

Severe traumatic brain injury - clinical course and prognostic factors

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To my beloved family

*"Memories of our lives, of our works and our deeds will continue in others".
Words from a civil rights legend, Rosa Parks.*

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ABSTRACT

Traumatic brain injury (TBI) constitutes a major health problem and is a leading cause of long-term disability and death. Patients with severe traumatic brain injury, S-TBI, comprise a heterogeneous group with varying complexity and prognosis. The primary aim of this thesis was to increase knowledge about clinical course and outcome with regard to prognostic factors. Papers I, II and III were based on data from a prospective multicentre observational study from six neurotrauma centers (NCs) in Sweden and Iceland of patients (n=103-114), 18-65 years with S-TBI requiring neurosurgical intensive care or collaborative care with a neurosurgeon (the "PROBRAIN" study). Paper IV and V were performed on a regional subset (n=37).

In Paper I, patients with posttraumatic disorders of consciousness (DOC) were assessed as regards relationship between conscious state at 3 weeks and outcomes at 1 year. The number of patients who emerged from minimally conscious state (EMCS) 1 year after injury according to status at 3 weeks were: coma (0/6), unresponsive wakeful syndrome (UWS) (9/17), minimally conscious state (MCS) (13/13), anaesthetized (9/11). Outcome at 1 year was good (Glasgow Outcome Scale Extended (GOSE)>4) in half of the patients in MCS (or anaesthetized) at 3 weeks, but not for any of the patients in coma or UWS.

In Paper II, the relationships between clinical care descriptors and outcome at 1 year were assessed. A longer length of stay in intensive care, and longer time between discharge from intensive care and admission to inpatient rehabilitation, were both associated with a worse outcome on the GOSE. The number of intervening care units between intensive care and rehabilitation, was not significantly associated with outcome at 1 year.

In Paper III, the clinical course of cognitive and emotional impairments as reflected in the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) and the Hospital Anxiety and Depression Scale (HADS) were assessed from 3 weeks to 1 year together with associations with outcomes GOSE and Rancho Los Amigos Cognitive Scale-Revised (RLAS-R) at 1 year. Cognition improved over time and appeared to be stable from 3 months to 1 year.

In Paper IV, clinical parameters, the clinical pathways from injury to 3 months after discharge from the NC in relation to outcomes 3 months post-injury. Ratings on the RLAS-R improved significantly over time. Eight patients had both “superior cognitive functioning” on the RLAS-R and “favourable outcome” on the GOSE. Acute transfers to the one regional NC was direct and swift, transfers for postacute rehabilitation scattered patients to many hospitals/hospital departments, not seldom by several transitional stages.

In Paper V, an initial computerized tomography of the brain (CT_i) and a further posttraumatic brain CT after 24 hours (CT₂₄) were evaluated according to protocols for standardized assessment, the Marshall and Rotterdam classifications. The CT scores only correlated with clinical outcome measures (GOSE and RLAS-R) at 3 months, but failed to yield prognostic information regarding outcome at 1 year. A prognostic model was also implemented, based on acute data (CRASH model). This model predicted unfavourable outcomes for 81% of patients with bad outcome and for 85% of patients with favourable outcome according to GOSE at 1 year. When assessing outcomes per se, both GOSE and RLAS-R improved significantly from 3 months to 1 year.

The papers in this study point both to the generally favourable outcomes that result from active and aggressive management of S-TBI, while also underscore our current lack of reliable instruments for outcome prediction. In the absence of an ability to select patients based on prognostication, the overall favourable prognosis lends support for providing active rehabilitation to all patients with S-TBI. The results of these studies should be considered in conjunction with the prognosis of long-term outcomes and the planning of rehabilitation and care pathways. The results demonstrate the importance of a combination of active, acute neurotrauma care and intensive specialized neurorehabilitation with follow-up for these severely injured patients.

Key words: Severe traumatic brain injury, outcome, rehabilitation, prognosis

ABBREVIATIONS

ATV all-terrain vehicle
BAC blood alcohol concentration
BNIS Barrow Neurological Institute Screen for Higher Cerebral Functions
CI confidence interval
CPP cerebral perfusion pressure
CRASH Corticosteroid randomisation after significant head injury
CRS-R Coma Recovery Scale Revised
CT Computed tomography
CT_i Initial Computed tomography
CT₂₄ Computed tomography nearest 24 hours after trauma
DAI Diffuse axonal injury
DOC disorders of consciousness
DT Datortomografi
EDH epidural haematoma
EMCS emerging from the minimally conscious state
fMRI functional magnetic resonance imaging
GCS Glasgow Coma Scale
GOS Glasgow Outcome Scale
GOSE Glasgow Outcome Scale Extended
HADS Hospital Anxiety and Depression Scale
ICF International Classification of Functioning, Disability and Health
ICP Intracranial pressure
IMPACT International Mission for Prognosis and Clinical Trial database of traumatic brain injury
LOC Level of consciousness
LOSIC Length of stay in intensive care
LSS The law on support and service for certain people with disabilities
MAP mean arterial blood pressure
MCS minimally conscious state
MRI magnetic resonance imaging
NC Neurotrauma Center
NHR Northern Health Region
NMDA N-methyl-D-aspartate
OR odds ratio
PET positron emission tomography
POCON Prospective Observational Cohort Neurotrauma study
PTA Posttraumatic amnesia
PT-DOC post-traumatic disorders of consciousness

PTV Persistent vegetative state
RLS85 Swedish Reaction level scale
RLAS-R Rancho Los Amigos Cognitive Scale Revised
RPAP Rivermead Post-traumatic Amnesia Protocol
SPSS Statistical Package for the Social Sciences
SD standard deviation
SDH Subdural haematoma
TBI Traumatic brain injury
S-TBI severe traumatic brain injury
UWS unresponsive wakefulness syndrome
VS vegetative state

SAMMANFATTNING PÅ SVENSKA

Traumatisk hjärnskada (Traumatic brain injury/TBI) är en av de vanligaste orsakerna till funktionsnedsättning hos personer i arbetsför ålder. Skadan medför stort personligt lidande, drabbar även anhöriga, och innebär stora kostnader såväl för den enskilde som för samhället. Patienter med svår traumatisk hjärnskada (severe traumatic brain injury S-TBI), utgör en heterogen grupp med varierande komplexitet och prognos. Det primära målet med denna avhandling är att öka kunskapen om kliniskt förlopp och prognostiska faktorer vid S-TBI. Studierna I, II och III baseras på data från en prospektiv multicenter observationsstudie (PROBRAIN studien) från sex neurotraumacentra (NCs) i Sverige och Island. Inkluderade patienter (n=103-114) var i åldrarna 18-65 år, med svår traumatisk hjärnskada, som vårdats på neurointensivvårdsavdelning eller annan intensivvårdsavdelning i samråd med neurokirurg. Exklusionskriterier var patienter som avled inom 3 veckor efter skadan. Studierna IV och V baseras på en regional subpopulation i multicenterstudien PROBRAIN (n=37), och omfattar patienter från norra Sverige.

I studie I var patienter med medvetandestörning vid 3 veckor upp till 1 år undersökta och jämförda beträffande medvetandegrad vid 3 månader och utfall vid 1 år. De patienter som förbättrades till bättre än minimalt medvetande tillstånd ("emerged from minimally conscious state", EMCS) 1 år efter skadan jämfört med medvetandetillstånd vid 3 veckor var för koma: 0/6, för vegetativt tillstånd/icke-responsivt vakenhets tillstånd (unresponsive wakeful syndrome UWS) (9/17), för minimalt medvetande tillstånd (minimally conscious state MSC) (13/13), och för sederade/sövda patienter (9/11). Gott utfall vid 1 år på skalan (Glasgow Outcome Scale Extended GOSE>4) skattades för hälften av patienterna som bedömdes vara i ett minimalt medvetande tillstånd eller varit sövda vid 3 veckor men inte för de som bedömdes vara komatösa eller bedömdes vara i ett vegetativt/icke-responsivt vakenhetstillstånd.

I studie II undersöktes relationen mellan vårdvägar, vårdtid inom neurointensivvård, tiden mellan neurointensivvård och intag på rehabiliteringsavdelning och utfall vid 1 år. Längre vårdtid vid neurointensivvård och längre tid mellan neurointensivvård och intag på vårdavdelning för rehabilitering var faktorer som var associerade med ett sämre utfall enligt GOSE. Antalet förflyttningar mellan olika vårdavdelningar under tiden mellan utskrivning från neurointensivvård och rehabilitering var inte signifikant associerat med utfall vid 1 år.

I studie III, undersöktes det kliniska förloppet av kognitiva och emotionella funktionsnedsättningar med Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) och Hospital Anxiety and Depression Scale (HADS) från 3 veckor till 1 år jämfört med utfallet vid 1 år på GOSE och Ranchos Los Amigos Cognitive Scale-Revised (RLAS-R). Kognitiv funktionsnivå förbättrades över tid och föreföll vara stabil från 3 månader till 1 år. BNIS delskalor "orientering" och "visuospatial och visuell problemlösning" var associerade med GOSE och RLAS-R vid 1 år.

I studie IV, studerades kliniska parametrar, vårdvägar från skadetillfället fram till 3 månader efter skadan för 37 patienter från Norra sjukvårdsregionen i Sverige i relation till utfall vid 3 månader efter skadan. Utfall enligt RLAS-R förbättrades signifikant över tid. Utmärkande var att akut transport till det enda neurotraumacentret i regionen fungerade väl emedan postakut förflyttning fram till rehabilitering kunde ske dels via olika sjukhus och ibland via olika avdelningar med olika vårdnivåer.

I studie V undersöktes hjärnan med datortomografi (DT) initialt och efter 24 timmar enligt Marshall och Rotterdam DT klassifikationer i relation till utfall på GOSE och RLAS-R vid 3 månader och 1 år. Dessa klassifikationer för DT var bara relaterade till GOSE och RLAS-R vid 3 månader. GOSE och RLAS-R förbättrades signifikant från 3 månader till 1 år. En prognostisk modell baserad på akuta data (CRASH) predicerade dåligt utfall för 81% av patienter med dåligt utfall och för 85% av patienterna med gott utfall enligt GOSE vid 1 år. Sammanfattningsvis skattades gott utfall på GOSE 1 år efter S-TBI hos majoriteten av patienterna. Vid prognostisering av långtidsutfall, rehabiliteringsplanering och planering av vårdvägar bör resultaten från dessa studier beaktas. Resultaten pekar på vikten av en kombination av aktiv akut neurotraumavård och intensiv neurorehabilitering med uppföljningar av dessa svårt skadade patienter.

PREFACE

For two decades, I have worked as a physician in rehabilitation medicine and neurorehabilitation at Umeå University hospital. My main interest has been rehabilitation after acquired brain injury. After some unexpectedly interesting and fundamentally instructive years in the early 1990s devoted to cognitive impairment at the Department of Psycho-geriatric Care at the Geriatric Center at Umeå University Hospital, I started my employment at the Center for Neurorehabilitation. Some of the patients at the psycho-geriatric department with dementia, progressive cognitive impairment and behavioural disorders had a previous history of severe traumatic brain injury (S-TBI), many years earlier. These patients had participated in rehabilitation programmes and improved but had then suffered a progression of cognitive disorders.

Neurorehabilitation in Sweden offers specialized rehabilitation after spinal cord injury, acquired brain injury and for patients with neurological disease, primarily to patients of working age. Patients with acquired brain injury after trauma, stroke, infections, tumours, hypoxia/anoxia and metabolic causes are assessed and treated at center of neurorehabilitation. Umeå University Hospital provides specialized care to the Northern Health Region (NHR), a region that covers almost half the total area of Sweden (136,373 km²), with a total of 900,000 inhabitants. As the NHR comprises mainly rural districts with geographically large but sparsely populated areas, with long distances between hospitals, the clinical setting in this part of the country differs substantially from the more urbanised, southern half of the country. It is a challenge to offer equal care to persons in the NHR. Specialized rehabilitation in the NHR after brain injury is offered at three county hospitals in addition to the neurorehabilitation department at Umeå University Hospital. My aim as a physician over the years has been to focus on the importance of rehabilitation and especially on rehabilitation after acquired brain injury. There are areas for improvement in brain injury rehabilitation for county councils and regions but resources are limited. It is important to identify current conditions and compare with other brain injury rehabilitation departments in Sweden and abroad. The "PROBRAIN" study was an excellent chance for me to be part of a Swedish-Icelandic multicentre study of patients with S-TBI and therefore I devoted all my strength and time to pursuing and implementing this project. The aim of the multicentre study for S-TBI is to increase knowledge about clinical course and outcome with regard to prognostic factors. With knowledge from this survey of a patient group that is already well-known as heterogeneous, my

personal contribution was to have a basis for the further improvement of the rehabilitation of patients with S-TBI in clinical practice at our department and in the NHR. I also hoped that the studies could bring valuable knowledge of how to improve information to persons with S-TBI and their relatives for better planning of care pathways, use of resources and the evaluation of treatment effects. My goals for the future are studies which focus on rehabilitation and the long-term follow-up of patients with S-TBI and their relatives, if possible, from a lifetime perspective.

LIST OF ORIGINAL PAPERS

- I. Godbolt AK, DeBoussard CN, Stenberg M, Lindgren M, Ulfarsson T, Borg J. Disorders of consciousness after severe traumatic brain injury: a Swedish-Icelandic study of incidence, outcomes and implications for optimizing care pathways. *J Rehabil Med.* 2013 Sep;45(8):741-8.
- II. Godbolt AK, Stenberg M, Lindgren M, Ulfarsson T, Lannsjö M, Stålnacke BM. Borg J, DeBoussard CN. Associations between care pathways and outcome 1 year after severe traumatic brain injury. *J Head Trauma Rehabil.* 2015 May-Jun;30(3):E41-51.
- III. Stenberg M, Godbolt AK, Nygren DeBoussard CN, Levi R, Stålnacke BM. Cognitive Impairment after Severe Traumatic Brain Injury, Clinical Course and Impact on Outcome: A Swedish-Icelandic Study. *Behav Neurol.* 2015;2015:680308.
- IV. Stenberg M, Koskinen LO D, Levi R, Stålnacke BM. Severe traumatic brain injuries in Northern Sweden: a prospective 2-year study. *J Rehabil Med.* 2013 Sep;45(8):792-800.
- V. Stenberg M, Koskinen LO D, Jonasson P, Levi R, Stålnacke BM. Computed Tomography and clinical outcome in patients with severe traumatic brain injury. Submitted.

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INTRODUCTION

Definition of traumatic brain injury (TBI)

Traumatic brain injury (TBI) occurs when “direct or indirect external destructive, mechanical force causes brain dysfunction with impaired consciousness. Typically focal change, coup and contrecoup injuries includes contusion and hematoma formation whereas diffuse microvascular change, occur over a more widespread area includes diffuse axonal injury (DAI), and each includes multiple types of subcellular, cellular and physiologic dysfunction. [1]. TBI can lead to a broad range of temporary or permanent impairments of a cognitive, physical or psychosocial nature. Pathology and severity of TBI can be defined or classified in different ways: e.g. by i) mechanism, ii) level of consciousness (LOC) or by iii) structural damage (neuroimaging).

Mechanism

If the skull remains intact after trauma, the head injury is described as a “closed head injury”. If, by contrast, penetration of the skull occurs, the head injury is described as being “open”. In most cases, the brain remains enclosed in the skull cavity and any intracranial volume expansion, for example due to haematoma or oedema, will increase the intracranial pressure, thereby causing further brain injury. Closed head injury is caused by rotational and/or decelerational forces and resulting brain damage is categorized as being focal or diffuse. Focal brain injury comprises hematoma and/or contusions of different sizes, in one or several locations. Diffuse brain injury, by contrast, is widespread, a result of microscopic damage, typically in the subcortical white substance. Such damage may be impossible to visualize by ordinary neuroimaging but may nevertheless have disastrous consequences. Focal and diffuse

pathologies often coexist and contribute to morbidity [2]. Diffuse changes also include diffuse axonal injury (DAI) caused by rapid rotational movement, acceleration or deceleration force, which causes axonal disruption, leading to impaired function and also to diffuse microvascular damage with leakage of chemicals, further contributing to brain damage [3,4,5,6]. More recent studies indicate more generalized abnormalities after S-TBI, involving widespread neuro-excitation and metabolic changes that ultimately may prove to be of therapeutic importance [1].

