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Traumatic brain injury in elderly patients

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Abstract

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The increase of elderly traumatic brain injury (TBI) patients constitutes a considerable challenge. The aim was therefore to specifically study elderly TBI patients with respect to patient characteristics, neurointensive care (NIC) and outcome, and to identify age specific features, which may be important for selection of patients and optimization of NIC in the elderly. Data from the Uppsala TBI-registry and collected physiological monitoring data from the NIC unit were analysed.

Between 1996–1997 and 2008–2009, patients ≥60 years had doubled from 16% to 30%. Despite the increase of elderly an overall favorable outcome was maintained at around 75% between the two periods and the elderly showed favorable outcome in slightly more than 50%.

Analysis of characteristics and outcome between 2008–2010 showed that fall accidents and acute subdural hematoma were more common in the elderly ≥65 years. Admission status and NIC treatment did not differ depending on age, except that a larger proportion of the elderly had surgery. Elderly ≥65 years showed a favorable outcome in 51% compared to 72% in the young.

Studies of patients ≥60 years treated 2008–2014 showed that high age, multiple injuries, low Glasgow coma motor score on admission and the use of mechanical ventilation were negative prognostic factors.

Elderly had different secondary insult patterns with a higher percentage of good monitoring time (%GMT) with high cerebral perfusion pressure (CPP), high mean arteria blood pressure (MAP) and high systolic blood pressure (SBP) and less %GMT with high intracranial pressure (ICP), low CPP and low MAP. On the contrary to the young, high %GMT with SBP>180 was associated with favorable outcome in the elderly, indicating that blood pressure probably should be treated differently in the elderly.

Elderly had worse pressure autoregulation (higher values of PRx) and spent longer time with higher PRx. Elderly also had higher optimal CPP and spent lower %GMT with CPP close to optimal CPP. High PRx correlated with mortality in elderly but pressure autoregulation influenced outcome less in the elderly.

Overall, the results show that elderly TBI patients differ in many aspects and more studies are warranted to increase knowledge and optimize NIC.

Keywords: Traumatic brain injury, Elderly, Outcome, Standardized neurosurgical intensive care, Quality register, Prognostic factors, Secondary insults, Neurointensive care monitoring, Pressure reactivity index, Optimal cerebral perfusion pressure, Cerebral autoregulation

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“Accidents and diseases occurring to the brain are not the most unfrequent affections that claim the assistance of surgery, and are at all times subjects demanding the practitioner's mature and deliberate investigation”

C. C. Wallis,1821
British surgeon

Till Mia, Sia och Siri

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Lenell S., Nyholm L., Lewén A., Enblad P. (2015) Updated periodic evaluation of standardized neurointensive care shows that it is possible to maintain a high level of favorable outcome even with increasing mean age. *Acta Neurochir*, 157(3):417–425

II. Merzo A., Lenell S., Nyholm L., Enblad P., Lewén A. (2016) Promising clinical outcome of elderly with TBI after modern neurointensive care. *Acta Neurochir*, 158(1):125–133

III. Lenell S., Nyholm L., Lewén A., Enblad P. (2019) Clinical outcome and prognostic factors in elderly traumatic brain injury patients receiving neurointensive care. *Acta Neurochir*, 161(6):1243–1254

IV. Lenell S., Lewén A., Howells T., Enblad P. (2021) Neurointensive care of traumatic brain injury in the elderly – age-specific secondary insult levels and optimal physiological levels to target needs to be defined. *Acta Neurochir*, 164(1):117–128

V. Lenell S., Swedung Wettervik S., Howells T., Hånell A., Lewén Anders., Enblad P. (2024) Cerebrovascular reactivity (PRx) and optimal cerebral perfusion pressure in elderly with traumatic brain injury. Acta Neurochir, 166, 62. https://doi.org/10.1007/s00701-024-05956-9

Contents

Abbreviations

%GMT	Proportion of Good Monitoring Time
AOR	Adjusted Odds Ratio
ASDH	Acute Subdural Hematoma
CBF	Cerebral Blood Flow
CI	Confidence Interval
CPP	Cerebral Perfusion Pressure
CPPopt	Optimal Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CVD	Cardiovascular Disease
CVP	Central Venous Pressure
DAI	Diffuse Axonal Injury
EDH	Epidural Hematoma
EVD	External Ventricular Drainage
GCS	Glasgow Coma Scale
GCS M	Glasgow Coma Scale Motor Score
GMT	Good Monitoring Time
GOS	Glasgow Outcome Scale
GOSE	Glasgow Outcome Scale Extended
ICP	Intracranial Pressure
IQR	Interquartile range
MAP	Mean Arterial Pressure
NIC	Neuro Intensive Care
OR	Odds Ratio
PRx	Pressure regulatory index
RLS	Reaction Level Scale 85
SBP	Systolic Blood Pressure
SpO_2	Pulse Oximetry Saturation
TBI	Traumatic Brain Injury
tSAH	Traumatic Subarachnoid Hemorrhage
ΔCPPopt	Difference between CPP and CPPopt (CPP-CPPopt)

Introduction

During the second half of the 20th century, the modern management of traumatic brain injury (TBI) has evolved with the establishment of specialized neurointensive care (NIC) units dedicated to preventing and treating secondary insults, e.g. increased intracranial pressure (ICP), hypotension and hypoxemia. Structured guidelines and local management protocols have been implemented in these units[1–3]. A gradual improvement in clinical outcomes has been observed[2,4]. There has also been a trend in many of the industrialized countries with a reduced incidence of severe TBI driven by public health interventions such as seatbelts and helmet legislations, and workplace safety regulations. On the other hand, TBI still constitutes a major global health problem. The magnitude of the problem is illustrated by an overview of TBI in Europe showing that the incidence of hospitalized TBI patients was 278.2/100 000 in 2012 (Sweden 451.5/100 000 in 2013)[5] and the mortality rate was 11.7/100 000 (Sweden 9.0/100 000 in 2013)[5]. Furthermore, patients with severe TBI have an increased risk of dying after discharge, for at least 8 years after the trauma[6]. Thus, there are still challenges ahead, especially as the population is changing with an increased proportion of elderly[7,8] and with that also an increase of elderly TBI patients[9].

Elderly people today are perceiving themselves healthier and they are living more active lives, and are at the same time prone to fall[7,10]. They often have a medical history with previous diseases or injuries[11]. For example, Hawley and coll. showed that TBI patients ≥65 years of age had a recorded medical history in 80% of the cases and only 1.1% had no pre-existing medical condition[12]. TBI in the elderly means special challenges for the NIC since the elderly with TBI require special considerations due to age-depended differences in injury mechanisms, brain and other organ functions, rehabilitation potential and prognosis, respectively[13,14]. Because of those factors and the experience of poor outcomes, there has often been an assumption of futility in treating elderly TBI patients and age cut-offs have often been implemented for offering surgery and NIC to the elderly[15]. However, there are elderly with severe TBI who recover, which indicates that chronological age and TBI severity alone are not sufficient to make a reliable prediction of prognosis[16–18]. In a CENTER-TBI study from 2022 of patients ≥65 years, it was found that about half of the elderly TBI patients were treated at an intensive care unit and that they had poorer global functioning, lower physical health-related quality of

life (HRQoL) and higher mortality, respectively, which was found to be associated with worse preinjury health[19]. However, a considerable amount of patients also made full recovery or partially returned to preinjury levels, which underlines that the elderly may also be possible to treat successfully[19]. Even though there have been many calls for more research in the field of TBI in the elderly, there are still major knowledge gaps regarding prognosis, treatment algorithms and outcomes in the era of modern NIC. The purpose of this thesis was therefore to try to overbridge those gaps in some aspects.

Review of TBI literature

Epidemiology

It has been estimated that between 28–69 million people worldwide will suffer from a TBI each year[20,21]. James and coll. found that between 1990 and 2016 there was a global increase in incidence (3.6%) and prevalence (8.4%) of TBI, which could be expected to continue as a result of increases in population density, population aging, and increasing use of transportation vehicles[20]. TBI constitutes a serious global challenge in patient suffering as well as high cost for society and is therefore often referred to as the silent epidemic[22]. In an epidemiological review of TBI in Europe by Brazinova and coll. a slightly decreasing trend in TBI incidence was observed (both on the national level and regionally) but there was no decrease in TBI mortality over time[23].

When looking at how the age distribution has changed over time, one clear example of the change is the inverted age pyramid with a dominance of the elderly observed in many developed countries, e.g. in Sweden (Figure 1). The changing age distribution also causes the epidemiology of TBI to change with an increase of elderly with TBI[10,24–28] and a changed dominating cause of injury from road traffic accidents to falls[23,26,27].

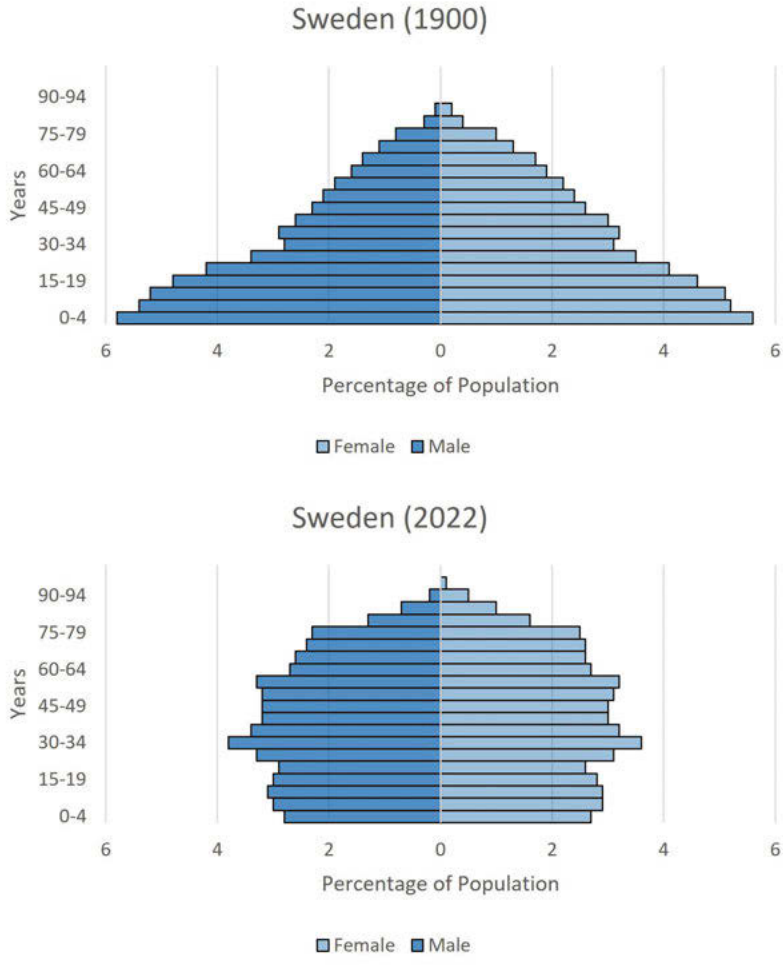

Figure 1. Comparison of age distribution in Swedish between 1900 and 2022 showing that the population pyramid has become inverted. Data Source: Statistics Sweden.

Clinical assessment

The most common clinical assessment scale used for TBI is the Glasgow Coma Scale (GCS)[29] created in 1972 and updated in 1974 (Table 1)[29]. The scale grades verbal response (5 grades), motor response (6 grades) and eye movements (4 grades), and the sum of the scores are presented as the GCS score.

Table 1. Glasgow Coma Scale (GCS)[29]. The best sum score of the eye, verbal and motor responses.

		Score
Eye response	Spontaneous	4
	To sound	3
	To pain	2
	No response	1
Verbal response	Orientated	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Motor response	Obeys commands	6
	Localize pain	5
	Flexion (withdrawal)	4
	Flexion (abnormal)	3
	Extension	2
	None	1

One problem with the GCS is the risk of overscoring the verbal and eye responses in intubated patients and patients with facial injuries, respectively. Therefore and to avoid a summary score The reaction level scale 85 (RLS) was developed in 1985 at Sahlgrenska University Hospital, Gothenburg, Sweden, by Starmark and coll. (Table 2)[30]. This scale consists of 8 levels where RLS 1 is fully awake and RLS 8 is no reaction. RLS has not gained international spread but is found advantageous and used routinely in some Swedish centers.

Table 2. Reaction Level Scale-85[30] and corresponding GCS Motor scores (GCS M)[29]. The subdivision of RLS level 3 into a and b is a local modification used in Uppsala University Hospital so that RLS can be translated into GCS M.

RLS-85		Corresponding GCS	
Response	Score	Motor response	Score
Alert and oriented	1	Obeys	6
Delayed/confused response	2	Obeys	6
Very delayed response/somnolent	3a	Obeys	6
Wards of pain	3b	Localizing	5
Localizes pain	4	Localizing	5
Withdrawing movements	5	Normal flexion/withdrawal	4
Stereotype flexion	6	Abnormal flexion	3
Stereotype extension	7	Extending	2
No response	8	No response	1

Injury types and radiological grading

Depending on the forces and mechanical dynamics of the trauma different types of injuries occur. These can be divided into focal as epidural haematoma (EDH), acute subdural haematoma (ASDH), intracerebral haematoma and contusions, or diffuse, i.e. diffuse axonal injury (DAI). EDH is more common in children and young adults and ASDH in older adults and in the elderly.
With the introduction of computed tomography (CT) scanning came the possibility to evaluate TBI radiologically. Characterization of the injury type and evaluation of midline shift, compression of sulci and basal cisterns, and ventricular size, respectively, could give information on injury severity and intracranial dynamics. A structured way to grade the injury radiologically was the Marshall score[31] where the presence of midline shift, compression of basal cisterns, diffuse injury/swelling, and mass lesions >/<25 cm^3, respectively, were assessed on the initial CT scan (Table 3). The final estimated Marshall score, which also takes into account if the findings led to the evacuation of mass lesions, correlates with the outcome and may be used for the prediction of prognosis[31].

Table 3. Marshall CT score[31].

Category	Definition
Diffuse injury I	No visible intracranial pathology seen on CT scan.
Diffuse injury II	Cisterns are present with midline shift 0–5 mm and/or lesion densities present. No high- or mixed-density lesion > 25 cc. May include bone fragments and foreign bodies.
Diffuse III (swelling)	Cisterns compressed or absent with midline shift 0–5 mm. No high- or mixed-density lesion >25 cc.
Diffuse IV (shift)	Midline shift >5. No high- or mixed-density lesion >25 cc.
Evacuated mass lesions	Any lesion surgically evacuated.
Non-evacuated mass lesions	High- or mixed-density lesion >25 cc. Not surgically evacuated.

There have been many attempts to improve the prognostic information from radiology assessment with newer scales. The Rotterdam CT score added evaluation of traumatic subarachnoid hemorrhage (tSAH) and intraventricular blood[32]. The Stockholm CT score used the midline shift as a continuous variable and had a separate more advanced scoring of tSAH[33]. The Helsinki CT score combined components from the Marshall score and Rotterdam score and weighed more the types of intracranial injury[34]. Which of the newer CT scales to use has been debated and there has been no consensus. Thelin and coll. compared the Marshall CT score, Rotterdam CT score, Helsinki CT score and

Stockholm CT scores and found that the Helsinki and Stockholm CT scores had a better predictability of outcome, and accounted that to the assessment of tSAH in the scales [35].

Primary and secondary brain injury

The impact of the trauma causes a *primary brain injury*, which generally is immediate and definitive. The primary injury is followed by a complex cascade of adverse events on the cellular level that give rise to *secondary brain injury*. The injury mechanisms on the cellular and chemical level have been well characterized, e.g. excitotoxicity, apoptosis, neuroinflammation, and mitochondrial dysfunction[36]. Many neuroprotective agents have been developed to inhibit such injury mechanisms but the results have so far been very disappointing in humans[36]. The primary brain injury makes the brain vulnerable and secondary brain injury may also be caused by clinical insults.

In 1975 Reilly first described that some TBI patients initially were awake and then deteriorated and died[37]. Rose and coll. studied the phenomenon with *talk-and-die cases* further and found that such patients suffered from one or more of the following secondary insults: delayed evacuation of intracranial hematoma, hypoxia, hypotension and poorly treated epilepsy and meningitis[38]. The interpretation was that that those insults caused secondary brain injury and since the occurrence could have been prevented or better treated the term *avoidable factors* was coined[38]. Today the concept of avoiding secondary insults and preventing secondary brain injury is the basis for the acute management and modern NIC[1–3].

Acute management

Patients with TBI should always be managed according to the Advanced Trauma Life Support (ATLS) principles[39] to avoid deficient airway, breathing and circulation, which are the most serious secondary brain insults. Neurological grade and pupil reactions should be assessed. An acute trauma CT scan should be performed including the whole body to assess the brain injury and to detect other injuries. Radiological detection of e.g. intra-abdominal bleedings before indirect clinical signs as hypotension occur may initiate prompt management and thus a secondary brain insult may be avoided. After the acute management, patients with moderate and severe injuries should be treated in a dedicated NIC unit with a continuous focus on avoiding secondary insults to the brain.

Neurointensive care

The main task of NIC is to prevent the primary injured brain from secondary insults to minimize additional secondary injury. Careful patient surveillance with regular wake-up tests and physiological monitoring of different modalities is crucial in NIC to detect emerging secondary insults. In addition to standard critical care monitoring, i.e. ECG, invasive arterial blood pressure, pulse oximetry (SpO_2) and core temperature, regular neuromonitoring includes monitoring of ICP and cerebral perfusion pressure (CPP).

More advanced multimodality neuromonitoring also includes e.g. neurochemical microdialysis monitoring, brain tissue oxygenation monitoring ($PbtO_2$), jugular bulb oxygen saturation monitoring ($SjvO_2$), and EEG monitoring[40].

The monitoring of ICP was first introduced in the 1950s[41,42] and further developed by Lundberg during the 1960s[42]. The main methods for invasive ICP monitoring are using an external ventricular drainage (EVD) system (golden standard) or an intraparenchymal pressure monitoring device. The EVD has the advantage that it can also be used to drain cerebrospinal fluid (CSF) to reduce the ICP.

CPP is the pressure gradient between mean arterial pressure (MAP) and ICP (CPP=MAP-ICP). The pressure dome for the arterial line is often placed at the level of the heart and the pressure dome for the EVD at the level of the lateral ventricle. Both transducer domes are also often placed at the level of the lateral ventricle to avoid an underestimation of CPP when the head is elevated.

The TBI management guidelines from the Brain Trauma Foundation recommend ICP target <22 mmHg and CPP target between 60–70 mmHg[1] and the European Braim injury consortium guidelines recommend ICP<20–25 mmHg and CPP between 60–70 mmHg[3]. There have been different trends in the CPP management during different eras and the current development is probably toward more individualized management.

CPP management

In 1995 Rosner and coll. reported a significant improvement in outcome, compared to other published treatment series at the time, with a CPP-oriented treatment targeting CPP ≥70 mmHg to avoid cerebral ischemia[43]. The CPP levels were reached and maintained by using systemic vasopressors and volume expansion. This concept was however challenged by others, e.g. by the Lund group considering high CPP to be dangerous because of the risk of brain edema and suggesting a CPP as low as 50 mmHg, which was found to be tolerable without risk of brain ischemia[44]. Today the current guidelines recommend a CPP between 60 and 70 mmHg to avoid ischemia as well as aggravating edema[1].

Cerebral pressure autoregulation-directed CPP management

Cerebral pressure autoregulation (Figure 2), first described by Lassen 1959, is the ability to maintain a relatively constant cerebral blood flow (CBF) despite broad variations of MAP (50–160 mmHg)[45,46].

In 1994 Lang and Chesnut proposed that monitoring of ICP could be used to optimize CPP according to an impaired autoregulation in a patient-specific fashion[47]. In 2000 they described a way of assessing cerebral pressure autoregulation using existing monitoring, to be able to set patient-specific CPP targets. This was done by manipulating MAP using infusions of phenylephrine and observing the reaction in CPP and ICP[48]. Three different ICP responses to blood pressure manipulations were observed: 1. Pressure-passive, 2. Pressure stable and 3. Pressure-active[48] (Figure 2). In a study by Howells and coll. analyzing monitoring data from Uppsala applying an ICP-directed management and from Edinburgh using a CPP-oriented management, it was shown that pressure-passive patients had better outcomes if treated with ICP-oriented therapy with relatively lower CPP targets and pressure-active patients had better outcomes if treated with CPP directed therapy with relatively higher CPP targets[49]. Observations that impaired pressure autoregulation after TBI is associated with poor outcome indicate that pressure autoregulation-directed therapy may be beneficial[50–52]. Therefore, continuous measures of autoregulation have been developed.

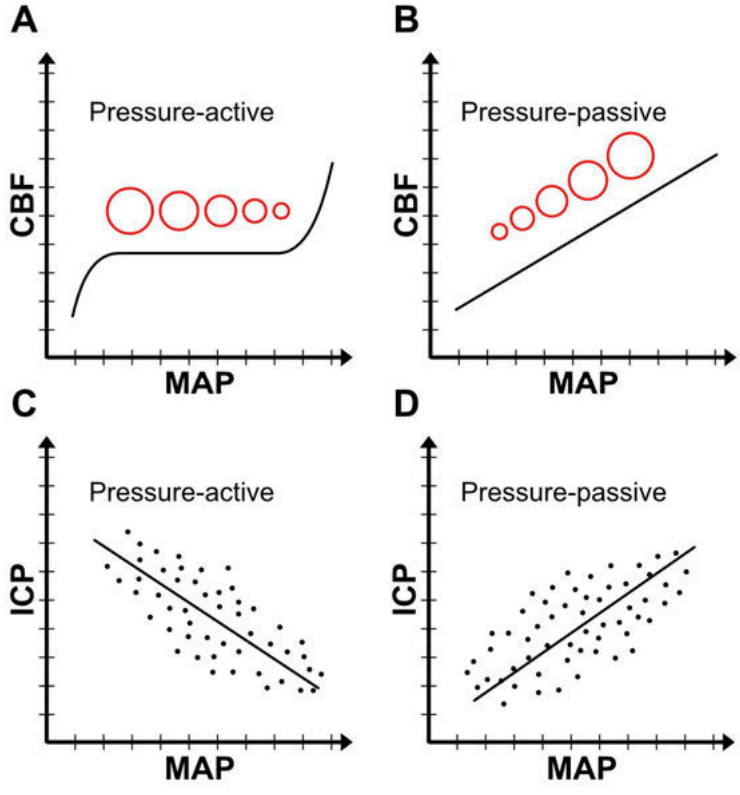

Figure 2. **A** Pressure-active patient with a classic Lassen curve[45]. The red circles illustrate the vasoconstriction of the arteries when MAP is increasing. **B** Pressure-passive patient with passive vasodilatation when MAP is increasing. **C** ICP plotted against MAP in a pressure-active patient. **D** ICP plotted against MAP in a pressure-passive patient.

Pressure regulatory index (PRx)

The Pressure regulatory index (PRx) was described by Czosnyka and coll. in 1997[51]. PRx is a moving Pearson's correlation between ICP and ABP (Figure 2). A positive value indicating impaired autoregulation[51]. A PRx above 0.2 showed a substantially higher risk of unfavorable outcome (81% unfavorable outcome)[51] and in many later studies, PRx has been proven to be strongly and independently correlated with outcome[50,53,54].

Variants of PRx

Several variants of PRx have been developed. $PRx_{55\text{-}15}$ was created to reduce the problem of PRx being relatively unstable and noisy. The input signals for PRx were modified to include the frequency components of ICP and ABP that are optimal for the analysis of cerebral autoregulation. This was done by using a bandpass 55–15 filter (passband of 0.018–0.067 Hz)[55].

The low-frequency autoregulation index (Lax) is similar to PRx but uses minute-by-minute data[56] for the correlation analysis. The advantage is that high-frequency data are not needed.

Long pressure reactivity index (L-PRx) is another alternative algorithm similar to PRx. This method uses 20-minute averages of MAP and ICP data for the linear Pearson's correlation. This index also shows a correlation to 6-month outcome[57].

Wavelet transform-based PRx (wPRx) is calculated by taking the cosine of the wavelet transform phase shift between ABP and ICP. The wPRx shows promise to be more stable in time, yield a more consistent CPPopt guidance, and have a stronger relationship with patient outcome[58].

Optimal CPP - CPPopt

Creating a plot with PRx (y-axis) in different CPP intervals (x-axis) produces typically a U-shaped curve. The bottom of the U-shaped curve represents the CPP level where pressure autoregulation works best, i.e. the optimal CPP (CPPopt)[59] (Figure 3). In the randomized trial COGiTATE by Tas and coll. it was shown that CPPopt-guided therapy was safe and feasible in TBI patients[60].

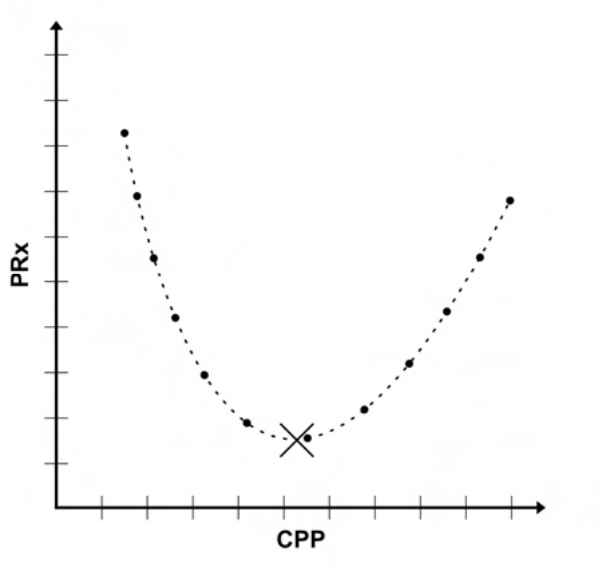

Figure 3. Optimal CPP (CPPopt)**.** PRx is plotted in CPP intervals. The lowest point of the U-shaped curve corresponds to CPPopt (the cross in the picture), which is the CPP level where pressure autoregulation works best.

Outcome assessment

In TBI, outcome can be assessed in many ways. The simplest grading is only looking at mortality during treatment and after discharge. In 1975 Jennett and coll. created the Glasgow Outcome Scale (GOS) assessing the outcome by categorization into dead, vegetative state, severe disability, moderate disability and good recovery[61]. The GOS was expanded by subdividing the best three categories into upper/lower and the modified scale was named GOS Extended (GOSE)[62], (Table 4). To improve the reliability of the GOSE scale structured interviews are to be used[63].

Table 4. GOS[61] and GOSE[62] outcome scale.

	GOS	GOSE	Level of function
Unfavorable outcome	1 = Dead	1 = Dead	Dead
	2 = Vegetative state	2 = Vegetative state	Unconscious
	3 = Severe disability	3 = Lower severe disability	Dependent – need frequent help
		4 = Upper severe disability	Dependent – need some help
Favorable outcome	4 = Moderate disability	5 = Lower moderate disability	Unable to participate in one or more life roles
		6 = Upper moderate disability	Limited in one or more roles
	5 = Good recovery	7 = Lower good recovery	Returned to normal life with some symptoms
		8 = Upper good recovery	Fully returned to normal life

Optimal management of elderly with TBI

The guidelines for NIC of patients with TBI are mostly based on data from younger patients and there is insufficient research on the elderly despite the change in population structure[10,64]. For example, large clinical TBI trials have often been made with age >65 years as an exclusion criteria[65–69]. Although the secondary insult prevention concept is one of the main reasons for the

improvement of NIC the best treatment as well as both the critical and optimal threshold levels probably differ between ages. This is underlined by studies in elderly patients with severe subarachnoid hemorrhage showing that the occurrence of defined secondary insults and the impact on outcome was age dependent[70,71]. It is desirable to extend the knowledge about optimal NIC management specifically in elderly TBI patients.

Special consideration for the elderly

Aging

With the generally improved health and functional level of the elderly, it is easy to forget that there is a declining organ function with increasing age-associated with the normal aging. Even if an elderly person has a high functional level, the organ function is reduced and needs to be considered in case of severe illness or trauma. The risk of comorbidities also increases with increasing age and also the amount of medication.

Aging of the brain

The normal aging of the brain consists of a decrease in brain volume/weight that starts as early as after 20 years of age and the decrease reaches 22% in males and 20% in females over a life span of 20–100 years[72]. However, longitudinal studies of healthy individuals have shown that brain shrinkage is complex and highly individual (except for the inferior parietal lobule)[73]. Shrinkage of the hippocampus, the entorhinal cortices, the inferior temporal cortex and the prefrontal white matter increased gradually over time while shrinkage in the hippocampus and the cerebellum accelerated with age[73]. With increasing age there is no global decrease of CBF but there is a bilateral focal decrease in the cingulate gyri, the parahippocampal gyri, the superior temporal gyri, the medial frontal cortices, the parietal cortices and the left insula and left inferior frontal cortex[74]. Blood-brain barrier permeability increases with age and is more common in patients with vascular dementia and white matter lesions[75]. Increasing age is also associated with progressive hemorrhagic insults which may be related to increased vascular rigidity and fragility[76]. Cerebral pressure autoregulation is maintained in healthy elderly individuals[77–81] but may have a delayed response compared to young[82].

Aging of other organ systems

The cardiovascular system undergoes many changes with age. With aging collagen increases and elastin decreases in the aorta, which leads to increased vessel stiffness. The increased stiffness leads to increased systolic blood pressure and lower diastolic pressure. Vascular aging alters the function of the endothelium with reduced vasodilatory and antithrombotic properties, which

leads to atherogenesis and thrombosis. Calcium accumulates in cardiovascular structures and cardiac valves[83]. In the elderly, sinus node intrinsic rate and atrioventricular (AV) conduction are slow, resulting in lower heart rates[84]. At the same time, the elderly have an increased incidence of cardiac arrhythmias[84].

In the respiratory system, there is a decline in mucociliary transport which together with changes in the connective lung tissue lead to decreased elasticity, reduced number of alveoli, increased alveolar duct size and decreased forced expiratory volume[84]. This in combination with a reduced cough strength due to reduced muscular strength leads to a decreased ability to clear secretions[85]. Accordingly, aging is associated with increased vulnerability to pulmonary infections and risk of respiratory failure[84].

The renal system experiences with aging, loss of the renal cortex, a decrease in the number and function of glomeruli, a decrease in renal blood flow, decreased glomerular filtration rate and decreased ability to concentrate urine[84].

Aging leads to a systemic decline in immune system effectiveness with higher pro-inflammatory cytokine secretion and a decrease in the ability to stimulate the immune response to antigens[84].

Aging is also associated with a decrease in muscle mass and function as well as a higher risk for malnutrition[84].

Comorbidities

With increasing age, the risk for comorbidities increases. The most common comorbidities in the elderly are hypertension (59.6%), hyperlipidemia (42.8%), ischemic heart disease (34.5%), diabetes (26.9%), arthritis (22.2), heart failure (18.0%), depression (10.7), chronic kidney disease (13.1%), osteoporosis (13.9%), Alzheimer disease (12.6%), chronic obstructive pulmonary disease (13.1%), arterial fibrillation (8.9%), cancer (7.4%), stroke (4.6%) and asthma (4.0%)[86]. In elderly 65–84 years of age the mean number of comorbidities is 2.6 and 64.9% have multimorbidity (two or more chronic morbidities) and by the age of ≥85 years the mean number of comorbidities is 3.62 and 81.5% has multimorbidity[87] In a study of comorbidities among patients admitted to a cardiac intensive care unit it was found that noncardiac comorbidities were associated with a stepwise increase in mortality, length of stay, noncardiac indications for intensive care unit admission, and increased utilization of critical care therapies[88].

Intrinsic capacity and frailty

Intrinsic capacity is composed of all the physical and mental capacities that an individual can draw on at any point in their life. It is at its peak in early adulthood and declines from midlife. With increasing aging, there is a diversity of

intrinsic capacity among elderly at the same biological age but most people experience a loss toward the end of their life. It is possible to increase intrinsic capacity with health interventions and the adoption of healthier lifestyles can positively modify the trajectory of intrinsic capacity[89].

According to WHO´s definition, frailty is a clinically recognizable state in which the ability of older people to cope with everyday tasks or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems. It is characterized by multisystem dysregulations, leading to a loss of dynamic homeostasis, reduced physiological reserve and greater vulnerability to subsequent morbidity and mortality, often manifested by maladaptive response to stressors, leading to a vicious cycle that results in functional and health outcome decline. Underlying components of frailty include a pro-inflammatory state, sarcopenia, anemia, relative deficiencies in anabolic hormones (androgens and growth hormone) and excessive exposure to catabolic hormones (cortisol), insulin resistance, compromised or altered immune function, micronutrient deficiencies and oxidative stress[89].

Instead of only using biological age for the clinical assessment of patients it is desirable to evaluate their intrinsic capacity and frailty in a broader sense. In the intensive care unit setting, the most used measure is the Clinical Frailty Scale (CFS) assessing physical activity, functional status, chronic illness burden, and cognition on a 7-degre scale[90].

Aims

General aims

To study elderly TBI patients to obtain an updated actual picture of patient characteristics, management, and outcome and to identify age-specific features, which may be important for the selection of patients and optimization of NIC in the elderly.

Specific aims

To evaluate the outcome and different characteristics (including age) of patients with TBI treated at Uppsala University Hospital 2008–2009 and compare with the period 1996–1997 and earlier periods when possible (Paper I).

To specifically study elderly patients (≥65 years) with TBI selected for NIC in comparison with younger patients (15–64 years) regarding the clinical characteristics and outcome (Paper II).

To examine outcomes in a larger group of elderly TBI patients (age ≥60 years) receiving NIC and to identify demographic- and treatment-related prognostic factors specifically in the elderly (Paper III).

To study the occurrence of secondary insults during NIC and the impact of outcome in different ages with particular focus on the elderly (age ≥65 years) (Paper IV).

To analyze PRx and CPPopt specifically in elderly TBI patients (age ≥65 years) during NIC and relate the results to outcome in comparison with younger patients (age 16–64) (Paper V).

Materials and Methods

Patient selection

Paper I

Time period 2008–2009 in comparison with the results from earlier periods. Patients aged 16–79 years. Elderly were defined as ≥60 years of age.

Paper II

Time period 2008–2010. Patients ≥15 years. Elderly were defined as ≥65 years of age.

Paper III

Time period of 2008–2014. Patients ≥60 years. Elderly were divided into patients 60–74 years of age and 75–89 years old.

Paper IV

Time period of 2008–2014. Patients ≥16 years. Elderly were defined as ≥65 years of age.

Paper V

Time period 2008–2018. Patients ≥16 years. Elderly were defined as ≥65 years of age.

Paper I, III and IV - Exclusion criteria

Patients were excluded for the following reasons: admitted to the NIC unit ≥5 days after the trauma or treated successfully at the NIC unit and discharged within 24 h, both pupils wide and non-reacting on arrival at the NIC unit or GCS score 3 and one wide pupil on admission (patients with probable predestined fatal/unfavorable clinical course judged in general not possible to treat)[91,92], gunshot wounds to the head and patients lost to follow-up.

Standardized NIC treatment protocol

In all five studies, the patients were treated according to the same standardized treatment protocol[2]. The treatment goals are presented in Table 5.

Table 5. Treatment goals.

ICP	<20 mmHg
SBP	>100 mmHg
CVP	0–5 mmH_2O
CPP	>60 mmHg
Blood glucose	5–10 mmol/L
PaO_2	12 kPa
Body temperature	<38°C
Hb	>100 g/L
Normovolemia to slight negative balance	
Electrolytes in normal ranges	

Unconscious patients (GCS M ≤5) were intubated and mechanically ventilated. Patients on mechanical ventilation were kept sedated with propofol (Propofol-®LipuroB, Braun Medical, Danderyd, Sweden) and received morphine for analgesia. Initially, they were moderately hyperventilated ($PaCO_2$ 4.0–4.5 kPa) with the aim of normoventilation as soon as ICP allowed. Neurological functions were regularly assessed with wake-up tests (usually 3–6 times/day, unless severe ICP elevations).

ICP was monitored in all unconscious patients (GCS M ≤5), regardless of age. In the case of coagulopathy, the placement of an ICP monitoring device was postponed until the coagulopathy had been corrected. An EVD was the first choice (with the pressure dome at the level of the lateral ventricles). An intraparenchymal pressure device was used when the ventricles were compressed or in the presence of coagulopathy. The arterial blood pressure was measured with the pressure dome at the heart level. Prophylactic anticonvulsants were not used.

Significant mass lesions in unconscious patients were evacuated. Elevated ICP was treated in an escalating regime. If the ICP increased ≥20 mmHg, in the absence of mass lesions, (CSF) was drained. Initially, small volumes (1–2 ml) were drained intermittently, when there was a risk of expanding hematoma and brain swelling. Later CSF was drained using an open system if needed, against a pressure of 15–20 mmHg.

If necessary, the ICP treatment was escalated with no wake-up tests, continuous sedation with propofol and stress reduction with ß1-antagonist metoprolol (Seloken®, AstraZeneca AB, Södertälje, Sweden) and α2-agonist clonidine (Catapresan®, Boehringer Ingelheim AB, Stockholm, Sweden) or dexmedetomidine (Dexdor®, Orion Corporation Orion Pharma, Espoo, Finland).

If the treatment above was insufficient to lower ICP, thiopental coma treatment and/or decompressive craniectomy were used as last-tier treatments, but more restrictively in the elderly.

Data sources

TBI-Registry

All patients treated at the NIC unit since 2008-01-01 at Uppsala University Hospital are registered in the *Uppsala Clinical Research Center* TBI-registry (https://www.ucr.uu.se/tbi/). Date of injury, cause of trauma, admission characteristics, NIC treatments and 6-months follow-up are registered. The registry is a local quality registry[93].

Physiological data collection

The physiological data was processed by the Odin software for data collection, visualization and analysis, developed in Edinburgh and Uppsala[94]. All bedside patient monitors at the NIC unit in Uppsala are connected to a local network and the data is forwarded to a central database at the hospital. The Odin server queries this database to extract the relevant data and display the data on the Odin client monitoring system at the bed spaces in the NIC unit[94] (Figure 4). All collected physiological data may also be processed and analyzed in retrospect within the hospital firewalls by the Odin Software[94].

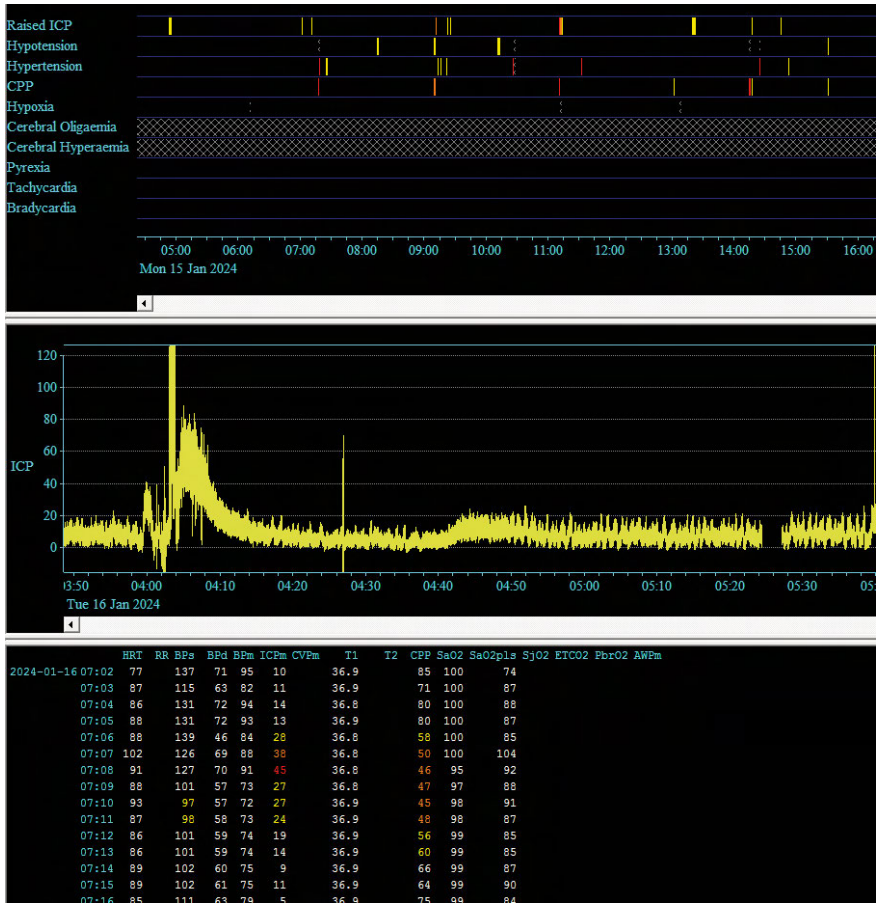

Figure 4. Screenshot of the bedside Odin monitor in the NIC unit.

