorous efficacy studies, which should be considered ethical to randomly assign treatments, are critically needed to identify the optimal dosage (that is, intensity and duration) and timing of different rehabilitation services in PICU and post-acute care settings. Studies are also needed to evaluate what factors moderate child's response to rehabilitation interventions, including age, preinjury conditions, severity of functional impairment and environmental support.

Importantly, pediatric TBI is a significant worldwide public health concern. The World Health Organization estimates that over 98% of pediatric TBI occur in the poorest countries with injury rates being five times higher than that in developed countries [232]. However, pediatric TBI research from developing countries are immensely lacking [233]. The availability of rehabilitation services and barriers to care for children in developing countries remain unclear. Further investigation is needed to characterize different rehabilitation services for children surviving severe TBI in lower- and middle-income countries. Moreover, a potential future research direction is evaluating the external validity of studies conducted in the US and other developed countries in lower- and middle-income countries to ensure the efficacy or effectiveness of certain rehabilitation interventions in different contexts. Identifying effective rehabilitation interventions and optimizing long-term care delivery will help to lower the morbidity burden of pediatric TBI around the world.

Appendix. Supplementary Materials

Table 14. Neuropsychological Measures and Parent/Guardian Rating Scales

Domains	Test	Age (years) at test	Source	Norm-referenced T scores
Overall intellectual functioning	Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III)	< 3	Child	FSIQ
	Wechsler Preschool and Primary Scale of Intelligence - 4th Edition (WPPSI-IV) Short Form	3 - <6	Child	
	Wechsler Abbreviated Scale of Intelligence - 2nd Edition (WASI-II)	>= 6	Child	
Verbal intellectual functioning	WPPSI-IV Short Form	3 - <6	Child	VIQ
Nonverbal intellectual functioning	WASI-II	>= 6	Child	NVIQ
Processing speed	WPPSI-IV - Animal Coding	4 - <6	Child	PS
	Wechsler Intelligence Scale for Children - 4th Edition (WISC-IV) - Processing Speed Index	6 - 16	Child	
	Wechsler Adult Intelligence Scale - 4th Edition (WAIS-IV) - Processing Speed Index	> 16	Child	
Memory and verbal learning Attention span Learning efficiency	California Verbal Learning Test – Child Version (CVLT-C)	5 - 16	Child	CVLT-ListA1 CVLT-ListA5
Delayed recall Inaccurate recall	California Verbal Learning Test – Adult Version (CVLT-II)	> 16	Child	CVLT-LDFR CVLT-FP
Cognitive flexibility	Delis-Kaplan Executive Function Scale (D-KEFS) – Verbal Fluency Subtest	8 - 16	Child	DKEFS-VF
Motor skills	Bruininks-Oseretsky Test of Motor Proficiency - 2nd Edition (BOT-2) - Short Form	>= 4	Child	BOT2-SF
Executive function	Behavior Rating Inventory of Executive Function Pre-school Version	2 - <6	Parent/Guardian	BRIEF-GEC
	Behavior Rating Inventory of Executive Function School-age Version	6 - 18	Parent/Guardian	
Behavior Internalizing	Child Behavior Checklist Pre-school Version	2 - <6	Parent/Guardian	CBCL-IN
Externalizing	Child Behavior Checklist School-age Version	6 - 18	Parent/Guardian	CBCL-EX

Table 15. Motor, Neuropsychological and Behavioral Impairments of Children in the Inpatient Rehabilitation and Non-Inpatient Rehabilitation Groups