Level of consciousness (LOC)

Level of consciousness (LOC), typically and historically assessed by Glasgow Coma Scale score (GCS) on admission [7] is the most widely used clinical instrument for assessment of severity of TBI. It consists of the sum score 3-15 of three different responses by eye, motor and verbal reaction and three different levels of sum scores describing three different levels of severity. Lower sum score GCS 3-8 indicates worst reaction: severe traumatic brain injury (S-TBI). The Reaction Level Scale (RLS85) is another 8-level hierarchic scale of reaction and this scale is widely used in Sweden [8]. RLS 4-8 assesses worst responsiveness: the patient is unconscious and classified as S-TBI. RLS scale can be translated to GCS score [9].

Structural damage (neuroimaging)

The third way to describe severity and pathology after TBI is by structural damage and this can be assessed by neuroimaging; computer tomography (CT) or magnetic resonance imaging (MRI). Acute CT scan of the brain is the most commonly used neuroimaging after TBI and it is used for acute survey and for deciding the further planning of acute care. Different classification systems have been

developed in an attempt to predict outcome, for example Marshall [10,85] and Rotterdam classification [11].

Epidemiology

Traumatic brain injury (TBI) is a global major health problem, predicted year 2020 to be the third leading cause of death and disability in the world [12]. Patients with TBI are a heterogeneous population and their subsequent state can vary from death or severe disability to full recovery. A study from Northern Sweden six to fifteen years after TBI reported a high degree of motor and cognitive function but also disability related to community reintegration and social participation even several years after injury [13]. Primary preventions such as seat belts, helmets and strict limitations for alcohol and drug use for motor vehicle drivers have reduced the number of TBI. However, the number of patients who survive S-TBI has increased due to improved chains of acute care, acute transportation systems, access to neurosurgery and modern neurointensive care. As a benefit of improved acute neurosurgical care and improved survival rates, there is an increased need for qualified neurorehabilitation [14]. Every year 15,000 – 20,000 persons in Sweden are hospitalized after TBI [15,16]. In a previous study 74% of hospital days were less than two days [16]. In a systematic review by Tagliaferri et al (2006) [17], the incidence of TBI in Europe was estimated at about 235/100,000/year. In a study from northern Sweden (2007), the incidence of TBI in all ages was reported as being even higher, 354/100,000/year and out of these, only 2% were classified as S-TBI [18]. Despite its relative rarity, S-TBI with an incidence of 3-12/100,000 per year [16,19] defined by acute Glasgow Coma Scale (GCS), total score 3-8, is the most common cause of death and long-

term disability in Western countries for young people and those of working age [20,21]. The mortality rate has been reported as 15-17/100,000/year [17]. In a European multicentre study, mortality for persons (>16 years) after six months with S-TBI was 40% [22] and in the Prospective Observational Cohort Neurotrauma (POCON), a study executed in 5 out of 11 specialized (Level I) trauma centres in the Netherlands with mortality 46% in patients (16-72 years) with S-TBI at 6-month post-injury follow-up [23]. TBI epidemiology and injury patterns have changed but case fatality rates remain high. [23]. Falls and motor vehicle related injuries are the leading causes of TBI [16,18,23,24]. Influence of alcohol or drugs at the time of injury is clearly indicated for persons with TBI; some studies have shown an incidence of 25-50% [17,25]. Injuries with S-TBI often involve great personal suffering and a reduced quality of life for patients and their relatives [26]. TBI also causes high societal costs [27]. Moreover, S-TBI may be associated with a higher risk (4.5 times) of Alzheimer's disease or dementia in general in a lifetime perspective [28,29].

Rehabilitation process after TBI

Care pathways

There are multiple logistical challenges presented at the acute stage of transfer of patients and rapid admission to Neuro trauma centers (NCs) and later after discharge from the NC transfer to intensive care if necessary or rehabilitation at a local hospital. It is also important to study care pathways after neuro-intensive care all the way to the person's home after discharge or to suitable accommodation. Admission to rehabilitation units and length of stay are usually decided by rehabilitation physicians according to local criteria. Previous studies have shown that delays between discharge from intensive care and admission to a rehabilitation unit are negatively associated with outcome one year after S-TBI [30]. Patients with S-TBI require hospitalization with different levels of care from acute care to a rehabilitation unit and are often discharged without a planned continuous care pathway. Acute care and rehabilitation come under different organizations which may affect treatment times and coordination.

Care pathways, NHR in Sweden

Outcome studies after S-TBI are mainly focused on injury severity; few studies have considered the effect of geographical factors [31]. The Northern Health Region (NHR) in Sweden which comprises mainly rural districts is a geographically large area that covers almost half of the total area of Sweden (136,373 km²). It differs substantially from the more urbanized southern half of the country. In the NHR, there are 900,000 inhabitants and a total of 13 hospitals (one of these is a single neuro trauma center, NC) that are very far apart.

Emergency transport is in many cases carried out by helicopters to the local hospital and then on to NC by helicopter, plane or car.

Neurointensive care

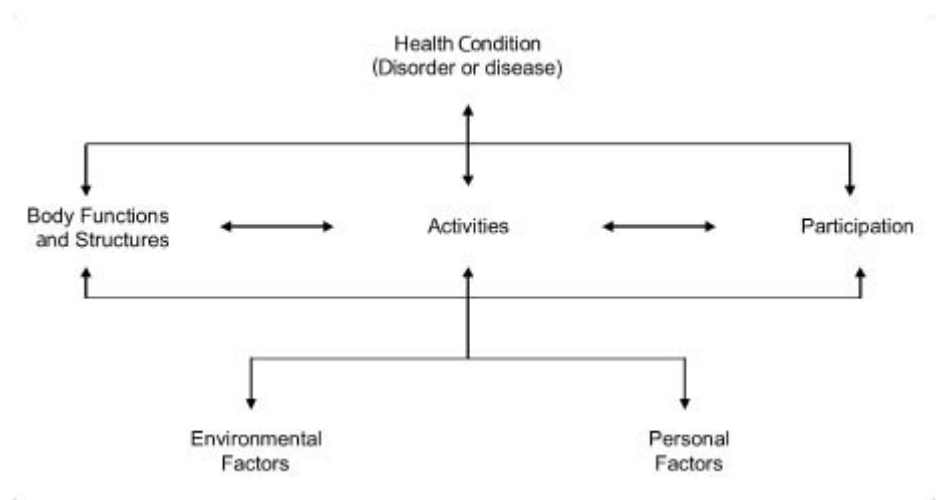
After admission to an NC with initial neurosurgery, neurointensive care is required to avoid ongoing brain damage and prevent secondary injuries after S-TBI such as brain swelling, increased intracranial pressure (ICP) and intracranial haemorrhage, and to provide the best conditions for the brain to recover after trauma. Neurosurgery and neurointensive care, observation and treatment in specialized neurotrauma centres are of importance. Secondary brain injury associated with lack of oxygen and pathological processes involving blood-brain barrier, oedema, release of chemicals factors with cell injury or death and swelling which can affects cerebrospinal circulation from the skull. The Lund concept is a modern protocol-driven concept for volume regulation of the brain and an aggressive neurointensive treatment after S-TBI, reducing brain swelling and improving oxygenation of the damaged brain, keeping intracerebral pressure (ICP) under control. [32,33]. After intensive care, admission to a rehabilitation ward is to be expected but delays and time for admission can differ, these patients can be dispersed among many different wards, each; of which rehabilitated only one or a few patients with very S-TBI per year [36].

Neurorehabilitation

The International Classification of Functioning, Disability and Health (ICF) from 2001 is a classification of health and health-related domains of a person in a context with environmental factors. It is the WHO framework for measuring health and disability from an individual and population perspective and it is very important in

neurorehabilitation. The ICF model shows five different components where body function and body structures is one of them. Activity and participation are separate. State of health is multifactorial and everything affects each other as well as environmental and personal factors. (Figure 1)

Figure 1.



There are available evidence that multidisciplinary specialized rehabilitation (multidisciplinary teams in departments with a defined responsibility for patients with S-TBI) programs for patients with S-TBI have beneficial effects when applied early or late post-injury as reported in recent reviews [34, 135]. A study from Southern Sweden reported that early formalized rehabilitation and an effective chain of medical and rehabilitation efforts resulted in shorter hospital stays and a good outcome after S-TBI [35]. A study from Denmark reported that centralized rehabilitation after S-TBI resulted in better

outcome compared with historical data from decentralized rehabilitation [36]. In a Norwegian quasi-experimental study, one of only a few prospective studies which compared two different treatment approaches of patients (aged 16-55 years) with S-TBI reported that patients who received early comprehensive rehabilitation to stimulate neuronal reorganization and functional recovery with a continuous chain of treatment showed better functional outcomes 12 months post-injury than patients in ordinary rehabilitation programs [30]. Borg et al. [37] recently reported that continued access to rehabilitation competencies after acute management for S-TBI is not standard procedure in Sweden. Data available from stroke studies have demonstrated recovery of function and functional reorganization of brain networks [38] this should principally be true also after TBI [37]. Several studies have reported that brain plasticity is activity driven and recovery is probably greater early after injury even though it can have some effect later post-injury [39]. Early onset of rehabilitation refers to medical stability, give time for spontaneous recovery with resolution of oedema, inflammatory infiltrate and reduction of disruption to functional networks. It is also of importance to minimize serious side effects such as pressure sores, malnutrition, focal spasticity, or contractures and making use of effective interventions such as for example beneficial effects of amantadine in patients with DOC [52,53]. There are a number of aspects to consider: the assessment of consciousness, awareness, neurological and cognitive functioning, regular medical mapping, radiological and neurophysiological conditions and treating disorders if necessary such as hydrocephalus and epilepsy after S-TBI. There is a need of rehabilitation programmes with specialized early interventions; like the description in a Danish study according to earlier recommendations like sensory stimulation, functional training

with guidance of movements in daily activity, early mobilization, supported sitting and standing even for comatose patients and inserting different rehabilitation interventions for different patients in an appropriate chain [36]. There is substantial evidence to support interventions for attention, memory, social communication skills, executive function, and for comprehensive-holistic neuropsychological rehabilitation after TBI [40]. There is some evidence for multimodal rehabilitation for persons with severe disorders of consciousness (DOC) [41].

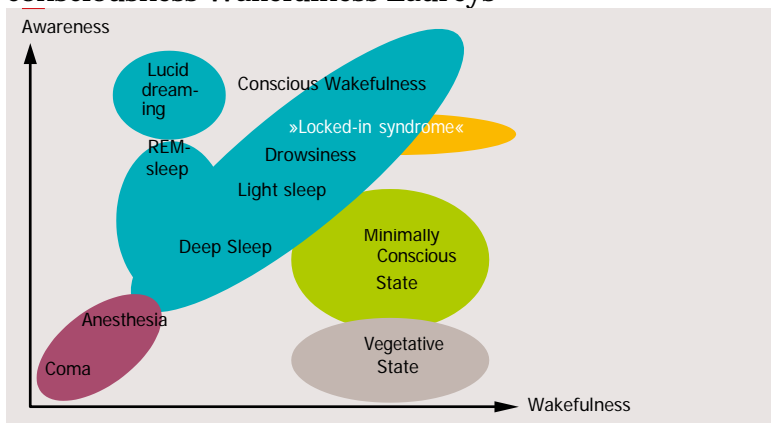
Disorders of consciousness (DOC) after S-TBI

Medical care has improved greatly and the number of persons who survive S-TBI has increased. Lives are saved. If the brain damage is very severe, the patient can have different levels of “disorders of consciousness” (DOC), initially a “coma state” and then recovery to a “vegetative state” (VS). Although in some non-traumatic cases patients may become in VS after a day or so, or without an initial period of coma. Jennett B et al 1972 [42] called this state “persistent vegetative state” (PVS) and after a month in this state the probability to recovery diminishes [42]. VS as a syndrome in search of a name have been described and named many times for example “the apallic syndrome” [43] and as early as 1899 Rosenblath reported about a young tightrope walker following a fall recovered after two weeks in coma “to become strangely awake” [44]. Persistent vegetative state (PVS) was recommended as the term of choice in the 1993 report of the American Neurological Association [45] and in the 1994 statement of the Multi-Society Task Force [46]. “Unresponsive wakefulness syndrome” (UWS) is a new proposed term for persistent vegetative state (VS) by Laureys et al 2010 [47] as changing the pejorative image to a descriptive term that indicates clinical signs

such as unresponsiveness and wakefulness with eye opening. UWS is the term that will be used instead of vegetative state (VS) continues. William James in 1890 defined the term “consciousness” as patients aware of themselves and the environment with two dimensions: wakefulness and awareness. Wakefulness can be present without awareness but awareness requires wakefulness [48]. The prevalence of UWS or for patients with a better awareness a “minimally conscious state” (MCS) [50] (See figure 2.) is not known because of a lack of earlier accepted diagnostic criteria. There are no codes of DOC in the International Classification of Diseases (ICD) 10th edition but these codes will be added in ICD-11 beta [64], which will be of importance for medical care planning in the future. For patients with DOC, it is important to differentiate patients in MCS from patients in UWS in order to offer specialized interventions and to plan further rehabilitation. Some patients with S-TBI who are initially assessed as being in a “coma state” do not survive more than about two-five weeks without a respirator [49]. Patients in “coma state” do not open their eyes and the best observation is some reflex movement of the limbs. Problems following S-TBI vary. Some of the patients with S-TBI could have a fast recovery, while others could remain in DOC entering UWS or MCS. When long-term (>4 weeks) pronounced disturbance of consciousness occurs, it is important to differentiate different levels of unconsciousness and awareness with active assessment as with JFK Coma Recovery Scale Revised (CRS-R) [82] an instrument that was established in acute specialized neurorehabilitation programmes. Patients assessed as being in a UWS are characterised by independent breathing, periods of sleep and wakefulness, giving spontaneous sound or movements and being able to open their eyes but there is no evidence of awareness of themselves or their environment or consciousness and they cannot

obey commands or make purposeful movements [48]. Recent studies about functional neuroimaging and cognitive evoked potential studies have shown new findings regarding awareness in some patients without behavioural responses to command [47]. Patients who improve to the MCS are able to follow simple prompts, gestures or verbally mediated yes or no responses, simple verbalization but have no functional communication and adequate affective behaviour to presented stimuli, contingent crying or laughing. They are partially conscious, localise noxious stimuli, can locate sound, can reach for objects and automatic movement such as scratching [50]. Misdiagnosis of UWS may occur and in a study from 2009 from Belgium, 41% of patients in UWS were found to be in MCS, when standardized assessment instruments were used such as Coma Recovery Scale Revised (CSR-R) [51]. However, most patients recover completely after S-TBI.

Figure 2. Content of consciousness: Awareness and level of consciousness Wakefulness Laureys



[Laureys S. Eyes open, brain shut. Sci Am. 2007;296:84-9] Permission to print from the author.