Admission characteristics

The following admission characteristics were retrieved from the TBI-registry: age, gender, medical history (previous brain injury, diabetes mellitus, hypertension/cardiovascular disease (CVD), anticoagulants, ethylism/substance abuse), accident mechanism, GCS and pupil status on admission, other injuries and CT findings (EDH, ASDH, contusions, DAI, tSAH, impression fracture, mixed injuries, normal CT and other). Missing data were collected from the patient records.

Marshall classification

In addition to the registered CT findings in the TBI-registry, all patients had their initial CT scans retrospectively evaluated and categorized according to Marshall[31] (Table 3).

NIC monitoring and Treatments

Information about ICP monitoring (EVD/intraparenchymal pressure device/no ICP monitoring), mechanical ventilation, craniotomies and evacuations, thiopental coma treatment and decompressive craniectomies were retrieved from the Uppsala TBI-registry and analyzed [93].

Physiological data processing

Physiological data were processed and analyzed using the Odin software[94]. For artifact detection, the trended data was pre-processed with median filters to detect sudden spikes (of non-physiological nature) and with a specialized algorithm to detect sudden drops to a constant value (usually zero). The data was further subject to manual review to verify, or if necessary correct, the automatic procedures. Time gaps in the monitoring, because of e.g. radiology examinations and surgical procedures, were automatically excluded by the Odin software. Remaining monitoring time is defined as good monitoring time (GMT).

For Paper IV, trended minute-by-minute data (median values of five samples during each sampled minute) were used for ICP, MAP, CPP, and systolic blood pressure (SBP) and proportion of GMT (%GMT) outside predefined physiological thresholds were analyzed.

For Paper V trended minute-by-minute data for blood pressure and ICP were used, and CPP was calculated. Pressure reactivity index (PRx), Optimal CPP (CPPopt) and the difference between CPP and CPPopt (ΔCPPopt) were calculated using high-resolution data of ICP and MAP waveforms (100 Hz).

Pressure reactivity index – PRx

PRx was calculated during 5 min from unfiltered ICP and ABP waveform data as the correlation of 30 contiguous averaged 10 s segments. A 5-minute moving window advanced through the patient data in increments of 10 seconds. Six values per minute were generated and the median value was then used for each minute[55].

Optimal CPP – CPPopt

For the determination of CPPopt, 5 min median CPP values were divided into intervals of 5 mmHg bins (range CPP 40–120) and the corresponding PRx values were averaged within these intervals. An automatic curve fitting was applied to determine the CPP value with the lowest PRx value. A 4-hour moving window of CPPopt is updated each minute[95].

Deviations from optimal CPP – ΔCPPopt

Deviations from CPPopt were denoted ΔCPPopt and calculated as the difference between actual CPP and calculated CPPopt (ΔCPPopt=CPP-CPPopt). The deviation ΔCPPopt was then used as %GMT grouped into ΔCPPopt <-5, ΔCPPopt ±5 and ΔCPPopt >5.

Patient follow-up and outcome

Follow-up was done at 6–12 months according to GOSE[63,96], by a few selected persons using standardized telephone interviews.

Statistical methods

Pearson's Chi 2 test was done manually with the help of Excel for the first paper and the more advanced statistical calculations in the following papers were done using IBM SPSS Statistics (IBM Corp, Armonk, NY). A p-value <0.05 was considered statistically significant.

Paper I

Differences between the study periods were compared using Pearson's Chi 2.

Paper II

A T-test was used to compare normally distributed values. For non-parametric values, the Mann-Whitney U test was used for independent data and the Wilcoxon test was used for dependent variables. Proportional numbers were assessed with the Chi 2 test.

Paper III

Pearson's Chi-squared test was used to compare different age groups. The contribution of patient and treatment variables to outcome was assessed by

univariate logistic regression analysis. Multiple logistic regression analysis was performed with favorable outcome (GOSE 5–8) as the dependent variable and with admission and treatment variables as explanatory variables. All explanatory variables were dichotomized except age which was used as a continuous variable (increase per year).

Paper IV

Differences between age groups were assessed with Pearson's Chi 2 test. Differences in occurrence of secondary insults between age groups were assessed by the Mann-Whitney U test. To evaluate the association between admission variables and physiological variables outside the thresholds, multiple linear regression was used. The relation between outcome and %GMT outside the thresholds was examined using univariate logistic regression analysis for the age groups and the age interaction was also analyzed.

Paper V

Differences in characteristics between the age groups were analyzed with Pearson's Chi 2 test. Non-parametric data were presented as a median with interquartile range and differences between groups were tested with Mann-Whitney U test.

To analyze the influence on outcome (favorable outcome and mortality) of PRx, CPPopt and ΔCPPopt, univariate logistic regression analysis was done with favorable outcome and mortality as dependent variables. Univariate analysis was also performed for GCS M, Marshall score and sex. Multiple logistic regression analysis was performed for favorable outcome and mortality with the explanatory variables GCS M, Marshall score, sex, %GMT with PRx>0.25 and %GMT with ΔCPPopt <-5/±5/>5 mmHg.

Ethics

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The studies were approved by the Local ethical review board.

Results

Paper I

The proportion of patients 60–79 years was doubled between 2008–2009 and 1996–1997 (16% to 30%, p<0.01) (Figure 5). The mean age of admitted patients increased from 41 to 45 years.

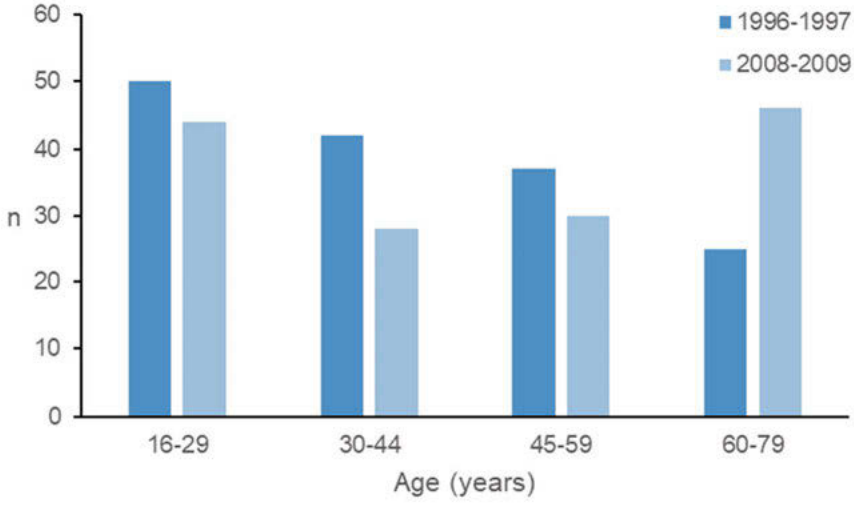

Figure 5. Comparison of age groups between time periods.

The distribution of admission GCS M grades was similar between the time periods. The dominating cause of trauma was motor vehicle accidents in both periods. A larger proportion of the patients underwent surgery in 2008–2009 compared to 1996–1996 (43% vs 32%, p<0.05). The proportion of favorable outcome was maintained at around 75% and there was no increase in patients with unfavorable or vegetative outcome when comparing 2008–2009 with 1996–1997. In the elderly ≥60 years, favorable outcome had decreased 13% (65% to 52%) from 1996–1997 to 2008–2009, mortality had increased 13% and unfavorable outcome was unchanged (Figure 6). The mean age of the patients who died was 48 years 1996–1997 and 62 years 2008–2009.

There was a higher mortality observed in patients who were admitted in GCS M ≥4 2008–2009 (10% vs 2.8%, p<0.05).

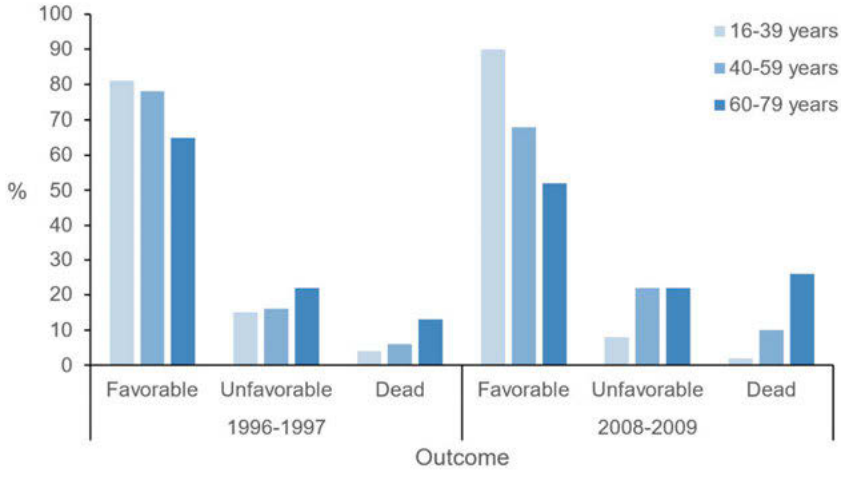

Figure 6. Outcome by age groups and period.

Paper II

In this study of 284 patients treated in 2008–2010, the proportion of elderly ≥65 years was 22% and the proportion of patients aged 16–64 was 78% (Table 6). There was a difference in sex distribution between the age groups with 36% females among the elderly and 16% in the young group. A larger proportion of the elderly had a medical history of diabetes mellitus and hypertension/CVD, and the use of anticoagulants was seven times more common in the elderly. Among the young, vehicle accidents were the most common cause (36%) while falls were most common in the elderly (81%). There was a difference in CT findings, where the elderly had ASDH more often (51% vs 18%). Extradural hematomas, mixed injuries, and DAI were more common in the young group (Table 6).

The median admission GCS M was 5 in both groups. There was no significant difference in mechanical ventilation (76% in both groups), ICP monitoring (elderly 44% and young 57%), and length of mechanical ventilation (elderly mean 8 days and young mean 6 days). Craniotomy for mass lesions was performed in 47% of the elderly and in 28% of the young ($p<0.01$). At discharge from the NIC unit, 29% of the elderly and 41% of the young ($p<0.05$) had improved consciousness from not being communicative (RLS ≤3) to becoming talkative (RLS 1–2).

Table 6. Demographic data of included patients.

	Elderly n (%)	**Younger n (%)**	**p-value**
No of patients	62 (22)	222 (78)	
Sex (female)	22 (36)	36 (16)	p<0.05
Medical history			
Previous brain injury	12 (20)	27 (13)	n.s.
Diabetes mellitus	9 (16)	9 (4)	p<0.05
Hypertension/CVD	28 (52)	21 (10)	p<0.001
Anticoagulation	25 (46)	12 (6)	p<0.001
Ethylism	12 (22)	37 (19)	n.s.
Accident mechanism			
Bicycle accident	0 (0)	10 (4)	n.s.
Fall accident	50 (81)	79 (36)	p<0.005
Vehicle accident	3 (5)	83 (37)	p<0.05
Pedestrian hit by vehicle	3 (5)	8 (4)	n.s.
Assault	2 (3)	14 (6)	n.s.
Sports injury	1 (2)	9 (4)	n.s.
Other	3 (5)	19 (9)	n.s.
CT findings			
ASDH	31 (50)	40 (18)	p<0.001
Contusions	19 (31)	78 (35)	n.s.
tSAH	4 (6)	18 (8)	n.s.
Mixed	4 (6)	28 (13)	p<0.001
EDH	0 (0)	20 (9)	p<0.05
Impression fracture	1 (2)	7 (3)	n.s.
Other	3 (5)	3 (1)	n.s.
DAI	0 (0)	26 (12)	p<0.05
Normal	0 (0)	3 (1)	n.s.

Some patients were not included in the analysis because of unknown data regarding previous brain injury (3 Elderly), diabetes mellitus (6 Elderly and 13 Young), hypertension (8 Elderly and 14 Young), anticoagulation (8 Elderly and 12 Young) and ethylism (7 Elderly and 24 Young).

At the follow-up, the elderly showed favorable outcome in 51% of the cases compared to 72% among the younger patients (p<0.05). Mortality was 25% in the elderly and 7% among the younger (p<0.05). There was no difference between the groups in unfavorable outcome (Figure 7).

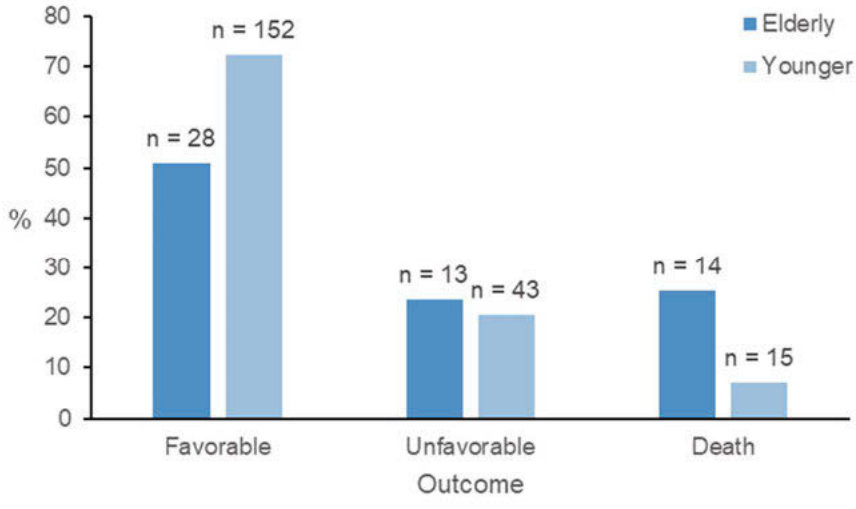

Figure 7. Outcome at 6 months.

Paper III

Two-hundred-twenty patients ≥60 years were included. The mean age was 70 years (range 60–86). At 6 months follow-up, 46% had a favorable outcome, 27% unfavorable and the mortality was 27%. One-hundred-seventy patients were within 60–74 years of age and 50 patients within 75–89 years of age. Overall, 26% were females, and there was no difference between the age groups. There was no difference in the cause of trauma between the age groups with fall accidents as the most common cause in 77% of all patients. In the group, 75–89 years of age, TBI under the influence of drugs/alcohol occurred in 6% compared to 25% in the group 60–74 years ($p<0.01$). Admission GCS M score was GCS M ≥4 in 90% of all included patients with no difference between the age groups.

ASDH was more common in the 75–89 years old (76% vs 34%, $p<0.001$) and contusions were less common (10% vs 35%, $p<0.01$) (Table 7). There were also differences in the Marshall classification of the initial CT scan where focal mass lesions (evacuated and non-evacuated mass lesions) were more common in the 75–89 years old (64% vs 41%, $p <0.01$). More than half of all patients (54%) had hypertension/CVD, 72% in the 75–89 years old and 48% among the younger ($p<0.01$). One in ten of the 75–89 year old had a history of ethylism in contrast to three out of ten in the 60–74 year old ($p<0.01$) (Table 7).

Antithrombotic drugs were common in the elderly, 37% overall, and in 62% of the 75–89-year-old and 30% of the 60–74 years old ($p<0.001$) (Table 7). Warfarin was more common in the 75–89-year-olds (42% vs 8%, $p<0.01$)

but there was no significant difference in the use of antiplatelets between the age groups (Table 7).

Table 7. Patient and trauma characteristics on admission.

Characteristics	All n (%)	60–74 n (%)	75–89 n (%)	p 60–74 vs 75–89	
Total	220	170	50		
Dominating injury type on CT					
ASDH	95 (43)	57 (34)	38 (76)	<0.001	***
Other	3 (1)	2 (1)	1 (2)		
DAI	2 (1)	2 (1)	0 (0)		
EDH	4 (2)	4 (2)	0 (0)		
Impression fracture	3 (1)	3 (2)	0 (0)		
Contusions	64 (29)	59 (35)	5 (10)	<0.001	***
Mixed	26 (12)	23 (14)	3 (6)	0.147	
Normal CT	0 (0)	0 (0)	0 (0)		
Traumatic SAH	23 (10)	20 (12)	3 (6)	0.242	
CT Marshall classification					
Diffuse injury I	2 (1)	2 (1)	0 (0)		
Diffuse injury II	80 (36)	69 (41)	11 (22)	0.016	*
Diffuse injury III	21 (9)	19 (11)	2 (4)		
Diffuse injury IV	14 (6)	9 (5)	5 (1)		
Evacuated mass lesion	68 (31)	48 (28)	20 (40)	0.114	
Non-evacuated mass lesion	35 (16)	23 (14)	12 (24)	0.075	
Diffuse injury I-IV	117 (53)	99 (58)	18 (36)	0.006	**
Focal mass lesion	103 (47)	71 (41)	32 (64)	0.006	**
Medical history of					
Brain injury/disease	45 (20)	33 (19)	12 (24)	0.480	
TBI	8 (4)	7 (4)	1 (2)		
Diabetes mellitus	36 (16)	25 (15)	11 (22)		
Hypertension/CVD	118 (54)	82 (48)	36 (72)	0.003	**
Ethylism	56 (25)	51 (30)	5 (10)	0.004	**
Antithrombotic drugs	82 (37)	51 (30)	31 (62)	<0.001	***
Antiplatelet	48 (22)	36 (16)	12 (24)	0.671	
Warfarin	34 (15)	13 (8)	21 (42)	<0.001	***
NOAC	8 (4)	7 (4)	1 (2)		
LMWH	6 (3)	4 (2)	2 (4)		

Non-vitamin K Oral Anticoagulants (NOAC) and Low Molecular Weight Heparin (LMWH).
* p<0.05, ** p<0.01 and *** p<0.001.

Eighty percent of the elderly patients were intubated and mechanically ventilated for a mean of 7 days (median 6, range 1–21) and 53% had ICP monitoring for a mean of 10 days (median 8, range 2–25). Regarding surgical treatment, 43% had a craniotomy done during the NIC and the most common reason was evacuation of ASDH (36%) followed by evacuation of contusions (11%). Four percent (9 patients in total, 7 patients 60–74 years and 2 patients 75–89 years) were treated with decompressive hemicraniectomy. There was a difference between the age groups where 60% of the 75–89 year old had a

craniotomy performed in contrast to 38% in the 60–74 year old patients ($p<0.01$).

Follow-up was done after 7.8 months in mean (median 7, range 5–28). Out of the 220 patients, 101 patients (46%) had a favorable outcome (GOSE 5–8), 60 patients (27%) had unfavorable outcome (GOSE 2–4) and 59 patients (27%) had died. When outcome was analyzed by 5–year subgroups there was a favorable outcome >40% and mortality <40% up until 75–79 years of age. There were clear trends that favorable outcome decreases with age and mortality increases. Unfavorable outcome did not show the same pattern and did not increase above 75 years of age (Figure 8).

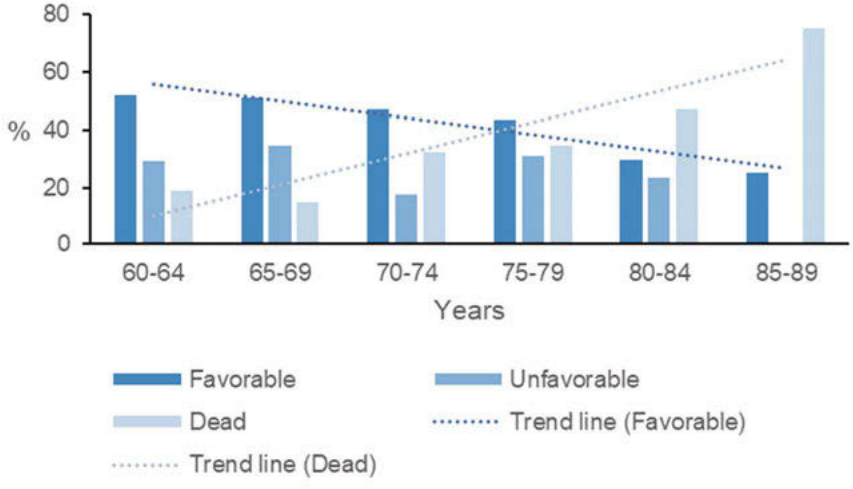

Figure 8. Outcome by 5-year age groups.

Univariate logistic regression analysis with favorable outcome as dependent variable for possible admission prognostic factors showed a negative correlation with age ($p<0.05$), GCS M ≤3 on admission ($p<0.01$), initial CT Marshall score evacuated mass lesion ($p<0.001$) and warfarin medication ($p<0.05$). A positive correlation with age was seen with initial CT Marshall score I-IV ($p<0.001$). Regarding possible treatment predictors, logistic regression analysis with favorable outcome as a dependent variable showed a negative correlation with craniotomy ($p<0.01$), evacuation of extracerebral hematoma ($p<0.05$) and mechanical ventilation ($p<0.001$).

A multiple logistic regression analysis for admission and treatment prognostic factors with favorable outcome as dependent variable showed a negative correlation with age ($p<0.05$), GCS M ≤3 on admission ($p<0.05$), multiple injuries ($p<0.05$), and mechanical ventilation ($p<0.01$) (Figure 9).

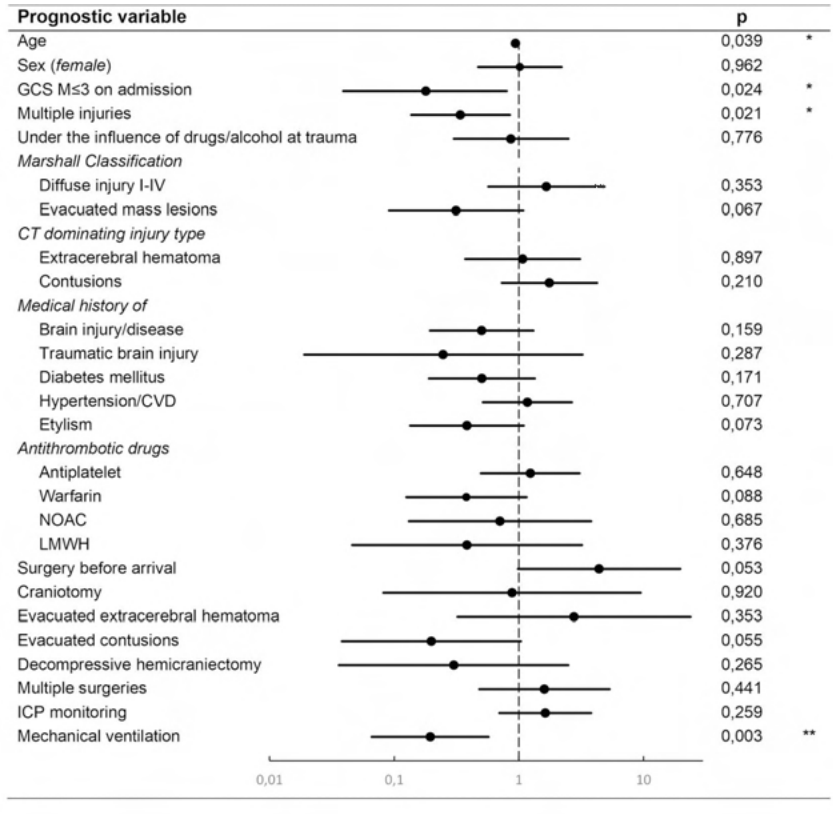

Figure 9. Prognostic model for favorable outcome. Multiple logistic regression analysis with favorable outcome as dependent variable. Non-vitamin K Oral Anticoagulants (NOAC) and Low Molecular Weight Heparin (LMWH). * $p<0.05$, ** $p<0.01$ and *** $p<0.001$.

Paper IV

Five-hundred-seventy patients were included, 151 elderly ≥65 years (mean 72.3, range 65–87) and 419 younger 16–64 years (mean 41.5, range 16–64).

When comparing the elderly with the younger, the elderly had the following significant differences in admission characteristics: a larger proportion of females (28.5% vs 19.6%, $p<0.05$), fall accidents (80.1% vs 42.0%, $p<0.001$), previous brain injury/disease (22.5% vs 11.0%, $p<0.001$), diabetes mellitus (18.5% vs 6.2%, $p<0.001$), hypertension/cerebrovascular disease (58.3% vs 13.8%, $p<0.001$), ongoing treatment with anticoagulants/antiplatelets (43.0% vs 7.9%, $p<0.001$), respectively, and smaller proportions of patients admitted from other hospitals (67.5% vs 82.3%, $p<0.001$), multiple injuries (17.9% vs 47.0%, $p<0.001$), the influence of drugs/alcohol (14.6% vs 34.1%, $p<0.001$),

vehicle accidents (7.3% vs 33.2%, p<0.001) and sports injury (0.7% vs 4.3% p<0.05), respectively.

When considering the radiological findings on the initial CT, the older patients had a significantly larger proportion of ASDH (51.7% vs 20.5%, p<0.001) and smaller proportions of DAI (0.0% vs 8.6%, p<0.001) and EDH (0.7% vs 11.5%, p<0.001). This was also reflected in the Marshall classification showing that the elderly had a lower proportion of Diffuse Injury I–IV (45% vs 77.6, p<0.001) and higher proportions of evacuated mass lesions (37.7% vs 16.5%, p<0.001) and non-evacuated mass lesion (17.2% vs 6%, p<0.001).

When comparing treatment characteristics, the elderly were operated with craniotomy more often (47.7% vs 32.7%, p<0.01) and the most common reason was evacuation of extracerebral hematoma (45.0% vs 23.6%, p<0.001). The younger group had more patients treated with hemicraniectomy (8.1% vs 3.3%, p<0.05) and thiopental (7.9% vs 0.7%, p<0.01).

There was no difference between the groups regarding ICP and CPP monitoring. Monitoring of blood pressure was more frequent in the elderly (95.36% vs 89.98%, p<0.05).

When looking at the occurrence of secondary insults, the occurrences of %GMT with MAP >120 and SBP >180 were more frequent in the elderly and the occurrences of ICP ≥20, CPP ≤60 and MAP ≤80 were more frequent among the young (Table 8).

Table 8. Occurrence of secondary insults by age group.

	Age 16–64		Age ≥65		16–64 vs ≥65[a]	
Physiological parameter	**Median %GMT**	**IQR %GMT**	**Median %GMT**	**IQR %GMT**	**p**	
ICP ≥20	6.26	1.39–17.01	3.14	0.73–9.05	0.005	**
CPP ≤60	5.52	2.05–11.79	2.51	1.16–1.94	0.001	**
CPP >100	1.27	0.51–5.25	6.37	1.96–18.57	0.000	***
MAP ≤80	23.01	10.67–39.49	17.51	8.75–32.68	0.040	*
MAP >120	0.48	0.17–1.77	1.31	0.36–5.52	0.000	***
SBP ≤100	0.75	0.25–2.39	0.71	0.25–1.83	0.499	
SBP >180	1.04	0.18–4.72	7.53	1.54–19.63	0.000	***

Interquartile range (IQR). [a] Difference between age groups tested with Mann-Whitney U test. * p<0.05, ** p<0.01 and *** p<0.001.

The multiple linear regression model with physiological variables as dependent variables and age ≥65 years, gender, GCS M, other injuries, extracerebral hematoma, and contusions as explanatory variables showed that age ≥65 years was an independent predictor for lower %GMT with ICP ≥20 and higher %GMT with CPP >100, MAP >120, and SBP >180, respectively.

The results from the logistic regression analyzes with favorable outcome and mortality as dependent variables and physiological parameters as explanatory variables are presented in Table 9 and Table 10. Low %GMT with CPP

>100 and SBP >180 were associated with higher odds of favorable outcome in the analysis of all ages (Table 9) and in the subanalysis of ages 16–64 years (Table 10). When the interaction with age was analyzed, there was a statistically significant interaction between age and %GMT with SBP >180 (p interaction=0.025) where the odds ratio (per unit increase in %GMT with SBP >180) was 1.007 (0.985–1.030) in patients≥65 years and 0.965 (0.937–0.994) in patients 16–64 years (Table 10).

High %GMT with ICP ≥20, CPP >100, and SBP ≤100 was associated with a higher risk of mortality in patients 16–64 years but not in the elderly (Table 10).

Table 9. Univariate logistic regression analysis of outcome (favorable outcome: GOSE 5–8 and mortality: GOSE 1) in relation to physiological variables.

	All ages		
Variable (%GMT)	**OR (CI 95%)**	**p**	
Favorable outcome model			
ICP ≥20	0.989 (0.967–1.002)	0.093	
CPP ≤60	1.001 (0.982–1.020)	0.926	
CPP >100	0.961 (0.940–0.984)	<0.001	***
MAP ≤80	1.007 (0.999–1.016)	0.097	
MAP >120	0.989 (0.960–1.006)	0.136	
SBP ≤100	0.992 (0.967–1.017)	0.531	
SBP >180	0.997 (0.960–0.994)	0.007	**
Mortality outcome model			
ICP ≥20	1.018 (1.002–1.034)	0.024	*
CPP ≤60	1.022 (0.999–1.045)	0.059	
CPP >100	1.034 (1.013–1.054)	<0.001	***
MAP ≤80	1.002 (0.991–1.014)	0.701	
MAP >120	1.021 (0.995–1.048)	0.115	
SBP ≤100	1.053 (1.023–1.083)	<0.001	***
SBP >180	1.035 (1.015–1.055)	<0.001	***

OR: Odds Ratio per one unit increase in %GMT. Confidence interval (CI). * p<0.05, ** p<0.01 and *** p<0.001.

Table 10. Univariate logistic regression analysis of outcome in relation to physiological variables and the interaction with age. Favorable outcome (GOSE 5–8) and mortality (GOSE 1) at follow-up.

	Age 16–64			Age ≥65		Age Interaction [a]	
Variable (%GMT)	**OR (CI 95%)**	**p**		**OR (CI 95%)**	**p**	**p**	
Favorable outcome model							
ICP ≥20	0.982 (0.967–0.997)	0.017	*	1.003 (0.977–1.030)	0.827	0.167	
CPP ≤60	1.002 (0.978–1.027)	0.874		0.993 (0.962–1.025)	0.669	0.663	
CPP >100	0.969 (0.942–0.997)	0.030	*	0.965 (0.929–1.002)	0.062	0.851	
MAP ≤80	1.009 (0.998–1.019)	0.107		0.998 (0.982–1.015)	0.833	0.294	
MAP >120	0.991 (0.957–1.027)	0.628		0.992 (0.961–1.025)	0.646	0.959	
SBP ≤100	0.998 (0.967–1.029)	0.885		0.965 (0.903–1.031)	0.294	0.374	
SBP >180	0.965 (0.937–0.994)	0.020	*	1.007 (0.985–1.030)	0.521	0.025	*
Mortality outcome model							
ICP ≥20	1.026 (1.005–1.048)	0.015	*	1.023 (0.994–1.054)	0.123	0.871	
CPP ≤60	1.028 (0.987–1.072)	0.180		1.028 (0.991–1.066)	0.134	0.989	
CPP >100	1.032 (1.002–1.063)	0.036	*	1.016 (0.989–1.045)	0.242	0.453	
MAP ≤80	1.003 (0.984–1.022)	0.759		1.010 (0.993–1.027)	0.244	0.594	
MAP >120	1.017 (0.957–1.080)	0.589		1.003 (0.971–1.035)	0.877	0.685	
SBP ≤100	1.067 (1.028–1.107)	<0.001	***	1.058 (0.993–1.127)	0.079	0.822	
SBP >180	1.048 (1.007–1.091)	0.022	*	1.001 (9.977–1.025)	0.953	0.052	

OR: Odds Ratio per one unit increase in %GMT. * $p<0.05$, ** $p<0.01$ and *** $p<0.001$. [a] Age interaction analyzed with multiple logistic regression for each physiological variable including Age ≥65, physiological variable and interaction (physiological parameter * Age ≥65). p-value for the interaction is presented.

Paper V

Four-hundred-seventy-one patients were included, 129 ≥65 years (median 78, IQR 68–75) and 342 16–64 years old (median 44, IQR 25–55). Looking at the patient characteristics the following significant differences were found between the age groups: elderly were more often males (82.2% vs 77.5%, p<0.001), had slightly higher GCSM-score (median 5, IQR 5–6 vs median 5, IQR 4–5, p=0.021), had higher Marshall score (median 5 vs 2, p<0.001) and had more craniotomies (64.3% vs 48.8%, p<0.005). There was no difference between the age groups regarding ICP monitoring. Last-tier treatment was less used in the elderly; decompressive craniectomies (4.7% vs 12.9%, p=0.010) and thiopental (3% vs 15.7%, p<0.001).

The elderly had less favorable outcome (GOSE 5–8: 39.5% vs 59.6%, p<0.001) and higher mortality (31.0% vs 10.8%, p<0.001).

Physiological monitoring data for the 10-day monitoring period are presented in Table 11. The elderly showed significantly higher median blood pressure, PRx, CPP and CPPopt. The elderly had a lower %GMT with ΔCPPopt ±5. The elderly also had significantly lower median ICP.

Table 11. Physiological features for the whole 10-day monitoring period.

	16–64 years	**≥65 years**	**p**	
MAP [a]	87.1 (83.4–92.3)	91.7 (87.3–96.7)	<0.001	***
SBP [a]	137.8 (129.9–147.4)	150.6 (140.0–158.5)	<0.001	***
ICP [a]	12.2 (8.7–14.8)	10.6 (7.2–12.9)	<0.001	***
CPP [a]	75.3 (70.7–81.0)	80.6 (76.1–89.1)	<0.001	***
CPPopt [a]	75.2 (71.6–79.6)	80.8 (75.8–87.2)	<0.001	***
PRx [a],	0.03 (-0.06–0.12)	0.10 (0.02–0.19)	<0.001	***
PRx >0 [b]	52.2 (42.0–63.5)	62.6 (51.2–71.8)	<0.001	***
PRx >0.25 [b]	26.9 (20.4–37.2)	36.6 (26.8–46.0)	<0.001	***
PRx >0.35[b]	19.5 (14.2–27.9)	26.0 (18.4–35.3)	<0.001	***
ΔCPPopt <-5 [b]	30.9 (23.0–40.2)	34.9 (25.7–44.0)	0.014	*
ΔCPPopt ±5 [b]	28.4 (23.4–34.2)	24.4 (20.5–27.9)	<0.001	***
ΔCPPopt >5[b]	33.1 (25.2–40.5)	33.9 (25.6–43.8)	0.236	

Difference between age groups tested with Mann-Whitney U test.
*p < 0.05, **p < 0.01, and ***p < 0.001. [a] median (IQR). [b] %GMT median (IQR).

When the temporal patterns of MAP, SBP, ICP, CPP, and PRx were analyzed by day and divided into favorable and unfavorable outcome, it seemed to be a tendency that patients ≥65 years with lower MAP day 8–10, lower SBP day 3–10 and higher PRx day 0–5 had more unfavorable outcome (Figure 10). In the young group, patients with higher PRx and higher MAP had significantly less favorable outcome during almost the whole time period (Figure 10). The temporal patterns of CPPopt and %GMT with ΔCPPopt <-5/±5/>5 showed no

significant differences between favorable and unfavorable outcome at any day in the elderly (Figure 10). In the young group, patients with unfavorable outcome had significantly higher median CPPopt on almost all days (days 1,2,5,7 and 9) and significantly lower %GMT with ΔCPPopt ±5 days 1, 4 and 5 (Figure 10).

Univariate logistic regression for favorable outcome showed in the young group significantly lower odds ratio (OR) for favorable outcome with increasing Marshall score and increasing %GMT with PRx >0.25, and significantly higher OR for favorable outcome with higher admission GCS M and %GMT ΔCPPopt ±5 (Table 12). In the elderly, no significant predictive variable was found (Table 13). Multiple logistic regression for favorable outcome in the young showed significantly higher adjusted odds ratio (AOR) for GCS M and significantly lower AOR for Marshall score and %GMT PRx >25 (Table 12). In the elderly, no significant predictive variable was found in the multivariate analysis (Table 13).

In the logistic regression model for mortality, the elderly were found to have significantly higher OR/AOR for mortality with increasing PRx, both in the univariate and multivariate analyzes (Table 13). Univariate analysis showed in the young group that increasing Marshall score, increasing %GMT with PRx >0.25 and increasing %GMT with ΔCPPopt <-5 were associated with higher OR for mortality, while lower GCS M and higher %GMT with CPPopt ±5 were associated with lower OR (Table 12). In the multiple regression analysis of the young group, a higher %GMT with PRx >0.25 was associated with significantly higher AOR for mortality and higher GCS M with lower AOR (Table 12).

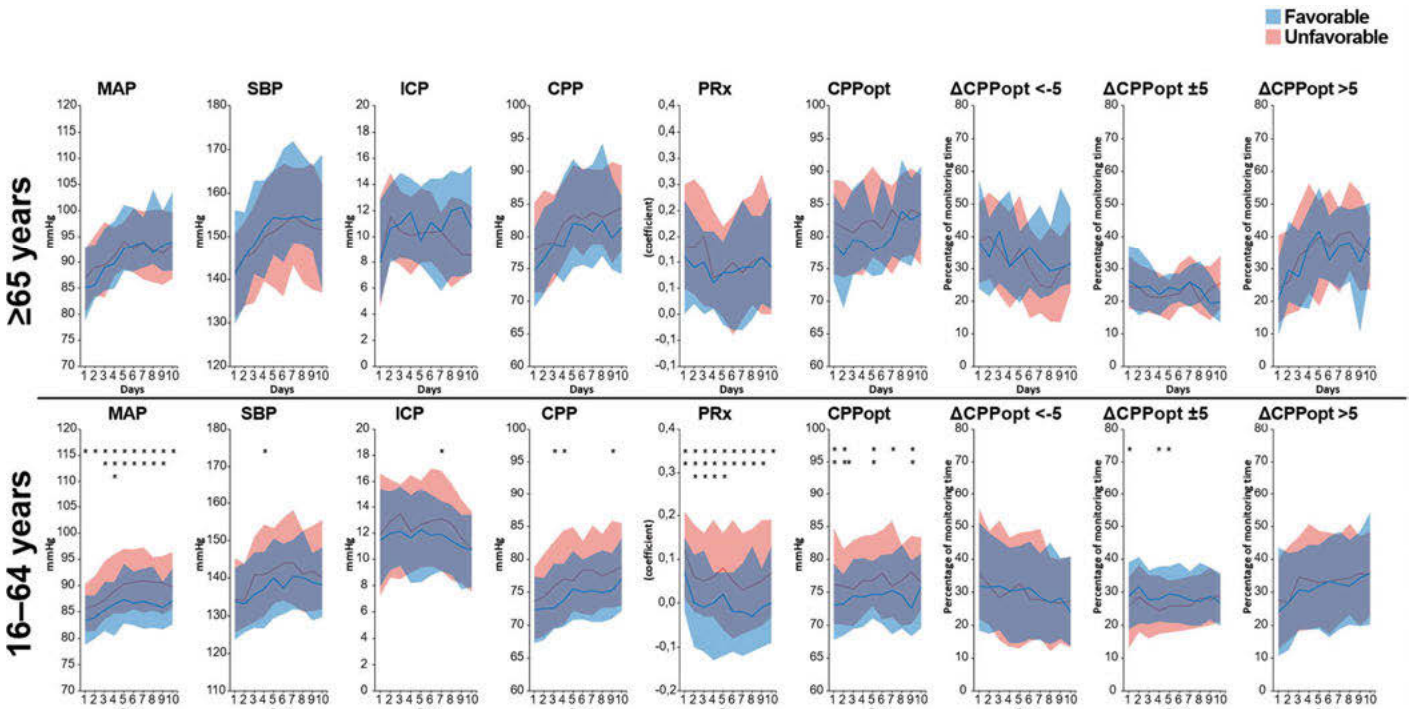

Figure 10. Temporal daily distribution of MAP, SBP, ICP, CPP and PRx by outcome and age group. Distribution of patients' daily mean values on group level for each physiological feature with the distribution presented as median (line) and IQR (band). Favorable outcome GOSE 5–8 and unfavorable GOSE 1–4. Difference between favorable and unfavorable tested for each day with Mann-Whitney U test. *p<0.05, **p<0.01, and ***p<0.001.