	Total	Non-inpatient rehabilitation	Inpatient rehabilitation	P
Beyond 1 SD from norm				
FSIQ	89 (45.2)	24 (42.1)	65 (46.4)	0.580
VIQ	67 (38.5)	15 (32.6)	52 (40.6)	0.338
NVIQ	74 (43.0)	16 (34.8)	58 (46.0)	0.187
PS	98 (60.9)	18 (40.0)	80 (69.0)	<0.001
Memory and Verbal Learning				
Attention span (CVLT-ListA1)	63 (42.0)	8 (19.5)	55 (50.5)	<0.001
Learning efficiency (CVLT-ListA5)	68 (45.3)	9 (22.0)	59 (54.1)	<0.001
Delayed recall (CVLT-LDFR)	75 (50.7)	15 (37.5)	60 (55.6)	0.051
Inaccurate recall (CVLT-FP)	47 (31.8)	10 (25.0)	37 (34.3)	0.283
Cognitive flexibility (DKEFS-VF)	48 (40.7)	9 (28.1)	39 (45.3)	0.090
Motor skills (BOT2-SF)	101 (63.5)	20 (45.5)	81 (70.4)	0.003
Executive function (BRIEF-GEC)	90 (47.1)	27 (49.1)	63 (46.3)	0.729
Behavior				
Internalizing (CBCL-IN)	59 (30.1)	23 (39.0)	36 (26.3)	0.075
Externalizing (CBCL-EX)	49 (25.0)	17 (28.8)	32 (23.4)	0.418
Beyond 1.5 SD from norm				
FSIQ	63 (32.0)	16 (28.1)	47 (33.6)	0.453
VIQ	45 (25.9)	8 (17.4)	37 (28.9)	0.126
NVIQ	57 (33.1)	11 (23.9)	46 (36.5)	0.120
PS	72 (44.7)	11 (24.4)	61 (52.6)	0.001
Memory and Verbal Learning				
Attention span (CVLT-ListA1)	47 (31.3)	5 (12.2)	42 (38.5)	0.002
Learning efficiency (CVLT-ListA5)	61 (40.7)	7 (17.1)	54 (49.5)	<0.001
Delayed recall (CVLT-LDFR)	61 (41.2)	10 (25.0)	51 (47.2)	0.015
Inaccurate recall (CVLT-FP)	36 (24.3)	7 (17.5)	29 (26.8)	0.239
Cognitive flexibility (DKEFS-VF)	38 (32.2)	5 (15.6)	33 (38.4)	0.019
Motor skills (BOT2-SF)	79 (49.7)	13 (29.6)	66 (57.4)	0.002

Table 15 (Continued)

	Total	Non-inpatient rehabilitation	Inpatient rehabilitation	P
Executive function (BRIEF-GEC)	63 (33.0)	23 (41.8)	40 (29.4)	0.099
Behavior				
Internalizing (CBCL-IN)	37 (18.9)	17 (28.8)	20 (14.6)	0.020
Externalizing (CBCL-EX)	29 (14.8)	10 (16.9)	19 (13.9)	0.577
Beyond 2 SD from norm				
FSIQ	40 (20.3)	12 (21.1)	28 (20.0)	0.868
VIQ	31 (17.8)	4 (8.7)	27 (21.1)	0.059
NVIQ	50 (29.4)	9 (19.6)	41 (33.1)	0.086
PS	55 (34.2)	5 (11.1)	50 (43.1)	<0.001
Memory and Verbal Learning				
Attention span (CVLT-ListA1)	27 (18.0)	2 (4.9)	25 (22.9)	0.010
Learning efficiency (CVLT-ListA5)	50 (33.3)	6 (14.6)	44 (40.4)	0.003
Delayed recall (CVLT-LDFR)	48 (32.4)	7 (17.5)	41 (38.0)	0.018
Inaccurate recall (CVLT-FP)	32 (21.6)	7 (17.5)	25 (23.2)	0.458
Cognitive flexibility (DKEFS-VF)	29 (24.6)	2 (6.3)	27 (31.4)	0.005
Motor skills (BOT2-SF)	55 (34.6)	9 (20.5)	46 (40.0)	0.020
Executive function (BRIEF-GEC)	43 (22.5)	14 (25.5)	29 (21.3)	0.536
Behavior				
Internalizing (CBCL-IN)	18 (9.2)	10 (16.9)	8 (5.8)	0.013
Externalizing (CBCL-EX)	13 (6.6)	6 (10.2)	7 (5.1)	0.216

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; NVIQ, Nonverbal Intelligence Quotient; PS, Processing Speed; CVLT-ListA1, California Verbal Learning Test – List A Trial 1; CVLT-ListA5, California Verbal Learning Test – List A Trial 5; CVLT-LDFR, California Verbal Learning Test – Long Delay Free Recall; CVLT-FP, California Verbal Learning Test – False Positives; DKEFS-VF, Delis Kaplan Executive Function Scale - Verbal Fluency; BOT2-SF, Bruininks-Oseretsky Test of Motor Proficiency Second Edition - Short Form; BRIEF-GEC, Behavior Rating Inventory of Executive Function – Global Executive Composite; CBCL-IN, Child Behavior Checklist – Internalizing scale; CBCL-EX, Child Behavior Checklist – Externalizing scale.