There is strong evidence that active rehabilitation interventions and more intensive rehabilitation programmes for patients with S-TBI

who are already in rehabilitation are associated with better function and that multidisciplinary rehabilitation affects outcome and there is strong evidence for a milieu-oriented model for patients with S-TBI [34]. Several studies have evaluated pharmacological treatment in patients with S-TBI. To optimize awareness and response to stimuli in patients with very S-TBI, a dopamine agonist and NMDA (N-methyl-D-aspartate) antagonist (amantadine) combined with interdisciplinary rehabilitation was used in a multicentre study. A clear effect of the amantadine in speeding improvement was noted without any side-effects. [52]. Amantadine is also considered to have a neuroprotective effect early after brain injury [53]. Other pharmacological treatments with the same purpose but without the same level of evidence are bromocriptine [54,55] and zolpidem [56]. For agitation that could not be managed by interpersonal intervention alone, antiepileptic drugs, especially carbamazepine, are recommended [57,58]. Benzodiazepines is considered to inhibit functional cerebral plasticity after brain injury [59]. A new area in neurorehabilitation is the knowledge of reorganization in the adult central nervous system after brain injury. Neuroplasticity can be influenced by different, specifically directed, active rehabilitation interventions [34,60]. This can be assessed by neuroimaging methods such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging and positron emission tomography (PET). Neurorehabilitation has the overall aim of an independent life as possible through improving a person's ability to cope from their own perspective and family member's goals with as full and independent life as possible through increased activity and better possibilities for participation. Successful rehabilitation has been determined on the basis of the patient's return to work. Mauriel Lezak summarizes in her book "Neuropsychological Assessment" (seen as a kind of standard

work) that employment is important because it leads to life structure, stability and gives the ability to live independently [61]. In contrast, Kersel et al 2001 [62] reported that return to work reduces the possibility of developing social contacts, increases isolation and entails higher levels of depression. Moreover, McCrimmon et al 2005 [61] found that patients with moderate to severe TBI who had not returned to work reported significantly higher levels of fatigue, depression and self-reported symptoms in comparison with patients who had returned to work. These different findings about factors related to return to work can be seen in the perspective of state of health in the ICF model. The Swedish and Icelandic insurance and healthcare systems for patients with S-TBI aim to offer all patients with S-TBI the medical care and rehabilitation needed when it is medically indicated. In 2012, for the first time, the National Board of Health and Welfare in Sweden [63] did a survey on the county and regional rehabilitation for people with moderate TBI and S-TBI based on a questionnaire to healthcare providers. This survey revealed a number of areas for improvement. In several counties, there were no guidelines for individuals with TBI, neither in terms of priority nor who should be offered rehabilitation. There is a lack of care programmes for rehabilitation after TBI and if there is a care programme, it does not cover the entire continuum of care. County Council directors are recommended to improve the management of rehabilitation for persons with TBI. The Swedish National Board of Health and Welfare stated that what determines whether a person is entitled to rehabilitation is whether he or she can benefit from rehabilitation and should not depend on whether the person is of working age. In 1997, the National Board of Health in Denmark [36] completed a review of the national state of rehabilitation for patients with TBI. Health insurance in Sweden gives access to assessment and

rehabilitation for patients with disorder of consciousness (DOC) and in December 2014, national recommendations were published in the Swedish medical journal [64] on the request of the Swedish Rehabilitation Physician Association. However, there are no national guidelines for rehabilitation after S-TBI, and admission to rehabilitation units and length of stay are usually decided by rehabilitation physicians according to local criteria. Patients with S-TBI have different problems and need different interventions and combinations of interventions and they benefit from routine follow-up so their needs for rehabilitation can be assessed [34].

Cognitive Impairment after S-TBI

Cognitive impairment is a common sequela of S-TBI. Most commonly, cognitive deficits are disorders of memory, attention [65] and speed of information-processing [66]. The demand for reliable screening instruments has increased so as to enable decisions to be made early in order to facilitate the further planning of care and rehabilitation. Chapman et al 1959 [67] described that cognitive impairment is not the only problem; frustration, inappropriate affective reactions, lack of spontaneity and avoiding challenges is also common. When affective disturbances are assessed, it is often done by questionnaires or rating scales [68,69,70,71]. Both thinking and feeling is important to maximize adaptive problem solving [72] as well as self-awareness [73,74]. It is important to distinguish between “mood” - a person’s subjective experience of feeling - and “affect”, described as an external manifestation of an individual’s feelings, thus physical and behavioural expression of mood [75]. Still there is a demand for cognitive retraining after rehabilitation programmes but many patients with S-TBI have emotional and motivational problems which require a different type of rehabilitation. These personality

difficulties do mostly not correlate to the specific brain tissue damage or level of severity of the TBI [76]. A patient with emotional distress in the rehabilitation process is a factor to be aware of; this could decrease with a holistic approach, intensive cognitive retraining and psychotherapeutic intervention and possibly maximize, if necessary, psychosocial recovery. An intensive programme for 6 hours a day, 5 days a week for 6 months showed that patients with self-awareness and acceptance of their disability after S-TBI was the best match for this program and that such patients need constant rehabilitation attention [77,78].

Global outcome after S-TBI

Patients with S-TBI are heterogeneous with varying complexity and prognosis, problems and outcome. In different studies, global outcome like survival/death, Glasgow Outcome Scale (GOS) [79] or Glasgow Outcome Scale Extended (GOSE) are used [80]. GOSE is an extended version of GOS and allows a more finely tuned categorization of post-traumatic disability. The Rancho Los Amigos Cognitive Scale (RLAS-R) is a clinical outcome scale for assessing cognitive improvement and recovery [81]. Parameters such as acute care, post–acute complications, level of function and interventions on neuroplasticity, which can be influenced by active rehabilitation [34] all have the potential to impact on outcome. Environmental factors and circumstances related to the patient are also important for outcome. Different instruments are used to evaluate activity, participation, sense of coherence, health-related quality of life, life satisfaction and self-awareness. All these identifications, clinical assessment, acute parameters, acute prognostic factors and outcome are of importance for a knowledge bank that is relevant for the design of appropriate rehabilitation programmes.

RATIONALE

In a recent Cochrane report about rehabilitation after S-TBI (2015), the authors concluded it would be beneficial to have a routine follow-up for the assessment of the needs for rehabilitation [34]. Problems vary after injury and different interventions and combinations of interventions are required. In the Cochrane report, there was strong evidence for better function from formal interventions and for active rehabilitation interventions with more intensive rehabilitation programmes for patients with S-TBI (already in rehabilitation). However, the context of multidisciplinary rehabilitation affected outcome. Multidisciplinary neurorehabilitation facility has been found to be more effective than rehabilitation in a nonspecialized facility in earlier studies [34,145]. Limited evidence in the Cochrane report indicated that early rehabilitation results in better outcome and there was strong evidence for milieu-oriented rehabilitation for patients with S-TBI and comprehensive cognitive interventions in a therapeutic environment [34]. In a review from 2011 Cicerone et al [40] reported that there is substantial evidence to support interventions for attention, memory, executive function, social communication skills and for comprehensive-holistic neuropsychologic rehabilitation after TBI. There is some evidence for multimodal rehabilitation for persons with severe disorders of consciousness (DOC) [41]. Recommendations from a consensus conference 1999 [143] were that all patients with S-TBI and in need of systematic assessment and rehabilitation should be offered this and with an early onset. A Norwegian study [141] from 2016 indicated that clinical pathways in which specialized neurorehabilitation departments and interventions according to evidence based recommendations and guidelines for the management of S-TBI [144] may contribute to

enhance independence in S-TBI patients [141]. Although this evidence was shown, there are no national guidelines for rehabilitation after S-TBI in Sweden. Admission to rehabilitation units and length of stay are usually decided according to local criteria, different priority or limited numbers of beds. There are no standards for care pathways after acute care. It is therefore important to increase knowledge about the clinical course and outcome of this heterogeneous group of patients with S-TBI and a subgroup, namely, patients with disorders of consciousness (DOC) with regard to acute prognostic factors and care pathways.

This thesis could contribute to better knowledge about level of function and progress of function at different points in time with follow-ups up to 1 year.

AIMS OF THE THESIS

The overall aim of this thesis was to increase knowledge about the clinical course and outcome in patients with S-TBI with regard to prognostic factors.

The specific aims were:

Paper I: To assess the rates of disorder of consciousness at three weeks, three months and one year after S-TBI, and to relate conscious state three weeks after the injury to outcome at one year.

Paper II: To investigate prospectively the relationship between care pathways for patients with S-TBI in the first year after the injury, and outcome at one year.

Paper III: To assess the clinical course of cognitive and emotional impairments in patients with S-TBI from three weeks to one year after trauma and to study associations with outcomes at one year.

Paper IV: To evaluate the clinical characteristics, injury descriptors and the care pathways from injury to three months after discharge in patients with S-TBI in Northern Sweden and to assess outcomes at three months post-injury.

Paper V: To investigate the relationships between CT scans as assessed by the Marshall and Rotterdam protocols and clinical outcomes at three months and one year post S-TBI and to evaluate the prognostic value of the CRASH model.

MATERIALS AND METHODS

Design

This thesis includes prospective observational studies conducted in a clinical setting with follow-up three months and one year after the injury. The first three papers are multicentre prospective, observational studies. Papers IV and V are population-based cohort studies.

Patients

Patients in Papers I-III were from the Swedish-Icelandic, multicentre study of patients with S-TBI, the “PROBRAIN” study, and included patients from 6 of 7 neurotrauma centers (NCs). Papers IV and V included patients from the Northern Health Region (NHR) treated at the NC at Umeå University Hospital (included patients as part of the “PROBRAIN” study). For a flowchart, see Figures 3-5.

Inclusion criteria were severe, non-penetrating, traumatic brain injury, with a lowest non-sedated Glasgow Coma Score (GCS) [7] of 3–8 or Reaction Level Scale score (RLS85) [8] of 4–8 in the first 24 hours after injury, age at injury was 18–65 years, with an injury requiring neurosurgical intensive care, or collaborative care with a neurosurgeon in another intensive care unit. Exclusion criteria were death or expected death within 3 weeks of injury. The participating NCs provide neurosurgical care to more than 80% of the population in Sweden and 100% in Iceland. The population of Sweden and Iceland aged 18-65 years comprises ~4.7 million persons (Papers I-III) and for the NHR, 525000 persons (Papers III-V). Patients were included from January 2010 to June 2011 in Paper I with extended recruitment until December 2011 at 2 centres (Papers II-V).

Data collection

Patients were recruited after contact with NCs on a weekly basis to identify eligible patients by rehabilitation physicians and then they underwent prospective clinical assessment at 3 points in time: 3 weeks (18-24 days), 3 months (75-105 days), and 1 year (350-420 days) after injury. The patient gave informed consent in cases where he or she had the capacity to do so. In the majority of cases, the patient lacked the capacity and the patient's nearest relative gave consent to inclusion. When the patient improved and at all follow-up occasions, patients gave a new mandate if they wanted to continue participation. After inclusion, acute prognostic and socioeconomic data were obtained from medical records. Additional background socioeconomic data and medical history were collected through interviews of relatives (if the patient was still unable to participate) as soon as possible after inclusion. Patients were considered to have a coexisting medical problem at the time of injury if any of the following were present: hypertension, diabetes, cardiac disorder, psychiatric disorder, renal failure, chronic obstructive airways disease, other significant medical problem. Data on care pathways were updated in conjunction with each follow-up to gather complete care pathway data during the first year after injury, as far as possible. Assessments took place in the patient's current care setting if possible (which in some cases was in the patient's home) or in a local outpatient department. Inclusion and follow-up were therefore designed to be independent of any decisions regarding care pathways and of any decision regarding admission to inpatient rehabilitation. Assessments were performed by rehabilitation physicians with assistance from rehabilitation nurses, psychologists, physiotherapists and occupational therapists. Assessments at each of the 3 points in time included both clinical examination and a battery of standardized

instruments, allowing description of the patient's condition according to the framework of the International Classification of Functioning, Disability and Health (ICF): bodily structure and function, activities and participation.

PAPER I

“Disorders of consciousness” (DOC) after S-TBI was assessed at three weeks, three months and one year to relate conscious state three weeks after injury to outcome at one year. The instruments relevant to this sub-study included the JFK Coma Recovery Scale Revised (CRS-R) [82], and the Glasgow Outcome Scale Extended (GOSE) [80]. The JFK CRS-R was used for all patients where a DOC was suspected on the basis of lack of functional communication and/or functional object use, with the exception of patients who remained sedated or anaesthetized. The CRASH prognostic model was used (available at: <http://www.crash2.lshtm.ac.uk/Risk%20calculator/index.html>) to calculate the percentage risk of an unfavourable outcome (equivalent to GOSE 1–4) at 6 months, for each patient, after conversion of RLS scores for those patients not assessed with the GCS.

PAPER II

The care pathways and their relationship to outcome one year after S-TBI were prospectively assessed with the presence or absence of complications that were recorded at each point of time in the study. Complications present three weeks after injury were considered in relation to possible delays in transfer to rehabilitation and outcome. The following possible complications were recorded: infection (meningitis, sepsis, wound infection, urinary tract infection, pneumonia, other stated infection), hydrocephalus, deep vein thrombosis, pulmonary embolism, heterotopic ossification, new fracture or new brain injury since the incident injury, other defined complication. The presence of tracheostomy, ongoing artificial ventilation and administration of oxygen three weeks after injury were considered as surrogates for respiratory complications in terms of difficulties in weaning from ventilation and/or persisting respiratory difficulties and were therefore also coded as representing complications. Bad outcome was assessed as GOSE 2-4 for patients alive and followed up 1 year after injury.

PAPER III

In this study, the clinical course of cognitive and emotional impairments in patients with S-TBI from three weeks to one year after trauma was assessed at three points in time and related to outcomes at one year. The data regarding education and earlier cognitive problems were obtained by interviews with patients and/or significant others. Patients were interviewed and administered the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) [68,89,90] for assessment of cognitive function, either by a clinical neuropsychologist or a physician who was a specialist in rehabilitation medicine. Pre-screening was performed initially to evaluate whether it was meaningful to attempt further testing. The BNIS was assessed at 3 weeks, 3 months, and 1 year after injury. The Hospital Anxiety and Depression Scale (HADS) [94] self-reporting instrument was used for screening of depression and anxiety. The HADS was assessed at 3 weeks, 3 months, and 1 year after injury. Outcome variables were GOSE [80] at 1 year and RLAS-R [81] at 3 weeks, 3 months, and 1 year. GOSE 1-4 was assessed as unfavourable and inferior function as RLAS-R 1-8.

PAPERS IV-V

Enrolled patients were treated at the NC at Umeå University Hospital NHR according to the “Lund” concept, which is standard protocol at this center [32]. For details, see [83,84]. The primary hospital performed an initial computed tomography (CT) scan of the brain. This investigation was often repeated upon arrival to the NC. Pictures were transferred electronically to the NC where a neuro-radiologist assessed the images (Papers IV-V).

In Paper IV, the clinical characteristics and injury descriptors of patients with S-TBI from the NHR were assessed together with care pathways from injury to three months after discharge and compared with outcomes at three months. The first CT scans were classified according to CRASH protocol and the Marshall [10,85] classification. Outcomes were assessed by GOSE [80] at 3 months after injury and RLAS-R [81] at 3 weeks and 3 months. GOSE 1-6 was assessed as unfavourable outcome and inferior functioning as RLAS-R I-VIII.

In Paper V, prospectively a senior neuro-radiologist (PJ), and a senior neuro-rehabilitationist (MS) assessed the first CT scan and subsequent CT scan nearest twenty-four hours after trauma according to the Marshall [10,85] and Rotterdam classification [11]. The relationships between CT scans assessed by the Marshall and Rotterdam protocols and clinical outcomes were investigated at three months and one year post injury on the GOSE and RLAS-R. The CRASH acute prognostic model [101] was used to predict the risk of unfavourable outcome at six months (used in Papers I-II). GOSE 1-4 was assessed as unfavourable outcome and inferior outcome as RLAS-R 1-6.

All the gathering of clinical outcome data was performed by one of the authors (MS) through patient assessment at 3 weeks and 3 months and 1 year post-injury. Socio-demographic data and data regarding pre-morbid health were gathered by interviews with patients and/or significant others, also performed by MS. Data regarding injury characteristics and length of stay at the NC were retrieved from the medical records.

INSTRUMENTS

Table 1. Overview of instruments.

| | Study I | Study II | Study III | Study IV | Study V |
|---|---------|----------|-----------|----------|---------|
| Glasgow Outcome Scale Extended, GOSE | x | x | x | x | x |
| Rancho Los Amigos Scale of cognitive functioning-revised, RLAS-R | | | x | x | x |
| Coma Recovery Scale revised, CRS-R | x | | | | |
| CRASH acute prognostic model | x | x | | | x |
| The Barrow Neurological Institute Screen for higher cerebral functions BNIS | | | x | | |
| The Hospital Anxiety and Depression Scale HADS | | | x | | |
| The Marshall CT classification | | | | x | x |
| The Rotterdam CT classification | | | | | x |

Glasgow Coma Scale (GCS) [7] is the most widely used scale for assessing patients' responses at admission and consists of eye-opening, motor and verbal responses. It is of importance to assess patient without sedation or intubation and note if they are under the influence of drugs or alcohol. Acute intensive care starts at the place of the accident and even before emergency transportation; patients are therefore often sedated at admission and a new assessment of LOC is necessary. GCS have different scores for different responses and consist of a sum score of 3 to 15. Higher scores indicate better responses. GCS scores of 13 to 15 correspond to mild TBI, GCS scores of 9 to 12 moderate TBI, and GCS scores of 3 to 8 S-TBI. See Table 2. The incidence of TBI severity are as follows: mild/moderate/severe; 22:1.5:1.1 [17].