Table 12. Univariate and multiple logistic regression analysis (whole 10-day period) with favorable outcome and mortality as dependent variables for patients 16–64 years old.

		16–64 years					
		Univariate logistic regression			Multiple logistic regression		
	Variable	**OR (95% CI)**	**p**		**AOR (95% CI)**	**p**	
Favorable model[a]	Sex (male)	1.005 (0.599–1.686)	0.985		1.134 (0.628–2.046)	0.676	
	GCS M on admission	1.852 (1.499–2.288)	<0.001	***	1.914 (1.484–2.467)	<0.001	***
	Marshall score	0.763 (0.655–0.889)	<0.001	***	0.809 (0.679–0.964)	0.018	*
	PRX >0.25 (%GMT)	0.964 (0.948–0.980)	<0.001	***	0.973 (0.953–0.993)	0.009	**
	ΔCPPopt <-5 (%GMT)	0.995 (0.979–1.011)	0.520		1.211 (0.854–1.718)	0.282	
	ΔCPPopt ±5 (%GMT)	1.048 (1.016–1.082)	0.003	**	1.287 (0.866–1.912)	0.213	
	ΔCPPopt >5 (%GMT)	0.987 (0.968–1.005)	0.164		1.184 (0.835–1.679)	0.343	
Mortality model[b]	Sex (male)	0.783 (0.330–1.860)	0.580		0.830 (0.292–2.358)	0.726	
	GCS M on admission	0.648 (0.514–0.818)	<0.001	*	0.784 (0.562–0.995)	0.046	*
	Marshall score	1.313 (1.048–1.645)	0.018	*	1.243 (0.949–1.627)	0.114	
	PRX >0.25 (%GMT)	1.057 (1.035–1.080)	<0.001	***	1.029 (1.000–1.058)	0.046	*
	ΔCPPopt <-5 (%GMT)	1.040 (1.013–1.067)	0.003	**	1.118 (0.715–1.750)	0.625	
	ΔCPPopt ±5 (%GMT)	0.915 (0.865–0.969)	0.002	**	1.066 (0.643–1.768)	0.803	
	ΔCPPopt >5 (%GMT)	0.980 (0.949–1.012)	0.221		1.107 (0.707–1.733)	0.658	

*p<0.05, **p<0.01, and ***p<0.001. [a]Nagelkerke R Square = 0.254. [b]Nagelkerke R Square = 0.176.

Table 13. Univariate and multiple logistic regression analysis (whole 10-day period) with favorable outcome and mortality as dependent variables for patients ≥65 years old.

		≥65 years				
		Univariate logistic regression			Multiple logistic regression	
	Variable	OR (95% CI)	p		AOR (95% CI)	p
Favorable model[a]	Sex (male)	0.616 (0.234–1.624)	0.328		0.858 (0.302–2.439)	0.774
	GCS M on admission	1.186 (0.864–1.629)	0.292		1.158 (0.823–1.630)	0.401
	Marshall score	0.949 (0.763–1.180)	0.636		0.958 (0.758–1.212)	0.721
	PRX >0.25 (%GMT)	0.983 (0.960–1.006)	0.148		0.986 (0.960–1.013)	0.300
	ΔCPPopt <-5 (%GMT)	1.001 (0.978–1.025)	0.932		0.905 (0.535–1.533)	0.711
	ΔCPPopt ±5 (%GMT)	1.024 (0.972–1.079)	0.364		0.907 (0.496–1.658)	0.751
	ΔCPPopt >5 (%GMT)	0.991 (0.965–1.018)	0.502		0.897 (0.529–1.520)	0.685
Mortality model[b]	Sex (male)	0.968 (0.364–2.575)	0.948		1.084 (0.357–3.292)	0.887
	GCS M on admission	0.822 (0.605–1.115)	0.208		0.879 (0.616–1.254)	0.477
	Marshall score	1.196 (0.944–1.515)	0.137		1.159 (0.888–1.513)	0.278
	PRX >0.25 (%GMT)	1.044 (1.017–1.071)	0.001	**	1.035 (1.005–1.066)	0.023
	ΔCPPopt <-5 (%GMT)	1.015 (0.991–1.041)	0.227		1.117 (0.637-1.961)	0.699
	ΔCPPopt ±5 (%GMT)	0.983 (0.930–1.038)	0.535		1.127 (0.594–2.140)	0.714
	ΔCPPopt >5 (%GMT)	0.986 (0.959–1.015)	0.343		1.108 (0.630–1.947)	0.722

*p<0.05, **p<0.01, and ***p<0.001. [a]Nagelkerke R Square = 0.049. [b]Nagelkerke R Square=0.135.

The combined effect of PRx/CPP and PRx/ΔCPPopt, respectively, on the outcome (GOSE) was explored by creating heatmaps. The heatmap interaction analysis of PRx and ΔCPPopt showed a clear difference between the age groups where the elderly had a much more dispersed distribution with their centers for favorable outcome around PRx 0 (range -0.5–0.5) and ΔCPPopt -10 (range -20–0) and the younger patients with their centers around PRx -0.5 (range -0.75–0) and ΔCPPopt closer to zero (range -10–10) (Figure 11). The density plots showed almost the same centers in both age groups (marginally lower PRx center in the younger group) but with a wider field for the elderly (Figure 11).

The elderly also had a more dispersed center in the PRx/CPP heatmap mostly with PRx between -0.5–0.5 and CPP between 60–80, in contrast to the younger group where the field had a more distinct center at approximately PRx -0.3 (range PRx -0.7–0.4) and CPP 65 (range CPP 50–80). The density plots showed almost the same center in both age groups (marginally lower PRx center in the younger) but with a wider field in the elderly group (Figure 12).

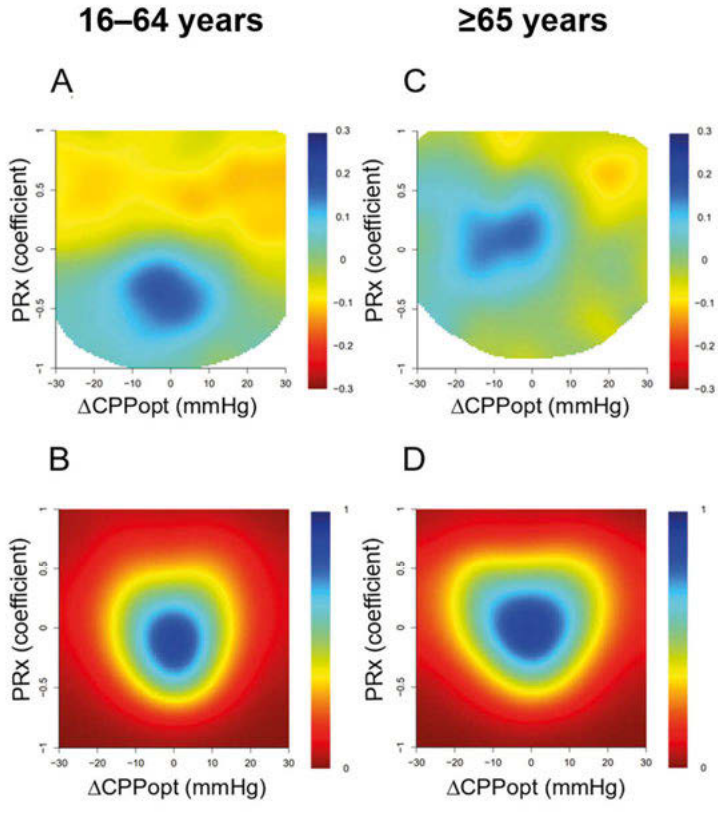

Figure 11. The combined effect of PRx and ΔCPPopt on clinical outcome. The figure illustrates the combined association of the percentage of monitoring time (%GMT) for absolute PRx and ΔCPPopt values with GOSE (A and C) and density plots with the data frequency of certain PRx and ΔCPPopt combinations (B and D). The %GMT for the concurrent combination of PRx and ΔCPPopt during the 10 days was calculated and correlated with GOSE. The jet color range denotes the value of the correlation coefficients, where blue color indicates favorable and red color indicates unfavorable outcome. Pixels with less than five patients with 5 min of monitoring with a certain combination of PRx and ΔCPPopt were colored white.

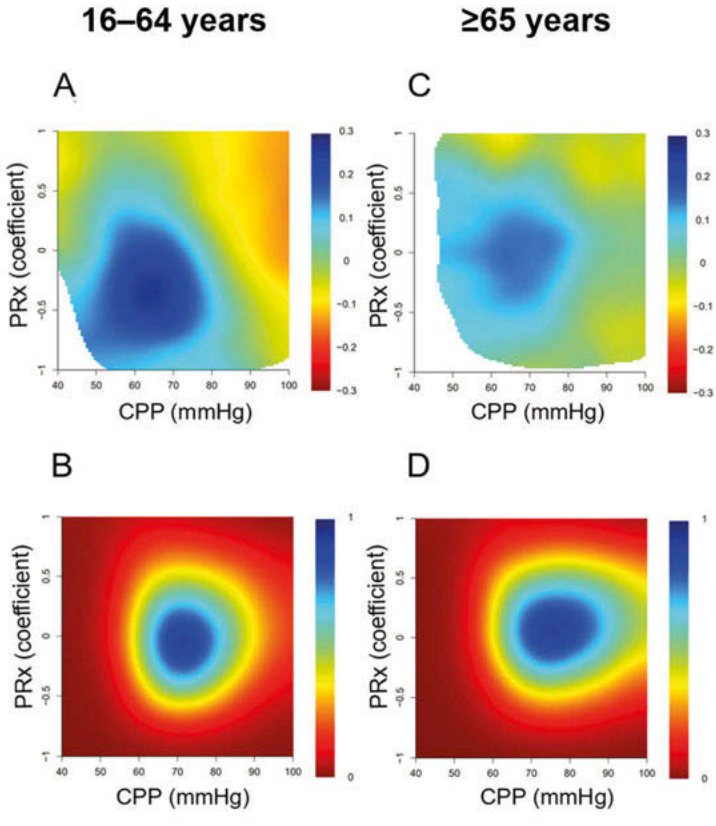

Figure 12. The combined effect of PRx and CPP on clinical outcome. The figure illustrates the combined association of the percentage of monitoring time (%GMT) for absolute PRx and CPP values with GOSE (A and C) and density plots with the data frequency of certain PRx and CPP combinations (B and D). The %GMT for the concurrent combination of PRx and CPP during the 10 days was calculated and correlated with GOSE. The jet color range denotes the value of the correlation coefficients, where blue color indicates favorable and red color indicates unfavorable outcome. Pixels with less than five patients with 5 min of monitoring with a certain combination of PRx and CPP were colored white.

Discussion

Paper I

There has been a successive improvement of outcome for TBI patients during the introduction of NIC at the Uppsala University Hospital from 1980–1981 to 1987–1988 and to 1996–1997[2,4]. However, when the results from 2008–2009 were analyzed, no further improvement in outcome was found. This could be explained by that no major changes in the treatment had been introduced between the last two periods and that the quality of NIC had culminated or was close to culminating. Another explanation could be that the patient's characteristics had changed.

We found that patients ≥60 years of age had doubled, from 16% to 30%. This finding was expected since the mean age in Sweden increases gradually. In 2009, 18% of the population was above 65 years of age and in 2060, 25% of the inhabitants are expected to be above 65 years[8]. There was no change in admission GCS M grades or predominating cause of trauma. There was a larger proportion of patients who underwent surgery 2008–2009. When assessing mortality in patients with GCS M ≥4 there had been a substantial increase. However, the mean age of the patients who died had increased from 48 to 62 years between the time periods. Detailed analyzes of the patients who died showed that many deaths could be explained by aggravating patient-related factors.

The findings that a large proportion of patients with favorable outcome at around 75% was maintained despite that the proportion of patients ≥60 years of age doubled may indicate that the quality of NIC had increased or at least was unchanged. The study underlines the need for more studies of TBI in the elderly to improve the management in that particular group of TBI patients which requires special considerations. A favorable outcome of slightly more than 50% indicates that the elderly may be treated with relatively good results and should be candidates for NIC.

Paper II

The focus of this study was to evaluate the demographics, management and outcome in the elderly receiving NIC and compare them with younger patients. The proportion of patients ≥65 years was 22%, which not was

unexpected. There was a clear difference in cause of trauma between the young and the old where falls were much more common in the elderly. This finding is well in line with what has been observed by many others[97–100]. The elderly are more prone to falls due to orthostatic hypotension, vertigo, diabetes mellitus, poor vision, insufficient physiotherapy and unsuitable home environments[101,102]. The type of TBI also differed by age group. Patients ≥65 years had a higher proportion of ASDH, and younger patients had a higher degree of EDH, DAI and mixed injuries. The differences in injury patterns are mainly explained by the different causes of trauma and have also been demonstrated by others[103–105]. The distribution of GCS M score on admission was the same in both groups.

There was no difference in NIC treatment regarding the length of stay, proportion of patients mechanically ventilated and the duration of mechanical ventilation, which suggest that there was no significant difference in the NIC treatment depending on age. Patients ≥65 had surgery in a higher proportion (47% vs 28%) which is likely to be explained by the different injury types where patients ≥65 years had more ASDH.

Favorable outcome was achieved in 72% of the young and 51% of the patients ≥65 years at 6 months follow-up. The mortality increased with age. However, 51% favorable outcome in patients ≥65 years appears to be a relatively good result compared with the results of other earlier studies reporting mortality over 50% and unfavorable outcome between 74–90% in patients ≥65 years[16,103,106–110]. Another interesting finding was that 61% of the young had a favorable outcome after craniotomy compared to 22% in patients ≥65 years of age. This was regardless if the patients ≥65 years were awake or unconscious before the surgery. Thus, it appears that the consciousness level at admission does not solely define the functional outcome in the elderly, meaning that the elderly do not necessarily have a bad outcome despite being unconscious. It would be desirable to have a more accurate prognostic prediction to select elderly patients for NIC treatment and surgery.

Paper III

In this study of 220 patients ≥60 years receiving modern NIC, it was found that those patients had a fair chance of favorable outcome (46%) and that the risk of unfavorable outcome was 27% and the risk of mortality was 27%. High age, multiple injuries, and GCS M ≤3 on admission had a negative correlation with favorable outcome. This was anticipated and others have also made similar observations in elderly[111–114]. We found that mechanical ventilation had a negative correlation with favorable outcome. Barnato and coll. found that the elderly treated in intensive care with mechanical ventilation who survived had worse functional outcome[115]. The observed worse outcome associated with mechanical ventilation likely depends both on the severity of the brain injury

as well as on the development of systemic complications. It is important to emphasize that the findings should not restrict older patients from mechanical ventilation [116].

In the two previous studies there was a high incidence of antithrombotic drugs among the elderly. It was therefore desirable to have a closer look at that, since a negative impact on outcome could be expected and has been reported by others. Karni and coll. reported a 50% mortality rate for traumatic head injury in the elderly with anticoagulants[117]. Lavoie and coll. showed that preinjury warfarin in elderly with closed head injury was related to a more severe head injury and a higher likelihood of death[118]. Franko and coll. showed that warfarin carried a six-fold increase in TBI mortality and that mortality and occurrence of intracerebral hemorrhage increased with higher international normalized ratio (INR)[119]. We found in our material that antithrombotic drugs were as common as 37% in the elderly overall and that 62% of the 75–89 year old had such drugs. Warfarin was most common in the 75–89 years old (42%) and antiplatelets in the 60–74 years old (16%). However, we did not find any significant correlation between favorable outcomes and treatment with antiplatelets and/or warfarin. In line with our results, Ganetsky and coll. found in 2017 in a large study of 939 TBI patients with ground-level falls and antiplatelets or anticoagulants, a low incidence of clinically significant intracranial hemorrhage (<5%) and no difference between anticoagulation and antiplatelet therapy[120]. Possible reasons why antithrombotic drugs did not show any prognostic value in our material could be several: 1. In our referral area, patients on warfarin have frequent check-ups which reduces the risk for overtreatment with too high INR. 2. National guidelines are followed requiring CT examination after mild head trauma when on anticoagulation and prompt reversal of warfarin in case of intracranial hemorrhages. 3. Standardized NIC which minimizes secondary insults may prevent the worsening of intracranial hemorrhages. However, we believe that it is reasonable to assume that anticoagulation therapy increases the risk worsening of TBI and that anticoagulation therapy in some instances may complicate the insertion of ICP devices or surgical treatment, but it does not make successful treatment impossible.

Paper IV

The proportion of elderly patients ≥65 years was 26%. The most common cause of trauma in the elderly was fall accidents which is in line with paper II and paper III as well as many other reports[7,12,24,26,97–100,108,121,122]. There was a higher percentage of females among the elderly (29%) which was also seen in paper II. Dams O'Conner and coll. also reported an increasing proportion of women with increasing age[121]. This finding may be associated with the predominance of women in the older ages[123].

We found differences in the physiological variables and occurrence of secondary insult depending on age. The elderly spent a higher %GMT with high CPP, high MAP and high SBP and less %GMT with high ICP, low CPP and low MAP. Similar findings have been observed by Czosnyka and coll.[124]. The multivariate logistic regression analysis showed that age ≥65 was an independent explanatory factor for higher %GMT with high CPP, high MAP and high SBP. This could to some extent be due to a higher degree of hypertension and cardiovascular diseases in the elderly.

The crucial questions are how high SBP may influence clinical outcome and if this influence is the same regardless of age. The logistic regression analysis showed that high %GMT with SBP >180 was significantly negatively related to favorable outcome overall in patients of all ages and in patients 16–64 years old. Interestingly when looking at the analysis of the age interaction in patients ≥65 there was a significant interaction for SBP >180 with an OR for favorable outcome of 1.007 (per unit increase in %GMT with SBP >180). This indicates that high systolic blood pressure probably should be treated differently in elderly patients. The finding that high blood pressure in the elderly may be advantageous has also been shown by Utomo and coll. who found that patients ≥65 years with a SBP on arrival at the hospital in the range of 131–150 mmHg, compared to patients with SBP of <130 mmHg, had a higher odds of independent living at 6 months[125].

Paper V

In this paper, cerebral pressure autoregulation was studied in 129 elderly (≥65 years) and compared with 342 younger patients (16-64 years). The elderly had higher median values of PRx (worse pressure autoregulation) and spent longer time with higher PRx. It appears that elderly TBI patients differ in pressure autoregulation characteristics, which also is supported by Czosnyka and coll. who found an association between higher PRx and increasing age[124]. A difference in pressure autoregulation characteristics was further supported by that elderly were found to have higher CPPopt and lower %GMT with ΔCPPopt ±5.

High PRx has been shown to be associated with poor outcome in several studies[51,58,124,126]. Regarding the temporal patterns by outcome, the overall impression was that %GMT with CPP close to CPPopt, above CPPopt or below CPPopt influenced outcome less in the elderly. This impression was strengthened by the multiple logistic regression analysis which showed in the young group that high PRx, and as expected also worse GCS M and high Marshall score, were associated with unfavorable outcome, and high PRx and worse GCS M with increased mortality. In the elderly, there was an increased mortality with high PRx but no other variables including ΔCPPopt showed to be significant. The heatmaps were also consistent with that pressure

autoregulation may influence outcome less in the elderly since the elderly had a more dispersed pattern for favorable outcome both regarding PRx/CPP and PRx/CPPopt.

It is unclear why young and elderly TBI patients show different pictures concerning autoregulation. There is limited knowledge about pressure autoregulation in the elderly in general. Studies in healthy individuals have shown that aging does not impair cerebral autoregulation[77–81], but that the vascular reactivity may be delayed[82]. One can speculate whether the elderly have a more vulnerable autoregulation, and if the differences in injury types, effects of aging in general and presence of comorbidities may play a role.

More studies are warranted on pressure autoregulation both in elderly individuals and in elderly TBI patients. At present, this study indicates that CPPopt-guided therapy for the elderly with TBI may be less promising.

Limitations

The results may not be generalizable because they come from a single center and may be influenced by the local management applied. It should also be noted that the patient materials in the included studies partly were the same.

Furthermore, there is always a risk of selection bias since only elderly patients judged to have a reasonable chance for favorable outcome were accepted for NIC. There may also be a risk of more reluctance to treat the elderly accepted for NIC. However, it was found that elderly had a higher degree of surgery and did not differ with regard to mechanical ventilation, length of mechanical ventilation and ICP monitoring.

Conclusions

The patient characteristics had changed between the periods 1996–1997 and 2008–2009. Patients ≥60 years old had doubled and a larger proportion underwent surgery in the second period. The elderly had worse outcome than the younger patients, although relatively good with a favorable outcome at slightly more than 50%. The mean age of patients who died increased from 48 to 64, and of the patients who died many had aggravation patient-related factors. Despite the increase in elderly an overall favorable outcome was maintained between the periods at around 75% (Paper I).

Falls were much more common in the elderly. The elderly had a higher proportion of ASDH and younger patients more often had EDH, DAI and mixed injuries. There were no differences in the distribution of GCS M score on admission and NIC treatment depending on age. The elderly showed a higher proportion of surgery. Favorable outcome was achieved in 72% of the young and 51% of the patients ≥65 years. The mortality increased with age (Paper II).

Favorable outcome was 47% for patients 60–74 years and around 30% for patients 75–84 years. High age, multiple injuries, low GCS M on admission, and the use of mechanical ventilation were found to be significant negative prognostic factors (Paper III).

The elderly differed in relation to younger patients in their physiological variables and the occurrence of secondary insults. They spent higher %GMT with high CPP, high MAP and high SBP and less %GMT with high ICP, low CPP and low MAP. Age ≥65 was an independent explanatory factor for higher %GMT with high CPP, high MAP and high SBP. High %GMT with SBP >180 was significantly negatively related to favorable outcome overall in patients of all ages and in patients 16–64 years old. In the elderly there was an interaction for SBP >180 with an OR for favorable outcome of 1.007 (per unit increase in %GMT with SBP >180). This indicates that high systolic blood pressure may be beneficial and probably should be treated differently in the elderly patients (Paper IV).

Elderly showed higher values of PRx (worse pressure autoregulation) and spent longer time with higher PRx. The elderly TBI patients differed in pressure autoregulation characteristics with higher CPPopt and lower %GMT with ΔCPPopt ±5. The elderly had different temporal patterns where %GMT with CPP close to CPPopt, above CPPopt or below CPPopt influenced outcome less in the elderly. Multiple logistic regression analysis showed in the young group that high PRx, worse GCS M and high Marshall score were associated with unfavorable outcome, and high PRx and worse GCS M with increased mortality. In the elderly, there was an increased mortality with high PRx but no other variables including ΔCPPopt proved to be significant. Overall, the findings indicate that pressure autoregulation may influence outcome less in elderly TBI patients and CPPopt-guided therapy may therefore be less promising in the elderly (Paper V).

Summary in Swedish – sammanfattning på svenska

Traumatisk hjärnskada (THS) utgör en stor utmaning såväl globalt som nationellt p.g.a. stort lidande både för patienter och anhöriga, och stor belastning på samhällets resurser. Modern neurointensivvård har resulterat i allmänt förbättrade behandlingsresultat. De senaste årtiondena med skadepreventivt arbete, så som bl.a. säkerhetskrav på arbetsplatser, utveckling av vägnät och trafikregler, bättre fordon och krav på bälte, har dessutom lett till en minskning av THS i den utvecklade världen. Under samma tid har vår åldersstruktur förändrats genom att vi lever allt längre och har ett längre aktivt liv med bevarad funktionsnivå. Detta har lett till att antalet äldre patienter med THS hela tiden ökar, vilket innebär en stor utmaning för framtidens sjukvård. Tidigare har det funnits en uppfattning, baserad på tidigare dåliga erfarenheter, att avancerad hjärnskadevård för de äldre varit utsiktslös. Den kliniska forskningen kring äldre med THS har varit mycket begränsad och alla behandlingsriktlinjer baseras på studier av yngre patienter med THS, trots att behandlingen av äldre sannolikt kräver speciella anpassningar. Vissa studier talar för att även äldre med THS kan behandlas relativt framgångsrikt men det är ett starkt behov av fler studier på äldre för att kunna optimera neurointensivvården för denna särskilda grupp av patienter.

Målet med denna avhandling var att speciellt studera äldre med THS för att kunna få en uppdaterad bild gällande deras karaktäristika, hur de behandlas och hur behandlingsresultaten utfaller med förhoppning att kunna identifiera ålderspecifika egenskaper som kan vara viktiga för rätt patientval och optimering av neurointensivvården för de äldre med THS. Data från Uppsala THS-register och s.k. monitoreringsdata från de olika kontinuerliga övervakningsteknikerna som används i neurointensivvården analyserades.

Mellan 1996–1997 och 2008–2009 hade andelen THS patienter ≥60 år fördubblats, från 16% till 30%. Trots ökningen av andelen äldre patienter visade sig behandlingsresultaten vara väsentligen oförändrade med omkring 75% som återgick till ett självständigt liv. Även de äldre uppvisade relativt bra behandlingsresultat med drygt 50% som återgick till ett självständigt liv.

Analys av de äldre patienternas karakteristika och behandlingsresultat under perioden 2008–2010 visade att fallolyckor och akuta subduralhematom (blödningar mellan den hårda hjärnhinnan och hjärnan) var vanligare bland de äldre ≥65 år medan de yngre oftare hade diffus hjärnskada (diffus axonal

injury), blödningar mellan benet och den hårda hjärnhinnan (epiduralhematom) och en blandning olika skadetyper. Det förelåg inga skillnader i neurologiskt status vid ankomst till neurointensivvårdsavdelningen-NIVA eller vad gällde neurointensivvårdsbehandlingen förutom att de äldre oftare genomgick skallingrepp. De äldre ≥65 år uppvisade relativt bra behandlingsresultat med 51% som återgick till ett självständigt liv (72% för yngre).

Studier av en större grupp patienter ≥60 år som vårdats på NIVA 2008–2014 visade att hög ålder, andra skador utöver THS, dåligt neurologiskt status vid ankomst till NIVA och vård i respirator vara negativa prognostiska faktorer hos de äldre. Bland de mellan 60–74 år återgick 47% till ett självständigt liv och 30% av de mellan 75–84 år.

Analys av övervakningsdata från neurointensivvården visade att äldre jämfört med yngre hade ett annat mönster med högt cerebral perfusionstryck (CPP; skillnaden mellan blodtrycket och intrakraniella trycket) och högt blodtryck större andel av tiden, och högt intrakraniellt tryck, lågt CPP och lågt blodtryck mindre andel av tiden. Till skillnad från de yngre visade sig högt blodtryck vara associerat med bättre behandlingsresultat för de äldre ≥65 år. Detta talar för att de blodtrycksmål som ska eftersträvas under neurointensivvården eventuellt bör vara olika för äldre och yngre patienter.

Övervakningsdata från neurointensivvården användes också för att studera patienternas förmåga till s.k. ”pressure autoregulation” av blodflödet i hjärnan, dvs den normala förmågan att upprätthålla ett konstant blodflöde i hjärnan när blodtrycket varierar (när blodtrycket går upp drar blodkärlen ihop sig och när blodtrycket sjunker vidgas blodkärlen). Vid störd pressure autoregulation stiger intrakraniella trycket när blodtrycket går upp pga att kärlen vidgas och sjunker när blodtrycket går ner pga att kärlen blir mindre medan det är tvärt om när autoregulationen fungerar. Förmågan till pressure autoregulation kan beräknas genom att mätvärdena för blodtrycket och intrakraniella trycket korreleras (PRx). Äldre visade sig ha sämre autoregulation (högre värden av PRx) och spenderade längre tid med höga PRx jämfört med yngre. Äldre hade också högre optimalt CPP (CPPopt; CPP-nivån där PRx är lägst/bäst) och de äldres CPP låg mindre del av tiden nära CPPopt jämfört med yngre. Högt PRx (dålig autoregulation) var associerat med ökad mortalitet för de äldre men pressure autoregulation påverkade behandlingsresultaten mindre än för de yngre. Resultaten talar för att s.k. pressure autoregulation styrd CPP behandling är mindre lovande för äldre med THS.

Sammanfattningsvis så ökade andelen äldre med THS som behövde neurointensivvård. De äldre hade andra karaktäristika vad det gäller olycksorsak och typ av intrakraniell skada jämfört med de yngre. De äldre blev behandlade med samma behandlingsintensitet som de yngre under neurointensivvården frånsett att de opererades oftare vilket kan förklaras av att de hade högre andel akuta subduralhematom. Äldre ≥65 år uppvisade relativt bra behandlingsresultat vilket starkt talar för att de bör vara kandidater för neurointensivvård även i högre åldrar i selekterade fall. De äldre hade annorlunda

övervakningsmönster när insamlade data från neurointensivvårdens övervakningsmetoder analyserades och resultaten talade för att högre blodtryck är bättre för de äldre men dåligt för yngre. Försämrad pressure autoregulation var associerat med högre mortalitet för de äldre men pressure autoregulation påverkade behandlingsresultaten mindre än för de yngre vilket talar för att individualiserad CPP behandling utifrån förmågan att autoreglera sannolikt är mindre lovande för äldre med THS än för yngre. Det är angeläget med ytterligare studier på gamla med THS för att öka kunskapen och kunna optimera neurointensivvården för denna grupp av patienter.

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References

1. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery*. 2017;80(1):6-15. doi:10.1227/NEU.0000000000001432
2. Elf K, Nilsson P, Enblad P. Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care*: *Critical Care Medicine*. 2002;30(9):2129-2134. doi:10.1097/00003246-200209000-00029
3. Maas AI, Dearden M, Teasdale GM, et al. EBIC-guidelines for management of severe head injury in adults. European Brain Injury Consortium. *Acta Neurochir (Wien)*. 1997;139(4):286-294. doi:10.1007/BF01808823
4. Wärme PE, Bergström R, Persson L. Neurosurgical intensive care improves outcome after severe head injury. *Acta neurochir*. 1991;110(1-2):57-64. doi:10.1007/BF01402049
5. Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *The Lancet Public Health*. 2016;1(2):e76-e83. doi:10.1016/S2468-2667(16)30017-2
6. Baguley IJ, Nott MT, Howle AA, et al. Late mortality after severe traumatic brain injury in New South Wales: a multicentre study. *Medical Journal of Australia*. 2012;196(1):40-45. doi:10.5694/mja11.10090
7. Lennartsson C, Heimerson I. Elderly people's health: Health in Sweden: The National Public Health Report 2012. Chapter 5. *Scandinavian Journal of Public Health*. 2012;40(9 Suppl):95-120. doi:10.1177/1403494812459468
8. Schweden, ed. *Sveriges framtida befolkning 2009 - 2060: = The future population of Sweden 2009 - 2060*. SCB; 2009.
9. Roozenbeek B, Maas AIR, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol*. 2013;9(4):231-236. doi:10.1038/nrneurol.2013.22
10. Gardner RC, Dams-O'Connor K, Morrissey MR, Manley GT. Geriatric Traumatic Brain Injury: Epidemiology, Outcomes, Knowledge Gaps, and Future Directions. *Journal of Neurotrauma*. 2018;35(7):889-906. doi:10.1089/neu.2017.5371
11. Dams-O'Connor K, Gibbons LE, Landau A, Larson EB, Crane PK. Health Problems Precede Traumatic Brain Injury in Older Adults. *J Am Geriatr Soc*. 2016;64(4):844-848. doi:10.1111/jgs.14014
12. Hawley C, Sakr M, Scapinello S, Salvo J, Wrenn P. Traumatic brain injuries in older adults—6 years of data for one UK trauma centre: retrospective analysis of prospectively collected data. *Emerg Med J*. 2017;34(8):509-516. doi:10.1136/emermed-2016-206506
13. Moriokah T. Problems in Neurosurgical Operations on Elderly Patients From the Viewpoint of Anesthesiology. :8.

14. Stefan M, Lino LI, Fernandez G. Medical Consultation and Best Practices for Preoperative Evaluation of Elderly Patients. *Hospital Practice*. 2011;39(1):41-50. doi:10.3810/hp.2011.02.373
15. Hernesniemi J. Outcome following head injuries in the aged. *Acta neurochir*. 1979;49(1-2):67-79. doi:10.1007/BF01809175
16. De Bonis P, Pompucci A, Mangiola A, et al. Decompressive craniectomy for elderly patients with traumatic brain injury: it's probably not worth the while. *J Neurotrauma*. 2011;28(10):2043-2048. doi:10.1089/neu.2011.1889
17. Lilley EJ, Williams KJ, Schneider EB, et al. Intensity of treatment, end-of-life care, and mortality for older patients with severe traumatic brain injury. *Journal of Trauma and Acute Care Surgery*. 2016;80(6):998-1004. doi:10.1097/TA.0000000000001028
18. Taussky P, Hidalgo ET, Landolt H, Fandino J. Age and Salvageability: Analysis of Outcome of Patients Older than 65 Years Undergoing Craniotomy for Acute Traumatic Subdural Hematoma. *World Neurosurgery*. 2012;78(3-4):306-311. doi:10.1016/j.wneu.2011.10.030
19. Van Der Vlegel M, Mikolić A, Lee Hee Q, et al. Health care utilization and outcomes in older adults after Traumatic Brain Injury: A CENTER-TBI study. *Injury*. 2022;53(8):2774-2782. doi:10.1016/j.injury.2022.05.009
20. James SL, Theadom A, Ellenbogen RG, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2019;18(1):56-87. doi:10.1016/S1474-4422(18)30415-0
21. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg*. 2018;130(4):1080-1097. doi:10.3171/2017.10.JNS17352
22. Coburn K. Traumatic brain injury: the silent epidemic. *AACN Clin Issues Crit Care Nurs*. 1992;3(1):9-18. doi:10.4037/15597768-1992-1002
23. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. *Journal of Neurotrauma*. Published online December 19, 2018:neu.2015.4126. doi:10.1089/neu.2015.4126
24. Iaccarino C, Carretta A, Nicolosi F, Morselli C. Epidemiology of severe traumatic brain injury. *Journal of Neurosurgical Sciences*. 2018;62(5):8.
25. Koskinen S, Alaranta H. Traumatic brain injury in Finland 1991–2005: A nationwide register study of hospitalized and fatal TBI. *Brain Injury*. 2008;22(3):205-214. doi:10.1080/02699050801938975
26. Peeters W, Majdan M, Brazinova A, Nieboer D, Maas AIR. Changing Epidemiological Patterns in Traumatic Brain Injury: A Longitudinal Hospital-Based Study in Belgium. *Neuroepidemiology*. 2017;48(1-2):63-70. doi:10.1159/000471877
27. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir*. 2015;157(10):1683-1696. doi:10.1007/s00701-015-2512-7
28. Pedersen K, Fahlstedt M, Jacobsson A, Kleiven S, von Holst H. A National Survey of Traumatic Brain Injuries Admitted to Hospitals in Sweden from 1987 to 2010. *Neuroepidemiology*. 2015;45(1):20-27. doi:10.1159/000381780
29. Teasdale G, Jennett B. ASSESSMENT OF COMA AND IMPAIRED CONSCIOUSNESS: A Practical Scale. *The Lancet*. 1974;304(7872):81-84. doi:10.1016/S0140-6736(74)91639-0

30. Starmark JE, Stålhammar D, Holmgren E. The Reaction Level Scale (RLS85). Manual and guidelines. *Acta Neurochir (Wien)*. 1988;91(1-2):12-20. doi:10.1007/BF01400521
31. Marshall LF, Marshall SB, Klauber MR, et al. A new classification of head injury based on computerized tomography. *Journal of Neurosurgery*. 1991;75(Supplement):S14-S20. doi:10.3171/sup.1991.75.1s.0s14
32. Maas AIR, Hukkelhoven CWPM, 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;57(6):1173-1182. doi:10.1227/01.NEU.0000186013.63046.6B
33. Nelson DW, Nyström H, MacCallum RM, et al. Extended analysis of early computed tomography scans of traumatic brain injured patients and relations to outcome. *J Neurotrauma*. 2010;27(1):51-64. doi:10.1089/neu.2009.0986
34. Raj R, Siironen J, Skrifvars MB, Hernesniemi J, Kivisaari R. Predicting Outcome in Traumatic Brain Injury: Development of a Novel Computerized Tomography Classification System (Helsinki Computerized Tomography Score). *Neurosurgery*. 2014;75(6):632. doi:10.1227/NEU.0000000000000533
35. Thelin EP, Nelson DW, Vehviläinen J, et al. Evaluation of novel computerized tomography scoring systems in human traumatic brain injury: An observational, multicenter study. Menon D, ed. *PLoS Med*. 2017;14(8):e1002368. doi:10.1371/journal.pmed.1002368
36. McConeghy KW, Hatton J, Hughes L, Cook AM. A review of neuroprotection pharmacology and therapies in patients with acute traumatic brain injury. *CNS Drugs*. 2012;26(7):613-636. doi:10.2165/11634020-000000000-00000
37. Reilly PL, Graham DI, Adams JH, Jennett B. Patients with head injury who talk and die. *Lancet*. 1975;2(7931):375-377. doi:10.1016/s0140-6736(75)92893-7
38. Rose J, Valtonen S, Jennett B. Avoidable factors contributing to death after head injury. *Br Med J*. 1977;2(6087):615-618.
39. ATLS Subcommittee, American College of Surgeons' Committee on Trauma, International ATLS working group. Advanced trauma life support (ATLS®): the ninth edition. *J Trauma Acute Care Surg*. 2013;74(5):1363-1366. doi:10.1097/TA.0b013e31828b82f5
40. Le Roux P, Menon DK, Citerio G, et al. The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a list of recommendations and additional conclusions: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Neurocrit Care*. 2014;21 Suppl 2(Suppl 2):S282-296. doi:10.1007/s12028-014-0077-6
41. Guillaume J, Janny P. [Continuous intracranial manometry; physiopathologic and clinical significance of the method]. *Presse Med (1893)*. 1951;59(45):953-955.
42. Lundberg N, Troupp H, Lorin H. Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report. *J Neurosurg*. 1965;22(6):581-590. doi:10.3171/jns.1965.22.6.0581
43. Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. *J Neurosurg*. 1995;83(6):949-962. doi:10.3171/jns.1995.83.6.0949
44. Eker C, Asgeirsson B, Grände PO, Schalén W, Nordström CH. Improved outcome after severe head injury with a new therapy based on principles for brain

volume regulation and preserved microcirculation. *Crit Care Med*. 1998;26(11):1881-1886. doi:10.1097/00003246-199811000-00033
45. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev*. 1959;39(2):183-238. doi:10.1152/physrev.1959.39.2.183
46. Lassen NA. AUTOREGULATION OF CEREBRAL BLOOD FLOW. *Circ Res*. 1964;15:SUPPL:201-204.
47. Lang EW, Chesnut RM. Intracranial pressure. Monitoring and management. *Neurosurg Clin N Am*. 1994;5(4):573-605.
48. Lang EW, Chesnut RM. A bedside method for investigating the integrity and critical thresholds of cerebral pressure autoregulation in severe traumatic brain injury patients. *Br J Neurosurg*. 2000;14(2):117-126. doi:10.1080/02688690050004534
49. Howells T, Elf K, Jones PA, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. *Journal of Neurosurgery*. 2005;102(2):311-317. doi:10.3171/jns.2005.102.2.0311
50. Sorrentino E, Diedler J, Kasprowicz M, et al. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. *Neurocrit Care*. 2012;16(2):258-266. doi:10.1007/s12028-011-9630-8
51. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous Assessment of the Cerebral Vasomotor Reactivity in Head Injury. *Neurosurgery*. 1997;41(1):11-19. doi:10.1097/00006123-199707000-00005
52. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke*. 1996;27(10):1829-1834. doi:10.1161/01.str.27.10.1829
53. Balestreri M, Czosnyka M, Steiner LA, et al. Intracranial hypertension: what additional information can be derived from ICP waveform after head injury? *Acta Neurochir (Wien)*. 2004;146(2):131-141. doi:10.1007/s00701-003-0187-y
54. Petkus V, Preiksaitis A, Chaleckas E, et al. Optimal Cerebral Perfusion Pressure: Targeted Treatment for Severe Traumatic Brain Injury. *Journal of Neurotrauma*. 2020;37(2):389-396. doi:10.1089/neu.2019.6551
55. Howells T, Johnson U, McKelvey T, Enblad P. An optimal frequency range for assessing the pressure reactivity index in patients with traumatic brain injury. *J Clin Monit Comput*. 2015;29(1):97-105. doi:10.1007/s10877-014-9573-7
56. Depreitere B, Güiza F, Van den Berghe G, et al. Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe traumatic brain injury based on minute-by-minute monitoring data. *J Neurosurg*. 2014;120(6):1451-1457. doi:10.3171/2014.3.JNS131500
57. Sánchez-Porras R, Santos E, Czosnyka M, Zheng Z, Unterberg AW, Sakowitz OW. 'Long' pressure reactivity index (L-PRx) as a measure of autoregulation correlates with outcome in traumatic brain injury patients. *Acta Neurochir*. 2012;154(9):1575-1581. doi:10.1007/s00701-012-1423-0
58. Liu X, Donnelly J, Czosnyka M, et al. Cerebrovascular pressure reactivity monitoring using wavelet analysis in traumatic brain injury patients: A retrospective study. *PLOS Medicine*. 2017;14(7):e1002348. doi:10.1371/journal.pmed.1002348
59. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Critical Care Medicine*. 2002;30(4):733-738.