Table 16. Unadjusted and Adjusted Associations of Inpatient Rehabilitation Versus Non-Inpatient Rehabilitation with Motor, Neuropsychological and Behavioral Impairments in Children with Severe Traumatic Brain Injury (M=15 imputations)

	No selection bias adjustment				**Adjustment for selection biases**			
	Unadjusted		**Confounder-adjusted**		**Weighted for children consenting for outcome assessments**		**Weighted for children alive at hospital discharge**	
Inpatient rehabilitation vs. Non-inpatient rehabilitation (ref)	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Beyond 1 SD from norm								
FSIQ	1.19 (0.64-2.22)	0.580	1.03 (0.38-2.81)	0.952	0.93 (0.34-2.59)	0.892	1.05 (0.39-2.86)	0.922
VIQ	1.41 (0.69-2.88)	0.339	1.23 (0.32-4.81)	0.762	1.32 (0.35-5.00)	0.681	1.44 (0.42-4.94)	0.564
NVIQ	1.60 (0.79-3.22)	0.189	1.44 (0.41-5.01)	0.566	1.37 (0.39-4.81)	0.622	1.42 (0.42-4.73)	0.568
PS	3.33 (1.63-6.81)	0.001	1.98 (0.49-8.02)	0.336	1.75 (0.44-7.02)	0.427	1.74 (0.44-6.90)	0.433
Memory and Verbal Learning								
Attention span (CVLT-ListA1)	4.20 (1.78-9.92)	0.001	2.03 (0.60-6.93)	0.257	1.99 (0.58-6.80)	0.270	2.13 (0.66-6.88)	0.208
Learning efficiency (CVLT-ListA5)	4.20 (1.83-9.62)	<0.001	2.13 (0.60-7.60)	0.244	2.16 (0.60-7.78)	0.238	2.53 (0.71-9.01)	0.152
Delayed recall (CVLT-LDFR)	2.08 (0.99-4.38)	0.053	1.72 (0.54-5.50)	0.363	1.78 (0.55-5.75)	0.335	2.02 (0.64-6.41)	0.23
Inaccurate recall (CVLT-FP)	1.56 (0.69-3.54)	0.285	1.16 (0.30-4.54)	0.826	1.37 (0.35-5.31)	0.651	1.09 (0.28-4.17)	0.904
Cognitive flexibility (DKEFS-VF)	2.12 (0.88-5.11)	0.094	1.09 (0.15-7.77)	0.935	1.10 (0.16-7.78)	0.923	1.19 (0.16-8.74)	0.864
Motor skills (BOT2-SF)	2.86 (1.40-5.85)	0.004	1.86 (0.60-5.74)	0.283	1.88 (0.64-5.57)	0.253	1.81 (0.61-5.40)	0.285
Executive function (BRIEF-GEC)	0.90 (0.48-1.68)	0.728	0.94 (0.36-2.45)	0.898	1.06 (0.41-2.79)	0.901	1.00 (0.38-2.62)	0.995
Behavior								
Internalizing (CBCL-IN)	0.56 (0.29-1.07)	0.077	0.62 (0.22-1.74)	0.358	0.58 (0.20-1.72)	0.325	0.67 (0.24-1.91)	0.457
Externalizing (CBCL-EX)	0.75 (0.38-1.50)	0.419	1.04 (0.39-2.78)	0.936	1.11 (0.42-2.97)	0.835	1.06 (0.38-2.93)	0.912
Beyond 1.5 SD from norm								
FSIQ	1.29 (0.66-2.55)	0.453	0.90 (0.27-2.92)	0.856	0.88 (0.26-2.91)	0.830	0.84 (0.27-2.63)	0.761
VIQ	1.93 (0.82-4.53)	0.130	0.79 (0.18-3.40)	0.747	0.76 (0.18-3.22)	0.711	0.92 (0.23-3.74)	0.913
NVIQ	1.83 (0.85-3.94)	0.123	1.25 (0.30-5.15)	0.753	1.15 (0.28-4.76)	0.844	1.08 (0.27-4.25)	0.911
PS	3.43 (1.58-7.41)	0.002	1.55 (0.38-6.31)	0.541	1.40 (0.32-6.10)	0.650	1.28 (0.29-5.75)	0.745

Table 16 (Continued)