The Swedish Reaction Level Scale (RLS85) [8] is another classification of LOC. This scale is an 8-point hierarchic scale where scores of 4 to 8 indicate worst responsiveness, corresponding to S-TBI. At some NCs in Sweden, RLS is the most commonly used scale. RLS can be converted to GCS in order to be compared in worldwide studies. Conversion studies of these scales have been carried out, thus, RLS 8 = GCS 3, RLS 7 = GCS 4, RLS 6 = GCS 5, RLS 5 = GCS 6, RLS 4 = GCS 7 [9,86]. In Paper I-V, GCS is used. See Table 3.

Table 2. Glasgow Coma Scale (GCS)

| | | |
|------------------------|-------------------------------|------|
| Eye response | Open spontaneously | 4 |
| | Open to verbal command | 3 |
| | Open in response to pain | 2 |
| | No response | 1 |
| Verbal response | Talking/Orientated | 5 |
| | Confused speech/Disorientated | 4 |
| | Inappropriate words | 3 |
| | Incomprehensible sounds | 2 |
| | No response | 1 |
| | | |
| Motor response | Obeys commands | 6 |
| | Localizes to pain | 5 |
| | Flexion/withdrawal | 4 |
| | Abnormal flexion | 3 |
| | Extension | 2 |
| | No response | 1 |
| TOTAL SCORE | | 3-15 |

Teasdale G. & Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81-84.

Table 3. Reaction Level Scale (RLS85)

| Clinical descriptor | Responsiveness | Score |
|-------------------------|--|-------|
| Alert | No delay in response | 1 |
| Drowsy or confused | Responsive to light stimulation | 2 |
| Very drowsy or confused | Responsive to strong stimulation | 3 |
| Unconscious | Localizes but does not ward off pain | 4 |
| Unconscious | Withdrawing movements on pain stimulation | 5 |
| Unconscious | Stereotype flexion movements on pain stimulation | 6 |
| Unconscious | Stereotype extension movements on pain stimulation | 7 |
| Unconscious | No response on pain stimulation | 8 |

Starmark JE, Stålhammar D, Holmgren E. The Reaction Level Scale (RLS85). Manual and guidelines. Acta Neurochir (Wien). 1988;91(1-2):12-20.

JFK Coma Recovery Scale –Revised, (CRS-R) is an instrument used to assess DOC [82]. This instrument was first described by Giacino and colleagues in 1991 and was restructured at 2004. The purpose of using the CRS-R is to help assessment of persons with DOC as a prognostic assessment and for the further planning of treatment. The CRS-R was recently recommended by the American Congress of Rehabilitation Medicine for the assessment of possible “disorders of consciousness” (DOC) and has good reliability and validity [87,88].

This scale consists of 23 items with six subscales; auditory (0-4), visual (0-5), motor (0-6), oral (0-3), communication (0-2), arousal (0-3). Total score is 0-23; estimated time is 25 minutes. This subscale consists of hierarchically-arranged items associated with brain stem, subcortical and cortical processes where lowest items correspond to reflex activity and highest items purposeful response. The CRS-R has been used in TBI outcome research. The Swedish version was produced in 2008-2009 by Godbolt AK, Jonasson, Sörbo A, Tengvar C and Borg J.

The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) [68,89,90] is a cognitive screening test with seven subscales for speech and language functions, orientation, attention/concentration, visuospatial and visual problem solving, memory, affect and the patient's own ability to perceive cognitive ability and awareness of their abilities with 1-10 tasks after different types of brain injury early post-injury. The instrument was developed by Prigatano GP et al during the nineties with a focus on cognitive function, affective disturbances and self-awareness in early stages of brain injury. This instrument was used in Paper III. It was translated and validated in Sweden through cooperation with scientists in Malmö and Göteborg, Sweden. BNIS takes 15-20 minutes to perform, preferably acute or subacute at bedside. This survey should if necessary be followed by a detailed neuropsychological assessment. The BNIS test comprises a pre-screen test (level of arousal 3 p, basic communication 3 p, and cooperation 3 p) to judge if the person is testable. The three items in the BNIS pre-screening must be assessed and the patients must score at least two points on each of the items in order for it to be meaningful to continue. Lower scores indicate that the patient will not be able to do the BNIS [68,89,90]. Total score for pre-screen and the screening test is 6 to 50 p and total for the seven subscales 41 p. BNIS has good reliability and validity [91]. The total score (maximum 50 points) represents the results from the pre-screen plus the 7 subscale scores (speech and language 15 p, orientation 3 p, attention/concentration 3 p, visuospatial and visual problem solving 8 p, memory and learning 7 p, affect (generating happy versus angry affect, perception of facial affect, affect control, and ability to generate spontaneity) 4 p, and awareness of own performance 1 p). A total subscale score can be obtained, as well as a total BNIS raw score that is converted to an age-

corrected standard *T*-score. Higher scores reflect a higher level of functioning. If the total BNIS score is below 47 points, further cognitive investigation is recommended [92]. The BNIS has been validated for a Swedish population [91,93].

The Hospital Anxiety and Depression Scale (HADS) was used to screen for presence and degree of anxiety and depression. It consists of 14 items (7 items in each subscale) which are assessed on a 4-point Likert scale (range 0–3), where the total score is the sum of each subscale (range 0– 21) [94]. Cut-offs for both subscales of 8 or higher were used to determine “caseness” [95]. The HADS is an established screening tool for anxiety and depression and it has been used previously in patients with TBI [96]. The HADS has acceptable reliability, sensitivity and specificity in assessing symptom severity in anxiety and depression in various populations [97]. The HADS was assessed at 3 weeks, 3 months and 1 year after injury.

CT findings

Computerized tomography (CT) assesses findings such as focal lesion, mass lesion or diffuse brain injury in patients with S-TBI [98, 99,100]. CT scan of the brain is an important assessment in the acute setting for further decisions about surgical planning and neuro-intensive care. A prognostic model such as “Corticosteroid randomisation after significant head injury”, the CRASH online model [101], includes CT findings with indirect signs of increased intracranial pressure (ICP) and major radiological indicators of poor outcome such as midline shift, obliteration of the third ventricle or basal cisterns and diffuse hemispheric swelling [102]. Different classification systems such as the Marshall [10, 85] and Rotterdam classifications [11] are two examples of useful structured

investigations and these classification systems have been used in several studies such as prognostic [103] and mortality studies after S-TBI [104].

The Marshall CT classification [10,85] is a descriptive classification of morphological abnormalities as depicted by CT scanning, see Table 4. Marshall CT classifications I-IV comprise a diffuse injury severity rating scale and V-VI reflect a mass lesion. This classification is a commonly used predictor of clinical outcome. In Paper V, we dichotomized Marshall CT scores into two groups (in accordance with Andelic et al. [30]) Marshall classifications I-II defined as “less severe brain injury” and Marshall classifications III-VI defined as “more severe brain injury” [30].

Table 4. Marshall CT classification

| Marshall CT classification | |
|-------------------------------------|---|
| Diffuse injury I | Diffuse injury, no visible intracranial pathologic change seen on CT |
| Diffuse injury II | Cisterns are present with shift 0-5 mm and/or lesion densities present No high or mixed density lesion >25 ml. May include bone fragments and foreign bodies. |
| Diffuse injury (swelling) III | Cisterns compressed or absent with shift 0-5 mm. No high or mixed density lesion >25ml |
| Diffuse injury (shift) IV | Shift >5 mm No high or mixed density lesion > 25 ml |
| Evacuated mass lesion (EML) V | Any lesion surgically evacuated. |
| Non-evacuated mass lesion (NEML) VI | High or mixed density lesion > 25 ml, not surgically evacuated |

Marshall LF, Bowers Marshall S, Klauber MR, van Berkum Clark M, Eisenberg H M, Jane JA, et al. A new classification of head injury based on computerized tomography. J Neurosurg 1991;75: S14–S20

The Rotterdam CT score. This classification is used for clinical application for individual patients. Maas et al (2005) [11] translated a

logistic regression model into a score chart with a prognostic score according to CT characteristics and for the probability of mortality in patients with moderate or S-TBI brain injury and includes 6 points that are consistent with the motor score of the GCS and the Marshall classification. Rotterdam CT scores were used in Paper V. The presence of traumatic subarachnoid haemorrhage (tSAH) is a strong predictor of outcome and mortality in S-TBI [105,106,107,108,109], intraventricular blood and status of the basal cisterns while epidural mass lesion is a favourable predictor [11]. See Table 5.

Table 5. Rotterdam CT score

| | | Score |
|--|-------------------------------|--------------|
| Basal cisterns | | |
| | Normal | 0 |
| | Compressed | 1 |
| | Absent | 2 |
| Midline shift | | |
| | No shift or shift \leq 5 mm | 0 |
| | Shift > 5 mm | 1 |
| Epidural mass lesion | | |
| | Present | 0 |
| | Absent | 1 |
| Intraventricular blood or subarachnoid haemorrhage | | |
| | Absent | 0 |
| | Present | 1 |
| Sum score | | +1 |

Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery*. 2005 Dec;57(6):1173-82; discussion 1173-1182.

Outcome assessment

Outcome variables were survival/death, GOSE [80] and RLAS-R [81] at 3 months and 1 year after trauma. In previous studies, different dichotomization has been used for these two scales for

good/favourable or bad/unfavourable outcome, for example, global outcome as “unfavourable outcome” (GOSE 1-4) in accordance to unfavourable outcome used in the CRASH study [101] and in accordance with previous GOS classification [103]. In four of the Papers (I-III and V), GOSE 1-4 were dichotomized as “unfavourable outcome”. In Paper IV, GOSE 1-6 were dichotomized as “unfavourable outcome”/“bad recovery” in accordance with some other earlier studies [30,110,111,112]. There were different cut-offs on the RLAS-R scale: RLAS-R IX–X (Papers III and IV) were dichotomized as “superior functioning” while RLAS-R I–VIII were dichotomized as “inferior outcome”. RLAS-R classification in Paper V were RLAS-R VII–X as “favourable outcome” (minimal assistance for daily living to modified independent) while RLAS-R I–VI represented “unfavourable outcome” (with two different levels: I-III total assistance and IV-VI maximum to moderate assistance).

Glasgow Outcome Scale Extended (GOSE) [80] extends the 5 categories of the previously developed GOS [113] to 8, thereby increasing its sensitivity. With a structured interview, to identifying of specific criteria. GOSE has been developed for a more detailed categorization and has good interrater reliability [80] and validity [114] and is an established measure of global outcome after traumatic brain injury. The patient’s overall rating is based on the lowest outcome category indicated on the scale. GOSE 1 corresponds to death. GOSE scores 2 -4 (“vegetative state” – “lower and upper severe disability”) are considered as a “bad” outcome. GOSE scores 2-4, are described as dependent on others for activities of daily living. GOSE scores 5-8 are often described as “good” outcome. Some

characteristics for patients assessed as GOSE score 5 (lower moderate disability): are able to work only in a sheltered workshop or non-competitive job, or currently unable to work and unable to participate; rarely, if ever, take part in social and leisure activities and have constant daily and intolerable quick temper, irritability, anxiety, insensitivity to others, mood swings, depression and unreasonable or childish behaviour. Those with GOSE scores 5 to 8 are independent at home: individuals with GOSE scores 5 to 6 lack or have a reduced ability to work while those with GOSE score 7 have some impact on social life and leisure activities and symptoms that are similar to those of patients with post-concussion, GOSE 8 indicates recovery . See Table 6.

Table 6. Glasgow Outcome Scale Extended (GOSE)

| | | |
|---|---------------------------|-----|
| 1 | Death | D |
| 2 | Vegetative state | VS |
| 3 | Lower severe disability | SD- |
| 4 | Upper severe disability | SD+ |
| 5 | Lower moderate disability | MD- |
| 6 | Upper moderate disability | MD+ |
| 7 | Lower good recovery | GR- |
| 8 | Upper good recovery | GR+ |

Lindsay Wilson JT, Laura EL, Pettigrew, Graham, Teasdale M. Structured Interviews for Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for their use. J Neurotrauma 1998; 15:5 73–585.

Rancho Los Amigos Cognitive Scale Revised, Levels of Cognitive Functioning (RLAS-R) [81] is a medical scale with scores from 1 to 10, representing 10 states of cognitive and behavioural functioning through which patients with TBI typically progress, see Table 7. Typical progress in recovery from S-TBI is a period of impaired consciousness to a posttraumatic confusional state with amnesia and then improvement of attention, memory, and executive capacities [1]. Coma, UWS and MCS to a high degree correspond to the three first levels RLAS-R I-III. The posttraumatic confusional state and posttraumatic amnesia correspond to the next three levels RLAS-R IV-VI and the post-confusional period corresponds to levels VII-VIII [115]. The RLAS originally had 8 levels but the revision added levels 9 and 10 to better reflect the highest levels of recovery. Higher scores indicate improved functioning. The bottom level is “No Response, Total Assistance”, and the top level is “Purposeful, Appropriate: Modified Independent”. Patients are thus assessed by reaction to stimuli, ability to follow instructions, presence of confusion, behaviour with and without meaning, cooperation, attention, ability to maintain attention to the environment, verbal ability, memory, orientation and higher cognitive ability.

Table 7. Rancho Los Amigos Scale of Cognitive Functioning-Revised (RLAS-R)

| Level | |
|-------------|--|
| <i>I</i> | <i>No Response: Total Assistance</i> |
| <i>II</i> | <i>Generalized Response: Total Assistance</i> |
| <i>III</i> | <i>Localized Response: Total Assistance</i> |
| IV | Confused/Agitated: Maximum Assistance |
| V | Confused, Inappropriate Non-Agitated: Maximum Assistance |
| VI | Confused, Appropriate: Moderate Assistance |
| VII | Automatic, Appropriate: Minimal Assistance for Daily Living |
| VIII | Purposeful, Appropriate: Stand-By Assistance |
| IX | Purposeful, Appropriate: Stand-By Assistance on Request |
| X | Purposeful, Appropriate: Modified Independent |

Hagen C, Malkmus D, Durham P. Levels of cognitive functioning. In: Professional Staff Association of Rancho Los Amigos Hospital, editors. Rehabilitation of the head injured adult: comprehensive physical management. Downey, CA: Rancho Los Amigos Hospital Inc.; 1987.

Acute prognostic model

The CRASH (Corticosteroid Randomization After Significant Head Injury) acute prognostic model is a model based on data from a study with 10,008 patients [101] and is validated with another big study, the IMPACT study, with over 8,686 patients. A prognosis calculator has been developed and is available online for risk of mortality at 14 days and risk of unfavourable outcome at 6 months. This model has been used in Papers I, II and V and the presented parameters were country, age, acute GCS, pupils react to light, major extracranial injury, acute CT findings as presence of petechial haemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid bleeding and non-evacuated hematoma. This prognostic model and calculator have been used in a previous study at NC at Umeå University Hospital. The CRASH prognosis calculator was found to overestimate the risk of mortality and unfavourable outcome at six month in a population of 47 patients with S-TBI and ICP-targeted therapy based on the Lund concept. Assessment and decisions in individual patients are therefore considered to be doubtful in this study [116]. We used the online calculator for the CRASH prognostic model (*available at <http://www.crash2.lshtm.ac.uk/Risk%20calculator/index.html>*) to calculate the percentage risk of an unfavourable outcome equivalent to GOSE 1-4 at 6 months, for each patient, after conversion of RLS scores for those patients not assessed with the GCS. In Paper V, the CRASH model predicted risk for unfavourable outcome at 6 months cut-off $\geq 50\%$.