60. Tas J, Beqiri E, van Kaam RC, et al. Targeting Autoregulation-Guided Cerebral Perfusion Pressure after Traumatic Brain Injury (COGiTATE): A Feasibility Randomized Controlled Clinical Trial. *Journal of Neurotrauma*. 2021;38(20):2790-2800. doi:10.1089/neu.2021.0197
61. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1(7905):480-484. doi:10.1016/s0140-6736(75)92830-5
62. Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. *J Neurol Neurosurg Psychiatry*. 1981;44(4):285-293. doi:10.1136/jnnp.44.4.285
63. Wilson JTL, Pettigrew LEL, Teasdale GM. Structured Interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for Their Use. *Journal of Neurotrauma*. 1998;15(8):573-585. doi:10.1089/neu.1998.15.573
64. Gaastra B, Longworth A, Matta B, et al. The ageing population is neglected in research studies of traumatic brain injury. *British Journal of Neurosurgery*. 2016;30(2):221-226. doi:10.3109/02688697.2015.1119240
65. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive Craniectomy in Diffuse Traumatic Brain Injury. *N Engl J Med*. 2011;364(16):1493-1502. doi:10.1056/NEJMoa1102077
66. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. *N Engl J Med*. 2016;375(12):1119-1130. doi:10.1056/NEJMoa1605215
67. Maas AI, Murray G, Henney H, et al. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. *The Lancet Neurology*. 2006;5(1):38-45. doi:10.1016/S1474-4422(05)70253-2
68. Marshall LF, Maas AIR, Marshall SB, et al. A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. *Journal of Neurosurgery*. 1998;89(4):519-525. doi:10.3171/jns.1998.89.4.0519
69. Nichol A, French C, Little L, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. *The Lancet*. 2015;386(10012):2499-2506. doi:10.1016/S0140-6736(15)00386-4
70. Ryttlefors M, Howells T, Nilsson P, Ronne-Engström E, Enblad P. Secondary insults in subarachnoid hemorrhage: occurrence and impact on outcome and clinical deterioration. *Neurosurgery*. 2007;61(4):704-714; discussion 714-715. doi:10.1227/01.NEU.0000298898.38979.E3
71. Ryttlefors M, Howells T, Ronne-Engström E, Nilsson P, Enblad P. Neurointensive care is justified in elderly patients with severe subarachnoid hemorrhage—an outcome and secondary insults study. *Acta Neurochir*. 2010;152(2):241-249. doi:10.1007/s00701-009-0496-x
72. Svennerholm L, Boström K, Jungbjer B. Changes in weight and compositions of major membrane components of human brain during the span of adult human life of Swedes. *Acta Neuropathol*. 1997;94(4):345-352. doi:10.1007/s004010050717
73. Raz N, Lindenberger U, Rodrigue KM, et al. Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers. *Cerebral Cortex*. 2005;15(11):1676-1689. doi:10.1093/cercor/bhi044
74. Martin AJ, Friston KJ, Colebatch JG, Frackowiak RS. Decreases in regional cerebral blood flow with normal aging. *J Cereb Blood Flow Metab*. 1991;11(4):684-689. doi:10.1038/jcbfm.1991.121

75. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease--systematic review and meta-analysis. *Neurobiol Aging*. 2009;30(3):337-352. doi:10.1016/j.neurobiolaging.2007.07.015
76. Oertel M, Kelly DF, McArthur D, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. *Journal of Neurosurgery*. 2002;96(1):109-116. doi:10.3171/jns.2002.96.1.0109
77. Yam AT, Lang EW, Lagopoulos J, et al. Cerebral autoregulation and ageing. *Journal of Clinical Neuroscience*. 2005;12(6):643-646. doi:10.1016/j.jocn.2004.08.017
78. Lipsitz LA, Mukai S, Hamner J, Gagnon M, Babikian V. Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. *Stroke*. 2000;31(8):1897-1903. doi:10.1161/01.str.31.8.1897
79. Carey BJ, Eames PJ, Blake MJ, Panerai RB, Potter JF. Dynamic cerebral autoregulation is unaffected by aging. *Stroke*. 2000;31(12):2895-2900. doi:10.1161/01.str.31.12.2895
80. Narayanan K, Collins JJ, Hamner J, Mukai S, Lipsitz LA. Predicting cerebral blood flow response to orthostatic stress from resting dynamics: effects of healthy aging. *Am J Physiol Regul Integr Comp Physiol*. 2001;281(3):R716-722. doi:10.1152/ajpregu.2001.281.3.R716
81. Franke WD, Allbee KA, Spencer SE. Cerebral blood flow responses to severe orthostatic stress in fit and unfit young and older adults. *Gerontology*. 2006;52(5):282-289. doi:10.1159/000094609
82. Heckmann JG, Brown CM, Cheregi M, Hilz MJ, Neundörfer B. Delayed cerebrovascular autoregulatory response to ergometer exercise in normotensive elderly humans. *Cerebrovasc Dis*. 2003;16(4):423-429. doi:10.1159/000072567
83. Paneni F, Diaz CC, Libby P, L üscher TF, Camici GG. The Aging Cardiovascular System. *Journal of the American College of Cardiology*. 2017;69(15):1952-1967. doi:10.1016/j.jacc.2017.01.064
84. Brunker LB, Boncyk CS, Rengel KF, Hughes CG. Elderly Patients and Management in Intensive Care Units (ICU): Clinical Challenges. *Clin Interv Aging*. 2023;18:93-112. doi:10.2147/CIA.S365968
85. Freitas FS, Ibiapina CC, Alvim CG, Britto RR, Parreira VF. Relationship between cough strength and functional level in elderly. *Rev Bras Fisioter*. 2010;14(6):470-476.
86. Salive ME. Multimorbidity in Older Adults. *Epidemiologic Reviews*. 2013;35(1):75-83. doi:10.1093/epirev/mxs009
87. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*. 2012;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2
88. Miller PE, Thomas A, Breen TJ, et al. Prevalence of Noncardiac Multimorbidity in Patients Admitted to Two Cardiac Intensive Care Units and Their Association with Mortality. *Am J Med*. 2021;134(5):653-661.e5. doi:10.1016/j.amjmed.2020.09.035
89. WHO TEAM, Ageing and Health (AAH), Maternal, Newborn, Child & Adolescent Health & Ageing (MCA). *WHO Clinical Consortium on Healthy Ageing: Topic Focus - Frailty and Intrinsic Capacity*.; 2016.
90. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489-495. doi:10.1503/cmaj.050051

91. Andrews BT, Pitts LH. Functional recovery after traumatic transtentorial herniation. *Neurosurgery*. 1991;29(2):227-231. doi:10.1097/00006123-199108000-00010
92. Combes R, Fauvage B, Jacquot C, et al. Severe head injuries: An outcome prediction and survival analysis. :5.
93. Nyholm L, Howells T, Enblad P, Lewén A. Introduction of the Uppsala Traumatic Brain Injury register for regular surveillance of patient characteristics and neurointensive care management including secondary insult quantification and clinical outcome. *Upsala Journal of Medical Sciences*. 2013;118(3):169-180. doi:10.3109/03009734.2013.806616
94. Howells T, Piper I, Souter M, Miller J, Jones P. Design of a research database for the study of secondary insults following head injury. *Journal of Neurotrauma*. 1995(12):471-472.
95. Aries MJH, Czosnyka M, Budohoski KP, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury*: *Critical Care Medicine*. 2012;40(8):2456-2463. doi:10.1097/CCM.0b013e3182514eb6
96. Teasdale GM, Pettigrew LEL, Wilson JTL, Murray G, Jennett B. Analyzing Outcome of Treatment of Severe Head Injury: A Review and Update on Advancing the Use of the Glasgow Outcome Scale. *Journal of Neurotrauma*. 1998;15(8):587-597. doi:10.1089/neu.1998.15.587
97. Fletcher AE, Khalid S, Mallonee S. The epidemiology of severe traumatic brain injury among persons 65 years of age and older in Oklahoma, 1992–2003. *Brain Injury*. 2007;21(7):691-699. doi:10.1080/02699050701426873
98. Ingebrigtsen T, Mortensen K, Romner B. The epidemiology of hospital-referred head injury in northern Norway. *Neuroepidemiology*. 1998;17(3):139-146. doi:10.1159/000026165
99. Mosenthal AC, Livingston DH, Lavery RF, et al. The Effect of Age on Functional Outcome in Mild Traumatic Brain Injury: 6-Month Report of a Prospective Multicenter Trial: *The Journal of Trauma: Injury, Infection, and Critical Care*. 2004;56(5):1042-1048. doi:10.1097/01.TA.0000127767.83267.33
100. Styrke J, Stålnacke BM, Sojka P, Björnstig U. Traumatic Brain Injuries in a Well-Defined Population: Epidemiological Aspects and Severity. *Journal of Neurotrauma*. 2007;24(9):1425-1436. doi:10.1089/neu.2007.0266
101. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology*. 2010;21(5):658-668. doi:10.1097/EDE.0b013e3181e89905
102. Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc*. 2011;59(1):148-157. doi:10.1111/j.1532-5415.2010.03234.x
103. Howard MA, Gross AS, Dacey RG, Winn HR. Acute subdural hematomas: an age-dependent clinical entity. *J Neurosurg*. 1989;71(6):858-863. doi:10.3171/jns.1989.71.6.0858
104. Stocchetti N, Paternò R, Citerio G, Beretta L, Colombo A. Traumatic Brain Injury in an Aging Population. *Journal of Neurotrauma*. 2012;29(6):1119-1125. doi:10.1089/neu.2011.1995
105. Thompson HJ, McCormick WC, Kagan SH. Traumatic Brain Injury in Older Adults: Epidemiology, Outcomes, and Future Implications: TRAUMATIC BRAIN INJURY AND OLDER ADULTS. *Journal of the American Geriatrics Society*. 2006;54(10):1590-1595. doi:10.1111/j.1532-5415.2006.00894.x

106. Brazinova A, Mauritz W, Leitgeb J, et al. Outcomes of patients with severe traumatic brain injury who have Glasgow Coma Scale scores of 3 or 4 and are over 65 years old. *J Neurotrauma*. 2010;27(9):1549-1555. doi:10.1089/neu.2010.1315
107. Gan B, Med M, Lim J, Ng I. Outcome of Moderate and Severe Traumatic Brain Injury Amongst the Elderly in Singapore. 2004;33(1):5.
108. Hukkelhoven CWPM, Steyerberg EW, Rampen AJJ, et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. *Journal of Neurosurgery*. 2003;99(4):666-673. doi:10.3171/jns.2003.99.4.0666
109. Jennett B, Teasdale G, Braakman R, Minderhoud J, Heiden J, Kurze T. Prognosis of patients with severe head injury. *Neurosurgery*. 1979;4(4):283-289. doi:10.1227/00006123-197904000-00001
110. Tokutomi T, Miyagi T, Ogawa T, et al. Age-associated increases in poor outcomes after traumatic brain injury: a report from the Japan Neurotrauma Data Bank. *J Neurotrauma*. 2008;25(12):1407-1414. doi:10.1089/neu.2008.0577
111. Mosenthal AC, Lavery RF, Addis M, et al. Isolated Traumatic Brain Injury: Age Is an Independent Predictor of Mortality and Early Outcome: *The Journal of Trauma: Injury, Infection, and Critical Care*. 2002;52(5):907-911. doi:10.1097/00005373-200205000-00015
112. Susman M, DiRusso SM, Sullivan T, et al. Traumatic Brain Injury in the Elderly: Increased Mortality and Worse Functional Outcome At Discharge Despite Lower Injury Severity: *The Journal of Trauma: Injury, Infection, and Critical Care*. 2002;53(2):219-224. doi:10.1097/00005373-200208000-00004
113. Vollmer DG, Torner JC, Jane JA, et al. Age and outcome following traumatic coma: why do older patients fare worse? *Journal of Neurosurgery*. 1991;75(Supplement):S37-S49. doi:10.3171/sup.1991.75.1s.0s37
114. Part 2: early indicators of prognosis in severe traumatic brain injury. *Journal of Neurotrauma*. 2000;17(6_7):555-555. doi:10.1089/neu.2000.17.555
115. Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among Elderly Survivors of Mechanical Ventilation. *Am J Respir Crit Care Med*. 2011;183(8):1037-1042. doi:10.1164/rccm.201002-0301OC
116. Ely EW, Evans GW, Haponik EF. Mechanical ventilation in a cohort of elderly patients admitted to an intensive care unit. *Ann Intern Med*. 1999;131(2):96-104. doi:10.7326/0003-4819-131-2-199907200-00004
117. Karni A, Holtzman R, Bass T, et al. Traumatic head injury in the anticoagulated elderly patient: a lethal combination. *Am Surg*. 2001;67(11):1098-1100.
118. A L, S R, D C, et al. Preinjury warfarin use among elderly patients with closed head injuries in a trauma center. *The Journal of trauma*. 2004;56(4). doi:10.1097/01.ta.0000066183.02177.af
119. Franko J, Kish KJ, O'Connell BG, Subramanian S, Yuschak JV. Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. *J Trauma*. 2006;61(1):107-110. doi:10.1097/01.ta.0000224220.89528.fc
120. Ganetsky M, Lopez G, Coreanu T, et al. Risk of Intracranial Hemorrhage in Ground-level Fall With Antiplatelet or Anticoagulant Agents. *Acad Emerg Med*. 2017;24(10):1258-1266. doi:10.1111/acem.13217
121. Dams-O'Connor K, Cuthbert JP, Whyte J, Corrigan JD, Faul M, Harrison-Felix C. Traumatic Brain Injury among Older Adults at Level I and II Trauma Centers. *Journal of Neurotrauma*. 2013;30(24):2001-2013. doi:10.1089/neu.2013.3047

122. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *The Lancet Neurology*. 2008;7(8):728-741. doi:10.1016/S1474-4422(08)70164-9
123. Guralnik JM, Balfour JL, Volpato S. The ratio of older women to men: Historical perspectives and cross-national comparisons. *Aging Clin Exp Res*. 2000;12(2):65-76. doi:10.1007/BF03339893
124. Czosnyka M, Balestreri M, Steiner L, et al. Age, intracranial pressure, autoregulation, and outcome after brain trauma. *Journal of Neurosurgery*. 2005;102(3):450-454. doi:10.3171/jns.2005.102.3.0450
125. Utomo WK, Gabbe BJ, Simpson PM, Cameron PA. Predictors of in-hospital mortality and 6-month functional outcomes in older adults after moderate to severe traumatic brain injury. *Injury*. 2009;40(9):973-977. doi:10.1016/j.injury.2009.05.034
126. Dias C, Silva MJ, Pereira E, et al. Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study. *Neurocrit Care*. 2015;23(1):92-102. doi:10.1007/s12028-014-0103-8

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CLINICAL ARTICLE - BRAIN INJURY

Updated periodic evaluation of standardized neurointensive care shows that it is possible to maintain a high level of favorable outcome even with increasing mean age

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Abstract
Background Periodic evaluation of neurointensive care (NIC) is important. There is a risk that quality of daily care declines and there may also be unrecognized changes in patient characteristics and management. The aim of this work was to investigate the characteristics and outcome for traumatic brain injury (TBI) patients in the period 2008–2009 in comparison with 1996–1997 and to some extent also with earlier periods.
Methods TBI patients 16–79 years old admitted from 2008 to 2009 were selected for the study. Glasgow Coma Scale Motor score at admission (GCS M), radiology, surgery, and outcome (Glasgow Outcome Extended Scale) were collected from Uppsala Traumatic Brain Injury Register.
Results The study included 148 patients (mean age, 45 years). Patients >60 years old increased from 16 % 1996–1997 to 30 % 2008–2009 ($p<0.01$). The proportion of GCS M 4–6 were similar, 92 vs. 93 % (NS). In 1996–1997 patients, 73 % had diffuse injury (Marshall classification) compared to 77 % for the 2008–2009 period (NS). More patients underwent surgery during 2008–2009 (43 %) compared to 1996–1997 (32 %, $p<0.05$). Good recovery increased and mortality decreased substantially from 1980–1981 to 1987–1988 and to 1996–1997, but then the results were unchanged in the 2008–2009 period, with 73 % favorable outcome and 11 % mortality. Mortality increased in GCS M 6–4, from 2.8 % in 1996–1997 to 10 % in 2008–2009 ($p<0.05$); most of the patients that died had aggravating factors, e.g., high age, malignancy.
Conclusions A large-proportion favorable outcome was maintained despite that patients >60 years with poorer prognosis doubled, indicating that the quality of NIC has increased or at least is unchanged. More surgery may have contributed to maintaining the large proportion of favorable outcome. For future improvements, more knowledge about TBI management in the elderly is required.

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Keywords Traumatic brain injury · Standardized neurosurgical intensive care · Periodic evaluation · Outcome · Quality register

Introduction

It has been shown by many that the outcome after traumatic brain injury (TBI) improves with the development of neurointensive care (NIC) [2, 3, 6, 9, 10, 12, 19]. There has not yet been any breakthrough for neuroprotective drugs [11] and high-quality NIC is still crucial for further improvements of treatment results. We have earlier been able to demonstrate successively improved results by comparing the time periods 1980–1981, 1987–1988 [19], and 1996–97 [6]. During the last time period, we had implemented standardized management protocols for the NIC and maximum attention was paid to the importance of avoiding secondary insults through staff lectures and the introduction of new routines where the occurrence of secondary insults should be reported orally at the bedside rounds and recorded in checklists by the responsible nurses [6, 14]. Since the last period, the Uppsala Traumatic Brain Injury Register for quality assurance of NIC has been established [13]. The principles for our NIC have not been changed. There is always a risk that the quality of daily routine care declines and there may also be unrecognized changes in patient characteristics and small shifts in management. Therefore, we found it desirable to evaluate another 2-year period 10 years after the last review and take advantage of the

information available in The Uppsala TBI register. The specific aim was to investigate the treatment results and characteristics of the patients of 2008–2009 in comparison with the previously most recent reported period of 1996–1997 and to some extent also with earlier periods.

Materials and methods

Referral of patients and the TBI register

The Department of Neurosurgery at the University Hospital in Uppsala, Sweden, provides neurosurgical care for the central part of Sweden with a population of approximately 2 million people. Most patients are initially managed at local hospitals according to ATLS principles and then referred to Uppsala (the most distant local hospital 382 km away) [7]. Since 2008, all patients with TBI admitted to our NIC are included in the Uppsala Traumatic Brain Injury register [13] from which all data can be extracted.

Patients

To be able to compare the results with the previous period [6, 19], we used the same inclusion and exclusion criteria. All TBI patients between the age of 16 and 79 years admitted to the NIC unit at the Uppsala University Hospital between 2008 and 2009 were eligible for the study. In total, 168 patients were identified, and after exclusion of 20 patients, 148 patients remained in the study. The patients were excluded for the following reasons: (1) the patients were admitted to the NIC unit≥5 days after the trauma (n=4), or were treated successfully at the NIC unit within 24 h (n=6); (2) patients had both pupils wide and non-reacting on arrival at the NIC unit (n=3) (i.e., patients with an obvious predestined fatal clinical course [1, 4] in whom it could not be assessed retrospectively if active treatment had been initiated); (3) patients had gunshot injuries (n=1) and patients lost to follow-up (n=6).

Neurointensive care

All patients were treated according to the same standardized management protocols as in the previously evaluated time period of 1996–1997 [6]. The standardized management protocols are summarized below.

Basal treatment

Head elevation was 30° to facilitate venous outflow and prohibit ventilator-associated pneumonia. Unconscious patients (Glasgow Coma Motor Score (GCS M) 1–5) were intubated and received propofol infusion (Propofol-LipuroB. Braun Medical AB, Danderyd, Sweden) as sedation and morphine injections or infusions as analgetics. The sedation was interrupted repeatedly and neurological wake-up tests were performed [16]. The patients were initially moderately hyperventilated ($PaCO_2$ 4.0–4.5 kPa) but gradually normoventilated as early as possible when the intracranial pressure (ICP) allowed. Extracerebral hematomas and contusions causing significant mass effect were surgically evacuated except in cases where coagulopathia was resistant to therapy. ICP was monitored in all patients with GCS M 1–5 using an intraventricular drainage catheter if possible or intracerebral probes if the ventricles were compressed.

Treatment goals were as follows: ICP≤20 mmHg, cerebral perfusion pressure (CPP)≥60 mmHg, systolic blood pressure >100 mmHg, CVP 0–5 mmHg, pO_2>12kPa, blood glucose 5–10 mmol/l, electrolytes within normal range, normovolemia and body temperature<38 °C. Prophylactic anticonvulsants were not given.

If no mass effect existed, intermittent drainage of small volumes (approximately 1–2 ml) of cerebrospinal fluid (CSF) was applied. The reason for not using a continuously open drainage system early was to maintain control over the intracranial dynamics and to avoid the development of slit ventricles and inaccurate ICP readings during the period when the risk of expanding mass lesions was highest. If the ICP was controlled by intermittent drainage for a reasonable period of time (around 1–3 days) without signs of progressive impairment or inadequate ICP registration due to compressed ventricles, the ventricular drainage was kept open and CSF was drained against a pressure level of 15–20 mmHg. This was always preceded by a CT-scan to exclude expanding mass lesions and slit ventricles. If the ICP was increased despite basal treatment, the following steps were followed:

Step 1a - Continuous sedation and stress reduction

Re-evaluation with the purpose of identifying significant mass lesions requiring surgery, existing avoidable factors, or inadequate sedation level. No wake-up tests until stabilization of ICP. Infusion of 0.2–0.3 mg/kg/24 h β1-antagonist Metoprolol (Seloken, AstraZeneca AB, Södertälje, Sweden) and injections of α2-agonist Clonidin (Catapresan, BoehingerIngelheim AB, Stockholm, Sweden) (0.5–1.0 μg/kg × 8 or the same dose as an infusion) were given to reduce the physiological stress response and thereby avoid ICP spikes and aggravation of cerebral edema [5].

Step 1b - Barbiturate coma treatment

If previous treatments are insufficient to reduce the increased ICP, thiopental infusion was used (Pentocur, Abcur AB, Helsingborg, Sweden). The infusion was started with a bolus dose of 4–8 mg/kg given as repeated 50 mg doses until ICP< 20 mmHg or blood pressure became unstable. After this, a continuous infusion of 5–10 mg/kg/24 h was given for around

6 h and thereafter 2–5 mg/kg/24 h. The lowest possible dose to keep ICP<20 mmHg was used and burst-suppression on electroencephalogram was not a goal. During this treatment, a CPP of 50 mmHg was allowed. Thiopental concentrations> 380 μmol/l were avoided.

Step 2 - Decompressive craniectomy

Decompressive craniectomy was advised under the following conditions: (1) Step 1b was unsuccessful in reducing ICP< 20 mmHg; (2) Step 1b caused severe adverse effects; (3) If too high doses/concentrations of thiopental were needed with risk of complications.

A hemicraniectomy was done if there was a shift of the mid-line but no significant mass lesions to remove. Bilateral frontotemporal craniectomies with sparing of a bone ridge at the mid-line were done if no shift was present. The ambition should always be to remove as large bone flaps as possible and a duraplasty should be performed to ensure adequate decompression.

Evaluation of outcome

The clinical outcome was assessed after around 6 months by a selected number of persons using structured telephone interviews for the extended Glasgow Outcome Scale (EGOS) [17, 18].

Statistical methods

To compare the groups, Pearson's Chi-square analyses were used. When comparing differences in gender and outcome, Yates' Chi-square was used when expected numbers were less than 5. A p value<0.05 was considered as a statistically significant difference.

Results

Patient characteristics on admission

The age distribution had changed from 1996–1997, showing a decreasing number of patients with increasing age, to 2008–2009, which showed a bimodal distribution with the highest number of patients in the age groups 16–29 years and 60–79 years (Fig. 1). The proportion of patients>60 years had increased from 16 to 30 % between those time periods (p<0.01, Table 1). The distribution in different admission GCS M grades was similar in the two time periods with the majority of patients in GCS M 4–5 grade (Fig. 2, Table 1).

In the 1996–1997 period, 73 % (112/154) patients were classified as diffuse injury I-IV according to the Marshall classification [6, 8] compared to 77 % (114/148) in the 2008–2009 period (NS) (Table 2). Extra-cranial injuries were present in 36 % of the patients in the 1996–1997 period and in 39 % of the patients in the 2008–2009 period (NS) (Table 1). The most predominating causes of trauma were motor vehicle accidents in both periods (29.2 % for 1996–1997 and 29.7 % for 2008–2009) (Table 3).

Surgery

A larger proportion of the patients underwent surgery in the 2008–2009 period compared to the 1996–1996 period (43 % (64/148) vs. 32 % (49/154), p<0.05) (Table 2). Among patients classified as evacuated mass lesions and non-evacuated mass lesions (i.e., all focal mass lesions), 94 % (32/34) of the

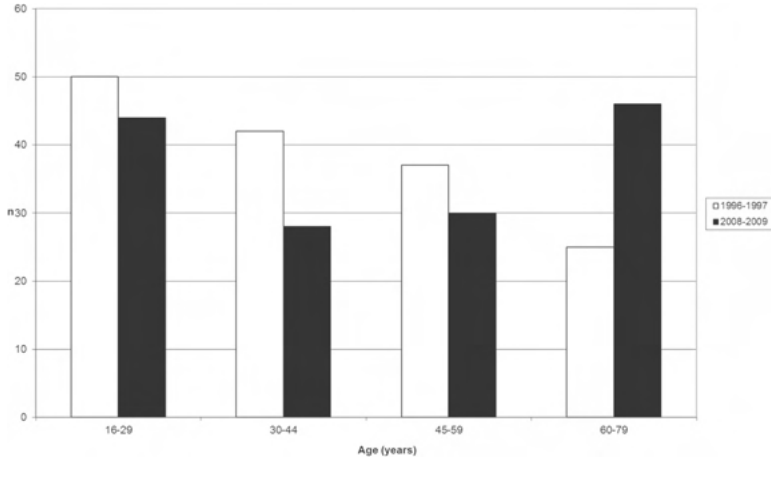

Fig. 1 Age distribution by period

Table 1 Comparative summary of periods

	1980–1981[a]	1987–1988[a]	1996–1997[b]	2008–2009	Chi-square test (1996–1997 vs. 2008–2009)
Numbers	49	72	154	148	
Referrals (%)	75	65	80	82	NS
Mean age, years	37	36	41	45	
>60 years (%)	16	18	16	30	$p<0.01$
GCS M≥4 (%)	40	42	92	93	NS
Epidural hematoma (%)	16	8	9	9	NS
Multiple injuries[c] (%)	18	18	36	39	NS
Outcome GCS M 1–6 (%)					
Mortality	41	31	6	11	NS
Favorable outcome	34	48	78	74	NS
Outcome GCS M≥4 (%)					
Mortality	40	27	2.8	10	$p<0.05$
Favorable outcome	40	69	84	80	NS

[a] [19]

[b] [6]

[c] Associated chest injury, abdominal injury (requiring surgery), or major fracture (one or more extremity or spinal fracture)

patients were operated on before discharge in 2008–2009 compared to 62 % (26/42) in 1996–1997 ($p<0.05$) (Table 2).

Clinical outcome

Follow-up of the patients treated in 2008–2009 after 10 months in mean (median, 9, range, 1–28) showed that 45 % had good recovery (GR) (33.8 % higher GR and 10.7 % lower GR), 28 % moderate disability (MD) (16.2 % higher MD and 11.5 % lower MD), and 16 % severe disability (SD) (6.8 % higher SD and 9.5 % lower SD). No patient was in a vegetative state (VS). At the time of follow-up, 17 of the patients (11.5 %) had died. Seven patients had died at the NIC unit and ten patients had died after discharge from the NIC. Figure 3 shows the clinical outcome according to GOS in four time periods. The proportion of patients in GR increased and the proportion of diseased patients decreased substantially from 1980 to 1981, 1987 to 1988, and 1996 to 1997, but then the results did not change significantly to from 2008 to 2009 (Table 1). The patients who died in 1996–1997 had an average age of 48 years, while the patients who died in 2008–2009 had an average age of 61 years (Table 5). The proportions of

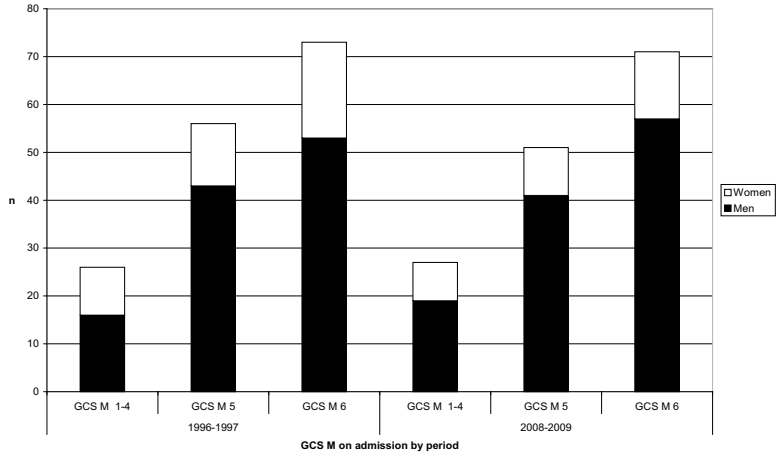

Fig. 2 Glasgow Coma Scale Motor score (GCS M) by period

Table 2 Initial CT Marshall category and surgery

CT-category[a]	Definition	1996-1997[b] (n / surgery)	2008-2009 (n / surgery)
DI I	No visible intracranial injury on CT scan	0 / 0	1 / 0
DI II	Cisterns present, midline shift 0-5 mm and/or lesion densities present (< 25 cm3)	70 / 10	85 / 18
DI III	Cisterns compressed or absent, midline shift 0-5 mm. Lesion densities < 25 cm3	36 / 10	18 / 8
DI IV	Midline shift > 5 m, lesion densities < 25 cm3	6 / 3	10 / 6
DI I-IV		**112 / 23**	**114 / 32**
		N.S	
EML	Any lesion surgically evacuated	1 / 1	23 / 23
NEML	High- or mixed-density lesion > 25 cm3, not surgically evacuated	41 / 25	11 / 9
EML + NEML		**42 / 26**	**34 / 32**
		$p < 0.05$	
Total		**154 / 49**	**148 / 64**
		$p < 0.05$	

[a] *DI I* diffuse injury I, *DI II* diffuse injury II, *DI III* diffuse injury III, *DI IV* diffuse injury IV, *EML* evacuated mass lesion, *NEML* nonevacuated mass lesion [8]

[b] [6]

patients with SD and patients in VS were virtually unchanged over time (Fig. 3). Patients in higher GCS M on admission had better outcomes in both periods (Fig. 4, Table 4).

Subgroup analysis showed that mortality had increased in patients with GCS M 4–6, from 2.8 % in 1996–1997 to 10 % in 2008–2009 ($p<0.05$), while the proportion of patients with a favorable outcome (GR+MD) was not significantly changed (Table 1). When mortality in the 2008–2009 period was analyzed in detail, older patients (60–79 years) had higher mortality ($p<0.001$) and lower favorable outcome ($p<0.01$) (Fig. 5). Favorable outcome (GR+MD) was seen in 75 % (88/117) of the men and in 61 % (19/31) of the women (NS). Unfavorable (SD+VS) 13 % (15/117) of the men and in 29 % (9/31) of the women (NS). Of the men, 12 % died (14/117) and 10 % (3/31) of the women (NS). The 17 patients treated in 2008–2009 who were dead at the time of follow-up were judged to have died as a direct or indirect consequence of the trauma (Table 5). Aggravating factors were present in the large majority of the cases, which also applies to 1996–1997 (Table 5).

Table 3 Causes of accidents

Cause of accident	1996–1997[a] (*n*/%)	2008–2009 (*n*/%)
Motor vehicle occupant	45/29.2	44/29.7
Pedestrian	18/11.7	11/7.4
Cyclist	3/1.9	5/3.3
Work	15/9.7	8/5.4
Domestic	7/4.5	19/12.8
Sport	16/10.4	5/3.4
Assault	6/3.9	10/6.8
Fall under the influence of alcohol	35/22.7	27/18.2
Other	7/4.5	18/12.2
Unknown	2/1.3	1/0.7

[a] [6]

For the 2008–2009 period, 12 of the patients who died were 60 years or older. The youngest patient (patient 1) had a traumatic vertebrobasilar dissection, which led to severe cerebral ischemia. Patient 2 was involved in an explosion accident and arrived to the NIC unit in GCS M grade 2. Patients 3, 4, and 5 all had cancer diagnoses. Patients 6, 7, and 8 all had severe alcohol abuse. Patient 9 had an acute subdural hematoma diagnosed 2 days after the trauma and he was admitted in GCS M 3. Patients 10, 11, and 12 had large acute subdural hematomas, which were evacuated in their local hospitals on vital indication. Two of these patients were admitted in GCS M grade 2–3 and the third was 79 years old. Patients 13 and 14 were found in GCS M 1 at the scene of the accident when the emergency team arrived and patient 13 was also cyanotic. Patient 15 was 78 years

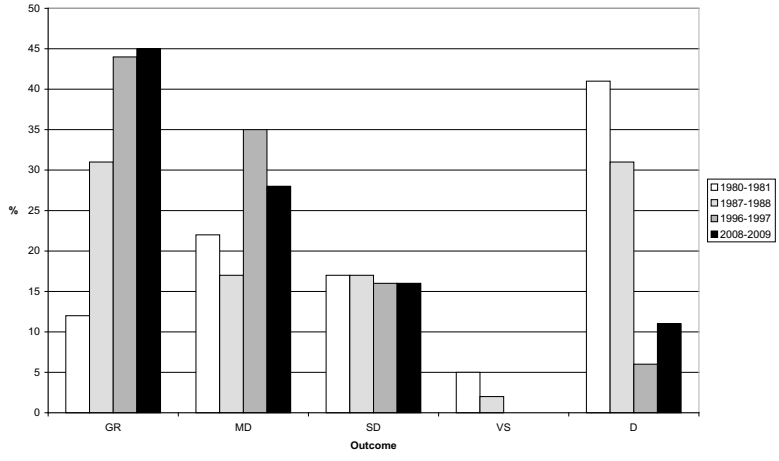

Fig. 3 Clinical outcome according to Glasgow Outcome Scale (GOS) by period

old and was on Warfarin medication. Patient 16 had chronic kidney disease and Alzheimer's disease. Patient 17 was a 72-year-old patient who underwent multiple operations because of expansive hygromas and who had coagulase-negative staphylococcus (CoNS) meningitis. One of the patients who died during the NIC could be classified as "Talk and die". This patient was 78 years old and on Warfarin treatment (patient 15).

Discussion

A substantial successive improvement of outcome after TBI, have been shown during the development of NIC, when the periods 1980–1981, 1987–1988 and 1996–1997 have been compared [19, 6] (Fig. 3). The updated evaluation of the standardized NIC in Uppsala for the time period 2008–2009 did not show any significant changes in clinical outcome overall when the results were compared with the 1996–1997 period (Fig. 3). The neurological grade on admission according to the GCS M score was also virtually the same for the two periods (Fig. 2). The major observation was that the proportion of patients>60 years was doubled, which apparently did not influence the overall clinical outcome substantially despite that the proportion of favorable outcome was lower and the mortality higher in this

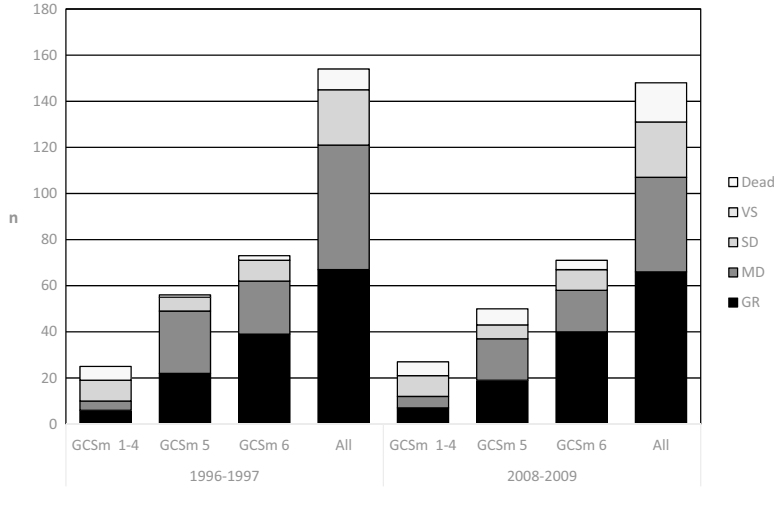

Fig. 4 Clinical outcome according to Glasgow Outcome Scale (GOS) by admission Glasgow Coma Scale Motor score (GCS M)

Table 4 Clinical outcome by admission GCS M grade

GOS	GCS M *n* (%) 1996–1997/*n* (%) 2008–2009			
	6	5	1–4	All
GR	39 (53)/40 (56)	22 (39)/19 (38)	6 (24)/7 (26)	67 (44)/66 (45)
MD	23 (32)/18 (25)	27 (48)/18 (36)	4 (16)/5 (19)	54 (35)/41 (28)
SD	9 (12)/9 (13)	6 (11)/6 (12)	9 (36)/9 (33)	24 (16)/24 (16)
VS	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Dead	2 (3)/4 (6)	1 (2)/7 (14)	6 (24)/6 (22)	9 (6)/17 (11)
Total	73 (100)/71 (100)	56 (100)/50 (100)	25 (100)/27 (100)	154 (100)/148 (100)

age group (Fig. 5). When the mortality for the two time periods was compared for patients in GCS M 4–6, the mortality was significantly higher during the last period. An analysis of mortality by year showed that the increased mortality mainly was ascribed to 2009, 14 % (9/61) compared to 9.2 % (8/87) 2008 and preliminary analysis of 2010 showed 5.0 % mortality (data not presented). Therefore, the observed increased mortality for patients in GCS M 4–6 is probably not an indication that the quality of NIC has decreased in general but more probable a temporary increase in mortality 2009, which appears to be explained by aggravating factors in the large majority of patients with fatal outcomes (Table 5). On the contrary, maintaining the large proportion of favorable outcomes despite that the proportion of patients>60 years with poorer prognosis had increased may indicate that the quality of NIC rather has increased or at least is unchanged. The observation that a larger proportion of patients underwent surgery (Table 2) may indicate that more active surgery may have contributed to that the large proportion of favorable outcome was maintained.