Memory and Verbal Learning								
Attention span (CVLT-ListA1)	4.51 (1.64-12.41)	0.003	1.31 (0.33-5.16)	0.703	1.21 (0.31-4.79)	0.787	1.31 (0.36-4.79)	0.679
Learning efficiency (CVLT-ListA5)	4.77 (1.95-11.68)	<0.001	1.87 (0.47-7.40)	0.371	1.84 (0.47-7.28)	0.383	2.09 (0.55-7.95)	0.280
Delayed recall (CVLT-LDFR)	2.68 (1.19-6.03)	0.017	1.63 (0.48-5.62)	0.434	1.71 (0.50-5.81)	0.392	1.87 (0.57-6.09)	0.297
Inaccurate recall (CVLT-FP)	1.73 (0.69-4.34)	0.243	0.92 (0.18-4.77)	0.917	1.10 (0.20-5.91)	0.909	0.98 (0.19-5.08)	0.982
Cognitive flexibility (DKEFS-VF)	3.36 (1.18-9.59)	0.023	1.50 (0.17-13.24)	0.713	1.58 (0.18-13.85)	0.680	1.90 (0.20-18.00)	0.575
Motor skills (BOT2-SF)	3.21 (1.52-6.77)	0.002	2.40 (0.69-8.39)	0.168	2.34 (0.69-7.97)	0.173	2.07 (0.62-6.95)	0.237
Executive function (BRIEF-GEC)	0.58 (0.30-1.11)	0.100	0.63 (0.24-1.65)	0.345	0.70 (0.26-1.88)	0.482	0.65 (0.25-1.70)	0.379
Behavior								
Internalizing (CBCL-IN)	0.42 (0.20-0.88)	0.022	0.54 (0.18-1.60)	0.265	0.48 (0.15-1.53)	0.216	0.50 (0.16-1.55)	0.230
Externalizing (CBCL-EX)	0.79 (0.34-1.82)	0.578	1.00 (0.28-3.54)	0.996	1.03 (0.28-3.84)	0.959	1.25 (0.33-4.77)	0.747
Beyond 2 SD from norm								
FSIQ	0.94 (0.44-2.00)	0.868	0.48 (0.14-1.69)	0.250	0.48 (0.12-1.83)	0.279	0.43 (0.12-1.56)	0.198
VIQ	2.81 (0.92-8.52)	0.068	1.11 (0.17-7.33)	0.912	1.12 (0.18-7.13)	0.901	1.38 (0.25-7.70)	0.712
NVIQ	2.68 (0.97-7.37)	0.057	0.80 (0.11-5.52)	0.819	0.75 (0.11-5.20)	0.768	0.77 (0.13-4.41)	0.767
PS	6.06 (2.23-16.47)	<0.001	1.55 (0.32-7.48)	0.584	1.43 (0.28-7.25)	0.661	1.22 (0.24-6.28)	0.816
Memory and Verbal Learning								
Attention span (CVLT-ListA1)	5.80 (1.31-25.74)	0.021	3.12 (0.33-29.70)	0.322	3.84 (0.34-42.91)	0.274	2.65 (0.40-17.44)	0.310
Learning efficiency (CVLT-ListA5)	3.95 (1.53-10.18)	0.004	1.10 (0.23-5.30)	0.907	1.18 (0.24-5.77)	0.835	1.18 (0.24-5.70)	0.835
Delayed recall (CVLT-LDFR)	2.88 (1.17-7.12)	0.021	1.41 (0.37-5.42)	0.615	1.51 (0.39-5.79)	0.545	1.64 (0.46-5.80)	0.445
Inaccurate recall (CVLT-FP)	1.42 (0.56-3.60)	0.460	0.66 (0.12-3.52)	0.625	0.83 (0.16-4.43)	0.832	0.71 (0.13-3.70)	0.683
Cognitive flexibility (DKEFS-VF)	6.86 (1.53-30.83)	0.012	3.06 (0.54-17.36)	0.204	3.13 (0.54-18.07)	0.198	3.92 (0.63-24.40)	0.141
Motor skills (BOT2-SF)	2.59 (1.14-5.90)	0.023	2.15 (0.51-9.09)	0.295	2.17 (0.52-8.99)	0.286	1.71 (0.44-6.69)	0.442
Executive function (BRIEF-GEC)	0.79 (0.38-1.65)	0.536	1.28 (0.44-3.69)	0.649	1.47 (0.51-4.25)	0.480	1.26 (0.41-3.85)	0.686
Behavior								
Internalizing (CBCL-IN)	0.30 (0.11-0.82)	0.018	0.42 (0.11-1.68)	0.221	0.37 (0.09-1.58)	0.181	0.36 (0.08-1.52)	0.163
Externalizing (CBCL-EX)	0.48 (0.15-1.48)	0.200	0.67 (0.17-2.57)	0.558	0.66 (0.17-2.62)	0.554	0.81 (0.19-3.42)	0.776

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; NVIQ, Nonverbal Intelligence Quotient; PS, Processing Speed; CVLT-ListA1, California Verbal Learning Test – List A Trial 1; CVLT-ListA5, California Verbal Learning Test – List A Trial 5; CVLT-LDFR, California Verbal Learning Test – Long Delay Free Recall; CVLT-FP, California Verbal Learning Test – False Positives; DKEFS-VF, Delis Kaplan Executive Function Scale - Verbal Fluency; BOT2-SF, Bruininks-Oseretsky Test of Motor Proficiency Second

Edition - Short Form; BRIEF-GEC, Behavior Rating Inventory of Executive Function – Global Executive Composite; CBCL-IN, Child Behavior Checklist – Internalizing scale; CBCL-EX, Child Behavior Checklist – Externalizing scale.

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