Lund Concept

A modern protocol-driven concept for volume regulation of the brain and an aggressive neurointensive treatment after S-TBI, the “Lund concept” focuses on reducing brain swelling and improving oxygenation of the damaged brain, keeping intracerebral pressure (ICP) under control. Prompt removal of intracranial hematomas if necessary after head trauma is an important acute measure but besides that avoiding secondary damage by elevated intracerebral pressure (ICP) is a priority. The cause of death after a head trauma is often impaction of the brain stem because of brain swelling. Vasogenic oedema due to a damaged blood brain barrier is what neurointensive care focuses on. In Sweden, state-of-the-art medical treatment of patients with S-TBI comprises this standardized protocol-driven therapy, according to an intracranial pressure (ICP) oriented protocol such as the “Lund concept” [32,33,117,118]. The Lund concept has been evaluated in a number of outcome studies that have shown favourable results and was offered to patients at the neurotrauma center (NC) in our region NHR [14,83,119]. Patients are sedated with Midazolam, receive continuous fentanyl for analgesia, are mechanically normo-ventilated (PaCO_2 4.5–5.5 kPa, PaO_2 kept \geq 12 kPa) and initially nursed in a supine position with no head elevation. Normovolaemia is maintained with preferably albumin infusion (Serum albumin \geq 40 g/l) and packed red blood cells (haemoglobin \geq 110 g/l). These levels are maintained and a neutral to slightly negative fluid balance is achieved by using furosemide as needed. The limits for blood glucose and serum sodium are normal (\geq 135 mmol/l). Normovolaemia is kept by infusions of metoprolol and clonidine. It is desirable to normalize mean arterial blood pressure (MAP), minimize fluid leakage through the capillary membrane, and reduce stress mediated by the sympathetic nervous system. A

minimum cerebral perfusion pressure (CPP) of 50 mmHg is accepted but the aim is to preserve CPP at 60-70 mmHg. To reduce an elevated/ rising ICP (> 20 mmHg), possible additional interventions are low-dose barbiturates, ventriculostomy with intermittent drainage, and/or decompressive craniectomy.

ICP_{Max}

Hourly mean ICPs were calculated by using all the minute-to-minute ICP values during the first 5 days. ICP_{Max} was defined as the mean ICP of the hour with the highest ICP during the five first days and was measured with the intention to assess the potential secondary damage of the brain. The mean ICP_{Max} for the first 5 days were also calculated reported in Paper V.

Statistical analysis

Data are reported as frequencies or medians and IQR and means. In all the five studies, differences between groups were analysed using non-parametric tests, Mann-Whitney test (Papers I-V). For the study of paired observations, Wilcoxon's signed rank test was used (Papers III, IV, V). For the analyses of bivariate correlations, Spearman's correlation coefficient was used (Papers II and III). The Chi-square test was used for the comparison of proportions (Papers III, IV, V). Logistic regression analysis was performed to study relationships between several variables and outcomes (Papers II and III). The statistical significant level was set at $p < 0.05$ in Papers I, II, IV and V and $p < 0.01$ in Paper III.

The statistical analysis in Papers I and II was performed using Statistical Package for the Social Sciences (SPSS) version 20.0, in Paper III SPSS version 21.0, in Paper IV SPSS version 19.0 and in Paper V SPSS version 22.0.

Ethical considerations

In all the studies, the patients gave written informed consent in cases where he or she had the capacity to do so. When the patient lacked capacity, the patient's nearest relative gave consent to inclusion. No adverse events occurred during any of the tests. The studies were approved by the regional Ethical Review Board of Stockholm, Sweden (no 2009/1644-31/3).

RESULTS

Papers I, II and III were based on data from the prospective multicenter observational study for S-TBI (the “PROBRAIN” study) from six of seven neurotrauma centers (NCs) in Sweden and Iceland of patients (n=103-114), 18-65 years with S-TBI requiring neurosurgical intensive care or collaborative care with a neurosurgeon. Papers IV and V were part of this multicenter study (n=37). Falls was the most common cause of injury 44%- 54%, for an overview of recruitment and clinical data in Papers I-V, see Table 8.

Table 8. Overview of recruitment and clinical data.

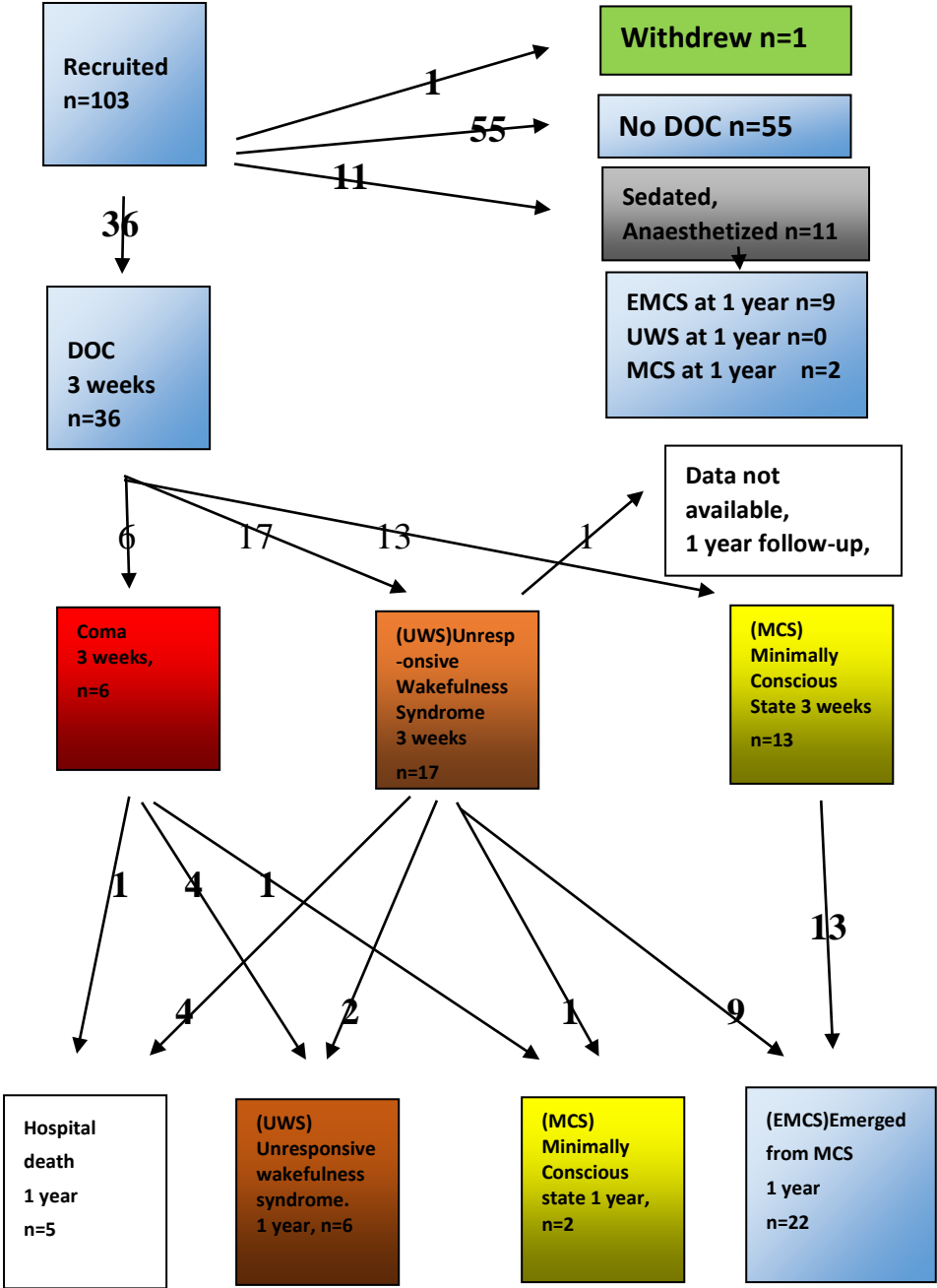
| | Paper I | Paper II | Paper III | Paper IV | Paper V |
|---|-------------|------------|------------|------------------|------------|
| Recruited, n (%) | 103 (90) | 114 (100) | 114 (100) | 37 (33) | 37 (33) |
| 3 weeks, n (HD) | 102 (0) | 111 (1) | 111 (1) | 37 (1) | - |
| 3 months, n (HD) | 96 (3) | 105 (5) | 105 (5) | 32 (5) | 32 (5) |
| 1 year, n (HD) | 78 (5) | 100 (7) | 100 (7) | - | 31 (6) |
| Follow-up | 1 year | 1 year | 1 year | 3 months | 1 year |
| Approximated number of adults aged 18-65 years | 4,700,000* | 4,700,000* | 4,700,000* | 525,000** | 525,000** |
| Age at injury, years, median, (range) | 41 (17-65) | 42 (17-65) | 42 (17-65) | 45 (17-64) | 45 (17-64) |
| Worst unsdated GCS score during first 24 h, median (range) | 5 (3-8) | 5 (3-8) | 5 (3-8) | 5 (3-8) | 5 (3-8) |
| Gender | | | | | |
| Male/female/missing % | 67/24/9 | 66/23/11 | 66/23/11 | 70/30/0 | 70/30/0 |
| Previous brain injury requiring Hospitalization, n (%) | 15 (15) | 18 (16) | 18 (16) | 12 (32) | 12 (32) |
| Known drug or alcohol abuse at time of injury n (%) | 27 (26) | 34 (28) | 34 (28) | 11 (30) | 11 (30) |
| Length of stay in intensive care, LOSIC, days, median (range) | 17.5 (1-54) | 17 (1-78) | 17 (1-78) | 17(2-54) n=34 | 16 (2-54) |
| GOSE 1 at 1 year, n (%) | 5 (5) | 7 (6) | 7 (6) | 5 (14) | 6 (16) |
| GOSE 2 at 1 year, n (%) | 6 (6) | 7 (6) | 7 (6) | 2 (5) | 1 (3) |
| GOSE 3 at 1 year, n (%) | 22 (22) | 23 (20) | 23 (20) | 9 (24) | 5 (14) |
| GOSE 4 at 1 year, n (%) | 6 (6) | 6 (5) | 6 (5) | 2 (5) | 1 (3) |
| GOSE 5 at 1 year, n (%) | 10 (10) | 12 (11) | 12 (11) | 7 (19) | 2 (5) |
| GOSE 6 at 1 year, n (%) | 0 (0) | 12 (11) | 12 (11) | 3 (8) | 0 (0) |
| GOSE 7 at 1 year, n (%) | 19 (19) | 21 (18) | 21 (18) | 2 (5) | 9 (24) |
| GOSE 8 at 1 year, n (%) | 12 (12) | 17 (15) | 17 (15) | 6 (16) | 13 (35) |
| Missing n (%) | 3 (3) | 2 (2) | 2 (2) | 1 (3) | 0 (0) |
| Withdraw n (%) | 18 (17) | 7 (6) | 7 (6) | 0 (0) | 0 (0) |
| Total n | 101 | 114 | 114 | 37 | 37 |

HD= Hospital Death, *Sweden and Iceland, **Northern Health Region in Sweden.

PAPER I

In Paper I, 103 patients were recruited from 6 neurosurgical intensive care units in Sweden and Iceland, and acute data were entered for 102 patients (one patient withdrew consent). At three months, 3 patients had died and 4 withdrawn from the study, 96 patients continued (93%). One year post-injury, 5 patients had died and 18 withdrawn (17%), 78 continued (76%) and study status was missing for one person. Median length of intensive care of 17.5 days indicated that these patients had the most “severe” brain injuries. Most injuries were due to transport accidents and falls. Data on the relationship between conscious state at 3 weeks and outcome at 1 year are shown in Figure 3. The percentage of patients with DOC at 3 weeks (n=36) and who emerged from a minimally conscious state (EMCS) at 1 year was 61% (n=22) and 82% of the sedated anaesthetized patients at 3 weeks were conscious at 1 year.

Figure 3. Flowchart of patients through Paper I.



Patients in unresponsive wakefulness syndrome (UWS) 3 weeks after injury

Of the 17 patients in UWS at 3 weeks, by 3 months, 5 remained in UWS, 6 had improved to MCS, 4 had emerged from MCS, and 2 were dead, missing data for one. The outcome 1 year after injury for these patients, according to the GOSE, was 1 (dead, $n = 4$), 2 (vegetative state, $n = 3$), 3 (lower severe disability, $n = 7$), 4 (upper severe disability, $n = 2$), missing data ($n = 1$). Note, that GOSE level 2, associated with the description “vegetative state” actually includes some patients in MCS, explaining the apparent discrepancy. At first assessment 3 weeks after injury, scores on the CRS-R (maximum 23), for patients found to be in UWS ranged from 0 to 7. Correlation between CRS-R score at 3 weeks and outcome at 1 year for these patients, according to the GOSE, was poor, with a correlation coefficient of 0.29.

Patients in minimally conscious state 3 weeks after injury

Of the patients in a minimally conscious state (MCS) at 3 weeks, all 13 had emerged from MCS at 3 months. These patients scored median 12 on the CRS-R (range 6-19) at 3 weeks. GOSE for these 13 patients one year after injury varied from 3-7. Correlation between CRS-R score at 3 weeks and outcome at 1 year for these patients, according to the GOSE, was weak ($r = -0.19$). One year after injury, 4 of these patients were living at home without assistance, 8 were at home with assistance, and 1 was in a nursing home. One patient was working full-time (and could also drive).

Patients in coma or sedated/anaesthetized 3 weeks after injury

Of the 6 patients in coma at 3 weeks, by 3 months, 4 were in UWS, 1 was in MCS, none were better than MCS, and 1 was dead. The same figures were shown at one year follow-up. Of the 11 patients who were sedated/anaesthetized 3 weeks after injury, by 3 months, 1 was in UWS, 3 were in MCS, and 7 were better than MCS. One year after injury, none of these initially sedated patients remained in UWS, 2 were in MCS, and 8 were better than MCS. Only a few patients were treated with dopaminergic drugs at the time of study assessments. Of patients in UWS at any point during the study, none were being given such drugs at the 3-week assessment; at the 3-month assessment 1 patient (in UWS at 3 weeks, MCS at 3 months, and EMCS at 1 year) was being given Madopark (levodopa/benserazide combination), and one patient (coma at 3 weeks, UWS at 3 months, UWS at 1 year) was being given amantadine at 3 months but not at 1 year. One other patient (UWS at all study time-points) was being given amantadine at the 1-year assessment but not earlier.

Admission to specialized rehabilitation units

Of the 15 patients in UWS at 3 weeks who survived at least to 3 months, 14 were admitted to an inpatient specialized rehabilitation unit. Admission to a rehabilitation unit occurred on average 62 days after injury (standard deviation (SD) 46, range (26–198 days). All of the 13 patients in MCS 3 weeks after injury were admitted to inpatient rehabilitation units, a mean of 44 days after injury (SD 18, range 17–78).

Figure 4. Flowchart of patients Papers II and III

**PATIENTS
PAPERS II-III**

**BNIS
PAPER III**

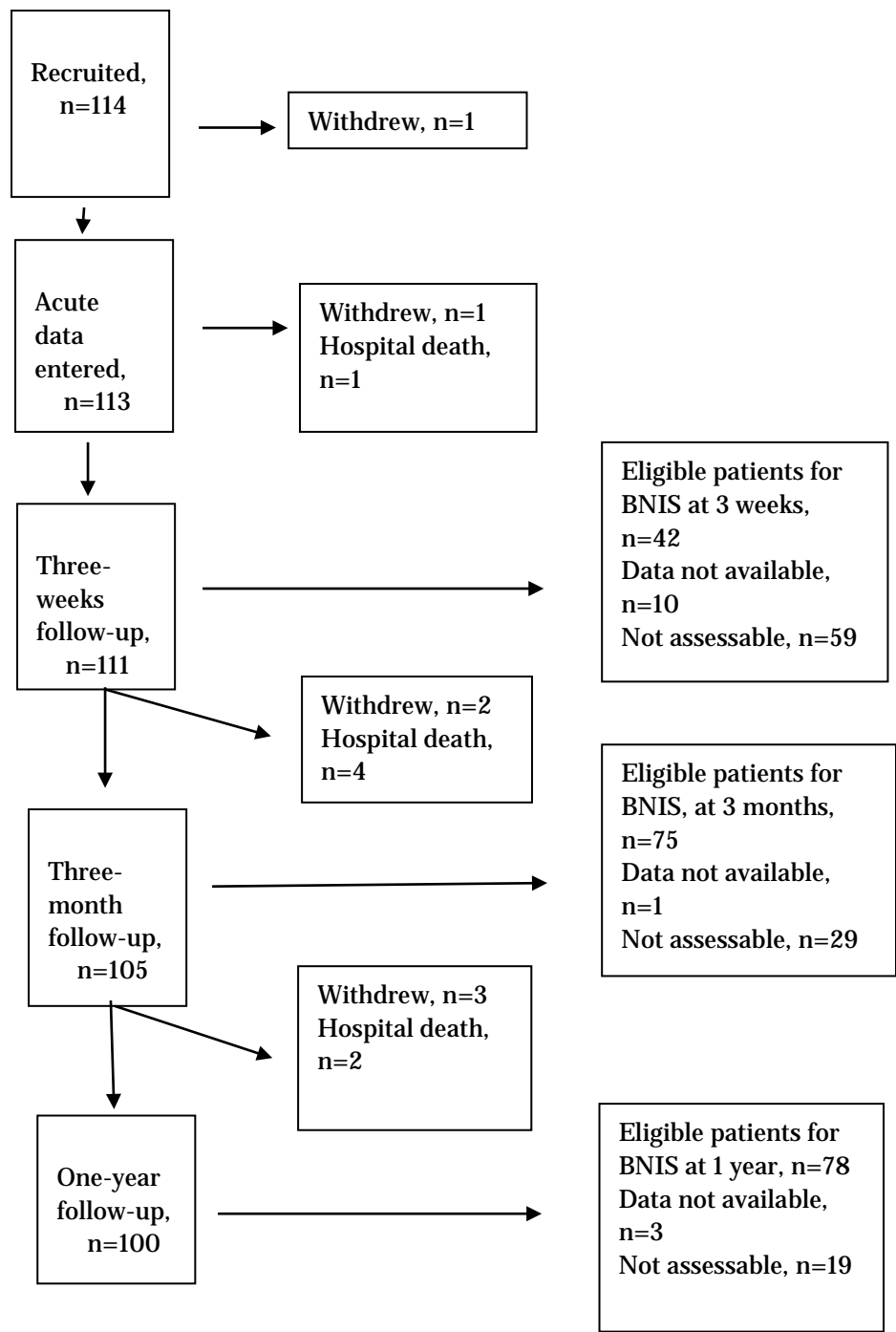


Figure 4 shows a flowchart of follow-up, withdrawals and deaths. For demographic details and summary statistics, see Table 8. Patients who withdrew were similar to those who continued in terms of age and median GCS and RLS.