The larger proportion of elderly in the latest evaluated period was expected. It is well known that the proportion of elderly in the population is increasing. In Sweden, the proportion of people≥65 years old has increased from 13.9 % in 1971 to 17.4 % in 2011 and is predicted to be 22.8 % in the year 2051 [15]. Furthermore, there is also an increase in the general health and activity of living among the elderly. Therefore, health-care faces a tremendous challenge to be able to offer elderly people adequate treatments in the future. We need a better mechanism for selection of elderly patients possible to treat and also to improve our understanding of age-specific pathophysiological mechanisms to be able to give the optimal care.

The finding that the results appeared to be virtually unchanged since the last updated period of 1996–1997 may indicate that the quality of NIC has culminated or is close to culminating. Therefore, in addition to optimizing the care of

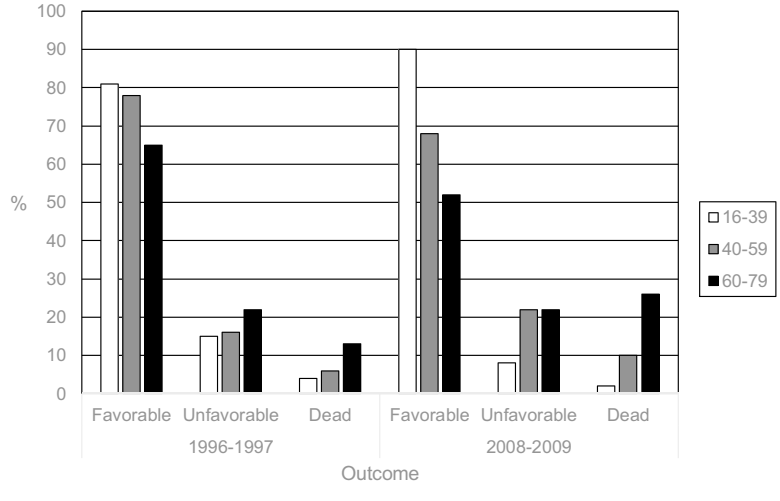

Fig. 5 Clinical outcome according to Glasgow Outcome Scale (GOS) by age

Table 5 Characteristics of patients who died

Patient no.	GCS M admission	GCS M discharge	Age	Aggravating factors
2008–2009				
1	5	4	19	Vertebrobasilar dissection
2	2	D[c]	43	Explosion accident
3	6	6	55	Small cell lung cancer
4	5	6	64	Operated for colon cancer 5 days prior to trauma. Suspected cerebral metastasis
5	5	4	68	Non-small cell lung cancer, severe heart disease
6	6	6	45	Severe alcohol abuse
7	6	6	60	Alcohol abuse, liver cirrhosis
8	2	D	64	Severe alcohol abuse
9	3	3	62	Large acute subdural hematoma diagnosed 2 days after trauma
10	2	D	64	Acute subdural hematoma evacuated at local hospital before transfer to Uppsala
11	3	D	73	Warfarin, acute subdural hematoma evacuated at local hospital before being transferred to Uppsala
12	5	D	79	Acute subdural hematoma evacuated at local hospital before transfer to Uppsala
13	4	4	75	GCS M 1 and cyanotic when EMT[a] arrived
14	5	6	52	GCS M 1, non-reacting pupils, and systolic BP 90 when EMT[a] arrived
15	6	D	78	Warfarin
16	5	D	79	Chronic kidney disease, diabetes mellitus 2, Alzheimer's dementia, and recent myocardial infarct
17	5	6	72	CoNS[b] meningitis, multiple intracranial surgeries
			(Mean 61)	
1996–1997[d]				
1	6	D	79	Renal carcinoma, chronic myelogenous leukemia, coagulopathy
2	6	4	57	Myeloma, coagulopathy
3	3	6	60	Mastocytosis, coagulopathy
4	3	4	47	Pneumonia 6 weeks after TBI
5	4	D	22	Septic shock
6	3	D	22	Penetrating heart injury
7	3	D	25	Trunk, spine, and extremity injuries
8	3	D	51	
9	3	D	71	
			(Mean 48)	

[a] *EMT* emergency medical technician

[b] *CoNS* coagulase-negative staphylococci

[c] *D* died before discharge

[d] [6]

elderly TBI patients, new approaches need to be developed and effective neuroprotective drugs need to be introduced in order to improve the results further.

Conclusions

A large proportion of favorable outcomes (78 %) was maintained despite that the proportion of patients>60 years old with poorer prognosis was doubled (16 to 30 %), which may indicate that the quality of NIC rather has increased or at least is unchanged. More active surgery may have contributed to that the large proportion of favorable outcomes was maintained. For further improvements of the results in the future, more knowledge about the optimal TBI management for the elderly is required, as well as an introduction of new approaches and effective neuroprotective drugs.

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Compliance with ethical standards

Conflict of interest None.

Research involving human participants The study was approved by the local ethical review board.

References

1. Andrews BT, Pitts LH (1991) Functional recovery after traumatic transtentorial herniation. Neurosurgery 29:227–231
2. Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R (1977) The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg 47:491–502
3. Bowers SA, Marshall LF (1980) Outcome in 200 consecutive cases of severe head injury treated in San Diego County: a prospective analysis. Neurosurgery 6:237–242
4. Combes P, Fauvage B, Colonna M, Passagia JG, Chirossel JP, Jacquot C (1996) Severe head injuries: an outcome prediction and survival analysis. Intensive Care Med 22:1391–1395
5. Eker C, Asgeirsson B, Grande PO, Schalen W, Nordstrom CH (1998) Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. Crit Care Med 26:1881–1886
6. Elf K, Nilsson P, Enblad P (2002) Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care. Crit Care Med 30:2129–2134
7. Fischerström A, Nyholm L, Lewén A, Enblad P (2014) Acute neurosurgery for traumatic brain injury by general surgeons in Swedish county hospitals: a regional study. Acta Neurochir (Wien) 156:177–185
8. Marshall LF, Marshall SB, Klauber MR, Clark MB, Eisenberg HM, Jane JA, Luerssen TG, Marmarou A, Foulkes MA (1991) A new classification of head injury based on computerized tomography. J Neurosurg 75:S14–S20
9. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part I: the significance of intracranial pressure monitoring. J Neurosurg 50:20–25
10. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part II: acute and chronic barbiturate administration in the management of head injury. J Neurosurg 50:26–30
11. McConeghy KW, Hatton J, Hughes L, Cook AM (2012) A review of neuroprotection pharmacology and therapies in patients with acute traumatic brain injury. CNS Drugs 26:613–636
12. Nordstrom CH, Sundbarg G, Messeter K, Schalen W (1989) Severe traumatic brain lesions in Sweden. Part 2: Impact of aggressive neurosurgical intensive care. Brain Inj 3:267–281
13. Nyholm L, Howells T, Enblad P, Lewén A (2013) Introduction of the Uppsala Traumatic Brain Injury register for regular surveillance of patient characteristics and neurointensive care management including secondary insult quantification and clinical outcome. Ups J Med Sci 118:169–180
14. Nyholm L, Lewén A, Fröjd C, Howells T, Nilsson P, Enblad P (2012) The use of nurse checklists in a bedside computer-based information system to focus on avoiding secondary insults in neurointensive care. ISRN Neurol 2012:903954
15. SCB Statistics Sweden: Statistical Database http://www.scb.se/en_/Finding-statistics/Statistical-Database/ Accessed 12 Jan 2014
16. Skoglund K, Hillered L, Purins K, Tsitsopoulos PP, Flygt J, Engquist H, Lewén A, Enblad P, Marklund N (2014) The neurological wake-up test does not alter cerebral energy metabolism and oxygenation in patients with severe traumatic brain injury. Neurocrit Care 20:413–426
17. Teasdale GM, Pettigrew LE, Wilson JT, Murray G, Jennett B (1998) Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. J Neurotrauma 15:587–597
18. Wilson JT, Pettigrew LE, Teasdale GM (1998) Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 15:573–585
19. Wärme PE, Bergström R, Persson L (1991) Neurosurgical intensive care improves outcome after severe head injury. Acta Neurochir (Wien) 110:57–64

Paper II

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CLINICAL ARTICLE - BRAIN INJURY

Promising clinical outcome of elderly with TBI after modern neurointensive care

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Abstract
Background The increasing number of elderly patients with traumatic brain injury (TBI) leads to specific neurointensive care (NIC) challenges. Therefore, elderly subjects with TBI need to be further studied. In this study we evaluated the demographics, management and outcome of elderly TBI patients receiving modern NIC.
Methods Patients referred to our NIC unit between 2008 and 2010 were included. Patients were divided in two age groups, elderly (E) ≥65 years and younger (Y) 64–15 years. Parameters studied were the dominant finding on CT scans, neurological motor skills and consciousness, type of monitoring, neurosurgical procedures/treatments and Glasgow Outcome Scale Extended score at 6 months after injury.
Results Sixty-two E (22 %) and 222 Y (78 %) patients were included. Falls were more common in E (81 %) and vehicle accidents were more common in Y patients (37 %). Acute subdural hematoma was significantly more common in E (50 % of cases) compared to Y patients (18 %). Intracranial pressure was monitored in 44 % of E and 57 % of Y patients. Evacuation of significant mass lesions was performed more common in the E group. The NIC mortality was similar in both groups (4–6 %). Favorable outcome was observed in 72 % of Y and 51 % of E patients. At the time of follow-up 25 % of E and 7 % of Y patients had died.
Conclusions The outcome of elderly patients with TBI was significantly worse than in younger patients, as expected. However, as much as 51 % of the elderly patients showed a favorable outcome after NIC. We believe that these results encourage modern NIC in elderly patients with TBI. We need to study how secondary brain injury mechanisms differ in the older patients and to identify specific outcome predictors for elderly patients with TBI.

Keywords Traumatic brain injury · Outcome · Elderly · Neurointensive care · Secondary injury

Introduction

Traumatic brain injury (TBI) is a very complex condition and particularly demanding to treat. Effective specific pharmacological patient treatments of the cellular and biochemical injury mechanisms do not exist, but advancements in neurointensive care have greatly contributed to improved patient outcomes over the last 20–30 years [8, 20]. Most studies about TBI-related changes in the intracranial pathophysiology are based on patients below the age of 65. With the increased number of elderly in the population [31] with more active lifestyles, we need better mechanisms to select treatable elderly patients. We also need to improve our understanding of age-specific pathophysiological changes to give optimal neurointensive care for every patient.

Elderly patients with TBI are challenging since many older patients have a high morbidity and mortality rate after surgery due to age-related physiological changes [34]. However, depending on the severity of the brain injury and premorbid status, some elderly TBI patients may recover well if they receive appropriate rehabilitation [12]. Unfortunately, less is known about age-related pathophysiological changes in TBI, which could influence the outcome. Recently, it was shown that elderly patients with TBI are more prone to losing vascular autoregulation control and cerebrovascular pressure reactivity [4]. It is

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reasonable to believe that more individualized patient care, targeted to age-specific aspects of the cerebral pathophysiology and individual requirements, would further improve outcomes. Therefore, the specific aim of this study was to study elderly (E) patients (≥65 years) with TBI selected for neurointensive care in comparison with younger (Y) patients (64-15 years) regarding the clinical characteristics and outcome to provide a basis for further studies of elderly patients.

Materials and methods

Patient selection and data collection

The Department of Neurosurgery at Uppsala University Hospital, Sweden, has a catchment area of approximately 2 million people. Most trauma patients are initially managed at local hospitals according to the ATLS concept and then transferred to our unit [10]. The study included 284 patients treated at the Uppsala University Hospital NIC unit from 2008 to 2010. Data were obtained from the Uppsala TBI register (www.ucr.uu.se/tbi) [27]. The register contains admission data including demographics, e.g., the mechanism of injury and injury classification. Some specific aggravating preconditions are sought, for example, previous brain disease/injury, diabetes mellitus, cardiovascular disease, alcohol overuse or ongoing anticoagulation therapy. The data from the NIC period include surgery, monitoring data, if and how long the patient was intubated, complications and the neurological condition at discharge. The register also includes 6-month outcome follow-up using the Glasgow Outcome Scale Extended (GOSE) score [40]. Specially trained nurses interview the patients by phone using a standard questionnaire. The GOSE score is used to categorize outcomes into three categories: favorable (good recovery, higher/lower; moderate disability, higher/lower), unfavorable (severe disability, higher/lower; vegetative) and death.

In this study, we divided the results into two age groups, E ≥65 years and Y 64–15 years. Neurological motor skills and consciousness were assessed according to the Reaction Level Scale (RLS) [27, 33] and Glasgow Coma Scale Motor (GCS M) scores [39] at admission and discharge from the NIC [27]. The dominant finding on the CT scans was used to categorize the TBI.

Standardized management

The patients were cared for according to standardized management protocols based on good laboratory practice (GLP) principles focusing on avoiding secondary insults [8]. Table 1 shows the target parameters used. Unconscious patients (RLS≥3b or GCS-M ≤5) were intubated and initially mildly hyperventilated (pCO_2 4.0–4.5 kPa). The intracranial pressure (ICP) and cerebral perfusion pressure (CPP) were continuously monitored in patients who were unconscious (RLS≥3b or GCS-M ≤5) or in situations where there was great risk of developing high intracranial pressure. The ventilation was gradually changed to normoventilation under strict surveillance of the ICP. Propofol and morphine were routinely given for sedation and analgesia. Normovolemic circulation and sufficient colloid osmotic pressure were aimed for. Infusion of 20 % albumin was commonly used to treat hypovolemia/hypotension. Fever was treated with paracetamol, a cooling blanket or chlorpromazine. Lesions (contusions and extracerebral hematomas) with significant mass effect were evacuated. In situations of increased ICP despite basic NIC treatment and if no mass lesion was present, the CSF was drained. If CSF drainage was not sufficient to reduce the ICP, a thiopental infusion was started. Finally, if the ICP was still refractory, a decompressive craniectomy was performed [8].

Table 1 Target parameters for the neurointensive care of patients with TBI at our NIC. ICP, intracranial pressure; CPP, cerebral perfusion pressure; CVP, central venous pressure; pCO_2, partial pressure of arterial carbon dioxide; pO_2, partial pressure of arterial oxygen; SaO_2, saturation of hemoglobin-binding sites in the bloodstream occupied by oxygen

Parameters	Goal
ICP	≤20 mmHg
CPP	≥60 mmHg
Systolic blood pressure	≥100 mmHg
CVP	0–5 mmHg
pCO_2	4.0–4.5 kPa
pO_2	≥12 kPa
SaO_2	≥96 %
Temperature	≤38 C

Data analysis and statistics

Data were analyzed using Microsoft Excel 2007® commercial software (Redmond, WA, USA), Statistica® (Statsoft, Tulsa, OK, USA) and SPSS® (Armonk, NY, USA). A T-test was used to compare normally distributed values. In nonparametric values (i.e., RLS, GCS-M, GOSE), the p-value was calculated using the Mann-Whitney U test for independent data and Wilcoxon test for dependent variables. Proportional numbers were assessed with the chi^2-test to test for significant differences. Parametric data are presented as means ± standard deviation. Nonparametric data are presented as median and quartile range.

Results

Demographics

Of the 284 patients included, 62 (22 %) were E and 222 (78 %) were Y. The mean age of the E group was 73 (±6)

years and of the Y group 39 (±16) years ($p<0.005$). In the older group 64 % were males and 36 % females. In the younger group, 84 % were males and 16 % females. The difference in the proportion of males and females in each age group was significant ($p<0.05$) (Table 2). For details regarding the medical history, accident mechanism and CT findings, see Table 2. In short, diabetes mellitus, preexisting cardiovascular disease (CVD) or/and hypertension and preinjury use of anticoagulants were statistically more common in the E group ($p<0.05$). Falls were more common in E (81 %, n=50) compared to Y patients (36 %, n=79) ($p<0.005$), and vehicle accidents were significantly more common in the Y (37 %, n=83) compared to E group (5 %, n=3) ($p<0.05$). Acute subdural hematoma (ASDH) was significantly more common in E (50 %, n=31) compared to Y patients (18 %, n=40) ($p<0.001$). Diffuse axonal injury (DAI), epidural hematoma (EDH) and mixed type of injury were significantly more frequent in the Y group (Table 2).

In the E group, 69 % presented with other injuries compared to 88 % in the Y group ($p<0.005$) (Table 2). The predominant injury in the Y patients was thoracic (including rib fractures), occurring in 61 patients. Spinal cord injury was only seen in two Y patients and in no E patients. No E patients suffered from extensive bleeding, while 13 Y patients were initially circulatory instable due to massive hemorrhage.

Table 2 Demographic data from the included patients. P-values were calculated by comparing E with Y patients. CVD, cardiovascular disease; ASDH, acute subdural hematoma; tSAH, traumatic subarachnoid hemorrhage; mixed, mixed type of injury; EDH, epidural hematoma; DAI, diffuse axonal injury. Some patients were not included in the analysis because of unknown data regarding previous brain injury (3 E), diabetes mellitus (6 E and 13 Y), hypertension (8 E and 14 Y), anticoagulation (8 E and 12 Y) and etylism (7 E and 24 Y)

	Elderly (E) N (%)	Younger (Y) N (%)	p-value
No. of patients	62 (22)	222 (78)	
Gender			
Male	40 (64)	186 (84)	p<0.05
Female	22 (36)	36 (16)	p<0.05
Medical history			
Previous brain injury	12 (20)	27 (13)	n.s.
Diabetes mellitus	9 (16)	9 (4)	p<0.05
Hypertension/CVD	28 (52)	21 (10)	p<0.001
Anticoagulants	25 (46)	12 (6)	p<0.001
Etylism	12 (22)	37 (19)	n.s.
Accident mechanism			
Bicycle accident	0 (0)	10 (4)	n.s.
Fall accident	50 (81)	79 (36)	p<0.005
Vehicle accident	3 (5)	83 (37)	p<0.05
Pedestrian hit by vehicle	3 (5)	8 (4)	n.s.
Assault	2 (3)	14 (6)	n.s.
Sports injury	1 (2)	9 (4)	n.s.
Other	3 (5)	19 (9)	n.s.
CT findings			
ASDH	31 (50)	40 (18)	p<0.001
Contusions	19 (31)	78 (35)	n.s.
tSAH	4 (6)	18 (8)	n.s.
Mixed	4 (6)	28 (13)	p<0.001
EDH	0 (0)	20 (9)	p<0.05
Impression fracture	1 (2)	7 (3)	n.s.
Other	3 (5)	3 (1)	n.s.
DAI	0 (0)	26 (12)	p<0.05
Normal	0 (0)	3 (1)	n.s.
Other injuries	43 (69)	196 (88)	p<0.005

RLS and GCS M scores at admission

The median RLS value was 3.5 (2.0–4.0) equally in the older and younger group. The median GCS M value was 5 (5.0–6.0) in both groups (Table 3).

NIC

Length of stay, ICP monitoring and length of artificial ventilation

The mean length of stay (LOS) in the E group was 12 (±13) days and in the Y group was 11 (±10) days (n.s.) (Table 4). A total of 154 patients [44 % of E and 57 % of Y patients ($p=0.056$)] received intracranial pressure monitoring (intraparenchymatous pressure monitoring and/or intraventricular drainage) (Table 4). The majority of patients in both the E and Y groups (approximately 76 %, respectively) were treated with a ventilator (Table 4). The mean duration of ventilator treatment was insignificantly higher among Y patients (mean 8 days) compared to E (mean 6 days) (Table 4).

Table 3 Neurological score at admission and discharge. NIC mortality in numbers and percentage. RLS, reaction level scale [33]; GCS M, Glasgow coma score Motor [39]; NIC, neurointensive care

	Elderly		Younger		
	Median	Quartile	Median	Quartile	p-value
RLS admission	3.5	2.0–4.0	3.5	2.0–4.0	n.s.
GCS-M admission	5.0	5.0–6.0	5.0	5.0–6.0	n.s.
RLS discharge	2.0	2.0–3.5	2.0	1.0–2.0	p<0.05
GCS-M discharge	6.0	5.0–6.0	6.0	6.0–6.0	p=0.09

Table 4 Numbers and percentage of different treatments during NIC. P-values were calculated by comparing E patients with Y. ICP, intracranial pressure; ASDH, acute subdural hematoma; EDH, epidural hematoma. In some cases, operations were done for several indications (e.g., evacuation of both extracerebral hematoma and contusions). Therefore, the sum of surgeries for each diagnosis category exceeds the total number of craniotomies and number of patients

	Elderly N (%)	Younger N (%)	p-value
Mean LOS	12 days	11 days	n.s.
Mechanical ventilation	47 (76)	168 (76)	n.s.
Mean LOV	6 days	8 days	n.s.
ICP monitoring	27 (44)	127 (57)	p=0.056
Craniotomy	29 (47)	63 (28)	p<0.01
ASDH	25 (40)	25 (11)	p<0.001
EDH	0	18 (8)	p<0.001
Contusions	6 (9)	18 (8)	n.s.
Hemicraniectomy	1 (2)	17 (8)	p=0.07
Thiopental treatment	0	21 (10)	p<0.005
Mean duration		6 days	
Surgery at local hospital	4 (6)	17 (8)	n.s.
NIC mortality	4 (6)	10 (4)	n.s.

Neurosurgery

Ninety-two of the patients underwent a craniotomy because of mass lesions: 47 % (n=29) of E and 28 % (n=63) of Y patients (p<0.001) (Table 4). The type of injury leading to surgery differed between E and Y patients (Table 4). Six percent (n=4) of E and 8 % (n=17) of Y patients underwent acute surgery because of a life-threatening mass lesion at a local hospital before admission to the NIC unit (n.s.) (Table 4).

Thiopental treatment

None of E vs. 10 % (n=21) of Y patients received thiopental treatment because of refractory high ICP (p<0.005) (Table 4). The mean duration of thiopental treatment was about 6 days (Table 4).

Meningitis

In the E group, 2 % (n=1) suffered from meningitis with a positive bacterial culture, which was similar to the Y group (2 %, n=5).

Outcome

Neurological grade at discharge and NIC mortality

At discharge, the median RLS at discharge was 2 and median GCS M was 6 in both the E and Y groups (Table 3). The mortality rate in E patients during NIC was 6 % (n=4); all died of circulatory arrest. The Y group had 4 % (n=10) NIC mortality (Table 4). Four of the Y patients died because of circulatory arrest, and the six remaining patients died as a result of total brain infarction.

Change in the RLS and GCS M scores during NIC

During the NIC period, the percentage of patients who talked at admission (RLS 1–2) and later deteriorated (RLS ≥3 at discharge) was 5 % (n=3) in the E and zero in the Y group (p<0.05). Moreover, 29 % (n=18) of E and 41 % (n=92) of Y patients (p<0.05) improved in consciousness from being in a more severe state (RLS≥3) to RLS 1–2 (talkative) at NIC discharge (substantial recovery).

Six-month GOSE

Seventy-two percent (n=152) of Y patients had favorable 6-month outcomes vs. 51 % (n=28) of E patients (p<0.05) (Fig. 1). The mortality at follow-up was 25 % (n=14) in the E and 7 % (n=15) in the Y group (p<0.05) (Fig. 1). The proportion of favorable outcome declined in combination with increased mortality with increasing age (Fig. 2).

Outcome after surgery

The clinical outcomes after surgery for different types of injury are presented in Table 5. Overall, after surgery (i.e., craniotomy because of a mass lesion) favorable outcome in the E group was 22 % (n=6) compared to 61 % (n=35) in the Y group (p<0.05) (Table 5). The proportion of unfavorable outcomes and mortality was higher in the E compared to the younger group (Table 5). Subgroup analysis showed that 16 E and 36 Y patients who were awake (RLS 1–3) at admission were subsequently operated on because of a mass lesion (Table 6). Moreover, 11 E and 21 Y patients who were unconscious (RLS 4–8) at admission underwent craniotomy (Table 6). Among the E patients who were unconscious at admission and operated on, 18 % had a favorable outcome, whereas approximately 82 % had a poor outcome (Table 6). In the group with awake E patients at admission, the proportion of favorable outcomes after surgery was 25 % (Table 6). There was no significant difference in outcome after surgery in the E group between unconscious and conscious patients. It is notable that even in the worse group (RLS 4–8) some E patients had a favorable outcome after surgery (18 %, n=2)(Table 6). In the Y group, 27 (74 %) patients who were awake at admission to the NIC had favorable outcomes, resulting in 26 % with poor outcomes in this group (Table 6). The mortality rate was 24 % in the most severe cases (RLS 4–8 at admission). The proportion of favorable outcomes was 38 % in this severe group (p<0.05) (Table 6).

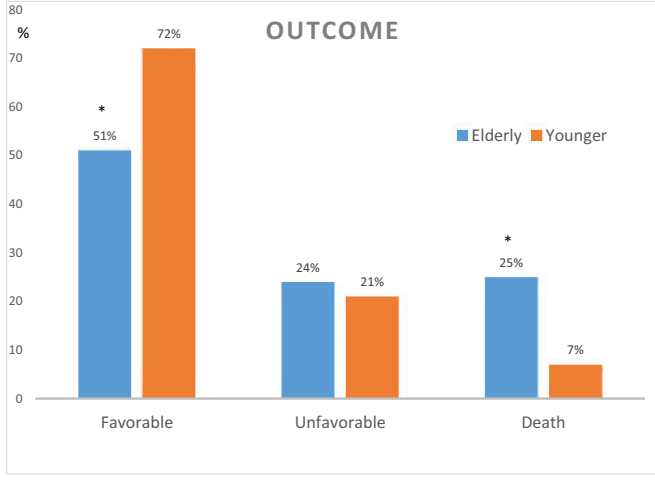

Fig. 1 Distribution of 6-month GOSE outcomes stratified into favorable (good recovery, higher/lower; moderate disability, higher/lower), unfavorable (severe disability, higher/lower; vegetative) and death. *Statistically significant difference between E and Y patients ($p<0.05$). Glasgow Outcome Scale Extended (GOSE) [40]. Patients with unknown outcome (6 E and 12 Y patients) were excluded from the outcome analysis but included in the descriptive part of the study

Discussion

The number of elderly people in society is increasing along with more active lifestyles. The incidence of TBI in the elderly has doubled the last 18 years [29]. In our previous TBI material the proportion of elderly patients >60 years was 16 % [8] compared to 22 % in the present study (>65 years). It is known that elderly patients with TBI fare far worse than younger patients [2, 3, 5, 13, 15, 16, 18, 23–25, 32, 35, 38, 42, 43]. However, to our knowledge there are only a few recent papers describing the results after neurointensive care of the current status [13, 24, 35]. The increasing number of elderly patients with TBI leads to difficult considerations regarding optimizing and individualizing patient care as well as reflections on quality of life in elderly TBI patients. Therefore, it is very important to increase our knowledge regarding elderly patients with TBI. In this article, we aimed to evaluate the demographics, management and outcome of elderly TBI patients receiving modern NIC as a starting point for further analysis of elderly patients with TBI. Our main findings confirmed the results of previous studies showing that the outcome of elderly patients with TBI is significantly worse than in the younger population. It was however notable that 51 % of the elderly had a favorable outcome. Furthermore, elderly patients undergoing a craniotomy because of an extracerebral hematoma with mass effect generally have a poor prognosis.

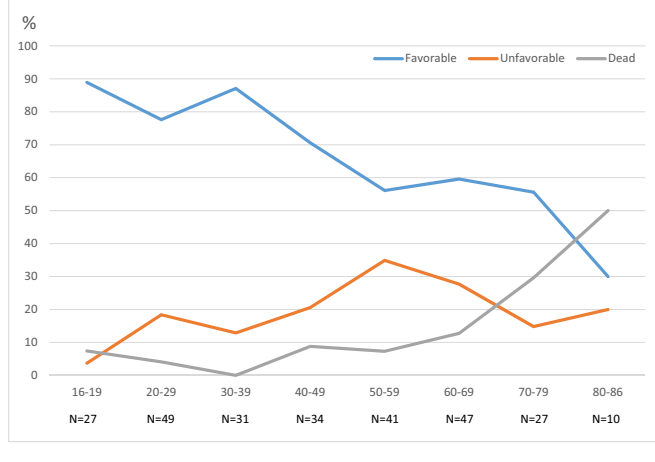

Fig. 2 Proportion of favorable outcomes and death at 6 months after injury in 10-year patient age periods. There was an apparent strong relationship between increased age and worsened outcome

Table 5 Six-month GOSE outcomes in patients operated on with craniotomy because of significant mass lesions. GOSE parameters are stratified into favorable (good recovery, higher/lower; moderate disability, higher/lower) unfavorable (severe disability, higher/lower; vegetative) and death. P-values were calculated by comparing E and Y patients. ASDH, acute subdural hematoma; EDH, epidural hematoma

Surgery		Elderly N (%)	Younger N (%)	p-value
ASDH	Favorable	5 (21)	12 (57)	n.s.
	Unfavorable	10 (42)	4 (19)	n.s.
	Death	9 (37)	5 (24)	p<0.05
EDH	Favorable	0	14 (82)	
	Unfavorable	0	2 (12)	
	Death	0	1 (6)	
Contusions	Favorable	2 (40)	9 (56)	n.s.
	Unfavorable	1 (20)	4 (25)	n.s.
	Death	2 (40)	3 (19)	n.s.
Hemicraniectomy	Favorable	0	9 (60)	
	Unfavorable	0	5 (33)	
	Death	1 (100)	1 (7)	
All	Favorable	6 (22)	35 (61)	p<0.05
	Unfavorable	11 (41)	15 (27)	n.s.
	Death	10 (37)	7 (12)	p<0.005

However, some have a favorable outcome even if they are unconscious preoperatively. We will discuss the results in detail.

Pre-NIC factors

A main question is whether the poorer results in the elderly after TBI are due to the brain injury or to an overall age-related weakness and premorbid status leading to a more complicated medical state. In our study, 20 % of the E population compared to 13 % in the Y group suffered from previous brain injury/disease (n.s.). We found a significant difference between the rates of preexisting diabetes mellitus (16 % of E and 4 % of Y patients). Diabetes mellitus leads to various systemic complications (e.g., chronic inflammation [26]), which may have adverse effects on secondary brain injury. Nearly half of the elderly suffered from CVD/hypertension or were treated with anticoagulants. This finding differed significantly from the younger group (10 % suffered from CVD/hypertension and 5 % were treated with anticoagulants). Preexisting anticoagulant treatment has been associated with worsened outcome [19, 22]. Therefore, it is clear that several unavoidable factors exist in the elderly such as preexisting brain pathology, chronic inflammation/diabetes mellitus and coagulopathy, reasonably contributing to increased secondary brain injury and poorer outcomes.

Table 6 Six-month GOSE outcome in patients after craniotomy divided by neurological status at admission. RLS 1–3 (awake) and RLS 4–8 (unconscious). P-values reflect differences between patients in the RLS 1–3 and RLS 4–8 groups

Admission RLS:		RLS 1–3	RLS 4–8	
Outcome		N (%)	N (%)	p-value
Elderly	Favorable	4 (25)	2 (18)	n.s.
	Unfavorable	6 (38)	5 (45)	n.s.
	Dead	6 (38)	4 (36)	n.s.
Younger	Favorable	27 (74)	8 (38)	p<0.05
	Unfavorable	7 (21)	8 (38)	n.s.
	Dead	2 (5)	5 (24)	p<0.05

In our study the most frequent injury mechanism in the elderly was falls (in 81 %), whereas in the younger group motor vehicle accidents were the most frequent (in 37 %). These results are similar to what others have published [11, 17, 24, 36]. There are several reasons why fall accidents among the elderly are more common, such as age-related muscle weakness, inappropriate medication, insufficient physiotherapy, orthostatic hypotension, vertigo, diabetes mellitus, poor vision and unsuitable home environments, to mention a few [6, 28]. In our article, half of the elderly group suffered from ASDH, a significantly larger proportion than in the younger group where DAI, EDH and mixed type of injury occurred more commonly. This injury distribution is in line with other studies [15, 35, 41] and may be explained by the injury mechanism. The increased risk of ASDH in the elderly due to reduced brain volume cannot be influenced. However, some causes of falls in the elderly could reasonably be prevented by improved medical care and living environments for the elderly. Organized training programs for the elderly are also currently receiving much attention [7].

The RLS and GCS-M at NIC admission did not differ between the older and younger group. The RLS and GSC-M were 3.5 and 5, respectively, in both age groups. These results are consistent with studies showing similar admission GCS scores between age groups [43]. However, in a recent study elderly patients had better GCS scores than younger TBI patients with similar TBI severity [30], suggesting that the brain injury could be worse in older patients with similar GCS scores as younger patients. This means that if the neurological scores at admission are equal between the age groups, the elderly could still have a more extensive brain injury. This effect is likely due to the fact that both the RLS and GCS scales are primarily consciousness scales and that elderly patients with reduced brain size can harbor a larger or more widespread injury before developing decreased consciousness due to a mass effect.

NIC

In our study, elderly and younger patients had a similar LOS in our NIC unit (approximately 11–12 days in both groups). Likewise, there were no significant differences in terms of ventilator treatment (occurring in 76 % of both groups), duration of ventilator treatment (6–8 days both groups) and NIC mortality rate (4–6 %). These findings are in line with other reports [12]. Ventilator treatment should not be restricted for older patients when an indication appears [9]. Our results confirm that we did not withhold ventilator treatment from the elderly if needed. However, artificial ventilation in the elderly is associated with a higher risk of side effects, such as the development of critical illness polyneuropathy, which could have a large effect on the outcome [14]. Further studies need to clarify the extent of this complication in our material.

The intracranial pressure was monitored in 44 % of E and 57 % of Y patients (n.s.). We have previously shown a strong compliance (79 %) with the standardized management protocols recommending that all unconscious patients not responding to commands (i.e., RLS>3a and GCS-M ≤5) should have ICP monitoring [1]. When we investigated the reasons for not monitoring the ICP in cases where it was indicated according to the protocol, reasonable explanations were found, e.g., coagulopathy [27]. Therefore, we believe we did not withhold ICP monitoring in elderly patients simply because of age. Other centers have published 47 % compliance with the Brain Trauma Foundation ICP monitoring guidelines [37]; we therefore consider our results regarding ICP monitoring guideline compliance satisfactory. Further studies need to address the differences between the number of secondary insults between elderly and younger patients during NIC.

Six-month outcome

We found that the overall mortality was significantly different between the age groups, i.e, 25 % and 7 % in the E and Y group, respectively ($p<0.05$). Favorable outcome was seen in 72 % of the Y and 51 % of the E group at 6 months. We also observed a clear graphical trend of an age-related decrease in favorable outcome after 40 years of age (Fig. 2).

Even if the mortality was clearly higher in the elderly, we believe that a 51 % favorable 6-month outcome in the elderly group is a good result compared to previously published results showing favorable outcomes in the elderly in only 7.9 %, 23 % and 32.2 % [13, 16, 21]. For those aged >65 years, mortality was over 50 % and unfavorable outcome 74–90 % in other studies [2, 5, 13, 15, 16, 18, 42].

Surgery

A key question is whether older patients benefit from surgical evacuation of mass lesions. In our study, 93 of all patients underwent a craniotomy because of a significant mass lesion: 47 % (n=29) of the elderly and 28 % (n=63) of younger group ($p<0.001$). The majority of the younger patients who underwent craniotomy had a favorable outcome (61 %). This stood in sharp contrast to the older patients, with favorable outcomes in 22 %. We found no significant difference in the outcome after surgery in the older patients when comparing whether they were awake or unconscious before surgery (25 vs. 18 % favorable outcome, respectively, Table 6). Thus, the consciousness level at admission does not solely define the functional outcome in the elderly, meaning that the elderly do not die because of the severity of the initial brain injury per se. This is opposed to what is seen in younger patients. A majority of the younger patients (74 %) who were awake at admission had favorable outcomes after surgery, and only 5 % of them died. The mortality rate in the unconscious group was significantly higher (24 %). Likewise, the rate of favorable outcome after surgery in the younger patients with RLS 4–8 at admission was significantly lower than in awake patients (38 % vs. 74 %, $p<0.05$).

Given that the chance of favorable outcome is significantly lower in the elderly, it would be desirable to have better methods for more accurate prognostic prediction to select patients for meaningful surgical intervention.

Limitations of the study

This study obviously contains several limitations that need to be addressed in the future. To mention a few, we only studied patients admitted to our department. From clinical practice we know that patients of high age with severe TBI tend not to be transferred but instead treated conservatively at a local hospital. Thus, there may be a selection bias between younger and older patients that could have had an impact on the relatively good outcome ratio in the elderly group. Another important factor regards the characteristics decisive for each outcome category. We need to determine the common denominator for patients doing worse but also for elderly patients doing well despite an initial low GCS.

Concluding remarks

Although the elderly did far worse than younger patients after TBI, as many as 51 % had a favorable outcome with modern NIC. In the elderly, the outcome after surgery did not differ significantly between patients who were awake or unconscious preoperatively, indicating that it is not solely the primary brain injury per se that limits the outcome in the elderly. Instead, it is more likely that it is the primary and secondary brain injury in combination with other contributing factors

associated with increased age, such as general weakening, use of anticoagulants and increased risk of complications, that determines the clinical outcome. We believe that age by itself should not be a reason for withholding treatment in elderly patients with TBI. To further improve the management of elderly patients with TBI we need better instruments for patient selection for active treatment and withdrawal of NIC. We also will need to advance targeted individualized NIC in the elderly and to improve the overall rehabilitative care after the NIC period. This article is an initial study preparing for such following investigations of the pathophysiology in elderly patients with TBI. This is urgent because of the quickly increasing proportion of active elderly people in the population.

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Compliance with ethical standards

Ethics The study was approved by the local ethics committee.

Conflict of interest All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW, Foundation BT, Surgeons AAoN, Surgeons CoN, Joint Section on Neurotrauma and Critical Care AANSC (2007) Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. J Neurotrauma 24(Suppl 1):S37–44
2. Brazinova A, Mauritz W, Leitgeb J, Wilbacher I, Majdan M, Janciak I, Rusnak M (2010) Outcomes of patients with severe traumatic brain injury who have Glasgow Coma Scale scores of 3 or 4 and are over 65 years old. J Neurotrauma 27:1549–1555
3. Cagetti B, Cossu M, Pau A, Rivano C, Viale G (1992) The outcome from acute subdural and epidural intracranial haematomas in very elderly patients. Br J Neurosurg 6:227–231
4. Czosnyka M, Balestreri M, Steiner L, Smielewski P, Hutchinson PJ, Matta B, Pickard JD (2005) Age, intracranial pressure, autoregulation, and outcome after brain trauma. J Neurosurg 102:450–454
5. De Bonis P, Pompucci A, Mangiola A, Paternoster G, Festa R, Nucci CG, Maviglia R, Antonelli M, Anile C (2011) Decompressive craniectomy for elderly patients with traumatic brain injury: it's probably not worth the while. J Neurotrauma 28: 2043–2048
6. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E (2010) Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. Epidemiology 21:658–668
7. El-Khoury F, Cassou B, Charles MA, Dargent-Molina P (2013) The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. BMJ 347:f6234
8. Elf K, Nilsson P, Enblad P (2002) Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care. Crit Care Med 30:2129–2134
9. Ely EW, Evans GW, Haponik EF (1999) Mechanical ventilation in a cohort of elderly patients admitted to an intensive care unit. Ann Intern Med 131:96–104
10. Fischerstrom A, Nyholm L, Lewen A, Enblad P (2014) Acute neurosurgery for traumatic brain injury by general surgeons in Swedish county hospitals: a regional study. Acta Neurochir (Wien) 156:177–185
11. Fletcher AE, Khalid S, Mallonee S (2007) The epidemiology of severe traumatic brain injury among persons 65 years of age and older in Oklahoma, 1992-2003. Brain Inj 21:691–699
12. Frankel JE, Marwitz JH, Cifu DX, Kreutzer JS, Englander J, Rosenthal M (2006) A follow-up study of older adults with traumatic brain injury: taking into account decreasing length of stay. Arch Phys Med Rehabil 87:57–62
13. Gan BK, Lim JH, Ng IH (2004) Outcome of moderate and severe traumatic brain injury amongst the elderly in Singapore. Ann Acad Med Singap 33:63–67
14. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G (2008) Clinical review: critical illness polyneuropathy and myopathy. Crit Care 12:238
15. Howard MA, Gross AS, Dacey RG, Winn HR (1989) Acute subdural hematomas: an age-dependent clinical entity. J Neurosurg 71: 858–863
16. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, Murray GD, Maas AI (2003) Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg 99:666–673
17. Ingebrigtsen T, Mortensen K, Romner B (1998) The epidemiology of hospital-referred head injury in northern Norway. Neuroepidemiology 17:139–146
18. Jennett B, Teasdale G, Braakman R, Minderhoud J, Heiden J, Kurze T (1979) Prognosis of patients with severe head injury. Neurosurgery 4:283–289
19. Karni A, Holtzman R, Bass T, Zorman G, Carter L, Rodriguez L, Bennett-Shipman VJ, Lottenberg L (2001) Traumatic head injury in the anticoagulated elderly patient: a lethal combination. Am Surg 67:1098–1100
20. Lenell S, Nyholm L, Lewen A, Enblad P (2015) Updated periodic evaluation of standardized neurointensive care shows that it is possible to maintain a high level of favorable outcome even with increasing mean age. Acta Neurochir (Wien) 157:417–425
21. McIntyre A, Mehta S, Janzen S, Aubut J, Teasell RW (2013) A meta-analysis of functional outcome among older adults with traumatic brain injury. NeuroRehabilitation 32:409–414
22. Mina AA, Knipfer JF, Park DY, Bair HA, Howells GA, Bendick PJ (2002) Intracranial complications of preinjury anticoagulation in trauma patients with head injury. J Trauma 53:668–672
23. Mosenthal AC, Lavery RF, Addis M, Kaul S, Ross S, Marburger R, Deitch EA, Livingston DH (2002) Isolated traumatic brain injury: age is an independent predictor of mortality and early outcome. J Trauma 52:907–911
24. Mosenthal AC, Livingston DH, Lavery RF, Knudson MM, Lee S, Morabito D, Manley GT, Nathens A, Jurkovich G, Hoyt DB, Coimbra R (2004) The effect of age on functional outcome in mild traumatic brain injury: 6-month report of a prospective multicenter trial. J Trauma 56:1042–1048

25. Mushkudiani NA, Engel DC, Steyerberg EW, Butcher I, Lu J, Marmarou A, Slieker F, McHugh GS, Murray GD, Maas AI (2007) Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma 24:259–269
26. Nguyen DV, Shaw LC, Grant MB (2012) Inflammation in the pathogenesis of microvascular complications in diabetes. Front Endocrinol (Lausanne) 3:170
27. Nyholm L, Howells T, Enblad P, Lewén A (2013) Introduction of the Uppsala Traumatic Brain Injury register for regular surveillance of patient characteristics and neurointensive care management including secondary insult quantification and clinical outcome. Ups J Med Sci 118:169–180
28. Panel on Prevention of Falls in Older Persons AGS, British Geriatrics S (2011) Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc 59:148–157
29. Ramanathan DM, McWilliams N, Schatz P, Hillary FG (2012) Epidemiological shifts in elderly traumatic brain injury: 18-year trends in Pennsylvania. J Neurotrauma 29:1371–1378
30. Salottolo K, Levy AS, Slone DS, Mains CW, Bar-Or D (2014) The effect of age on Glasgow Coma Scale score in patients with traumatic brain injury. JAMA Surg 149:727–734
31. SCB (2009) The future population of Sweden 2009-2060. Demographic reports 2009:1 http://www.scb.se/statistik/_publikationer/BE0401_2009I60_BR_BE51BR0901ENG.pdf Accessed August 28, 2015
32. Sendroy-Terrill M, Whiteneck GG, Brooks CA (2010) Aging with traumatic brain injury: cross-sectional follow-up of people receiving inpatient rehabilitation over more than 3 decades. Arch Phys Med Rehabil 91:489–497
33. Starmark JE, Stålhammar D, Holmgren E (1988) The Reaction Level Scale (RLS85). Manual and guidelines. Acta Neurochir (Wien) 91:12–20
34. Stefan M, Iglesia Lino L, Fernandez G (2011) Medical consultation and best practices for preoperative evaluation of elderly patients. Hosp Pract (1995) 39:41–51
35. Stocchetti N, Paternò R, Citerio G, Beretta L, Colombo A (2012) Traumatic brain injury in an aging population. J Neurotrauma 29:1119–1125
36. Styrke J, Stålnacke BM, Sojka P, Björnstig U (2007) Traumatic brain injuries in a well-defined population: epidemiological aspects and severity. J Neurotrauma 24:1425–1436
37. Talving P, Karamanos E, Teixeira PG, Skiada D, Lam L, Belzberg H, Inaba K, Demetriades D (2013) Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. J Neurosurg 119:1248–1254
38. Taussky P, Widmer HR, Takala J, Fandino J (2008) Outcome after acute traumatic subdural and epidural haematoma in Switzerland: a single-centre experience. Swiss Med Wkly 138:281–285
39. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. Lancet 2:81–84
40. Teasdale GM, Pettigrew LE, Wilson JT, Murray G, Jennett B (1998) Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. J Neurotrauma 15:587–597
41. Thompson HJ, McCormick WC, Kagan SH (2006) Traumatic brain injury in older adults: epidemiology, outcomes, and future implications. J Am Geriatr Soc 54:1590–1595
42. Tokutomi T, Miyagi T, Ogawa T, Ono J, Kawamata T, Sakamoto T, Shigemori M, Nakamura N (2008) Age-associated increases in poor outcomes after traumatic brain injury: a report from the Japan Neurotrauma Data Bank. J Neurotrauma 25:1407–1414
43. Vollmer DG, Torner JC, Jane JA, Sadovnic B, Charlebois D, Eisenberg HM, Foulkes MA, Marmarou A, Marshall LF (1991) Age and outcome following traumatic coma: why do older patients fare worse? J Neurosurg Spec Suppl 75:S37–S49

Paper III

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ORIGINAL ARTICLE - BRAIN TRAUMA

Clinical outcome and prognostic factors in elderly traumatic brain injury patients receiving neurointensive care

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Abstract

Background The probability of favorable outcome after traumatic brain injury (TBI) decreases with age. Elderly, ≥ 60 years, are an increasing part of our population. Recent studies have shown an increase of favorable outcome in elderly over time. However, the optimal patient selection and neurointensive care (NIC) treatments may differ in the elderly and the young. The aims of this study were to examine outcome in a larger group of elderly TBI patients receiving NIC and to identify demographic and treatment related prognostic factors.

Methods Patients with TBI ≥ 60 years receiving NIC at our department between 2008 and 2014 were included. Demographics, co-morbidity, admission characteristics, and type of treatments were collected. Clinical outcome at around 6 months was assessed. Potential prognostic factors were included in univariate and multivariate regression analysis with favorable outcome as dependent variable.

Results Two hundred twenty patients with mean age 70 years (median 69; range 60–87) were studied. Overall, favorable outcome was 46% (Extended Glasgow Outcome Scale (GOSE) 5–8), unfavorable outcome 27% (GOSE 2–4), and mortality 27% (GOSE 1). Significant independent negative prognostic variables were high age ($p < 0.05$), multiple injuries ($p < 0.05$), GCS M ≤ 3 on admission ($p < 0.05$), and mechanical ventilation ($p < 0.001$).

Conclusions Overall, the elderly TBI patients ≥ 60 years receiving modern NIC in this study had a fair chance of favorable outcome without large risks for severe deficits and vegetative state, also in patients over 75 years of age. High age, multiple injuries, GCS M ≤ 3 on admission, and mechanical ventilation proved to be independent negative prognostic factors. The results underline that a selected group of elderly with TBI should have access to NIC.

Keywords Traumatic brain injury · Elderly · Outcome · Quality register · Neurointensive care · Prognostic factors

Abbreviations

TBI	Traumatic brain injury
NIC	Neurointensive care
GOSE	Extended Glasgow Outcome Scale
GCS	Glasgow Coma Scale
GCS M	Glasgow Coma Scale motor response
ATLS	Advanced Trauma Life Support
CVD	Cardiovascular disease
ICP	Intracranial pressure
CT	Computed tomography
EVD	External ventricular drain
CPP	Cerebral perfusion pressure
SBP	Systolic blood pressure
CVP	Central venous pressure
CSF	Cerebrospinal fluid
ASDH	Acute subdural hematoma
EML	Evacuated mass lesions
INR	International normalized ratio
ICH	Intracerebral hematoma
OR	Odds ratio
EDH	Epidural hematoma
NOAC	Non-vitamin K antagonist oral anticoagulants
LMWH	Low molecular weight heparin

This article is part of the Topical Collection on *Brain trauma*

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Introduction

Outcome after traumatic brain injury (TBI) has improved over time with the development of neurointensive care (NIC) [3, 4, 9, 10, 26, 27, 30, 48] despite the fact that favorable outcome decreases with increasing age [16, 21, 28, 29, 38, 44], and there is an increasing proportion of elderly in the TBI population [17, 19, 33, 34]. The United Nations reports that the population aged 60 or older is growing faster than all the younger age groups and expects the number of persons over 60 years to be more than doubled by 2050 [46]. Elderly are prone to trauma from falls. One third of every person above 60 years and every other person above 80 years have a falling accident every year [23]. The management of elderly patients with traumatic head injury constitutes a tremendous challenge in the future. An updated periodic evaluation of NIC of TBI patients made by us showed substantial increase of the proportion of patients > 60 years treated from 16 to 30% between 1996–1997 and 2008–2009 [22]. Furthermore, when clinical outcome was evaluated in the elderly TBI patients who received NIC, 51% of patients age ≥ 65 had favorable outcome [28]. Those relatively favorable results indicate that elderly patients with TBI should not be excluded from NIC. However, the optimal patient selection and most beneficial treatments may differ in the elderly and the young. Elderly patients have comorbidities to a higher degree, are more likely to use anticoagulants, and respond less well to rehabilitation [5]. Therefore, it is important to gain more knowledge about elderly TBI patients. The aims of this study were to examine outcome in a larger group of elderly TBI patients receiving NIC and to identify demographic- and treatment-related prognostic factors specifically in the elderly.

Material and methods

Referral of patients

The Department of Neurosurgery at the Uppsala University Hospital in Sweden provides highly specialized NIC for a population of approximately 2 million people living in the central part of Sweden. Patients arriving at local hospitals are stabilized according to the ATLS principles and then referred to Uppsala for tertiary care (the most distant local hospital 382 km away) [11].

Patient selection and data collection

Information about clinical characteristics, management, and clinical outcome are recorded for all TBI patients treated at the NIC unit in Uppsala in the Uppsala Traumatic Brain Injury register [31].TBI patients ≥ 60 years of age registered between 2008 and 2014 were eligible for the study. In total, 249 patients were identified. After exclusion of 29 elderly patients, 220 remained to be the studied. The patients were excluded for the following reason: patients admitted to the NIC unit ≥ 5 days after the trauma ($n = 10$), or treated successfully at the NIC unit within 24 h ($n = 6$); patients with both pupils wide and non-reacting on arrival at the NIC unit ($n = 4$) (i.e., patients with an obvious predestined fatal clinical course [1, 7]); patients with gunshot wound to the head ($n = 1$); patients lost to follow-up ($n = 8$).

Data studied

The following parameters were studied: primary or secondary transfer, sex, age, cause of trauma, multiple injuries, trauma under influence of drugs/alcohol, acute surgery before arrival, GCS on admission, medical history (brain injury/disease, previous traumatic brain injury, diabetes mellitus, hypertension/cardiovascular disease (CVD), antithrombotic drugs (subgrouped by antiplatelet, warfarin, non-vitamin K antagonist oral anticoagulants (NOAC), and low molecular weight heparin (LMWH)), and ethylism), craniotomy, cause of craniotomy, decompressive hemicraniectomy, intracranial pressure (ICP) monitoring, mechanical ventilation, and NIC mortality.

Radiology

The computed tomography (CT) scans from the admission were classified retrospectively according to Marshall Classification [25] by one of the authors (S.L.).

Neurointensive care

All patients were treated according to the standardized escalated management protocol, described in detail earlier [10], and summarized below:

Basal treatment All unconscious patients (Glasgow Coma Scale motor response (GCS M) ≤ 5) are intubated and mechanically ventilated. Intubated patients are moderately hyperventilated ($PaCO_2$ 4.0–4.5 kPa) on admission with the aim of normoventilation as soon as possible when ICP allows. Propofol (Propofol-LipuroB; Braun Medical, Danderyd, Sweden) is used for sedation and morphine for analgesia. ICP is monitored in unconscious patients using an external ventricular drain (EVD) or an intraparenchymal pressure probe. When EVD is used, ICP is measured with the pressure dome at the level of the lateral ventricles. Arterial blood pressure is measured with the pressure dome at heart level. Patients are positioned in bed with 30° head elevation to facilitate venous outflow. Clinical neurological status is monitored using frequent wake-up tests. Lesions causing significant mass effect, extracerebral hematomas or contusions, are surgically evacuated except when coagulopathy is resistant to

therapy. Prophylactic anticonvulsants are not used. Thromboprophylaxis are used when the risk for new intracranial bleedings are deemed low and continued until patients have been mobilized. Treatment goals are as follows: ICP < 20 mmHg, cerebral perfusion pressure (CPP) > 60 mmHg, systolic blood pressure (SBP) > 100 mmHg, central venous pressure (CVP) 0–5 cm H_20, pO_2 > 12 kPa, blood glucose 5–10 mmol/L, electrolytes within normal range, normovolemia, and body temperature < 38 °C. If ICP is increased > 20 mmHg without mass lesions, intermittent cerebrospinal fluid (CSF) drainage of small volumes (1–2 ml) are used during the early period when there are risks of expanding hematomas and brain swelling. Later, CSF is drained using an open system against a pressure level of 15–20 mmHg if needed.

Step 1A In case of persisting ICP problems, the treatment is escalated to Step 1A with no wake-up test. This entails continuous sedation with propofol and stress reduction with β1-antagonist metoprolol (Seloken®, AstraZeneca AB Södertälje, Sweden) (0.2–0.3 mg/kg/24 h as an infusion) and α2-agonist clonidin (Catapresan®, BoehingerIngelheim AB Stockholm Sweden) (0.5–1.0 μg/kg × 8 or the same dose as an infusion).

Step 1B When the ICP problems continue, barbiturate coma treatment with infusion of thiopental (Pentocur, Abcur AB, Helsingborg, Sweden) is initiated provided that there is no shift of the midline. Bolus dose of 4–8 mg/kg is given as repeated 50 mg injections until ICP is < 20 mmHg followed by an infusion of 5–10 mg/kg/h for 6 h and thereafter 2–5 mg/kg/h as required to control ICP. The lowest possible dose is used to keep ICP < 20 mmHg and burst-suppression on electroencephalogram (EEG) is not the goal. During this treatment, a CPP as low as 50 mmHg is allowed. Thiopental concentration > 380 μmol/L is avoided. Because of the high risk of severe side effects with barbiturate coma treatment in elderly, this therapy was only exceptionally escalated to this step in old patients.

Step 2 Decompressive craniectomy [42] is used when Step 1B is insufficient to reduce ICP or when adverse effects of the thiopental treatment are observed. Bi-fronto-temporal craniectomies are done, sparing the bone ridge in the midline when there are no mass lesions. When there is a shift of the midline and no localized mass lesions to evacuate, a hemicraniectomy is done.

Evaluation of outcome

Clinical outcome was assessed after around 6 months using structured telephone interviews for the Extended Glasgow Outcome Scale (GOSE) [39, 43]. The interview was done by a few selected persons.

The outcome was categorized in favorable (GOSE 5–8), unfavorable (GOSE 2–4), and dead (GOSE 1).

Statistical methods

To compare different age groups, Pearson's Chi-squared test was used. Patients and treatment factors were analyzed using univariate logistic regression. Multivariate logistic regression analysis was performed with favorable outcome (GOSE 5–8) as dependent variable. Admission variables were included as explanatory variables, and admission together with treatment variables was also analyzed. All explanatory variables were dichotomized except age. IBM SPSS Statistics for Windows was used.

Results

Age distribution

The mean age of the 220 patients was 70 years (median 69; range 60–87). The age distribution showed that most of the patients were between 60 and 75 years (Fig. 1).

Patient characteristics on admission

The patient characteristics are presented in Table 1 for all patients > 60 years old, for patients 60–74 years old, and for patients 75–89 years old. There were 170 patients 60–74 years old and 50 patients 75–89 years old. There was no significant difference in sex between the two age groups. The most common cause of trauma was falls which occurred in 77% of all cases (170 patients). There was no significant difference between the two age groups. In both age groups, around 90% of the patients were admitted in GCS M ≥ 4. Multiple injuries were found in 25% of the 60–74-year-old patients and in 10% of the 75–89 years old ($p < 0.05$). Trauma under the influence of alcohol was almost 5 times as common in the 60–74-year-old patients compared to the older patients, 26% vs 6%, respectively, ($p < 0.01$).

Overall, the most common type of injury dominating TBI was acute subdural hematoma (ASDH; 43%) followed by contusions (29%). In the 60–74-year-old group, contusions were the dominating injury type, and occurred in 35% of the patients, compared to 10% in the 75–89-year-old group ($p < 0.001$). In the 75–89-year-old group, the dominating injury type was ASDH, occurring in 76% of the patients compared to 34% in the 60–74 years old ($p < 0.01$) (Table 1).

When the initial CT scans were classified according to Marshall Classification (Table 1), diffuse injury II was the most common class with 41% in patients 60–74 years old and 22% in patients 75–89 years old ($p < 0.05$). Evacuated mass lesion was the most common Marshall Classification in patients 75–89 years old and occurred in 40% of those patients.

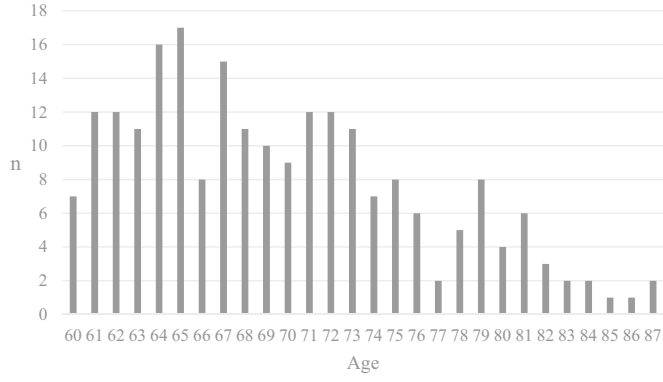

Fig. 1 Age distribution

Regarding the medical history (Table 1), 54% of all elderly had hypertension/CVD and 37% used antithrombotic drugs. One fifth of all 220 patients (20%) had a history of previous brain injury/disease before the trauma, but only 4% of those were a previous TBI. Among patients 60–74 years old, 48% had hypertension/CVD in the medical history compared to 72% in patients 75–89 years old ($p < 0.01$). Antithrombotic drugs were almost twice as common in 75–89-year-old patients compared to 60–74-year-old patients, 62% and 30%, respectively ($p < 0.001$). Looking at the specific antithrombotic drugs, warfarin was four times as common in 75–89-year-old patients compared to patients 60–74 years old; 42% vs 8%. Among patients 60–74 years old, 30% of had a history of ethylism compared to 10% among patients 75–89 years old ($p < 0.01$).

Management characteristics

Among all 220 elderly patients, 177 (80%) received mechanical ventilation for a mean of 7 days (median 6, range 1–21), and 118 (53%) had ICP monitoring for a mean of 10 days (median 8, range 2–25) (Table 2). Eighteen patients (8%) had been operated with evacuation of ASDH at the referring hospital due to acute herniation before arrival (Table 2). Ninety-five patients (43%) had a craniotomy done during NIC, most commonly due to ASDH which occurred in 80 patients (36%) followed by evacuation of contusions in 25 patients (11%). Decompressive hemicraniectomy was done in 9 patients (4%). Thirty patients 75–89 years old (60%) had a craniotomy compared to 65 patients 60–74 years old (38%) ($p \leq 0.01$). Three patients received thiopental.

Clinical outcome

Follow-up of surviving patients was made after 7.8 months in mean (median 7, range 5–28). When outcome was graded with the Extended Glasgow Outcome Scale, 43 patients (20%) were GOSE 8 (upper good recovery), 40 (18%) were GOSE 7 (lower good recovery), 10 (5%) were GOSE 6 (upper moderate disability), 8 (4%) were GOSE 5 (lower moderate disability), 21 (10%) were GOSE 4 (upper severe disability), 37 (17%) were GOSE 3 (lower severe disability), 2 patients (1%) were in GOSE 2 (vegetative state), and 59 patients (27%) were GOSE 1 (dead; 17 (8%) died at the NICU) (Fig. 2). The clinical outcome by age groups is summarized in Fig. 3. Patients 60–69 years old showed favorable outcome in around 50% of the cases and < 20% died. Patients 70–74 years old almost also showed favorable outcome in 50% of the cases and around 35% died. In patients 75–84 years of age, favorable outcome was around 30% and declined to 25% in patients 85–89 years old. Of the 60–74 years old, 11 patients (6%) died at the NICU compared with 6 (12%) in the 75–89 years old.

Prediction of prognosis

Univariate logistic regression analysis with favorable outcome (GOSE 5–8) as dependent variable (Table 3) showed the following significant patient variables (predictors): age ($p < 0.05$), GCS M ≤ 3 on admission ($p < 0.01$), diffuse injury Marshall score I–IV ($p < 0.001$), and Marshall score evacuated mass lesion (EML) ($p < 0.001$) and warfarin ($p < 0.05$). The following patient variables showed marginal significance (Table 3): extracerebral hematoma ($p = 0.08$), history of brain injury/disease ($p = 0.056$), and history of ethylism ($p = 0.066$) and antiplatelet ($p = 0.053$).

For the treatment variables, the significant variables were (Table 3): craniotomy ($p < 0.01$), evacuation of extracerebral hematoma ($p < 0.05$), and mechanical ventilation ($p < 0.001$).

Multivariate logistic regression analysis of admission variables showed that the significant independent variables were age ($p < 0.05$) and multiple injuries ($p < 0.05$). GCS M ≤ 3 on admission ($p = 0.052$) and EML ($p = 0.078$) showed marginal significance (Table 4).

Table 1 Characteristics on admission

Patient and trauma characteristics	All		60–74		75–89		*p* 60–74 vs 75–89	
	n	%	*n*	%	*n*	%		
Total	220		170		50			
Referrals	167	76	140	82	27	54	0.000	***
Sex (female)	61	28	44	26	17	34	0.260	
Male	159	72	126	74	33	66	0.260	
Multiple injuries	47	21	42	25	5	10	0.026	*
Under the influence of drugs/alcohol at trauma	47	21	44	26	3	6	0.003	**
Cause of trauma								
Bicycle accident	7	3	6	4	1	2		
Fall accident	170	77	132	78	38	76	0.807	
Vehicle accident	20	9	16	9	4	8		
Pedestrian hit by vehicle	9	4	6	4	3	6		
Assault	3	31	3	2	0	0		
Sports injury	1	0	0	0	1	2		
Other	10	5	7	4	3	6		
GCS motor response								
6 Obeys commands	106	48	80	47	26	52	0.539	
5 Localizes pain	68	31	55	32	13	26	0.393	
4 Withdraws (normal flexion)	24	10	17	1	7	14	0.425	
3 Stereotyped flexion	11	5	9	6	2	4		
2 Stereotyped extension	6	3	4	2	2	4		
1 None	5	2	5	3	0	0		
GCS M ≥ 4 on admission	198	90	152	89	46	92	0.592	
GCS M ≤ 3 on admission	22	10	18	11	4	8	0.592	
Dominating injury type on CT								
ASDH	95	43	57	34	38	76	0.000	***
Other	3	1	2	1	1	2		
DAI	2	1	2	1	0	0		
EDH	4	2	4	2	0	0		
Impression fracture[a]	3	1	3	2	0	0		
Contusions	64	29	59	35	5	10	0.001	***
Mixed	26	12	23	14	3	6	0.147	
Normal CT	0	0	0	0	0	0		
Traumatic SAH	23	10	20	12	3	6	0.242	
Initial CT Marshall Classification								
Diffuse injury I	2	1	2	1	0	0		
Diffuse injury II	80	36	69	41	11	22	0.016	*
Diffuse injury III	21	9	19	11	2	4		
Diffuse injury IV	14	6	9	5	5	1		
Evacuated mass lesion	68	31	48	28	20	40	0.114	
Non-evacuated mass lesion	35	16	23	14	12	24	0.075	
Diffuse injury I–IV	117	53	99	58	18	36	0.006	**
Focal mass lesion	103	47	71	41	32	64	0.006	**
Medical history of								
Brain injury/disease	45	20	33	19	12	24	0.480	
Traumatic brain injury	8	4	7	4	1	2		
Diabetes mellitus	36	16	25	15	11	22		
Hypertension/CVD	118	54	82	48	36	72	0.003	**
Ethylism	56	25	51	30	5	10	0.004	**
Antithrombotic drugs	82	37	51	30	31	62	0.000	***

Table 1 (continued)

Patient and trauma characteristics	All		60–74		75–89		*p* 60–74 vs 75–89	
	n	%	*n*	%	*n*	%		
Antiplatelet	48	22	36	16	12	24	0.671	
Warfarin	34	15	13	8	21	42	0.000	***
NOAC	8	4	7	4	1	2		
LMWH	6	3	4	2	2	4		

[a] All impression fractures also hade intracerebral or subarachnoidal blood

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

When admission variables and treatment variables were included in the multivariate logistic regression analysis, the significant independent variables were age ($p < 0.05$), GCS M ≤ 3 on admission ($p < 0.05$), multiple injuries ($p < 0.05$), and mechanical ventilation ($p < 0.01$). Variables that showed marginal significance were EML ($p = 0.067$), ethylism ($p = 0.073$), warfarin ($p = 0.088$), surgery before arrival ($p = 0.053$), and evacuated contusions ($p = 0.055$) (Table 5). Age was studied as a continuous variable so for every year in age there was a 0.94 odds ratio for favorable outcome, meaning the chance of favorable outcome decreased 6% with each increase of 1 year in age.

Discussion

Forty-six percent of the elderly over 60 years of age had favorable outcome (GOSE 5–8), while 27% had unfavorable outcome (GOSE 2–4), and 27% died (GOSE 1) (Fig. 3), which indicates that NIC may be beneficial for the elderly. The rate of favorable outcome was virtually unchanged up to 75 years of age and then a slight decrease was seen with more advanced age. Unfavorable outcome did not increase after 75 years of age; it appears as the reason for the slight decrease in the proportion of favorable outcome above 75 years of age was higher mortality rather than an increased

Table 2 Management characteristics

Management	All		60–74		75–89		*p* 60–74 vs 75–89	
	n	%	*n*	%	*n*	%		
Total	220		170		50			
Emergency craniotomy before arrival	18	8	13	8	5	10		
Craniotomy	95	43	65	38	30	60	0.006	**
Evacuation extracerebral hematoma[b]	87	40	58	34	29	58	0.002	**
Evacuation EDH	3	1	3	2	0	0		
Evacuation ASDH	80	36	52	31	28	56	0.001	**
Evacuation for both (EDH + SDH)	4	2	3	2	1	2		
Evacuation contusions[b]	25	11	21	12	4	8	0.394	
Decompressive hemicraniectomy	9	4	7	4	2	4		
Multiple surgeries	22	10	14	8	8	16	0.108	
ICP monitoring	118	53	96	56	22	44	0.120	
EVD only	21	10	19	11	2	4		
Intraparenchymal probe only	76	35	56	33	20	40	0.356	
EVD and intraparenchymal probe	21	10	21	12	0	0		
Days with ICP monitoring (mean)	9.5		10		7.4			
Mechanical ventilation	177	80	135	79	42	84	0.472	
Days with mechanical ventilation (mean)	7.4		7.6		6.8			

[b] Some patients evacuated both extracerebral hematoma and contusions

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

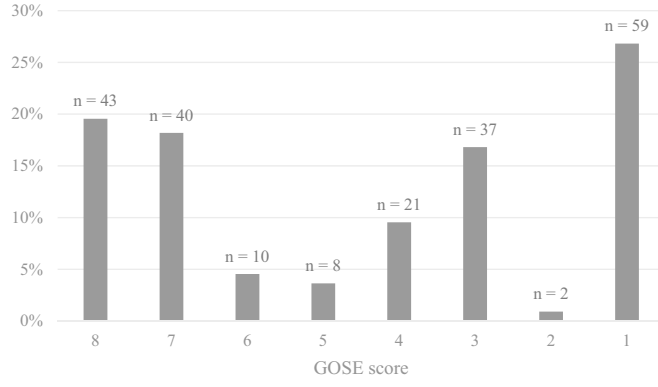

Fig. 2 GOSE score on 6-month follow-up

proportion of unfavorable outcome (Fig. 3). Those results are important to consider when to decide to offer NIC or not in an elderly TBI patient, taking also into consideration the general assumption that elderly are not afraid to die but to become dependent [41]. It should be emphasized, however, that these results cannot be extrapolated to the elderly population in general, since there was a selection of elderly patients judged to have a reasonable chance to achieve favorable outcome depending on, e.g., previous functional status, type of injury, level of consciousness, and co-morbidity. It is important to look at the characteristics of the elderly patients studied and try to identify prognostic factor in order to facilitate the selection of elderly TBI patients for NIC in the future.

The main cause of trauma in all elderly age groups was fall (Table 1), which is in accordance with our earlier findings [22, 28] as well as with the results of many other studies [8, 15, 17, 19, 23, 34, 36, 40]. Although there was a predominant injury mechanism, there was a notable significant difference between the age groups regarding several other characteristics (Table 1). The 60–74 years old were more often intoxicated at the time of trauma (26% vs 6%) and other injuries (25% vs 10%). They were also more likely to have contusions (35% vs 10%) and less likely to have ASDH (34% vs 76%). They had fewer cases of hypertension/CVD (48% vs 72%) and antithrombotic drugs (30% vs 62%, warfarin 8% vs 42%) and were more likely to have a history of ethylism (30% vs 10%). These findings highlight important differences between the 60–74-year-old group, and the 75–89-year-old group. The differences were also reflected in patient management with the older group having more craniotomies than the younger group (60% vs 38%). This may be explained by the fact that ASDH was more common among patients 75–89 years old and consistently it was also found that the reason for craniectomy was ASDH in 56% in the older age group compared to 31% in the younger group (Table 2).

Looking for prognostic predictors in the medical history, none of the following, such as previous brain injury/disease, previous traumatic brain injury, diabetes mellitus, and ethylism, had any significant impact on favorable outcome in the univariate analysis or the multivariate analyses, which was unexpected (Tables 3, 4, and 5). This of course does not exclude that those factors do not influence clinical outcome, but simply means that we were unable to show significant differences with our data. The reasons for that may be that some of those factors were present in too large proportions of the patients and others in too small proportions, and that a

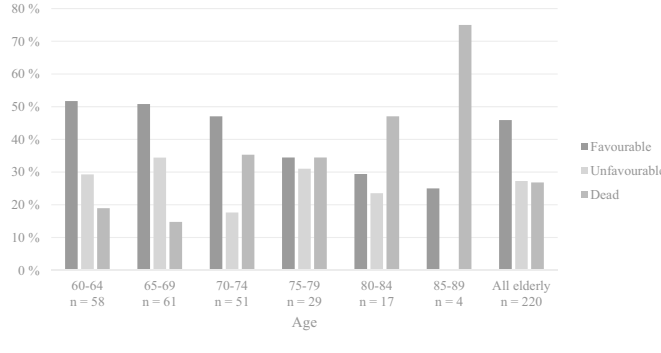

Fig. 3 Categorized outcome by age subdivided by 5 years. Outcome categorized in favorable (GOSE 5–8), unfavorable (GOSE 2–4), and dead (GOSE 1)

Table 3 Predictive value of admission and treatment variables for favorable outcome (univariate logistic regression analysis with favorable outcome (GOSE 5–8) as dependent variable)

Variables	Odds ratio	95% CI		*p*	
		Lower	Upper		
Age	0.948	0.908	0.989	0.013	*
Sex (female)	1.095	0.606	1.979	0.764	
GCS M ≤ 3 on admission	0.161	0.046	0.562	0.004	**
Multiple injuries	0.753	0.391	1.449	0.396	
Under the influence of drugs/alcohol at trauma	0.728	0.378	1.403	0.343	
Marshall Classification					
Diffuse injury I–IV	3.189	1.828	5.565	0.000	***
EML	0.299	0.160	0.560	0.000	***
NEML	0.751	0.360	1.567	0.445	
CT dominating injury type					
Extracerebral hematoma	0.619	0.361	1.059	0.080	
Contusions	1.646	0.916	2.956	0.096	
All other	1.082	0.591	1.981	0.797	
Medical history of					
Brain injury/disease	0.512	0.257	1.017	0.056	
Traumatic brain injury	0.160	0.019	1.323	0.089	
Diabetes mellitus	0.806	0.391	1.661	0.558	
Hypertension/CVD	0.900	0.528	1.534	0.699	
Ethylism	0.556	0.297	1.040	0.066	
Antithrombotic drugs	1.028	0.594	1.779	0.921	
Antiplatelet	1.899	0.993	3.632	0.053	
Warfarin	0.435	0.197	0.960	0.039	*
NOAC	1.186	0.289	4.866	0.813	
LMWH	1.184	0.234	5.998	0.839	
Surgery before arrival	0.845	0.326	2.188	0.728	
Craniotomy	0.412	0.237	0.716	0.002	**
Evacuated extracerebral hematoma	0.498	0.286	0.868	0.014	*
Evacuated contusions	0.418	0.167	1.045	0.062	
Decompressive hemicraniectomy	0.323	0.066	1.592	0.165	
Multiple surgeries	1.200	0.497	2.897	0.685	
ICP monitoring	0.634	0.371	1.082	0.095	
Mechanical ventilation	0.253	0.122	0.526	0.000	***

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

larger patient material is required to show significant differences in outcome. It is obvious that established prognostic factors from large patient materials of all ages cannot be disregarded in the decision-making process for which elderly TBI patients should be treated.

Antithrombotic drugs as a group had no negative impact on outcome in the univariate analysis. However, in a subgroup analysis, warfarin was a significant prognostic factor and antiplatelet therapy showed marginal significance ($p = 0.053$), but neither showed any significant independent contribution in the multivariate analysis (Table 4, Table 5). This finding is in contrast to the results of many earlier studies and needs to be discussed in particular. Karni et al. found a 50% mortality rate for traumatic head injury in elderly with anticoagulants [18]. Lavoie et al. showed that preinjury warfarin in elderly with closed head injury had more severe head injury and a higher likelihood of death [20]. Franko et al. showed that warfarin carries a six-fold increase in TBI-mortality and that mortality and occurrence of intracerebral hemorrhage increased with higher international normalized ratio (INR), especially INR over 4.0 where the mortality was found to be 50% and the risk of intracerebral hematoma (ICH) 75% [12]. Grandhi et al. found that warfarin and not antiplatelet medication influenced survival and need for neurosurgical intervention in the elderly [14]. Pieracci et al. found that the degree of anticoagulation rather than warfarin itself predicts adverse

Table 4 Prediction model of admission variables for favorable outcome (multivariate logistic regression analysis with favorable outcome (GOSE 5–8) as dependent variable)

Variables	Regression coefficient	SE	Wald X^2	Odds ratio	95% CI		p	
					Lower	Upper		
Intercept	4.114	2.032	4.101	61.192			0.043	*
Age	− 0.055	0.028	3.860	0.947	0.897	1.000	0.049	*
Sex (female)	0.056	0.366	0.023	1.057	0.516	2.167	0.879	
GCS M ≤ 3 on admission	− 1.350	0.696	3.765	0.259	0.066	1.014	0.052	
Multiple injuries	− 0.997	0.415	5.779	0.369	0.164	0.832	0.016	*
Under the influence of drugs/alcohol at trauma	− 0.135	0.492	0.076	0.874	0.333	2.290	0.783	
Marshall Classification								
Diffuse injury I–IV	0.521	0.478	1.189	1.684	0.660	4.300	0.275	
EML	− 0.910	0.516	3.114	0.403	0.147	1.106	0.078	
CT dominating injury type								
Extracerebral hematoma	0.464	0.458	1.027	1.591	0.648	3.903	0.311	
Contusions	0.296	0.416	0.508	1.345	0.595	3.036	0.476	
Medical history of								
Brain injury/disease	− 0.514	0.440	1.362	0.598	0.252	1.418	0.243	
Traumatic brain injury	− 1.425	1.259	1.281	0.240	0.020	2.837	0.258	
Diabetes mellitus	− 0.586	0.457	1.648	0.557	0.227	1.362	0.199	
Hypertension/CVD	0.015	0.387	0.001	1.015	0.476	2.165	0.970	
Ethylism	− 0.648	0.490	1.747	0.523	0.200	1.368	0.186	
Antithrombotic drugs								
Antiplatelet	0.540	0.434	1.548	0.523	0.200	1.368	0.213	
Warfarin	− 0.764	0.517	2.184	1.717	0.733	4.021	0.139	
NOAC	− 0.661	0.824	0.644	0.466	0.169	1.283	0.422	
LMWH	− 0.597	1.024	0.340	0.516	0.103	2.594	0.560	

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

outcome in TBI in elderly patients [35]. Ohm et al. showed that elderly with intracranial hemorrhage and antiplatelet therapy had increased mortality [32]. Wong et al. found in their study that clopidogrel increased mortality but not warfarin and aspirin [45]. There are also contradicting studies. In 2017, Ganetsky et al. examined 939 patients who had ground-level falls and antiplatelet therapy or anticoagulants, and found a low incidence of clinically significant intracranial hemorrhage (< 5%) and no difference between anticoagulation and antiplatelet therapy [13]. One could speculate that possible reasons for why anticoagulants did not have any prognostic significance in our study could be: (1) In our referral area, patients on warfarin have frequent check-ups which reduces the risk for overtreatment with too high INR. (2) National guidelines require CT examination after mild head trauma when on anticoagulation and prompt reversal of warfarin in case of intracranial hemorrhages. (3) Standardized NIC which minimizes secondary insults may prevent worsening of intracranial hemorrhages. Altogether, however, it is reasonable to assume that anticoagulation therapy increases the risk for worsening of the head injury and may under some circumstances complicate the insertion of ICP devices and surgical treatment, although such therapy doses not make successful management impossible.

Considering other possible prognostic factors analyzed in the univariate analysis, diffuse injury I–IV had a OR > 1 and seems to be associated with favorable outcome (most likely due to the large number of diffuse injury II, the least serious class in that group). EML had an OR 0.299 indicating less chance of good outcome (Table 3). Both craniotomy and evacuated extracerebral hematoma had a negative influence on good outcome in the univariate analysis as well as mechanical ventilation (Table 3).