PAPER II

Care pathways

Ninety-seven patients were transferred to an inpatient brain injury rehabilitation unit at some point during the first year after injury. Of these, 90 were alive and followed up at 1 year, 2 patients died after admitted to inpatient rehabilitation but before follow-up at 1 year, 4 had withdrawn from the study, and data were missing for 1. Another 5 patients died without having been transferred to a rehabilitation unit. Their median time from injury to first admission to inpatient rehabilitation was 28 days (range 9-198 days). Time from first discharge from intensive care to admission to inpatient rehabilitation was median 13 days (range, 0-176 days), and a substantial proportion of patients had to wait for several weeks. Eight surviving patients (7%) were known not to have been transferred to an inpatient brain injury rehabilitation service, 4 received rehabilitation (early outpatient rehabilitation, nursing home or a geriatric unit within a neurology facility) and 4 did not receive rehabilitation. Length of intensive care was shorter for those not receiving rehabilitation (median = 6 days; range, 5-17 days) than those receiving rehabilitation (median=17 days; range, 1-78 days). The most common care pathways for those patients who were transferred to inpatient rehabilitation (n = 97) was from intensive care to a neurosurgical ward and then to a rehabilitation unit (26%). Twenty-three patients (24%), were transferred directly from intensive care to a rehabilitation unit. Twenty patients (20%) were transferred from intensive care to a surgical ward and then to a rehabilitation unit. The remaining 29 patients (30%) received care at between 1 and 5 different intervening care units after intensive care discharge and before eventual transfer to a rehabilitation unit. The number of

intervening care units was not significantly associated with outcomes at 1 year.

Outcomes

Of the 100 patients that were alive and followed up one year after injury (including those who did not receive inpatient rehabilitation), 36 had a bad outcome on the GOSE (score 2-4), and data on GOSE were missing for 2. The CRASH acute prognostic model correlated poorly with actual outcome at 1 year ($r = -0.12$). Length of stay in intensive care ($r = -0.49$) and length of time between intensive care and admission to rehabilitation ($r = -0.30$) were more strongly correlated with outcomes.

A logistic regression model demonstrated that length of stay in intensive care, length of time between intensive care and rehabilitation admission, and the presence of post-acute complications contributed significantly to the variation in outcome and together explained 52% of the variation in the model. The CRASH model and the presence of pre-existing medical problems were not significantly related to outcome. Time between intensive care and rehabilitation admission was not significantly different for patients with and without complications at 3 weeks ($p = 0.11$), or for patients with and without major extracranial injury ($p = 0.59$), or for patients with and without pre-existing medical conditions ($p = 0.64$).

Length of inpatient rehabilitation stay was significantly inversely related to outcome, a bad outcome being associated with a longer stay in inpatient rehabilitation ($p = 0.0001$). Length of inpatient rehabilitation stay was median 34 days (range, 3-127 days) for patients with a good outcome and 64 days (range, 2-315 days) for patients with a bad outcome.

PAPER III

Figure 4 shows a flowchart depicting the study process and recruited and included patients in Paper III and patients who completed BNIS at 3 weeks, 3 months and 1 year. For demographic details and summary statistics, see Table 8.

The Barrow Neurological Institute Screen for Higher Cerebral Functions

It was possible to use the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) for assessment at three weeks after injury in 42 patients. 59 patients could not be assessed due to pre-screen, ongoing disorders of consciousness (DOC) or sedation. At 3 months, 75 patients were assessed and at one-year follow-up, 78 patients were assessed.

Both the BNIS total raw scores and *T*-scores improved significantly from 3 weeks to 3 months after injury (raw score: $p < 0.001$, *T*-score: $p < 0.001$) and from 3 months to 1 year on the raw score only ($p = 0.004$) and *T*-score ($p = 0.086$).

From 3 months to 1 year, no further significant improvements were found. At 3 months and 1 year, patients with more than 12 years of education had statistically significant higher scores than patients with less education on the subscales speech/language, orientation attention/concentration, memory affect and awareness ($p < 0.01$).

The Hospital Anxiety and Depression Scale (HADS).

Scores above cut-off for HADS anxiety occurred in 16 of 75 assessable patients at 3 months and in 16 of 74 patients at 1 year after injury.

HADS depression scores above cut-off occurred in 11 of 75 assessable patients at 3 months and in 15 of 74 patients at 1 year. Significant correlations were found between HADS depression and BNIS total at 3 months ($r = -0.302$, $p = 0.009$) and at one year ($r = -0.361$, $p = 0.002$).

Outcomes

The majority of patients (83%) who completed the BNIS at 3 weeks had favourable outcome on the GOSE at one year. Out of the patients who completed the BNIS at 3 months and at one year, “favourable” outcomes were reported for 80% and 76%, respectively.

Out of the patients who completed the BNIS at 3 weeks, “superior functioning” on the RLAS-R at 1 year was shown for 81%. The corresponding proportion on the RLAS-R at 1 year for patients completing the BNIS at 3 months was 73% and for patients completing the BNIS at 1 year 69%.

In a multivariate model, statistically significant associations were obtained for the BNIS subscales orientation and visuospatial and visual problem solving and “favourable outcome” on the GOSE at one year. The same subscales were also significantly associated with “superior functioning” on the RLAS-R at one year.

PAPER IV

Figure 5 shows a flowchart depicting the study process and recruited patients. A total of 37 patients were identified during the study period and included in the analyses and no patient withdrew. Falls were the most frequent cause of injury (54%) and 70% were males. Males had less education than the females. Education less than 12 years was reported for 62% of included patients and 65 % had an employment or as a student for more than 50%. More than half were married or cohabitating with or without children. The number of patients 18-25 years was nearly the same as for patients aged 26-49 and 50-65 years. Eighteen patients (49%) were under the influence of alcohol and/or drugs (as demonstrated by clinical assessment, anamnestic information and/or blood test) at the time of injury. Known current drug and/or alcohol abuse was present in 11 patients (30%). For demographic details and summary statistics, see Table 8.

Figure 5. Flowchart of patients through Papers IV and V

PAPERS IV-V

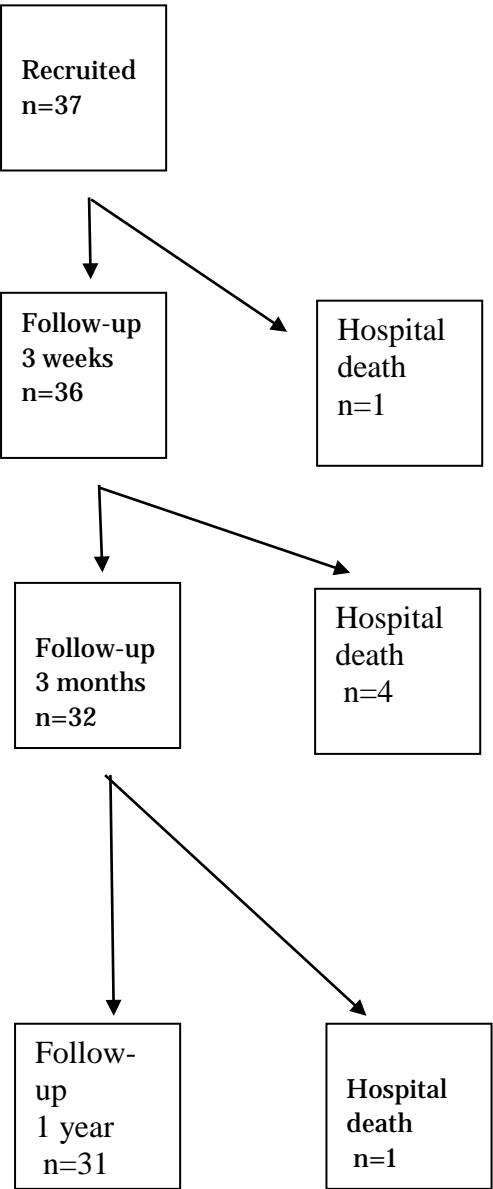


Figure 6. Acute care pathways from the Northern Health Region (NHR) to the neurotrauma center (NC) at Umeå University hospital.

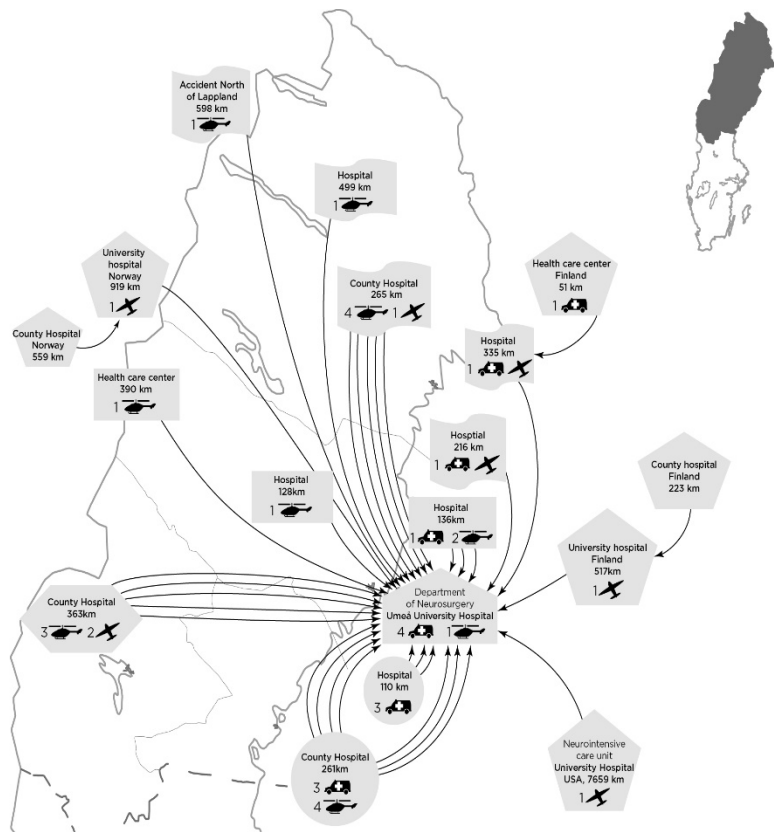
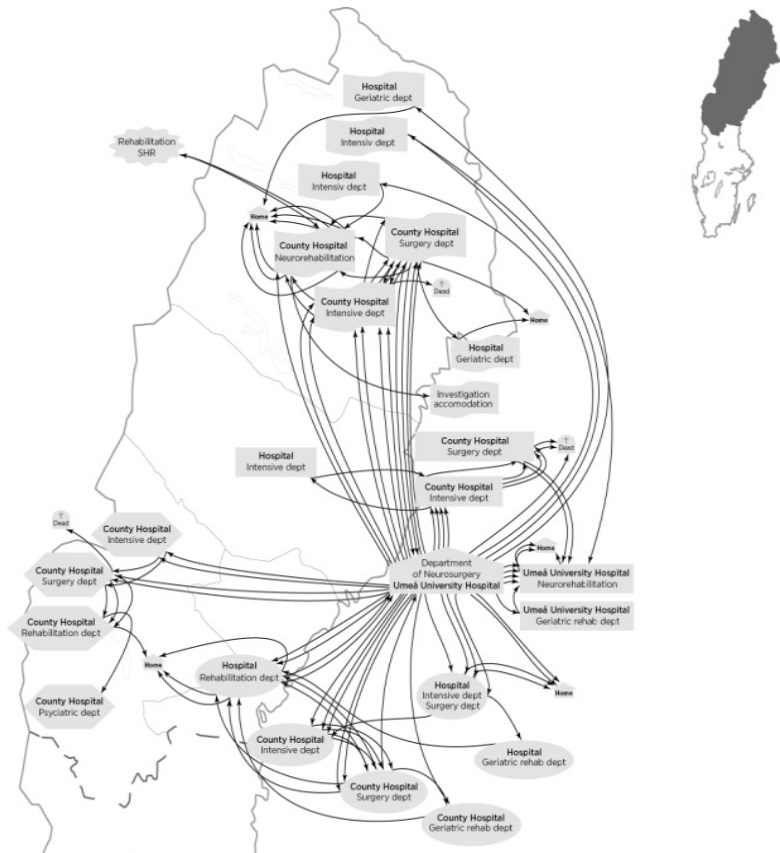


Figure 7. Care pathways from the NC Umeå University hospital to the NHR within 3 months.



Computed tomography scan

Time to first CT scan was less than 1 h for 11%, less than 3 h for 55% and less than 4 h for 82%. The first CT scan of the brain showed traumatic subdural hematoma in 73% of the patients, brain contusion (s) in 76% and traumatic subarachnoidal haemorrhage in 78% of the patients. The first CT was classified as Marshall I-II in 43% of the patients and Marshall III-VI in 57%.

Clinical outcomes

The RLAS-R scores improved significantly from 3 weeks (5.26 ± 3.07) to 3 months (8.0 ± 2.45) ($p < 0.001$), and 19 patients had “superior functioning” on the RLAS-R IX–X. Eight patients had both “superior functioning” on the RLAS-R and a “favourable outcome” on the GOSE 7–8.

Clinical care pathways.

Most patients (92%) were admitted directly to the regional neurotrauma centre (Figure 6). After discharge, patients were typically transferred back to one of several county or local hospitals (Figure 7). It was also common for them to be transferred between different departments within a given hospital.

PAPER V

See Figure 5 and the flowchart depicting the study process and recruited included patients in Paper V and for patient characteristics see table 8.

Hospital deaths occurred in 6 patients. One of these patients died at the NC due to respiratory complications. One of the fatalities suffered from multiple illnesses at the time of injury, two patients with very severe brain injury (GCS 3) died because of respiratory complications, one died because of inoperable traumatic intracranial aneurysm and one patient died from intracerebral bleeding after transportation from NC to the local hospital.

Fatalities (16%) had more severe injuries GCS median 3 (3-6) compared with survivors GCS median 5 (3-8) and a significantly higher mean age in comparison patients who survived (52.8 ± 17.8 vs. 41.3 ± 15.1 , $p = 0.048$). GCS 3 was seen in 24 % ($n=9$) of the included patients and hospital deaths occurred in 44% ($n=4$) of these patients.

A review at the NC to identify possibly missed patients revealed an additional 6 patients, all males, mean age $49.8 (\pm 9.6)$ age, GCS median 6.5 (4-7). These patients could not be included in the study, as they were identified later than 3 weeks post-injury (which is the latest time of inclusion as stipulated by the study protocol).

CT_i was assessed in all patients. A subsequent CT₂₄, according to the study protocol, was assessed in 34 patients. In this study, 41% of patients performed CT_i within 2 hours post-trauma. The mean time from trauma to CT_i was 2.7 ± 1.6 h ($n=31$). One patient was excluded because of delayed admission to hospital (15.2h). For 5 patients, the

exact elapsed time post-trauma could not be established, but was deduced to be within 22 hours. The mean time from trauma to CT₂₄ was 25.4 ± 12.4 h (n=30). Two patients were investigated by CT₂₄ after 60 hours due to clinical reasons. For CT characteristics, see Table 3.