When analyzing potential prognostic factors, it is of utmost importance to identify factors with independent prognostic information. The multivariate analysis of prognostic admission factors for favorable outcome showed that high age and multiple injuries had a significant independent negative prognostic value and low GCS showed marginal significance (p = 0.052) (Table 4), which was as expected and in accordance with other studies of elderly patients [6, 29, 38, 44]. When both treatment factors and admission factors were included in the multivariate analysis of prognostic factors for favorable

Table 5 Prediction model of admission and treatment variables for favorable outcome (multivariate logistic regression analysis with favorable outcome (GOSE 5–8) as dependent variable)

Variables	Regression coefficient	SE	Wald X^2	Odds ratio	95% CI		p	
					Lower	Upper		
Intercept	5.918	2.309	6.571	371.609			0.010	*
Age	−0.064	0.031	4.240	0.938	0.882	0.997	0.039	*
Sex (female)	0.019	0.394	0.002	1.019	0.471	2.204	0.962	
GCS M ≤ 3 on admission	−1.727	0.768	5.061	0.178	0.039	0.801	0.024	*
Multiple injuries	− 1.077	0.466	5.342	0.340	0.137	0.849	0.021	*
Under the influence of drugs/alcohol at trauma	− 0.152	0.535	0.081	0.859	0.301	2.449	0.776	
Marshall Classification								
Diffuse injury I–IV	0.508	0.547	0.861	1.661	0.569	4.855	0.353	
EML	− 1.157	0.631	3.359	0.314	0.091	1.084	0.067	
CT dominating injury type								
Extracerebral hematoma	0.070	0.541	0.017	1.073	0.371	3.098	0.897	
Contusions	0.564	0.449	1.575	1.757	0.729	4.238	0.210	
Medical history of								
Brain injury/disease	− 0.685	0.486	1.987	0.504	0.194	1.307	0.159	
Traumatic brain injury	− 1.398	1.313	1.133	0.247	0.019	3.241	0.287	
Diabetes mellitus	− 0.684	0.499	1.878	0.505	0.190	1.342	0.171	
Hypertension/CVD	0.158	0.419	0.141	1.171	0.515	2.664	0.707	
Ethylism	− 0.961	0.536	3.217	0.383	0.134	1.093	0.073	
Antithrombotic drugs								
Antiplatelet	0.212	0.465	0.209	1.237	0.497	3.075	0.648	
Warfarin	− 0.968	0.568	2.904	0.380	0.125	1.156	0.088	
NOAK	− 0.349	0.859	0.165	0.706	0.131	3.797	0.685	
LMWH	− 0.960	1.085	0.783	0.383	0.046	3.210	0.376	
Surgery before arrival	1.480	0.765	3.746	4.395	0.981	19.681	0.053	
Craniotomy	− 0.122	1.211	0.010	0.885	0.082	9.498	0.920	
Evacuated extracerebral hematoma	1.020	1.099	0.862	2.773	0.322	23.898	0.353	
Evacuated contusions	− 1.614	0.842	3.676	0.199	0.038	1.037	0.055	
Decompressive hemicraniectomy	− 1.202	1.078	1.243	0.301	0.036	2.488	0.265	
Multiple surgeries	0.473	0.614	0.595	1.605	0.482	5.344	0.441	
ICP monitoring	0.489	0.433	1.276	1.630	0.698	3.806	0.259	
Mechanical ventilation	− 1.637	0.548	8.910	0.195	0.066	0.570	0.003	**

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

outcome, age, low GCS, and multiple injuries all had significant independent negative prognostic value. Surgery before arrival (evacuated ASDH at the referring hospital) showed positive prognostic value of marginal significance ($p = 0.053$). Evacuation of contusions and extracerebral hematoma, which were significant prognostic factors in the univariate analysis, did not show any significant independent influence on clinical outcome, although evacuation of contusions had marginal significant ($p = 0.055$). Mechanical ventilation on the other hand proved to have independent negative predictive value for favorable outcome (OR 0.195) (Table 5). The reasonable explanation for that may be that mechanical ventilation is not completely dependent on the severity of brain injury but also related to other factors not included in the statistical analysis, e.g., various infections including lung infections and other adverse events. Barnato et al. also found that elderly treated at the intensive care unit who survived mechanical ventilation had worse functional outcome [2]. It is likely that the negative impact of mechanical ventilation on outcome depends both on a more severe brain injury requiring mechanical ventilation, and on the development of systemic complications, with which the elderly are less able to cope.

There are some study limitations that needs to be considered. This is a single-center study and the results may have been influenced by the local management applied, and therefore the results may not be completely generalizable. Furthermore, as mentioned earlier, there was a selection bias since predominantly patients judged to have a reasonable chance for favorable outcome were accepted for NIC. Therefore, the results need to be interpreted with caution.

While these results may at first look discouraging but for this group of elderly TBI patients, a relatively large proportion achieved favorable outcome, when they were treated according to modern NIC principles and the treatment did not cause a large proportion of patients with severe disability or vegetative state. Similar results have also been reported by others [24, 29,

37, 47]. Further studies are required focusing on the NIC specifically in elderly TBI patients concerning, e.g., secondary insults, ICP management, and cerebral perfusion thresholds, to find out if these areas holds the key to improve outcome.

Conclusion

This study shows that an appropriately selected group of elderly TBI patients receiving modern NIC have a fair chance of favorable outcome without large risks for severe deficits and vegetative state. Significant negative prognostic factors were high age, multiple injuries, low GCS M on admission, and the use of mechanical ventilation. The results underline that elderly with TBI should have access to NIC, when favorable outcome is as high as 47% for patients 60–74 years and around 30% for the patients between 75 and 84 years. Further research is needed about the selection of elderly patients and the optimal NIC management of elderly with TBI.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

The study was approved by the Local ethical review board.

Informed consent Informed consent was obtained from individual participants or the relatives if the participant did not have the decision-making capacity for informed consent.

References

1. Andrews BT, Pitts LH (1991) Functional recovery after traumatic transtentorial herniation. Neurosurgery 29:227–231
2. Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB (2011) Disability among elderly survivors of mechanical ventilation. Am J Respir Crit Care Med 183:1037–1042. https://doi.org/10.1164/rccm.201002-0301OC
3. Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R (1977) The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg 47:491–502. https://doi.org/10.3171/jns.1977.47.4.0491
4. Bowers SA, Marshall LF (1980) Outcome in 200 consecutive cases of severe head injury treated in San Diego County: a prospective analysis. Neurosurgery 6:237–242
5. Cheng C, Chi NC, Williams E, Thompson HJ (2018) Examining age-related differences in functional domain impairment following traumatic brain injury. Int J Older People Nursing:e12208. https://doi.org/10.1111/opn.12208
6. Chestnut RM, Ghajar J, Maas AIR, Marion DW, Servadei F, Teasdale G, Unterberg A, von Holst H, Walter BC (2000) Part 2: early indicators of prognosis in severe traumatic BRAIN injury. J Neurotrauma 17:555–555. https://doi.org/10.1089/neu.2000.17.555
7. Combes P, Fauvage B, Colonna M, Passagia JG, Chirossel JP, Jacquot C (1996) Severe head injuries: an outcome prediction and survival analysis. Intensive Care Med 22:1391–1395
8. Dams-O'Connor K, Cuthbert JP, Whyte J, Corrigan JD, Faul M, Harrison-Felix C (2013) Traumatic brain injury among older adults at level I and II trauma centers. J Neurotrauma 30:2001–2013. https://doi.org/10.1089/neu.2013.3047
9. Eker C, Asgeirsson B, Grande PO, Schalen W, Nordstrom CH (1998) Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. Crit Care Med 26:1881–1886
10. Elf K, Nilsson P, Enblad P (2002) Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care. Crit Care Med 30:2129–2134. https://doi.org/10.1097/01.CCM.0000025893.73582.52
11. Fischerström A, Nyholm L, Lewén A, Enblad P (2014) Acute neurosurgery for traumatic brain injury by general surgeons in Swedish county hospitals: a regional study. Acta Neurochir 156:177–185. https://doi.org/10.1007/s00701-013-1932-5
12. Franko J, Kish KJ, O'Connell BG, Subramanian S, Yuschak JV (2006) Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. J Trauma 61:107–110. https://doi.org/10.1097/01.ta.0000224220.89528.fc
13. Ganetsky M, Lopez G, Coreanu T, Novack V, Horng S, Shapiro NI, Bauer KA (2017) Risk of intracranial hemorrhage in ground-level fall with antiplatelet or anticoagulant agents. Acad Emerg Med 24:1258–1266. https://doi.org/10.1111/acem.13217
14. Grandhi R, Harrison G, Voronovich Z, Bauer J, Chen SH, Nicholas D, Alarcon LH, Okonkwo DO (2015) Preinjury warfarin, but not antiplatelet medications, increases mortality in elderly traumatic brain injury patients. J Trauma Acute Care Surg 78:614–621. https://doi.org/10.1097/TA.0000000000000542
15. Hawley C, Sakr M, Scapinello S, Salvo J, Wrenn P (2017) Traumatic brain injuries in older adults-6 years of data for one UK trauma Centre: retrospective analysis of prospectively collected data. Emerg Med J 34:509–516. https://doi.org/10.1136/emermed-2016-206506
16. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, Murray GD, Maas AI (2003) Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg 99:666–673. https://doi.org/10.3171/jns.2003.99.4.0666
17. Iaccarino C, Carretta A, Nicolosi F, Morselli C (2018) Epidemiology of severe traumatic brain injury. J Neurosurg Sci 62:535–541. https://doi.org/10.23736/S0390-5616.18.04532-0
18. Karni A, Holtzman R, Bass T, Zorman G, Carter L, Rodriguez L, Bennett-Shipman VJ, Lottenberg L (2001) Traumatic head injury in the anticoagulated elderly patient: a lethal combination. Am Surg 67:1098–1100
19. Koskinen S, Alaranta H (2008) Traumatic brain injury in Finland 1991-2005: a nationwide register study of hospitalized and fatal

TBI. Brain Inj 22:205–214. https://doi.org/10.1080/02699050801938975
20. Lavoie A, Ratte S, Clas D, Demers J, Moore L, Martin M, Bergeron E (2004) Preinjury warfarin use among elderly patients with closed head injuries in a trauma center. J Trauma 56:802–807
21. LeBlanc J, de Guise E, Gosselin N, Feyz M (2006) Comparison of functional outcome following acute care in young, middle-aged and elderly patients with traumatic brain injury. Brain Inj 20:779–790. https://doi.org/10.1080/02699050600831835
22. Lenell S, Nyholm L, Lewen A, Enblad P (2015) Updated periodic evaluation of standardized neurointensive care shows that it is possible to maintain a high level of favorable outcome even with increasing mean age. Acta Neurochir 157:417–425. https://doi.org/10.1007/s00701-014-2329-9
23. Lennartsson C, Heimerson I (2012) Elderly people's health: health in Sweden: the National Public Health Report 2012. Chapter 5. Scand J Public Health 40:95–120. https://doi.org/10.1177/1403494812459468
24. Li LF, Lui WM, Wong HH, Yuen WK, Leung GK (2017) Outcome after operative intervention for traumatic brain injuries in the elderly. Asian J Neurosurg 12:37–43. https://doi.org/10.4103/1793-5482.148787
25. Marshall LF, Marshall SB, Klauber MR, Clark MB, Eisenberg HM, Jane JA, Luerssen TG, Marmarou A, Foulkes MA (1991) A new classification of head injury based on computerized tomography. Spec Suppl 75:S14–S20. https://doi.org/10.3171/sup.1991.75.1s.0s14
26. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part I: the significance of intracranial pressure monitoring. J Neurosurg 50:20–25. https://doi.org/10.3171/jns.1979.50.1.0020
27. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part II: acute and chronic barbiturate administration in the management of head injury. J Neurosurg 50:26–30. https://doi.org/10.3171/jns.1979.50.1.0026
28. Merzo A, Lenell S, Nyholm L, Enblad P, Lewen A (2016) Promising clinical outcome of elderly with TBI after modern neurointensive care. Acta Neurochir 158:125–133. https://doi.org/10.1007/s00701-015-2639-6
29. Mosenthal AC, Lavery RF, Addis M, Kaul S, Ross S, Marburger R, Deitch EA, Livingston DH (2002) Isolated traumatic brain injury: age is an independent predictor of mortality and early outcome. J Trauma 52:907–911
30. Nordstrom CH, Sundbarg G, Messeter K, Schalen W (1989) Severe traumatic brain lesions in Sweden. Part 2: impact of aggressive neurosurgical intensive care. Brain Inj 3:267–281
31. Nyholm L, Howells T, Enblad P, Lewén A (2013) Introduction of the Uppsala Traumatic Brain Injury register for regular surveillance of patient characteristics and neurointensive care management including secondary insult quantification and clinical outcome. Ups J Med Sci 118:169–180. https://doi.org/10.3109/03009734.2013.806616
32. Ohm C, Mina A, Howells G, Bair H, Bendick P (2005) Effects of antiplatelet agents on outcomes for elderly patients with traumatic intracranial hemorrhage. J Trauma 58:518–522
33. Pedersen K, Fahlstedt M, Jacobsson A, Kleiven S, von Holst H (2015) A national survey of traumatic brain injuries admitted to hospitals in Sweden from 1987 to 2010. Neuroepidemiology 45:20–27. https://doi.org/10.1159/000381780
34. Peeters W, Majdan M, Brazinova A, Nieboer D, Maas AIR (2017) Changing epidemiological patterns in traumatic brain injury: a longitudinal hospital-based study in Belgium. Neuroepidemiology 48:63–70. https://doi.org/10.1159/000471877
35. Pieracci FM, Eachempati SR, Shou J, Hydo LJ, Barie PS (2007) Degree of anticoagulation, but not warfarin use itself, predicts adverse outcomes after traumatic brain injury in elderly trauma patients. J Trauma 63:525–530. https://doi.org/10.1097/TA.0b013e31812e5216
36. Sjörgen H, Björnstig U (1991) Injuries among the elderly in the home environment:detailed analysis of mechanisms and consequences. J Aging Health 3:107–125. https://doi.org/10.1177/089826439100300106
37. Stocchetti N, Paternò R, Citerio G, Beretta L, Colombo A (2012) Traumatic brain injury in an aging population. J Neurotrauma 29:1119–1125. https://doi.org/10.1089/neu.2011.1995
38. Susman M, DiRusso SM, Sullivan T, Risucci D, Nealon P, Cuff S, Haider A, Benzil D (2002) Traumatic brain injury in the elderly: increased mortality and worse functional outcome at discharge despite lower injury severity. J Trauma 53:219–223 discussion 223-214
39. Teasdale GM, Pettigrew LE, Wilson JT, Murray G, Jennett B (1998) Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. J Neurotrauma 15:587–597
40. Thomas KE, Stevens JA, Sarmiento K, Wald MM (2008) Fall-related traumatic brain injury deaths and hospitalizations among older adults–United States, 2005. J Saf Res 39:269–272. https://doi.org/10.1016/j.jsr.2008.05.001
41. Unterhofer C, Ho WM, Wittlinger K, Thome C, Ortler M (2017) "I am not afraid of death"-a survey on preferences concerning neurosurgical interventions among patients over 75 years. Acta Neurochir 159:1547–1552. https://doi.org/10.1007/s00701-017-3240-y
42. Wettervik TS, Lenell S, Nyholm L, Howells T, Lewen A, Enblad P (2018) Decompressive craniectomy in traumatic brain injury: usage and clinical outcome in a single centre. Acta Neurochir 160:229–237. https://doi.org/10.1007/s00701-017-3418-3
43. Wilson JT, Pettigrew LE, Teasdale GM (1998) Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 15:573–585
44. Vollmer DG, Torner JC, Jane JA, Sadovnic B, Charlebois D, Eisenberg HM, Foulkes MA, Marmarou A, Marshall LF (1991) Age and outcome following traumatic coma: why do older patients fare worse? Spec Suppl 75:S37–S49. https://doi.org/10.3171/sup.1991.75.1s.0s37
45. Wong DK, Lurie F, Wong LL (2008) The effects of clopidogrel on elderly traumatic brain injured patients. J Trauma 65:1303–1308. https://doi.org/10.1097/TA.0b013e318185e234
46. World Population Prospects (2017) The 2017 Revision, Volume II: Demographic Profiles. ST/ESA/SER.A/400. United Nations, Department of Economic and Social Affairs, Population Division
47. Wutzler S, Lefering R, Wafaisade A, Maegele M, Lustenberger T, Walcher F, Marzi I, Laurer H, TraumaRegister DGU (2015) Aggressive operative treatment of isolated blunt traumatic brain injury in the elderly is associated with favourable outcome. Injury 46:1706–1711. https://doi.org/10.1016/j.injury.2015.02.013
48. Wärme PE, Bergström R, Persson L (1991) Neurosurgical intensive care improves outcome after severe head injury. Acta Neurochir 110:57–64

Paper IV

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ORIGINAL ARTICLE - NEUROSURGICAL INTENSIVE CARE

Neurointensive care of traumatic brain injury in the elderly—age-specific secondary insult levels and optimal physiological levels to target need to be defined

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Abstract

Background Elderly patients with traumatic brain injury increase. Current targets and secondary insult definitions during neurointensive care (NIC) are mostly based on younger patients. The aim was therefore to study the occurrence of predefined secondary insults and the impact on outcome in different ages with particular focus on elderly.

Methods Patients admitted to Uppsala 2008–2014 were included. Patient characteristics, NIC management, monitoring data, and outcome were analyzed. The percentage of monitoring time for *ICP*, *CPP*, *MAP*, and *SBP* above-/below-predefined thresholds was calculated.

Results Five hundred seventy patients were included, 151 elderly ≥ 65 years and 419 younger 16–64 years. Age ≥ 65 had significantly higher percentage of $CPP > 100$, $MAP > 120$, and $SBP > 180$ and age 16–64 had higher percentage of $ICP \geq 20$, $CPP \leq 60$, and $MAP \leq 80$. Age ≥ 65 contributed independently to the different secondary insult patterens. When patients in all ages were analyzed, low percentage of CPP > 100 and SBP > 180, respectively, was significant predictors of favorable outcome and high percentage of $ICP \geq 20$, $CPP > 100$, $SBP \leq 100$, and $SBP > 180$, respectively, was predictors of death. Analysis of age interaction showed that patients ≥ 65 differed and had a higher odds for favorable outcome with large proportion of good monitoring time with $SBP > 180$.

Conclusions Elderly ≥ 65 have different patterns of secondary insults/physiological variables, which is independently associated to age. The finding that SBP > 180 increased the odds of favorable outcome in the elderly but decreased the odds in younger patients may indicate that blood pressure should be treated differently depending on age.

Keywords Traumatic brain injury · Elderly · Outcome · Secondary insults · Geriatric neurointensive care · Neurointensive care monitoring

Abbreviations

ASDH	Acute subdural hematoma
CPP	Cerebral perfusion pressure
CPPopt	Optimal cerebral perfusion pressure
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
CVP	Central venous pressure
DAI	Diffuse axonal injury
EDH	Epidural hematoma
EVD	External ventricular drainage
GCS M	Glasgow coma scale motor score
GMT	Good monitoring time
%GMT	Proportion of good monitoring time
GOSE	Glasgow outcome scale
ICP	Intra cranial pressure
MAP	Mean arterial pressure
NIC	Neurointensive care
OR	Odds ratio
SBP	Systolic blood pressure
TBI	Traumatic brain injury

This article is part of the Topical Collection on *Neurosurgical intensive care*

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Introduction

The introduction of neurointensive care (NIC), with focused efforts of avoiding secondary insults, has contributed to an increase of favorable outcome for traumatic brain injury (TBI) patients [2, 3, 8, 23, 27]. Despite this improvement, TBI still constitutes a large health problem. The magnitude of the problem is illustrated by a recent overview of TBI in Europe showing that the incidence of hospitalized TBI patients was 278.2/100 000 in 2012 (Sweden 2013, 451.5/100 000) and the mortality rate was 11.7/100 000 (Sweden 2013, 9.0/100 000) [21]. Despite that elderly (age ≥ 65 years) constituted only 29% of the hospitalized TBI patients, they contributed to 55% of the mortality [21]. It is obvious that the management of elderly TBI patients will be a tremendous challenge for the future for many reasons. In addition to higher mortality rate in the elderly [10, 17, 21], the elderly are an increasing part of the population and they live more active lives than before [10, 17, 18]. Traditionally, there has been some reluctance to treat these patients due to the previous experience of bad outcome, but more recently, larger numbers of elderly are treated [25, 30, 32, 33, 38]. Hence, it is urgent to obtain more knowledge about the optimal treatment of elderly TBI patients.

The NIC of patients with TBI in general is mostly based on data from younger patients and there is insufficient research in the elderly despite the change in population structure [9]. For example, large clinical TBI trials have often been made with age > 65 years as an exclusion criteria [5, 14, 19, 24, 26]. Although the secondary insult prevention concept is one of the main reasons for the improvement of NIC, it is likely that both critical and optimal threshold levels differ between ages. This is underlined by studies in elderly patients with severe subarachnoid hemorrhage showing that the occurrence of defined secondary insults and the impact on outcome was age-dependent [31]. In order to optimize the NIC of elderly TBI patients, it is desirable to identify the critical threshold levels for secondary insults and the optimal threshold levels to target, specifically in the older ages.

The aim of this investigation was therefore to study the occurrence of predefined secondary insults and the impact of outcome in different ages with particular focus on the elderly.

Material and methods

Patient selection and data collection

All TBI patients ≥ 16 years old receiving NIC at Uppsala University Hospital between 2008 and 2014 were retrieved from the Uppsala TBI registry [28]. In total, 663 patients were identified. The following patients were excluded as follows: recovery within 24 h after admission (11 patients), admission more than 5 days after trauma (23 patients), bilateral wide and unresponsive pupils (15 patients) or Glasgow coma scale score 3 and one wide pupil on admission (1 patient) (patients with probable predestined fatal/unfavorable clinical course judged in general not possible to treat [1, 4]), gunshot to head (4) and lost to follow up (39 patients). Finally, 570 patients remained to be analyzed.

Demographics and NIC management data

Demographic data and information about NIC management were obtained from the Uppsala TBI registry [28]. The following parameters were studied as follows: age, sex, primary or secondary transfer, Glasgow coma scale motor score (GCS M) on admission, type of injury, presence of multiple injuries, trauma under the influence of alcohol or drugs, cause of trauma, medical history (brain injury/disease, previous traumatic brain injury, diabetes mellitus, hypertension/cardiovascular disease (CVD), use of anticoagulants/antiplatelets), craniotomy, decompressive craniectomy, intracranial pressure monitoring, and mechanical ventilation. The type of injury was assessed on the initial CT-scan (dominating type of injury and Marshall CT score [22]).

Physiological data

Trended minute-by-minute data (median values of 5 samples during each sampled minute) was collected in real time from the Philips monitors in our ICU using the Odin software [12]. The Philips monitors forward the data to a central database within the hospital, which is queried by the Odin server to extract the relevant data which is stored centrally and displayed on Odin client systems at the ICU bedspaces. The patient data stored and processed by the Odin software is also kept within the hospital firewall. The trended data used in this study were preprocessed with median filters to detect sudden spikes that appeared to be non-physiological, and a specialized algorithm detected sudden drops to a constant value (usually zero). The data were further subject to manual review to verify, and if necessary correct, the automatic procedures. Time gaps from, e.g., radiology examination and surgical procedure were automatically excluded by the Odin software. The monitoring time left was defined as good monitoring time (GMT).

For the purpose of evaluating physiological NIC monitoring data (intra cranial pressure, ICP; cerebral perfusions pressure, *CPP*; mean arterial pressure, *MAP*; and systolic

blood pressure, SBP), *GMT* data from the start of monitoring to the end of the seventh monitoring day was studied.For ICP and *CPP* analyses, at least 12 h of *ICP* data was required. Using the Odin software, the proportions of good monitoring time (*%GMT*) spent above-/below-predefined threshold levels were calculated for $ICP \geq 20$, $CPP \leq 60$, $CPP > 100$, $MAP \leq 80$, $MAP > 120$, $SBP \leq 100$, and $SBP > 180$. The thresholds originated mainly from our protocol treatment goals [8].

Neurointensive care protocol

All patients were treated according to the same standardized treatment protocol [8]. Unconscious patients (GCS $M \leq 5$) had mechanical ventilation. Patients on mechanical ventilation were kept sedated with propofol (Propofol-LipuroB; Braun Medical, Danderyd, Sweden) and received morphine for analgesia. They were initially moderately hyperventilated ($PaCO_2$ 4.0–4.5 kPa) with the aim of normoventilation as soon as ICP allowed ($ICP < 20$ mmHg). Wake-up tests were performed regularly (usually 3–6 times/day unless severe ICP elevations) to assess neurological function. All unconscious patients (GCS $M \leq 5$), regardless of age, had also ICP monitoring, except in the case of coagulopathy. An external ventricular drainage system (EVD) (with the pressure dome at the level of the lateral ventricles) was the first choice and an intraparenchymal pressure device was chosen if the ventricles were compressed. Arterial blood pressure was measured with the pressure dome at heart level. Prophylactic anticonvulsants was not used. The treatment goals according to the standardized management protocol were as follows: $ICP < 20$ mmHg, $SBP > 100$ mmHg, central venous pressure (CVP) 0–5 mmH_2O, $CPP > 60$ mmHg, blood glucose 5–10 mmol/L, normovolemia, $Pa0_2 > 12$ kPa, electrolytes within normal ranges, and body temperature < 38 °C.

Mass lesions in unconscious patients were evacuated.

Raised ICP was treated in a stepwise fashion. If ICP increased ≥ 20 mmHg without mass lesions, cerebrospinal fluid (CSF) was drained from the EVD. Initially small volumes (1–2 ml) were drained intermittently, when there were risk of expanding hematomas and brain swelling. Later CSF was drained using an open system against a pressure level of 15–20 mmHg if needed. If raised ICP persisted, the treatment was escalated with no wake-up tests, continuous sedation with propofol, and stress reduction with ß1-antagonist metoprolol (Seloken®, AstraZeneca AB Södertälje, Sweden) (0.2–0.3 mg/kg/24 h as an infusion) and α2-agonist clonidin (Catapresan®, BoehingerIngelheim AB Stockholm Sweden) (0.5–1.0 µg/kg × 8 or the same dose as an infusion). Thiopental coma treatment and/or decompressive craniectomy were last tier treatment option but were initiated more restrictively in the elderly.

Outcome

The NIC mortality was assessed. Follow-up was done after 6 months, using the extended Glasgow outcome scale (GOSE), by structured telephone interviews done by a few selected persons[34, 39].

Statistics

Differences in the characteristics between age groups were analyzed with Pearsons Chi 2 test.

Mann-Withney *U* test was used to compare occurrence of secondary insults between the age groups.

Multiple linear regression analysis was done to examine if age ≥ 65 years and admission variables as gender, GCS M, other injuries, extracerebral hematoma, and contusions contributed to the *%GMT* above/below secondary insult thresholds for the physiological variables.

To evaluate if the %GMT above/below secondary insult thresholds for the physiological variables was associated with outcome, univariate logistic regression analysises were made with favorable outcome (GOSE 5–8) and survival (GOSE 2–8) as dependent variables. To evaluate whether associations differed by age (age 16–64 vs age ≥ 65), multiple logistic regression models were fitted including age, a physiological variable and age by physiological variable interaction as independent variables. The odds ratios (ORs) for physiological variables are reported for each age-group, regardless of the significance of interaction.

$p < 0.05$ was considered statistically significant. All statistical analyses were carried out in IBM SPSS Statistics for Windows except for Pearsons Chi 2 which was done with Microsoft Excel 365.

Results

Admission characteristics

For all patients, the mean age was 49.7 years (range 16–94). The age distribution showed one peak at around 20 years of age and another peak around 60–65 years of age (Supplementary Information 1). There were 151 patients ≥ 65 years (mean 72.3 range 65–87) and 419 between 16 and 64 (mean 41.5 range 16–64) years of age. Patient characteristics from admission are presented in Table 1. When the age groups of ≥ 65 years and 16–64 years were compared, the older patients showed significantly larger proportions of women (28.5% vs 19.6%), fall accidents (80.1 vs 42.0%), previous brain injury/disease (22.5% vs 11.0%), diabetes mellitus (18.5 vs 6.2%), hypertension/cerebrovascular disease (58.3% vs

Table 1 Patient characteristics by age group

	All		Age 16–64		Age ≥ 65		Age 16–64 vs ≥ 65[a]
	n	%	*n*	%	*n*	%	*p*
No. of patients	570		419		151		
Referrals from other hospitals	447	78.4	345	82.3	102	67.5	< 0.001 ***
Sex (female)	125	21.9	82	19.6	43	28.5	0.023 *
GCS M ≥ 4 on admission	518	90.9	382	91.2	136	90.1	0.687
GCS M ≤ 5 on admission	310	54.4	233	55.6	77	51.0	0.329
Multiple injuries	224	39.3	197	47.0	27	17.9	< 0.001 ***
Under the influence of drugs/alcohol at trauma (confirmed)	165	28.9	143	34.1	22	14.6	< 0.001 ***
Cause of trauma							
Bicycle accident	16	2.8	14	3.3	2	1.3	
Fall accident	297	52.1	176	42.0	121	80.1	< 0.001 ***
Vehicle accident	150	26.3	139	33.2	11	7.3	< 0.001 ***
Pedestrian hit by vehicle	24	4.2	17	4.1	7	4.6	0.762
Assault	33	5.8	30	7.2	3	2.0	0.020
Sports injury	19	3.3	18	4.3	1	0.7	0.033 *
Other	31	5.4	25	6.0	6	4.0	0.355
Medical history							
Brain injury/disease previously	80	14.0	46	11.0	34	22.5	< 0.001 ***
Traumatic brain injury previously	18	3.2	11	2.6	7	4.6	
Diabetes mellitus	54	9.5	26	6.2	28	18.5	< 0.001 ***
Hypertension/CVD	146	25.6	58	13.8	88	58.3	< 0.001 ***
Anticoagulants/Antiplatelets	98	17.2	33	7.9	65	43.0	< 0.001 ***
Ethylism	126	22.1	95	22.7	31	20.5	0.586

[a]Pearsons Chi 2 test, *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

13.8%), ongoing treatment with anticoagulants/antiplatelets (43.0% vs 7.9%), and significantly smaller proportions of patients admitted from other hospitals (67.5% vs 82.3%), multiple injuries (17.9% vs 47.0%), influence of drugs/alcohol (14.6% vs 34.1%), vehicle accidents (7.3% vs 33.2%), and sports injury (0.7% vs 4.3%). Regarding the dominating type of injury assessed on initial CT, the older patients had significantly larger proportion of acute subdural hematoma (51.7% vs 20.5%) and smaller proportion of diffuse axonal injury (DAI) (0.0% vs 8.6%) and epidural hematoma (0.7% vs 11.5%) (Table 2). There was no difference between the age groups in GCS M on admission (Table 1 and Supplementary Information 2).

NIC management and surgery

There were no significant differences between the age groups ≥ 65 years and 16–64 years regarding ICP monitoring (55.0% vs 62.5%) and mechanical ventilation (82.1% vs 77.3%) (Table 3). The proportion of patients treated with thiopental were significantly smaller in the old age group (0.7% vs 7.9%) (Table 3). The old group had significantly more craniotomies compared to the younger group (47.7% vs 32.7%) (Table 3).

Physiological data

Monitoring information regarding number of patients for each physiological parameter and age group is presented in Table 4. When the occurrences of physiological variables were analyzed as median *%GMT* (Table 5 and Fig. 1), there were statistically significant differences between the age groups: age ≥ 65 years had significantly higher *%GMT* with $CPP > 100$, $MAP > 120$, and $SBP > 180$ and age 16–64 years had significantly higher *%GMT* with $ICP \geq 20$, $CPP \leq 60$, and $MAP \leq 80$.

The multiple linear regression model with physiological variables as dependent variables and age ≥ 65 years, gender, GCS M, other injuries, extracerebral hematoma, and contusions as explanatory variables showed that age ≥ 65 years was an independent predictor for lower %GMT with $ICP \geq 20$ and higher *%GMT* with $CPP > 100$, $MAP > 120$, and $SBP > 180$ (Table 6). Higher GCS M score was an independent predictor for low %GMT with

Table 2 Radiological characteristics by age group

	All		Age 16–64		Age ≥ 65		Age 16–64 vs ≥ 65
	n	%	*N*	%	*n*	%	*p*
No. of patients	570		419		151		
Dominating CT finding							
ASDH	164	28.8	86	20.5	78	51.7	< 0.001 ***
EDH	49	8.6	48	11.5	1	0.7	< 0.001 ***
Contusions	171	30.0	132	31.5	39	25.8	0.192
DAI	36	6.3	36	8.6	0	0.0	< 0.001 ***
Mixed	68	11.9	53	12.6	15	9.9	0.378
Impression fracture	12	2.1	11	2.6	1	0.7	
Traumatic SAH	53	9.3	38	9.1	15	9.9	0.754
Normal	6	1.1	6	1.4	0	0.0	
Other	11	1.9	9	2.1	2	1.3	
Initial CT Marshall classification							
Diffuse injury	393	68.9	325	77.6	68	45.0	< 0.001 ***
Diffuse injury I	6	1.1	5	1.2	1	0.7	
Diffuse injury II	279	48.9	236	56.3	43	28.5	< 0.001 ***
Diffuse injury III	82	14.4	69	16.5	13	8.6	0.018 *
Diffuse injury IV	26	4.6	15	3.6	11	7.3	0.061
Focal mass lesion	117	20.5	94	22.4	23	15.2	0.060
Evacuated mass lesion	126	22.1	69	16.5	57	37.7	< 0.001 ***
Nonevacuated mass lesion	51	8.9	25	6.0	26	17.2	< 0.001 ***

[a]Pearsons Chi 2 test, $p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$

Table 3 Treatment characteristics by age group

	All		Age 16–64		Age ≥ 65		Age 16–64 vs ≥ 65[a]
	N	%	*n*	%	n	%	*p*
No. of patients	570		419		151		
Surgery							
Craniotomy at referring hospital	50	8.8	36	8.6	14	9.3	0.800
Craniotomy (yes/no)	209	36.7	137	32.7	72	47.7	0.001 **
Reasons for craniotomy[b]							
Extra cerebral hematoma	167	29.3	99	23.6	68	45.0	< 0.001 ***
EDH	35	6.1	34	8.1	1	0.7	0.001 **
ASDH	120	21.1	55	13.1	65	43.0	< 0.001 ***
Both (EDH + ASDH)	12	2.1	10	2.4	2	1.3	
Contusions	66	11.6	52	12.4	14	9.3	0.301
Hemicraniectomy	39	6.8	34	8.1	5	3.3	0.045 *
Multiple surgeries (yes/no)	61	10.7	43	10.3	18	11.9	0.572
Management, NIC							
ICP monitoring	345	60.5	262	62.5	83	55.0	0.103
EVD	65	11.4	47	11.2	18	11.9	0.816
Intraparenchymal pressure monitor	206	36.1	153	36.5	53	35.1	0.756
Both	74	13.0	62	14.8	12	7.9	0.032 *
Mean days with ICP monitoring	11.2		11.8		9.2		
Mechanical ventilation	448	78.6	324	77.3	124	82.1	0.218
Mean days ventilation	9.0		9.6		7.4		
Thiopenthal	34	6.0	33	7.9	1	0.7	0.001 **
Mean days with Thiopenthal	6.2		6.2		6		

[a]Pearsons Chi 2 test, $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$

[b]Multiple operations in some patients

Table 4 Monitoring by age group

	All	Age 16–64		Age ≥ 65		16–64 vs ≥ 65[a]
	N	*n*	%	*n*	%	*p*
No. of patients	570	419		151		
ICP	333	253	60.38	80	52.98	0.114
CPP	332	252[e]	60.14	80	52.98	0.126
MAP	521	377	89.98	144	95.36	0.043 *
SBP	521	377	89.98	144	95.36	0.043 *

[a]Pearsons Chi 2 test, *$p < 0.05$

[e]Continuous MAP data was missing in one patient with ICP monitoring

Table 5 Occurrence of secondary insults by age group

Physiological parameter	All patients		Age 16–64		Age ≥ 65		16–64 vs ≥ 65[d]
	Median %GMT[c]	IQR %GMT[c]	Median %GMT[c]	IQR %GMT[c]	Median %GMT[c]	IQR %GMT[c]	*p*
ICP ≥ 20	5.26	1.28–15.46	6.26	1.39–17.01	3.14	0.73–9.05	0.005 **
CPP ≤ 60	4.72	1.60–11.02	5.52	2.05–11.79	2.51	1.16–1.94	0.001 **
CPP > 100	1.97	0.62–8.10	1.27	0.51–5.25	6.37	1.96–18.57	0.000 ***
MAP ≤ 80	21.92	9.63–38.20	23.01	10.67–39.49	17.51	8.75–32.68	0.040 *
MAP > 120	0.59	0.21–2.52	0.48	0.17–1.77	1.31	0.36–5.52	0.000 ***
SBP ≤ 100	0.75	0.25–2.20	0.75	0.25–2.39	0.71	0.25–1.83	0.499
SBP > 180	2.10	0.23–7.81	1.04	0.18–4.72	7.53	1.54–19.63	0.000 ***

[c]*%GMT* denotes percentage of good monitoring time above/below the thresholds

[d]Mann-Whitney *U* test, *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

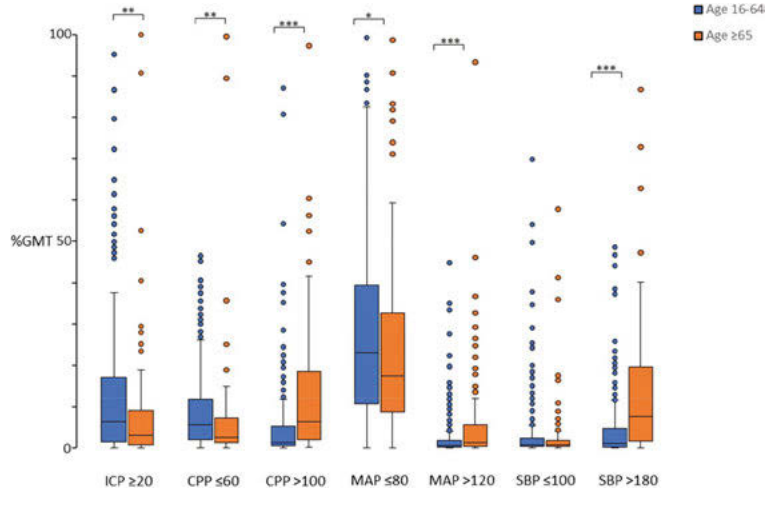

Fig. 1 Proportion of good monitoring time (*%GMT*) for different insult variables by age group. In the box plots, the horizontal black line marks the median, boxes extend from the 25th to the 75th percentile, vertical extending lines denote adjacent values (i.e., the most extreme values within 1.5 interquartile range of the 25th and 75th percentile of each group) and the dots denote observations outside the range of adjacent values (outliers).Mann–Whitney *U* test, *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

ICP ≥ 20 and *CPP* ≤ 60 (Table 6). Other injuries were found to be an independent predictor for lower *%GMT* with *ICP* ≥ 20, *CPP* > 100, *MAP* > 120, and *SBP* > 180 and for higher *%GMT* with *MAP* ≤ 80 (Table 6). Females showed significanly lower *%GMT* with *SBP* > 180 and higher *%GMT* with *SBP* ≤ 100. (Table 6).