The median (range) score of CT_i according to Marshall was 3 (1-6) and the corresponding results of CT₂₄ was 5 (1-6). The median (range) Rotterdam score of CT_i was 4 (2-6) and of CT₂₄ 3 (1-6). See Figures 1,2 and Table 4.

Non-evacuated mass lesion on the CT_i was seen in 19% (n=7/37) compared with 9% (n=3/34) on CT₂₄. Out of 27 patients with available CT_i and CT₂₄ and with detectable diffuse injury (Marshall I-IV) on the initial scan, 48% subsequently developed a mass lesion on CT₂₄, which was then evacuated. One patient who sustained high-energy trauma displayed findings of no pathological according to Marshall CT_i and CT₂₄. Nevertheless, the patient presented GCS 6 at admission and diffuse axonal injury on magnetic resonance imaging and GOSE 5 at one year. According to Rotterdam, 16 patients out of 34 (47%) showed improvement from CT_i to CT₂₄, whereas four patients (12%) deteriorated.

There was a positive correlation between Marshall CT_i and Rotterdam CT_i ($r = 0.716$, $p < 0.001$) but no significant correlation between Marshall CT₂₄ and Rotterdam CT₂₄ ($r = 0.077$, $p = 0.667$). Rotterdam CT₂₄ showed a negative correlation to GOSE at 3 months ($r = -0.421$, $p = 0.015$). There were negative correlations between Marshall CT_i and CT₂₄ and RLAS-R at 3 months (CT_i $r = -0.364$ $p = 0.044$; CT₂₄ $r = -0.425$, $p = 0.024$). However, Marshall and Rotterdam scores of CT_i and CT₂₄ did not correlate with the GOSE and RLAS-R scores at 1 year, this being the study endpoint as regards outcome.

GOSE improved significantly from 3 months (median 4.5 (1-8), mean 4.4 ± 2.3) to 1 year (median 7 (1-8); mean 5.5 ± 2.7 , $p=0.003$.) At 3 months, GOSE 1-4 was seen in 50% and GOSE 5-8 in 50%. At 1 year, GOSE 1-4 was seen in 36% and GOSE 5-8 in 64%. One patient was in a vegetative state at 1 year. Good recovery (GOSE 7-8) was seen in 59 % at 1 year. RLAS-R also improved significantly from 3 months (median 9 (2-1); mean 8.0 ± 2.4) to 1 year (median 10 (3-10); mean 8.9 ± 1.9 , $p=0.003$). At 1 year, RLAS-R 1-6 was seen in 10% and RLAS-R 7-10 in 90%, and 77% reached the highest level, i.e. “Stand-by assistance on request” and “Modified independent” (RLAS-R 9-10). One patient who was classified on CT_i as Marshall I (i.e. no visible intracranial pathologic change) had an initial score of GCS 6 and was classified as GOSE 5 at 1 year due to diffuse axonal injury. GCS on admission correlated with GOSE at 1 year ($r=0.366$, $p=0.026$). There were negative correlations between in-hospital total days and GOSE at 3 months and 1 year ($r= -0.419$, $p= 0.011$ and $r= -0.429$, $p= 0.008$) and between in-hospital total days and RLAS-R at 3 months and 1 year ($r= -0.738$, $p<0.001$ and $r= - 0.713$, $p<0.001$). The proportion of unfavorable outcome (GOSE 1-4) at 1 year was 31% for men and 46% for women. There were 4 patients with hospital death (GCS 3, GOSE 1) and unfavorable outcome (>95%) according to CRASH.

DISCUSSION

Main findings

This thesis describes patients of working age with S-TBI in Sweden and Iceland, a total of 114 patients recruited in a 2-year period, follow-up at 3 weeks, 3 months and 1 year post-injury, with further studies of three subgroups: i) 36 patients with DOC and 11 patients in sedation/anaesthetized at three weeks, ii) 42-78 patients who managed to complete cognitive screening, iii) 37 patients in the NHR, Sweden. This thesis is a result of collaboration with the “PROBRAIN” multicenter study, primarily descriptive. The number of included patients was relatively small although 80% of the population in Sweden and 100% of the population in Iceland were recruited. Therefore, some caution in interpretation is necessary. Global outcome (for all patients in the study/patients in the Northern Health Region) at 1 year was good and nearly two thirds (55%/64%) of these patients were assessed as GOSE 5-8, (33%/59% GOSE 7-8) but some patients died or ended up with severe disabilities GOSE 1-2 (12%/19%). Ninety-seven patients of the remaining 100 assessed patients were transferred to an inpatient brain injury rehabilitation unit at some point during the first year after injury. However, it is worth noting that rehabilitation was offered at different units, not only in a neurorehabilitation unit. Delays to rehabilitation unit were identified and delayed transfer was almost as common as patients transferred directly to rehabilitation and some waited longer than a month. The percentage of patients who received care at between 1 and 5 different intervening care units after intensive care discharge and before eventual transfer to a rehabilitation unit was 30%. The number of intervening care units was not significantly associated with outcome at 1 year. Sedated and anaesthetized patients or patients in

MCS at three weeks had a better prognosis than patients in coma or UWS. No patient in UWS was assessed better than GOSE 4 at one year (one missing). In accordance with an earlier Norwegian study, a delay from discharge from intensive care and admission to a rehabilitation unit was associated with worse outcome one year after injury [30]. The routines for transferring patients with severe TBI from the geographically large NHR Sweden to NC seemed to work very well but transfer from NC Umeå University hospital differed from one patient to another and no structured continuous care pathway was found. Cognition improved over time after the injury and appeared to be relatively stable from three months to one year. For the relatively small population from the Northern Health Region, neither an acute prognostic model (outcome at six months) nor acute repeated CT protocols could prove clinically useful correlation with outcome at one year.

Paper I

An understanding of the natural course of unresponsive wakeful syndrome (UWS) after S-TBI and recovery is of importance. The Multi-Society Task Force on persistent vegetative status (PVS) (1994) [48] performed a meta-analysis on recovery from UWS in 434 patients. The included studies had no standardized neurobehavioral assessment which was shown to be a more sensitive tool than clinical consensus for the establishment of differential diagnoses in patients with DOC, as misdiagnosis of UWS may occur in up to 40% of patients [51]. At that time, when the definition of minimally conscious state (MCS) [50] had not been established, it is likely that a number of patients who were judged as vegetative state in the Task Force report at one month were in MCS and therefore some of these patients had a better prognosis. Reported data in Paper I were assessed at three weeks postinjury and the relatively small group of patients, even though they represented 80% of the population of Sweden and 100% of the population of Iceland, meant that caution had to be applied to interpretation. A comparison of reported data from Paper I and the Multi-Society Task Force from 1994 showed that patients with UWS at 3 weeks who emerged to full consciousness (EMCS) at 3 months were quite similar, namely, 24% (Task Force 33%), and 53% (52% Task Force) at 1 year but a comparison of the patients who recovered consciousness (EMCS) at 3 months in Task Force with patients in UWS and MCS in our study at 3 weeks then there was a higher share of recovery in our study 57% (Task Force 33%) and 73% (52% Task Force) at 1 year. It is problematic to compare results with studies published more than twenty years ago. However, this may reflect the consequence of better access to NCs today and improved neurosurgical, modern neuro-intensive and neuro-rehabilitative care. The percentage of patients in UWS who

died or were still in UWS at three months in Paper I was 41% (67% Task Force). Long-term outcome for patients in conscious state UWS three weeks after injury was assessed at 1-year follow-up, the best level on the GOSE being 4 (upper severe disability), 13 % fulfilled this rating. GOSE 1-4 is described as unfavourable outcome. GOSE 2-4 with a need for assistance and further interventions of rehabilitation. Outcomes were also poor for patients in coma: 25% were dead and 75% in UWS which indicates that patients in coma state at three weeks have a poorer outcome. Reports have recently appeared in the literature on outcomes for selected groups of patients with disorders of consciousness from the point at which they are admitted to specialized rehabilitation programmes. Katz et al. [115] reported in a retrospective review of outcomes in 36 patients admitted to a slow-to-recover rehabilitation unit, of whom the 22 patients with S- TBI (8 in UWS at admission, 14 in MCS) were admitted a mean of 37 days after injury. Seven of the 8 UWS patients improved to MCS and 45% (number not stated) later emerged from MCS. Although follow-up periods differ, the figure of 45% who improved to better than MCS is not dissimilar from our figure of 53% 1 year after injury. Katz et al [115], reported that all of their patients admitted in MCS after TBI emerged from MCS during rehabilitation similar to our findings. It should be emphasized that such estimates are necessarily based on small numbers of patients. In a retrospective study from Italy of 259 patients admitted consecutively to a neurorehabilitation facility with acquired severe brain injury and admitted at different points in time 75 patients (29%) presented a UWS and 107 (41%) a MCS according to CRS-R. Thirty-six months after the acute event, 17 persons were still in UWS, 30 had died and 26 had regained some consciousness [120]. This reflects the need for a longer follow-up period even though this report did not only present data from S-TBI. In Paper I, outcome

was better for patients in MCS, 3 weeks after injury: 25% were assessed as lower good recovery (GOSE 7) and 25% as lower moderate disability (GOSE 5) at one year. Of the 15 patients in UWS at 3 weeks who survived at least to 3 months, 14 were admitted to an inpatient specialized rehabilitation unit. All patients with MCS at 3 weeks after injury were later admitted to inpatient rehabilitation units. The ongoing “PROBRAIN” study could have an impact on this because of the fact that patients were recruited by rehabilitation physicians who also underwent prospective clinical assessment at each point in time. A study from Norway [30] has shown that early initiation of an unbroken chain of rehabilitation improves outcomes after S-TBI. Post-traumatic disorders of consciousness (PT-DOC) occurred at one year after S-TBI in this paper with an incidence of approximately 1.4 per million people of working age. Because Sweden is a geographically large country, national standards are needed. Such standards already exist in some European countries, for example Scotland (2009) and Denmark (2006) [36,121]. Subacute rehabilitation and care with special standards and/or development of a DOC network and to promote further research are of importance. The development of a continuous chain of rehabilitation after S-TBI, which has been shown to improve outcomes but which was not in place for any patients in this study, should be prioritized.

Paper II

Patients with S-TBI may require a lengthy hospital stay and S-TBI can cause long-term disability. Paper II reported that delays between discharge from intensive care and admission to a rehabilitation unit were negatively associated with outcome one year after injury. Similar findings were also reported in an earlier study from Norway 2012 [30] and in a study from Norway 2016 [141] findings indicate

that clinical pathways without delay of admission to specialized department for rehabilitation may contribute to enhance independence. Medical stability is of importance before admission to rehabilitation but our data in Paper II could not determine whether a short period of a day or two between discharge from neuro-intensive care had a negative effect on outcome. Delays identified in Paper II were not short: the number of patients who had to wait longer than a month ($n=22$) was nearly as large as those transferred directly ($n = 23$). During the time between intensive care and inpatient rehabilitation, nearly a third of the patients received care at units that would not be expected to have specific knowledge of recovery after TBI. Some patients even received a short period of care in short-stay nursing homes before the initial rehabilitation stay. Delay in rehabilitation can depend of medical problems, extracranial injuries but often because of a lack of beds because of delays in discharge from rehabilitation to appropriate social care. These delays are well-known by rehabilitation professionals but not documented in a transparent way which would be of significance for creating a more smooth flow of patients and increasing access to rehabilitation. The presence of coexisting medical problems and major extracranial injury did not have a significant link to outcome and were not significantly related to the time between intensive care discharge and rehabilitation admission. However, our findings did provide support to the role of post–acute complications in contributing to poorer outcome. Patients with complications did not have a significantly longer time between intensive care discharge and rehabilitation admission than those without complications. The relationship between longer length of stay in intensive care (LOSIC) and worse outcome can be understood as complications during the intensive care period and secondary brain injury. Similar findings were reported in the PariS-TBI Study (2013),

that also found LOSIC to be an independent predictor of outcome at 1 year [122] and nearly a third of patients were discharged without inpatient rehabilitation [142]. LOSIC can differ because of variation of intensive care and treatment guidelines but standardized protocols such as the “Lund concept” and pressure on intensive care beds is extremely high at all centres and would reduce any difference. Our hypothesis that acute prognostic factors would be associated with outcome at 1 year has face validity and has been insufficiently considered in previous studies focusing on rehabilitation. We incorporated such acute prognostic variables into our data collection primarily to allow the evaluation of any additional contribution of delayed rehabilitation admission. We used the CRASH model to predict the risk of unfavourable outcome from acute prognostic variables. CRASH was not significantly related to actual outcome in our patients. Several factors may explain this apparent paradox. Assessment of outcome was at 6 months in the CRASH model but at 1 year in our study. Recovery continues after 6 months post injury [115] and the CRASH model may be missing improvements that have had an important long-term impact on patients’ functioning. Another factor is that the CRASH model included patients who died in the group with unfavourable outcome, and because our study evaluated the impact of rehabilitation care pathways, it was not meaningful to include patients who died before any rehabilitation was received. In addition, the CRASH study omitted any consideration of rehabilitation interventions. The CRASH model has also recently been shown to overestimate rates of unfavourable outcome in patients receiving intracerebral pressure-targeted neurosurgical treatment [116] according to the Lund concept [123] which is common in Sweden. Given the evidence for the effectiveness of rehabilitation [34], it is positive that the majority of patients did

eventually receive inpatient brain injury rehabilitation. A previous retrospective study [124] of a comparable group of patients with S-TBI receiving care in 2003-2004 at 3 neurosurgical centres in Sweden found that 17% were never admitted to rehabilitation compared with 7% of patients in Paper II. A Cochrane review reported the importance of rehabilitation for recovery of function after S-TBI depending on neuroplasticity, which can be influenced by active rehabilitation interventions. [34]. As regards access to rehabilitation for patients surviving S-TBI in Sweden and Iceland, the general health care insurance system in these countries gives access to rehabilitation for almost all patients but it is common for there to be delays in admission to several county hospitals, not only to specialized rehabilitation units. There is no planned continuous pathway and a lack of structured programmes. An quasirandomized study of S-TBI in Norway (2012) [30] because of a limited number of beds showed benefits of a continuous chain of care after S-TBI from neurosurgical intensive care to inpatient rehabilitation to discharge, with a better outcome for those who received early continuous rehabilitation starting in the intensive care compared with those who received ordinary rehabilitation without continuous pathways. [30]. A defined chain of care for all patients suffering from S-TBI would contribute to the optimization of care for all patients and support difficult discharge decisions and facilitate adequate follow-up.

Paper III

Our results in Paper III indicate that cognition improves over time after S-TBI and appears to be relatively stable from three months to 1 year. Since cognitive function was associated with outcomes, it seems that early screening of cognitive function could be of importance for rehabilitation planning in a clinical setting.

In this population of patients with S-TBI, it was feasible to use the BNIS instrument for the screening of cognitive functions as early as three weeks after injury in 42% of the patients. The screening made it possible to individualize interventions at the stage of recovery where neuroplasticity is maximal, with potential outcome benefits.

In Paper III, the patients who died had lower GCS while the patients who withdrew were younger and were less severely injured according to the GCS which could have had an influence on the result in this study. Falls were the most frequent cause in our population of working age adults while transport accidents were the second most common cause, just like those reported in some earlier Scandinavian studies [18,110] while motor vehicle injuries dominated, for example, in southern Europe, the USA and Australia [23,125,126]. The BNIS scores of the patients who completed the test at three weeks improved substantially at three months and further improvement was shown at 1 year, but the number of patients who completed the BNIS was relatively stable from 3 months to 1 year. There were only a few of the very severely injured patients who improved so much they were able to complete BNIS at the last follow-up at 1 year. When the BNIS total scores at three weeks were compared with the results reported by Borgaro and Prigatano [68] of a small population of S-TBI patients early after the injury (around 20 days), the patients in our study performed better and the scores were in fact higher than a group of patients with moderate TBI, but lower than a control group. This finding can in part be explained by differences regarding study populations and a large variation in the ranges of post injury time in the Borgaro and Prigatano study [68]. The BNIS scores at 1 year were in a range that was similar to another Swedish study [91], indicating that the long-term results are probably relatively consistent and in the same study, the BNIS was validated in a patient group from a

neurorehabilitation clinic where less than 9 years of schooling was defined as low education, as in the manual. In our study, low education was defined as being less than 12 years (in this study 35-40% of the patients) because the majority of the Swedish population continue to study at upper secondary school. Regardless of where the education level limit is set, it seems that the results in our study confirm earlier results of a link between education level and cognition [68,91]. The BNIS is a screening instrument that is made for practical clinical use and which indicates if comprehensive cognitive neuropsychological assessment should be proposed. It should be noted that according to the Swedish BNIS manual [127], the majority of our assessed patients at all the points in time gained scores that were below the cut-off (less than 47 points) which means they were recommended further testing but this proportion decreased over time from 84% to 74%.

In a clinical context, it is important to consider this in order to optimize the setting of realistic rehabilitation goals for each individual patient. When comparing the scores of the subscales at the different points in time, significant improvements in our study were only shown from three weeks to three months. The results at three months and at one year were in line with the previous Swedish results by Hofgren et al. [91]. Moreover, the majority of patients who completed the BNIS at all three points in time experienced “favourable outcome” on the GOSE and “superior functioning” on the RLAS. Higher scores on the orientation and visuospatial and visual problem-solving subscales at three months were also associated with good outcomes. Disorientation, a key component of posttraumatic amnesia, has often been studied in patients in the acute phase after TBI and it has been reported as a predictor of cognitive impairments after injury [128]. Borgaro et al [129] examined the usefulness of the BNIS for assessing

orientation in patients with TBI and concluded that the instrument was shown to be a sensitive measure of disorientation in these patients. The orientation, visuospatial and visual problem-solving subscales include basic domains of importance for independence inside and outside the patients' homes. It was therefore not surprising that these subscales were associated with outcome in the present study. In our study, awareness on the BNIS subscale was associated with the GOSE. This result is in line with earlier studies which have reported a relationship between self-awareness and long-term outcome in TBI patients [130]. In a study by Kelley et al. [131] impaired awareness was shown more than 5 years after TBI and awareness of cognitive function was found to predict return to work. Although awareness may improve over time, it seems to be a complex construct including varying aspects. Studies have reported depression and anxiety as a major cause of disability after TBI [132,133]. In the present study, there were negative relationships between the BNIS total score and the HADS anxiety and depression scores at one-year follow-up, indicating that patients with a cognitive dysfunction may also suffer from anxiety and depression symptoms over time. These findings confirm earlier results which have shown an association between self-reported depression and anxiety and poor performance on cognitive tests [134].

Paper IV

In Paper IV, 37 patients were included, survivors more than three weeks with S-TBI, from the NHR during 2 years. Injury characteristics of patients, their clinical pathways and outcome after three months were studied. In this rural area, which covers almost half of Sweden, most patients were nevertheless shown to be swiftly transported direct to the regional Neurotrauma Center (NC). Thus,

routines for pre-acute care seem to be well-established. Acute transportation to the NC was made by aircraft or helicopter in over 70% of cases and 82% of the included patients had made their first CT scan within 4 hours. By contrast, post-acute care after discharge from NC seemed to lack a structured care pathway since patients were transferred back to local hospitals at a fairly early stage, moved between departments and to different kinds of rehabilitation departments. The medical rationale of this dispersion is not clear. There were probably several reasons behind the differences between the acute and post-acute logistics. Although standardized treatment and specialized rehabilitation are also likely to be needed, the individual patient's differences and needs are factors that tend to grow in importance as the patient gradually becomes medically stabilized [34,135] and such aspects may have played a role in the choice of diverging pathways of the patients in the present study. Costs may be another operative factor, as each county has its own budget and has to cover the costs for patient care outside its jurisdiction. In addition, the severity of residual disability and projected prognosis was also likely to be a factor that determines the choice of post-acute clinical pathway. Well-organized pre-hospital transportation systems for patients with S-TBI have also been reported from rural regions of Norway [30]. In these areas, rehabilitation in the early phases is based on close collaboration between the neurosurgical departments and rehabilitation units, but capacity problems may delay inpatient rehabilitation [37]. Since similar difficulties with insufficient management routines in Sweden and Norway have been observed, researchers recently proposed a Scandinavian organization model that integrates neurointensive care and qualified rehabilitation, and ensures an effective chain of rehabilitation activities after S-TBI [37]. Differences in post-acute

pathways after S-TBI have also been demonstrated from other countries. In studies that have evaluated patients with S-TBI from rural and urban areas, poorer outcomes for rural residents have often been reported [31]. However, with an integrated acute and post-acute network of services, similar results have been shown for rural and urban groups in Australia [136]. These findings underline the importance of structured interventions in the early rehabilitation process.

The male patients in our study had a lower education level in comparison with the females, and more males than females were intoxicated at the time of injury. Alcohol use at the time of injury has been shown to be a risk factor for TBI [137,138]. In the present study, significantly more patients who were under the influence of alcohol at the time of injury had a history of previous TBI and were more often injured by high-energy trauma in comparison with the non-intoxicated patients. However, there was no significant difference between these groups on the outcomes three months post injury.

For assessment of outcomes, the GOSE and RLAS-R scales were used. Overall outcomes were surprisingly good in this group of severely injured patients, all patients improved significantly on the RLAS from 3 weeks to 3 months. At 3 months, 3 of the 19 patients in the 2 highest RLAS-R categories and 2 of the 8 patients with the highest GOSE levels had the lowest GCS score of 3 during the first 24 hours in the acute stage. Thus, the majority of the assessed patients experienced good recovery as regards cognitive and behavioural functioning, and around one quarter were considered as having both “superior cognitive functioning” [81] and a “favourable outcome” [80]. However, it is worth noting that even if positive results on the GOSE and the RLAS were measured, patients may still not be fully recovered at 3 months after the injury and may experience subtle deficits not

covered by these instruments. Therefore, it seems reasonable to assume that some of the patients were in need of further rehabilitation interventions and follow-up.

Paper V

To our knowledge, there are no previous studies using both Rotterdam and Marshall for study of outcome of comprehensive management and rehabilitation of S-TBI. In previous prognostic studies on mortality and outcome in TBI, Marshall or Rotterdam were utilized with a main focus on neurointensive care [9].

In this study, we found a negative correlation between Marshall and Rotterdam and the clinical outcome according to GOSE and RLAS-R at 3 months. However, there was no correlation between CT scores and GOSE or RLAS-R at one year post injury, indicating that analysis of CT acutely and within 24-48 hours lack predictive ability as regards long-term clinical outcome in S-TBI. Likewise, CRASH failed to predict outcome in this S-TBI population. Similar findings were reported by Olivecrona & Olivecrona [29], who used CRASH for prediction after S-TBI at six months. In previous research from our hospital, Marshall and Rotterdam CT_i and Marshall CT₂₄ correlated with the disability outcome GOS both at 3 months and at one year [9]. However, since GOSE is an extended version of GOS, these instruments are not completely comparable. It might be that prognostic prediction based on CT protocols lack sufficient sensitivity to provide more fine grained outcome assessments, particularly within a TBI subgroup comprising the most severe injuries. Another possible reason may be related to the inclusion criteria. The PROBRAIN study included patients who survived at three weeks, this was not a criteria in the previous study [9].

It is of particular clinical relevance that overall outcome among patients with severe TBI in our study was encouragingly favorable (GOSE 5-8, 64%) (GOSE 7-8, 59%), while instruments for prognostication failed to predict favourable/unfavourable outcome at one year. When interpreting data from this study, some distinguishing factors pertaining to this study population and design should be emphasized.

First, patients were somewhat older (mean age +6 years) than in some previous studies [5,9] on this topic. Second, in comparison with a prior study from our center [9], patients on average had lower GCS (5 vs 6), indicating more severe injury. Fatalities (16%) suffered more severe injuries (GCS 3) compared with survivors (GCS 5) and were also older (approximately +10 years). Third, this study was limited by the relatively small study population. However, S-TBI is rare in comparison with mild and moderate TBI. Also, the included patients in fact comprised a near-total population of incident S-TBI cases fulfilling selection criteria during two years. Furthermore, all data were collected by one of the authors, who also personally examined all patients during the course of the study, minimizing the amount of missing or secondary data. One fourth of the patients were initially classified as severely injured and with a minimal GCS score (3). Nevertheless, at 1 year, 44% of this subgroup was classified as “good recovery” on the GOSE (7-8), pointing to the importance of providing active care for all S-TBI patients [34,36,40,139].

Both a history of previous brain injury and indications of alcohol use at the time of injury have been shown to be risk factors for TBI [34,35]. Over one third of patients in our study had been hospitalized previously for TBI, and almost half were under the influence of

alcohol and/or drugs at the time of injury. This is a much higher rate of alcohol use in S-TBI patients than that recently reported in a Norwegian study (32%) [30]. These findings highlight the concept of high-risk populations and high-risk situations in conjunction with sTBI, and thus the need and potential for preventative measures.

CT of the brain remains a standard diagnostic tool for assessing TBI, and is also used for prediction of outcome. Since studies have shown that pathological intracranial changes in the brain often progress during the first 24 and even 48 hours, routine repeated CT scans have been proposed to capture intracranial dynamics [33]. In the present study, the proportion of “less severely injured” patients based on Marshall CT_i was higher than in some previous studies [9,31]. However, when comparing our results on CT₂₄, the percentage of severely injured patients was similar to these studies, as the severely injured group increased by more than 50% from CT_i to CT₂₄. Thus, it is to be emphasized that intracranial pathology after S-TBI commonly progress, so that repeat CT scans in the early stage often may be implicated, especially in light of clinical deterioration.

The majority of patients in our study experienced good recovery as regards disability and cognitive and behavioral functioning, and about two thirds were assessed as having good outcomes on both GOSE and RLAS-R. Those patients were independent as regards activities of daily living and did not need another person’s assistance at one year post injury.

In conclusion, the findings of this study proved negative as regards the predictive ability of CT and CRASH protocol on outcome prognostication at one year post injury in S-TBI. At the same time, good outcomes were found in about two thirds of survivors. The study

support to the notion that, as a rule, patients with S-TBI should be offered a combination of active and aggressive neurosurgical and neurointensive care and active and intensive neurorehabilitation, as a majority of these seriously injured patients showed favorable outcome by such management, and as our possibilities for early prognostication in the TBI subpopulation fails to identify who will benefit from aggressive management or not.

SUMMARY OF THE THESIS

In this thesis, we found that acute and repetitive CT of the brain assessed with classification scales could not serve as a prognostic factor for long-term outcome 1 year after injury. However, an initial CT of the brain and a CT within 24 hours is of importance for acute care planning. Patients recovered well, including patients in MCS and those who were sedated/anaesthetized at three weeks. Patients with S-TBI is a well-known heterogeneous group; this was confirmed in these papers. Patients who died were older and had more severe brain damage. There were only a few patients who were given pharmacological treatment to optimize awareness and response to stimuli, for example, Amantadine until follow-up at 1 year. Among the S-TBI patients, there was a relatively large group of patients with known drug or alcohol abuse. In comparison with previous studies, a large proportion had signs of influence of alcohol and/or drug use at the time of the injury compared with other studies. In this population of patients with S-TBI, it was feasible to use the BNIS instrument for the screening of cognitive functions as early as three weeks after injury in 38% of available patients. In order to find prognostic factors that describe the complexity of these patients and their needs for different interventions after acute care, this overall clinical study gave an opportunity to get better knowledge in several respects and provide a basis for new studies. A structured chain of care and specialized rehabilitation for patients with S-TBI, new guidelines for equal healthcare in urban and rural areas, and better information to care-providers, patients and their relatives are needed. The results from these papers can hopefully contribute to better information to patients and their relatives and thereby facilitate better planning of care pathways and use of resources.

Strengths and limitations

The studies have several strengths, such as a prospective multicenter observational design of S-TBI in Sweden and Iceland. Furthermore, in Papers IV and V, one of the authors examined all patients during the course of the studies and ensured that data were precisely and completely documented. The number of patients in these studies was rather small but comprised the total or near-total regional population of S-TBI patients injured during a two-year period.

However, the studies are based on clinical populations and have some limitations. Although the authors in Papers I-III had weekly contact with intensive care units, some eligible patients may have been missed from the recruitment process if they were admitted to and discharged from intensive care between contacts.

Confirming a diagnosis of unresponsive wakeful syndrome (UWS) or minimally conscious state (MCS) requires repeated assessment over time which was not possible within the design of Paper I, given that patients were assessed in whatever care setting was current at the study time-points. However, the use of the JFK Coma Recovery Scale Revised CRS-R is a strength in diagnostic accuracy.

Completeness of follow-up in Paper I of 81% patients (76% alive, 5% dead) and in Paper II of 94% (88% alive, 6% dead) one year after injury is acceptable, considering the necessity of obtaining consent from relatives at the start of the study. In Paper III, the follow-up rate of 69% completing the BNIS is satisfactory. Only 19 patients could not complete the BNIS at the one-year follow. In Papers IV and V, all patients who survived at three months and at one year participated in the follow-up.

Clinicians who assessed outcome at one year in the studies were not systematically blinded to acute data, which is a source of potential bias. Within reasonable study resources, it was not possible to arrange blinded follow-up at all locations and at the same time ensure completeness of follow-up and inter-rater reliability. The time interval between assessment at 3 months and one year can reasonably be expected to protect against this bias, as the relatively long period would make it unlikely that examiners would remember data from the acute phase at the time of follow-up.

The CRASH prognostic model was used in Papers I, II and V. The CRASH model predicts outcome 6 months after injury. We assessed outcome one year after injury as recovery may continue at least until this point in time for severely injured patients. These differing time-frames could explain why differences in outcome between patients in UWS and MCS 3 weeks after injury were not predicted by CRASH in Paper I and why the CRASH model failed to predict outcome for the population in Paper V.

Another limitation of the studies was that blood alcohol concentration was not measured in all patients, thus decreasing the accuracy in determining the contribution of alcohol to the early clinical picture and the presumed effects on outcome. Both alcohol and drug intake at the time of injury may depress the level of consciousness which could affect the classification of TBI.

However, longer follow-up is of importance. Additional descriptions of the complexity of these patients could provide better information for decision-makers and rehabilitation planning, and could be used in clinical practice and for further studies.

Conclusions

This thesis describes the clinical course and outcomes in patients with severe TBI with regard to prognostic factors.

- The patients in minimally conscious state or anaesthetized three weeks after injury were found to have a better prognosis than patients in coma or unresponsive wakefulness syndrome. This was not explained by acute prognostic models.
- A delay from discharge from intensive care and admission to a rehabilitation unit was associated with worse outcome one year after injury.
- Cognition improved over time after the injury and appeared to be relatively stable from three months to one year.
- The routines for transferring patients with severe TBI from the geographically large Northern Health Region in northern Sweden so they can be given well-monitored surgical care seemed to work very well. In contrast, the post-acute clinical pathways did not reflect as clearly an optimized medical and rehabilitative strategy.
- Neither acute CT protocols nor an acute prognostic model proved clinically useful correlations with outcomes one year after injury. At the same time, good outcomes were found in about two thirds of the patients.

Future considerations

During the course of work on this thesis, some further considerations and suggestions for further research have arisen.

- The small numbers of patients with disorders of consciousness indicate that a development of national standards for post-acute care for these patients is necessary to ensure good standards of care for everyone.
- Although outcomes were assessed at one year after injury, recovery may continue for longer than that. Further studies are needed with longer follow-up time.
- Validated questionnaires were used for the assessments. However, there is also a need for qualitative studies in order to get knowledge about the views of the patients and their nearest relatives concerning their situation after the injury.
- A high proportion of patients were reported to have a known drug or alcohol abuse at the time of injury. It is necessary to measure blood alcohol concentrations to determine the contribution of alcohol to the clinical picture and to the effects on outcomes.
- Health-economic studies to study costs of both the acute care but also longer-term care requirements would be of interest.
- Well-organized routines for admission to rehabilitation after severe TBI and for evidence-based treatment in the post-acute

stage should be considered as well as strategies to ensure standardized rehabilitation care in both rural and urban areas.

- Because of the specific epidemiology of S-TBI, it is important to inform of drug or alcohol use and its relation to S-TBI, prevent accidents, provide effective emergency care and neurorehabilitation, and there is a need for further studies of functioning and disability after S-TBI.

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