Table 6 Linear regression analysis of contribution from admission characteristics and age ≥ 65 to physiological variables

Physiological variable (*%GMT*)	Explanatory variable	level	*B*	*(95% CI)*	*p* value
ICP ≥ 20	Age ≥ 65	Yes	−0.05	(−0.10 to −0.10)	0.016 *
	Sex (female)	Yes	−0.04	(−0.08 to 0.01)	0.130
	GCS Motor Score	Per score increase	−0.02	(−0.04 to −0.01)	0.005 **
	Other injuries	Yes	−0.07	(−0.04 to −0.01)	0.001 **
	Extracerebral hematoma	Yes	−0.03	(−0.08 to 0.01)	0.166
	Contusions	Yes	−0.01	(−0.05 to 0.04)	0.744
CPP ≤ 60	Age ≥ 65	Yes	−0.02	(−0.05 to 0.01)	0.176
	Sex (female)	Yes	0.01	(−0.02 to 0.04)	0.594
	GCS Motor Score	Per score increase	−0.01	(−0.02 to 0.00)	0.046 *
	Other injuries	Yes	0.00	(−0.03 to 0.02)	0.836
	Extracerebral hematoma	Yes	−0.01	(−0.04 to 0.03)	0.687
	Contusions	Yes	−0.01	(−0.04 to 0.02)	0.486
CPP > 100	Age ≥ 65	Yes	0.06	(0.03 to 0.09)	0.000 ***
	Sex (female)	Yes	0.00	(−0.04 to 0.03)	0.846
	GCS Motor Score	Per score increase	0.00	(−0.01 to 0.02)	0.610
	Other injuries	Yes	−0.05	(−0.08 to −0.02)	0.000 ***
	Extracerebral hematoma	Yes	0.01	(−0.02 to 0.05)	0.469
	Contusions	Yes	−0.03	(−0.07 to −0.00)	0.043
MAP ≤ 80	Age ≥ 65	Yes	−0.02	(−0.06 to 0.02)	0.347
	Sex (female)	Yes	0.06	(0.01 to 0.10)	0.011 *
	GCS Motor Score	Per score increase	−0.01	(−0.02 to 0.01)	0.363
	Other injuries	Yes	0.09	(0.05 to 0.13)	0.000 ***
	Extracerebral hematoma	Yes	0.01	(−0.04 to 0.05)	0.809
	Contusions	Yes	0.00	(−0.05 to 0.05)	0.939
MAP > 120	Age ≥ 65	Yes	0.02	(0.01 to 0.04)	0.009 **
	Sex (female)	Yes	0.00	(−0.02 to 0.01)	0.828
	GCS Motor Score	Per score increase	0.00	(0.00 to 0.008)	0.522
	Other injuries	Yes	−0.03	(−0.04 to −0.02)	0.000 ***
	Extracerebral hematoma	Yes	0.00	(−0.02 to 0.02)	0.964
	Contusions	Yes	0.00	(−0.02 to 0.01)	0.636
SBP ≤ 100	Age ≥ 65	Yes	−0.01	(−0.02 to 0.01)	0.364
	Sex (female)	Yes	0.02	(0.01 to 0.04)	0.001 **
	GCS Motor Score	Per score increase	0.00	(−0.01 to 0.00)	0.116
	Other injuries	Yes	−0.01	(−0.02 to 0.00)	0.119
	Extracerebral hematoma	Yes	0.00	(−0.02 to 0.01)	0.732
	Contusions	Yes	−0.01	(−0.02 to 0.01)	0.455
SBP > 180	Age ≥ 65	Yes	0.08	(0.06 to 0.12)	0.000 ***
	Sex (female)	Yes	−0.03	(−0.05 to −0.01)	0.001 **
	GCS Motor Score	Per score increase	0.00	(−0.01 to 0.01)	0.474
	Other injuries	Yes	−0.03	(−0.05 to −0.01)	0.002 **
	Extracerebral hematoma	Yes	0.00	(−0.03 to 0.02)	0.745
	Contusions	Yes	0.01	(−0.02 to 0.03)	0.657

Multivariate linear regression analyses of each physiological variables as dependent and age ≥ 65, sex, GCS motor score, other injuries, extracerebral hematoma, and contusions as explanatory variables. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. Positive *B* coefficients indicate that the increasing value of the explanatory variable are associated with a larger %GMT of the dependent variable. Negative *B* coefficients indicate that the increasing value of the explanatory variable are associated with a lower %GMT of the dependent variable

Outcome

NIC mortality was higher in the old age group (≥ 65 years 8.6% and 16–64 years 2.4%, $p < 0.001$). Follow-up was made at 7 months in median (range 1–28, including patients who died before follow-up). For all ages, favorable outcome (GOSE 5–8) was observed in 62% (69% in 16–64 years and 42% in elderly) and 13% had died (6% in 16–64 years and 31% in elderly) (Fig. 2).

The results from the logistic regression analyses with favorable outcome and survival as dependent variables and physiological parameters as explanatory variables are presented in Table 7. Low *%GMT* with *CPP* > 100 and *SBP* > 180 were associated with a higher odds of favorable outcome. However, there was a statistically significant interaction between age and *%GMT* with *SBP* > 180 (p interaction = 0.025). The *OR* (per unit increase in *%GMT* with *SBP* > 180) was 2.07 (0.22–1731.66) in patients ≥ 65 years and − 0.03(0.00–0.57) in patients 16–64 years (Table 7). High *%GMT* with *ICP* ≥ 20, *CPP* > 100, *SBP* ≤ 100 were associated with a lower odds of survival (Table 7).

Discussion

Patient and management characteristics by age group

Patients ≥ 65 years of age constituted as much as 26% of all patients. Many of the patient characteristics found in relation to age were as expected. The most common cause of trauma in the elderly was fall accidents, which is in accordance with many other studies [7, 11, 13, 15, 16, 18, 20, 29, 35, 36]. There was a higher percentage of women among the elderly (29% vs 20%), which also was shown by Dams-O'Conner and coll., reporting an increasing proportion of women with increasing age (38.5% in 65–74 years, 50.4% in 75–84 years, and 62.2 in 85 years and older) [7]. The elderly more often had a medical history with previous diseases or injuries, e.g., 22.5% had a previous history of brain injury/disease, 58.3% hypertension/CVD, and 43% medicated with anticoagulants/antiplatelets. Similar results were found by Hawley and coll. showing that older TBI patients ≥ 65 had a recorded medical history in 80% and only 1.1% had no pre-existing medical condition [11]. The dominating injury type in the elderly was ASDH and diffuse injury was also less common according to the Marshall score. These findings are in line with that the dominating type of injury was falls in the elderly and that the elderly more often underwent craniotomy.

Secondary insults/physiological variables—occurrence and association to age

The pattern of secondary insults/physiological variables differed by age. The elderly (≥ 65 years) spent a higher proportion of GMT with high *CPP*, high *MAP*, and high *SBP* and less degree of high *ICP*, low *CPP*, and low *MAP* (Table 5). Similar findings were also observed by Czosnyka and coll. [6].

In order to find out whether the observed difference between the age groups was explained by age independently, a multiple linear regression analysis was performed including age ≥ 65 years as a explanatory factor for the different predefined secondary insults/physiological variables. The analysis showed that age ≥ 65 years was an independent explanatory factor for higher %GMT with *CPP* > 100, *MAP* > 120, and *SBP* > 180 (Table 6). This finding may to some extent be explained by higher degree of hypertension and cardiovascular diseases in the elderly (Table 1). The crucial question is whether higher pressures may influence outcome in a negative way in the elderly.

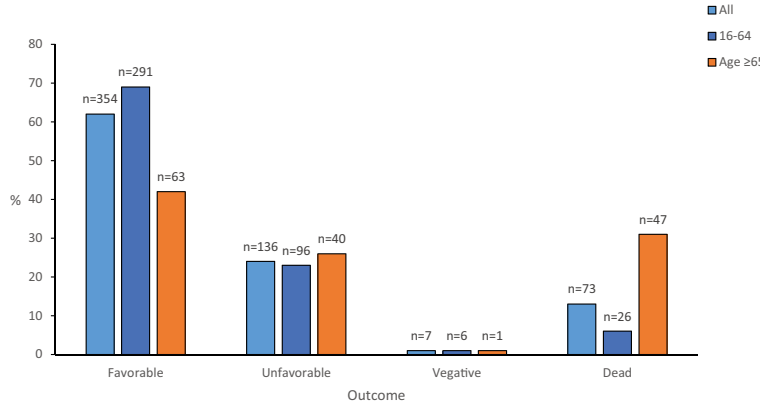

Fig. 2 Clinical outcome at follow-up. Favorable outcome (GOSE 5–8), unfavorable (GOSE 3–4), vegetative (GOSE 2), and dead (GOSE 1). Each bar represents the percentage of outcome within its age group. Absolute number of patients in each bar is presented above

Table 7 Univariate logistic regression analysis of outcome in relation to physiological variables and the interaction[d] with age

Physiological variable		All ages		Age 16–64			Age ≥ 65			Interaction
(%*GMT*)	***OR***	(95% CI)	***p***	***OR***	(95% CI)	***p***	***OR***	(95% CI)	***p***	***p*** value[d]
Model with favorable outcome as dependent										
ICP ≥ 20	0.33	(0.09–1.20)	0.093	0.16	(0.03–0.72)	0.017 *	1.34	(0.10–18.70)	0.827	0.167
CPP ≤ 60	1.09	(0.17–7.01)	0.926	1.22	(0.10–14.49)	0.874	0.50	(0.02–12.37)	0.669	0.663
CPP > 100	0.02	(0.00–0.19)	0.001 **	0.04	(0.00–0.74)	0.030 *	0.03	(0.00–1.20)	0.062	0.851
MAP ≤ 80	2.04	(0.88–4.76)	0.097	2.36	(0.83–6.72)	0.107	0.84	(0.17–4.24)	0.833	0.294
MAP > 120	0.17	(0.02–1.75)	0.136	0.42	(0.01–14.55)	0.628	0.47	(0.02–11.68)	0.645	0.959
SBP ≤ 100	0.45	(0.04–5.56)	0.531	0.80	(0.04–17.88)	0.885	0.03	(0.00–21.97)	0.294	0.374
SBP > 180	0.09	(0.02–0.53)	0.007 ***	0.03	(0.00–0.57)	0.020 *	2.07	(0.22–1731.66)	0.521	0.025 *
Model with survival as dependent										
ICP ≥ 20	0.17	(0.04–0.79)	0.024 *	0.07	(0.01–0.60)	0.015 *	0.10	(0.01–1.87)	0.123	0.871
CPP ≤ 60	0.11	(0.01–1.08)	0.059	0.06	(0.00–3.65)	0.180	0.06	(0.00–2.35)	0.134	0.989
CPP > 100	0.04	(0.01–0.27)	0.001 **	0.04	(0.00–0.81)	0.036	0.20	(0.01–3.00)	0.242	0.453
MAP ≤ 80	0.80	(0.25–2.57)	0.701	0.74	(0.11–5.01)	0.759	0.24	(0.07–1.96)	0.244	0.594
MAP > 120	0.12	(0.01–1.67)	0.115	0.19	(0.00–77.37)	0.589	0.78	(0.03–18.41)	0.877	0.685
SBP ≤ 100	00.01	(0.00–0.10)	0.000 ***	0.00	(0.00–0.063)	0.001 **	0.00	(0.00–1.93)	0.079	0.822
SBP > 180	0.03	(0.01–0.23	0.001 **	0.01	(0.00–0.51)	0.022 *	0.93	0.09 (0.09–9.97)	0.953	0.052

Favorable outcome (GOSE 5–8) and survival (GOSE 2–8) at follow-up. OR odds ratio per one unit increase in %GMT. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

OR > 1 indicates that an increasing value of %GMT is associated with a higher odds of favorable outcome/survival. *OR* < 1 indicates that an increasing value of *%GMT* is associated with a lower odds of favorable outcome/survival

[d]Analyzed with multiple logistic regression for the physiological variable, age ≥ 65, and interaction (physiological parameter × age ≥ 65, *p* value for the interaction is presented

Secondary insults/physiological variables-relation to clinical outcome and interaction by age

The logistic regression analysis of outcome (favorable and survival) for all patients indicated that high *%GMT* with $ICP > 20$, $SBP \leq 100$, $SBP > 180$, $CPP > 100$ not are beneficial. These findings, which may be summarized roughly as high *ICP*, low and high BP, and high *CPP* are bad, were not unexpected. Interestingly, when looking at the interaction analyses, the elderly had a higher AOR for favorable outcome.

Hence, blood pressure should probably be treated differently in younger and older patients. The finding that high blood pressures may be advantageous in elderly is supported by Utomo and coll. who found higher odds of independent living at 6 months for patients ≥ 65 years with a *SBP* on arrival at hospital in the range of 131–150 mmHg, compared to patients with *SBP* of < 130 mmHg[37].

ICP did not prove to be a significant predictor of outcome in the elderly. This finding should not be interpreted as if ICP is unimportant for outcome and does not need to be monitored in the elderly. Instead, this is probably an effect of the low burden of ICP insults thanks to effective detection and treatment. We have examined our material for events with $\%GMT\ ICP \geq 25$ and there was very few events in the elderly (median *%GMT* was 0.53, unpublished data). Monitoring of ICP in elderly with TBI is of importance and this has also been shown by You and coll. in a randomized trial of elderly with severe TBI who found lower in-hospital mortality and improved 6-month outcomes for the patients randomized to ICP monitoring [40]. We belive that extensive NIC monitoring is even more important in the elderly due to their increased vulnerability and this philosophy was clearly reflected in the observed numbers of elderly monitored in this study (Table 4), despite a larger proportion elderly using anticoagulants/antiplatelets.

Limitations

This is a single-center study and the results may therefore be influenced by the local management applied. Thus, the results may not be completely generalizable. There was a selection bias since only patients judged to have a reasonable chance for favorable outcome were accepted for NIC. Treatment bias also needs to be considered since all patients were treated to avoid secondary insults and the % GMT at insult level was in low general.

Furthermore, complete multiple logistic regression analyses for assessing the influence of secondary insults on outcome could not be done (to adjust, e.g., sex, GCS at admission, and injury type) due to the relative small number of patients. It was however possible to study the age interaction.

Conclusions

Elderly ≥ 65 years have different patterns of secondary insults/physiological variables, which to some extent is independently associated to age. When patients in all ages were analyzed, low %GMT with $CPP > 100$ and $SBP > 180$ were significant predictors of favorable outcome and high %GMT with $ICP \geq 20$, $CPP > 100$, $SBP \leq 100$, and $SBP > 180$ were positive predictors of death. The analysis of age interaction showed that patients ≥ 65 years differed and had a higher odds for favorable outcome and without a significant decrease in survival with large proportion of good monitoring time with $SBP > 180$.

This finding may indicate that blood pressure should be treated differently in younger and older patients. More TBI studies in the elderly are warrented to define specific guidelines regarding secondary insult definitions and optimal levels to target. Studies of pressure autoregulation and CPPopt are also desirable.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00701-021-05047-z.

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Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. The study was approved by the local ethical review board.

Informed consent Informed consent was obtained from individual participants or the relatives if the participant did not have the decision-making capacity for informed consent.

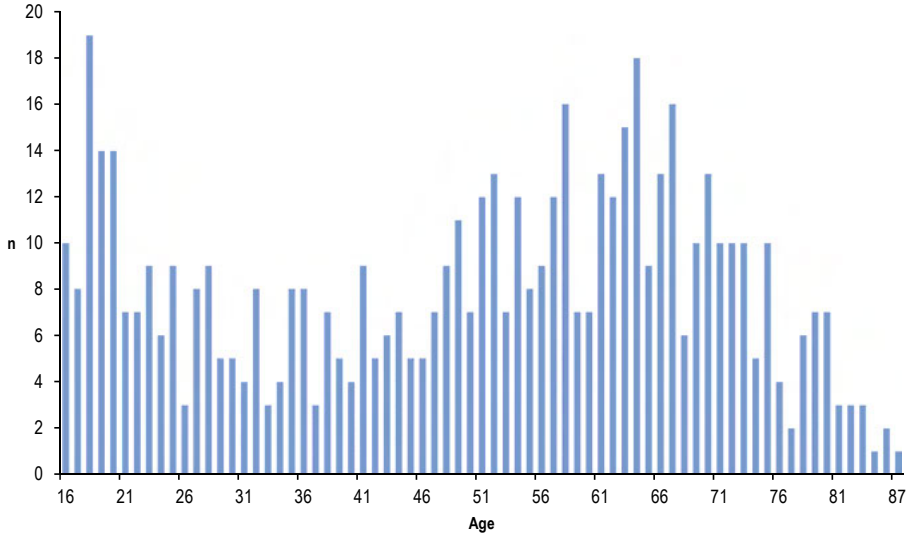
Conflict of interest The authors declare no competing interests.

References

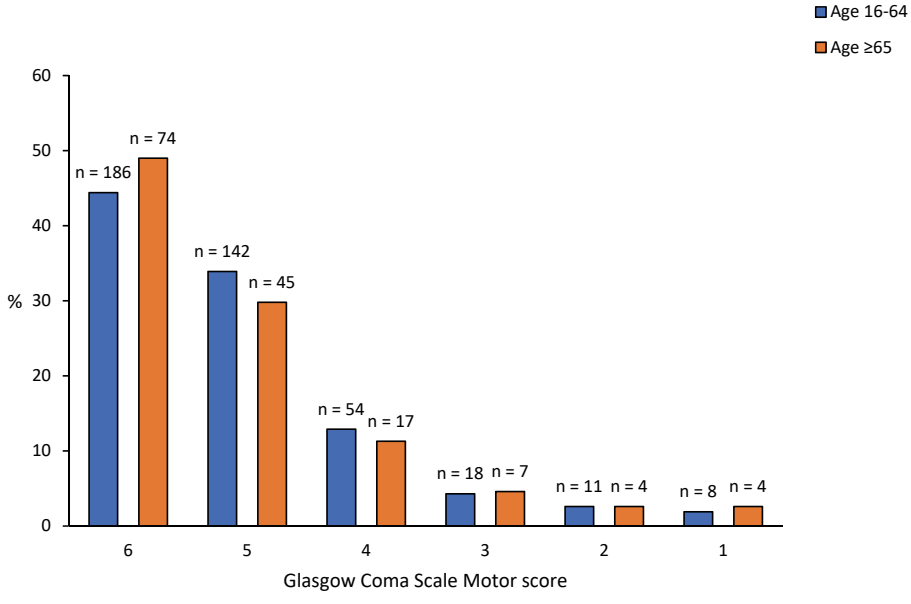
1. Andrews BT, Pitts LH (1991) Functional recovery after traumatic transtentorial herniation. Neurosurgery 29(2):227–231
2. Becker P, Ward JD, Young HF (1977) The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg 4:12
3. Bowers SA, Marshall LF (1980) Outcome in 200 consecutive cases of severe head injury treated in San Diego County: a prospective analysis. Neurosurgery 6(3):237–242
4. Combes R, Fauvage B, Jacquot C, Colonna M, Passagia JG, Chirossel JR, de Grenoble C Severe head injuries: an outcome prediction and survival analysis. 5
5. Cooper DJ, Rosenfeld JV, Murray L et al (2011) Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 364(16):1493–1502
6. Czosnyka M, Balestreri M, Steiner L, Smielewski P, Hutchinson PJ, Matta B, Pickard JD (2005) Age, intracranial pressure, autoregulation, and outcome after brain trauma. J Neurosurg 102(3):450–454
7. Dams-O'Connor K, Cuthbert JP, Whyte J, Corrigan JD, Faul M, Harrison-Felix C (2013) Traumatic brain injury among older adults at level I and II trauma centers. J Neurotrauma 30(24):2001–2013
8. Elf K, Nilsson P, Enblad P (2002) Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care*: Crit Care Med 30(9):2129–2134
9. Gaastra B, Longworth A, Matta B, Snelson C, Whitehouse T, Murphy N, Veenith T (2016) The ageing population is neglected in research studies of traumatic brain injury. Br J Neurosurg 30(2):221–226
10. Gardner RC, Dams-O'Connor K, Morrissey MR, Manley GT (2018) Geriatric traumatic brain injury: epidemiology, outcomes, knowledge gaps, and future directions. J Neurotrauma 35(7):889–906
11. Hawley C, Sakr M, Scapinello S, Salvo J, Wrenn P (2017) Traumatic brain injuries in older adults—6 years of data for one UK trauma centre: retrospective analysis of prospectively collected data. Emerg Med J 34(8):509–516
12. Howells T, Piper I, Souter M, Miller J (1995) Jones P Design of a research database for the study of secondary insults following head injury. J Neurotrauma 12:471–472
13. Hukkelhoven CWPM, Steyerberg EW, Rampen AJJ, Farace E, Habbema JDF, Marshall LF, Murray GD, Maas AIR (2003) Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg 99(4):666–673
14. Hutchinson PJ, Kolias AG, Timofeev IS et al (2016) Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med 375(12):1119–1130
15. Iaccarino C, Carretta A, Nicolosi F, Morselli C (2018) Epidemiology of severe traumatic brain injury. J Neurosurg Sci 62(5):8
16. Koskinen S, Alaranta H (2008) Traumatic brain injury in Finland 1991–2005: a nationwide register study of hospitalized and fatal TBI. Brain Inj 22(3):205–214
17. Lenell S, Nyholm L, Lewén A, Enblad P (2015) Updated periodic evaluation of standardized neurointensive care shows that it is possible to maintain a high level of favorable outcome even with increasing mean age. Acta Neurochir (Wien) 157(3):417–425
18. Lennartsson C, Heimerson I (2012) Elderly people's health: Health in Sweden: the National Public Health Report 2012. Chapter 5. Scand J Public Health 40(9 Suppl):95–120
19. Maas AI, Murray G, Henney H, Kassem N, Legrand V, Mangelus M, Muizelaar J-P, Stocchetti N, Knoller N (2006) Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurol 5(1):38–45
20. Maas AI, Stocchetti N, Bullock R (2008) Moderate and severe traumatic brain injury in adults. Lancet Neurol 7(8):728–741
21. Majdan M, Plancikova D, Brazinova A, Rusnak M, Nieboer D, Feigin V, Maas A (2016) Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. Lancet Public Health 1(2):e76–e83
22. Marshall LF, Marshall SB, Klauber MR, van Clark M, B, Eisenberg HM, Jane JA, Luerssen TG, Marmarou A, Foulkes MA, (1991) A new classification of head injury based on computerized tomography. J Neurosurg 75(Supplement):S14–S20
23. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part II: acute and chronic barbiturate administration in the management of head injury. J Neurosurg 50(1):26–30
24. Marshall LF, Maas AIR, Marshall SB et al (1998) A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. J Neurosurg 89(4):519–525
25. Merzo A, Lenell S, Nyholm L, Enblad P, Lewén A (2016) Promising clinical outcome of elderly with TBI after modern neurointensive care. Acta Neurochir (Wien) 158(1):125–133
26. Nichol A, French C, Little L et al (2015) Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. The Lancet 386(10012):2499–2506
27. Nordström C-H, Gör Sundbärg, Messeter K, Schalén W (1989) Severe traumatic brain lesions in Sweden. Part 2: impact of aggressive neurosurgical intensive care. Brain Inj 3(3):267–281
28. Nyholm L, Howells T, Enblad P, Lewén A (2013) Introduction of the Uppsala Traumatic Brain Injury register for regular surveillance of patient characteristics and neurointensive care management including secondary insult quantification and clinical outcome. Ups J Med Sci 118(3):169–180
29. Peeters W, Majdan M, Brazinova A, Nieboer D, Maas AIR (2017) Changing epidemiological patterns in traumatic brain injury: a longitudinal hospital-based study in Belgium. Neuroepidemiology 48(1–2):63–70
30. Raj R, Mikkonen ED, Kivisaari R, Skrifvars MB, Korja M, Siironen J (2016) Mortality in elderly patients operated for an acute subdural hematoma: a surgical case series. World Neurosurg 88:592–597
31. Ryttlefors M, Howells T, Nilsson P, Ronne-Engström E, Enblad P (2007) Secondary insults in subarachnoid hemorrhage: occurrence and impact on outcome and clinical deterioration. Neurosurgery 61(4):704–714; discussion 714–715
32. Shimoda K, Maeda T, Tado M, Yoshino A, Katayama Y, Bullock MR (2014) Outcome and surgical management for geriatric traumatic brain injury: analysis of 888 cases registered in the Japan Neurotrauma Data Bank. World Neurosurg 82(6):1300–1306
33. Taussky P, Hidalgo ET, Landolt H, Fandino J (2012) Age and salvageability: analysis of outcome of patients older than 65 years undergoing craniotomy for acute traumatic subdural hematoma. World Neurosurg 78(3–4):306–311
34. Teasdale GM, Pettigrew LEL, Wilson JTL, Murray G, Jennett B (1998) Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. J Neurotrauma 15(8):587–597
35. Thomas KE, Stevens JA, Sarmiento K (2005) Wald MM (2008) Fall-related traumatic brain injury deaths and hospitalizations among older adults — United States. J Safety Res 39(3):269–272

36. Thompson HJ, McCormick WC, Kagan SH (2006) Traumatic brain injury in older adults: epidemiology, outcomes, and future implications: traumatic brain injury and older adultS. J Am Geriatr Soc 54(10):1590–1595
37. Utomo WK, Gabbe BJ, Simpson PM, Cameron PA (2009) Predictors of in-hospital mortality and 6-month functional outcomes in older adults after moderate to severe traumatic brain injury. Injury 40(9):973–977
38. Wan X, Liu S, Wang S et al (2016) Elderly patients with severe traumatic brain injury could benefit from surgical treatment. World Neurosurg 89:147–152
39. Wilson JTL, Pettigrew LEL, Teasdale GM (1998) Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 15(8):573–585
40. You W, Feng J, Tang Q, Cao J, Wang L, Lei J, Mao Q, Gao G, Jiang J (2015) Intraventricular intracranial pressure monitoring improves the outcome of older adults with severe traumatic brain injury: an observational, prospective study. BMC Anesthesiol 16(1):35

Supplementary information 1. Age distribution



Supplementary information 2. Glasgow coma scale Motor score on admission by age group



Glasgow coma scale Motor score on admission. No significant differences between age 16-64 vs age ≥65, Pearsons Chi 2 test. Each bar represents the percentage of outcome within its age group. Absolut number of patients in each bar is presented above.

Paper V

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ORIGINAL ARTICLE

Cerebrovascular reactivity (PRx) and optimal cerebral perfusion pressure in elderly with traumatic brain injury

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Abstract

Purpose Cerebral perfusion pressure (CPP) guidance by cerebral pressure autoregulation (CPA) status according to PRx (correlation mean arterial blood pressure (MAP) and intracranial pressure (ICP)) and optimal CPP (CPPopt = CPP with lowest PRx) is promising but little is known regarding this approach in elderly. The aim was to analyze PRx and CPPopt in elderly TBI patients.

Methods A total of 129 old (≥ 65 years) and 342 young (16–64 years) patients were studied using monitoring data for MAP and ICP. CPP, PRx, CPPopt, and ΔCPPopt (difference between actual CPP and CPPopt) were calculated. Logistic regression analyses with PRx and ΔCPPopt as explanatory variables for outcome. The combined effects of PRx/CPP and PRx/ΔCPPopt on outcome were visualized as heatmaps.

Results The elderly had higher PRx (worse CPA), higher CPPopt, and different temporal patterns. High PRx influenced outcome negatively in the elderly but less so than in younger patients. CPP close to CPPopt correlated to favorable outcome in younger, in contrast to elderly patients. Heatmap interaction analysis of PRx/ΔCPPopt in the elderly showed that the region for favorable outcome was centered around PRx 0 and ranging between both functioning and impaired CPA (PRx range − 0.5–0.5), and the center of ΔCPPopt was − 10 (range − 20–0), while in younger the center of PRx was around − 0.5 and ΔCPPopt closer to zero.

Conclusions The elderly exhibit higher PRx and CPPopt. High PRx influences outcome negatively in the elderly but less than in younger patients. The elderly do not show better outcome when CPP is close to CPPopt in contrast to younger patients.

Keywords Pressure reactivity index · Optimal cerebral perfusion pressure · Cerebral autoregulation · Traumatic brain injury · Elderly · Neurointensive care monitoring

Abbreviations

CPP	Cerebral perfusion pressure
CPA	Cerebral pressure autoregulation
PRx	Pressure reactivity index
MAP	Mean arterial pressure
ICP	Intracranial pressure
CPPopt	Optimal CPP
TBI	Traumatic brain injury
ΔCPPopt	Difference between CPP and CPPopt
NIC	Neurointensive care
GCS M	Glasgow Coma Scale motor score
SBP	Systolic blood pressure
GOSE	Extended Glasgow outcome scale
EVD	External ventricular drainage system
CSF	Cerebrospinal fluid
GMT	Good monitoring time
% GMT	Proportion of GMT
IQR	Interquartile range
OR	Odds ratio
AOR	Adjusted odds ratio
DC	Decompressive craniectomy
CI	Confidence interval

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Introduction

The clinical outcome after traumatic brain injury (TBI) has improved substantially with the introduction of specialized neurointensive care (NIC) [3, 4, 9, 19, 20]. The current trend in NIC treatment of TBI is towards more individualized treatment. Cerebral pressure autoregulation (CPA) status may be one important factor to consider. Promising results indicate that, instead of using fixed cerebral perfusion pressure (CPP) goals, it may be beneficial to guide CPP according to CPA status and estimated optimal CPP (the CPP range where CPA works best) [5, 25, 26, 33, 34]. CPA can be monitored by using the pressure reactivity index (PRx), which is the correlation coefficient between mean arterial blood pressure (MAP) and intracranial pressure (ICP) over 5 min [5]. Optimal CPP (CPPopt) may be calculated continuously as the CPP with the lowest PRx over a chosen period of time (hours) [1]. CPA-guided CPP was found to be safe in a recent feasibility randomized clinical trial [30] and outcome studies are under discussion.

One important fact to consider in the further development of NIC towards more individualized management is the changing demographics of TBI. The proportion of elderly (age ≥ 65) is increasing both overall and among TBI patients [8, 14, 18, 22] and is expected to increase further over time. The management of elderly TBI patients is a tremendous future challenge. The elderly differ with a higher proportion of acute subdural hematoma, higher Glasgow Coma Scale motor score (GCS M) on admission, more often exhibit chronic diseases, such as hypertension and cardiovascular disease, and are more often pre-injury treated with antithrombotic drugs [14, 15, 27, 28]. The causes of the trauma are also often different with falls in the same plane being the main cause in elderly rather than high-energy injuries [7, 10, 12–14]. Despite the known differences between elderly and younger adults with TBI, all patients are still irrespective of age treated according to the same guidelines, which are based on research predominantly on younger patients. We found in our previous study that the elderly spent more time outside the treatment thresholds, with higher CPP and higher systolic blood pressure (SBP) but seemed to benefit from this in contrast to the young adults [16]. Low SBP was found to be critical to avoid in the elderly [16]. This raises the question of whether PRx and CPPopt are useful for guidance of treatment in the elderly. Only few TBI studies have focused on CPA in the elderly [2, 6, 8]. It has been shown that cerebrovascular resistance and reactivity may change with age and that PRx appears to be better in the younger ages [24]. More studies are warranted regarding CPA specifically in elderly TBI patients.

In this study, we aimed to analyze PRx and CPPopt specifically in elderly TBI patients during NIC and relate the results to outcome. We intend to use the younger patients for comparison.

Material and methods

Study design and patient selection

The Department of Neurosurgery at the Uppsala University Hospital, Sweden, provides neurosurgical care for a central part of Sweden, with a population of approximately 2 million people. Most TBI patients are initially treated at local hospitals according to advanced trauma life support principles and then referred to Uppsala for NIC (the most distant hospital is 382 km away).

All patients admitted to the NIC unit have since 2008 been included in the Uppsala Traumatic Brain Injury registry [23] where patients' characteristics, treatment characteristics, and 6-month follow-up are registered. Extended Glasgow outcome scale grade (GOSE) is assessed after around 6 months, by structured telephone interviews done by a few selected persons [31, 32].

All TBI patients admitted to Uppsala University Hospital between 2008 and 2018 aged ≥ 16 years who had available monitoring data were included in the study. Age, sex, GCS M, and GOSE were gathered from the Uppsala TBI registry. The first CT after trauma was classified according to Marshall [21], in retrospect by two of the authors (SL and TSW).

Neurointensive care

All patients were treated according to the same local standardized treatment protocol [9]. Briefly, unconscious patients (GCS M ≤ 5) were intubated, mechanically ventilated, and had ICP monitoring regardless of age (active waiting in cases with anticoagulants/coagulopathy). Propofol was used for sedation and opiates for analgesia. An external ventricular drainage system (EVD) was used as the first choice for ICP monitoring, and an intraparenchymal pressure device was chosen in case of compressed ventricles. The pressure dome for the EVD was placed at the level of the lateral ventricles, and the arterial blood pressure dome was placed at the heart level. Moderate hyperventilation was applied initially ($PaCO_2$ 4.0–4.5 kPa) and changed to normoventilation as soon as ICP permitted. Unless severe ICP elevations, regular wake-up tests were performed (3–6 times/day). Prophylactic anticonvulsants were not used. Significant mass lesions were evacuated.

The treatment goals were as follows: ICP < 20 mmHg, systolic blood pressure (SBP) > 100 mmHg, CPP > 60 mmHg, PaO_2 > 12 kPa, glucose 5–10 mmol/L, normovolemia, electrolytes within normal ranges, and body temperature < 38 °C. PRx and CPPopt were not available bedside.

Raised ICP was treated in a stepwise fashion[9]: (1) If ICP increased ≥ 20 mmHg without mass lesions, cerebrospinal fluid (CSF) was drained. Initially (first day/days) small volumes of 1–2 ml were drained intermittently. Later when the risk for expanding hematomas and brain swelling was decreased, CSF was drained (if needed) against a pressure level of 15–20 mmHg with a continuously open EVD. (2) If ICP remained increased the treatment was escalated. No wake-up tests were performed. Patients received continuous sedation, more morphine, and stress reduction with ß1-antagonist metoprolol (0.2–0.3 mg/kg/24 h as an infusion) and α2-agonist clonidine (0.5–1.0 µg/kg × 8 or the same dose as an infusion). (3) If the ICP treatment still was insufficient, thiopental coma treatment and/or decompressive craniectomy were used as last-tier treatments. This step was initiated more restrictively in the elderly.

Monitoring data processing

ICP and arterial monitoring data were recorded with the Odin software, developed at Uppsala University and the University of Edinburgh [11]. Collected data was screened and cleared from artifacts using the Odin software. The monitoring time left after the removal of artifacts and time gaps from, e.g., radiology examination and surgical procedures was entitled good monitoring (GMT). The proportion of GMT (% GMT) above/below certain predefined thresholds were calculated for PRx and CPPopt variables (see below).

Trended minute-by-minute data was collected for MAP, SBP, ICP, and CPP, respectively. PRx was calculated as a moving 5-min correlation of 10 s averages of ICP and MAP. PRx is presented as % GMT > 0.25. CPPopt was calculated as the CPP with the lowest PRx in the last 4 h, as described by Aries and colleagues [1]. Deviations from CPPopt were denoted ΔCPPopt and calculated as the difference between actual CPP and calculated CPPopt. ΔCPPopt is presented as % GMT with ΔCPPopt < − 5, ± 5, or > 5 mmHg, respectively [30].

Heatmap visualization

The combined effect of PRx/CPP and PRx/ΔCPPopt, respectively, on the outcome (GOSE) was explored by creating heatmaps. The heatmaps were generated by a custom-written-R-script, developed by one of the authors (AH) as earlier described in detail [29]. The PRx range was − 1 to + 1 with a 0.05 resolution, which was combined with CPP (range 40 to 100 mmHg), and ΔCPPopt (range − 30 to + 30 mmHg), with a 2-mmHg resolution. For each coordinate/pixel (combination of two thresholds) the % GMT was calculated for all patients and correlated with GOSE using the Spearman test. Smoothing filters were used, and values were then translated into the jet color range (red to blue) with red/blue color indicating a negative/positive association with unfavorable/favorable outcomes. Coordinates/pixels with less than five patients with at least 5 min of data were colored as white. Density plots were conducted to visualize the frequency of the percentage of monitoring time for certain combinations of PRx with CPP or ΔCPPopt. The resulting numbers were normalized (divided) by the highest count within the grid to yield density values ranging from 0 to 1 for each cell in the grid. The resulting values were smoothed and then transformed into colors using the jet color scale.

Statistics

Two age groups were analyzed, one old group ≥ 65 years of age and one young group 16–64 years old. Differences in characteristics between the age groups were analyzed with Pearson's chi^2 test. Non-parametric data were presented as median with interquartile range and differences between groups tested with Mann–Whitney *U*-test.

In order to analyze the influence on the outcome (favorable outcome (GOSE 5–8) and mortality) of PRx, CPPopt, and ΔCPPopt, univariate logistic regression analysis was done with favorable outcome and mortality as dependent variables. Univariate analysis was also performed for GCS M, Marshall score, and sex. Multiple logistic regression analysis was performed for favorable outcome and mortality with the explanatory variables GCS M, Marshall score, sex, % GMT with > 0.25, and % GMT with ΔCPPopt < − 5/ ± 5/ > 5 mmHg for favorable outcome and for mortality. IBM SPSS Statistics version 28.0.1.0 was used (IBM Corp, Armonk, NY).

A p-value < 0.05 was considered statistically significant. In tables and figures significant findings are marked with $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$.

Results

Among 471 patients who met the criteria for the study, 129 (27%) were ≥ 65 years old (old group), and 342 (73%) were between 16 and 64 years old (young group) (Table 1). The age distribution is provided as supplementary information in Online Resource 1. In the old group, 106 (82.2%) were males, the median GCS M was 5 (IQR 5–6), and the median Marshall score was 5 (IQR 2–5). In the young group, 265 (77.5%) were males, the median GCS M was 5 (IQR 4–5) and the median Marshall score was 2 (IQR 2–5).

ICP was monitored by an EVD in 87 cases, a parenchymatous pressure device in 280, and both in 103 (Table 1). The median ICP monitoring time was 11,684 min (IQR 6672–13,491), the median MAP monitoring time was 13,081 min (IQR 8980–13,818), and the median CPP monitoring time was 11,344 (IQR

Table 1 Patient characteristics

	16–64 years	≥ 65 years	*p*	
Patients, *n*	342	129		
Age (years), median (IQR)	44 (25–55)	71 (68–75)		
Sex (male), *n* (%)	265 (77.5)	106(82.2)	< 0.001[a]	***
GCS M at admission, median (IQR)	5(4–5)	5(5–6)	0.021[b]	*
Marshall score, median (IQR)	2(2–5)	5(2–5)	< 0.001[b]	***
ICP monitoring				
EVD, *n* (%)	60 (17.5)	27 (20.9)	0.398[a]	
Intraparenchymal devices, *n* (%)	196 (57.3)	84 (65.11)	0.124[a]	
Both, *n* (%)	86 (25.1)	17 (13.2)	0.005[a]	**
Neurointensive care treatment				
Craniotomy, *n* (%)	167 (48.8)	83 (64.3)	0.003[a]	**
DC, *n* (%)	44 (12.9)	6 (4.7)	0.010[a]	*
Thiopental, *n* (%)	53 (15.5)	4 (3)	< 0.001[a]	***
Outcome				
Favorable, *n* (%)	204 (59.6)	51 (39.5)	< 0.001[a]	***
Mortality, *n* (%)	37 (10.8)	40 (31.0)	< 0.001[a]	***

[a]Tested with chi^2-test

[b]Tested with Mann–Whitney *U*-test

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

6490–13,434). The number of patients with monitoring data for each day is provided as supplementary information in Online Resource 2. Median values of each physiological parameter and median values of % GMT spent above/within/below predefined thresholds for PRx and ΔCPPopt are presented for the whole studied monitoring period (10 days) by age group in Table 2. CPPopt was possible to calculate in 53.7% of GMT in the 16–64 years group and in 56.5% of GMT in the elderly group. There were highly significant differences between the age groups. The old group showed significantly higher MAP, higher SBP, lower ICP, higher CPP, higher (worse) PRx, higher CPPopt, higher % GMT with ΔCPPopt < − 5%, and lower % GMT with ΔCPPopt ± 5 (Table 2).

When the temporal patterns of MAP, SBP, ICP, CPP, and PRx were analyzed in the old group by day and divided into favorable outcome and unfavorable outcomes, it seemed to be a tendency that patients ≥ 65 years with lower MAP days 8–10, lower SBP days 3–10, and higher PRx days 0–5 had more unfavorable outcome (Fig. 1). In the young group, patients with higher PRx and higher MAP had significantly more unfavorable outcome during almost the whole time period (Fig. 1). Analysis of temporal patterns of CPPopt and % GMT with ΔCPPopt < − 5/ ± 5/ > 5 showed no significant

Table 2 Physiological features for the whole 10-day monitoring period

	16–64 years	≥ 65 years	*p*	
MAP, median (IQR)	87.1 (83.4–92.3)	91.7 (87.3–96.7)	< 0.001	***
SBP, median (IQR)	137.8 (129.9–147.4)	150.6 (140.0–158.5)	< 0.001	***
ICP, median (IQR)	12.2 (8.7–14.8)	10.6 (7.2–12.9)	< 0.001	***
CPP, median (IQR)	75.3 (70.7–81.0)	80.6 (76.1–89.1)	< 0.001	***
CPPopt, median (IQR)	75.2 (71.6–79.6)	80.8 (75.8–87.2)	< 0.001	***
PRx, median (IQR)	0.03 (− 0.06–0.12)	0.10 (0.02–0.19)	< 0.001	***
GMT PRx > 0, median % (IQR)	52.2 (42.0–63.5)	62.6 (51.2–71.8)	< 0.001	***
GMT PRx > 0.25, median % (IQR)	26.9 (20.4–37.2)	36.6 (26.8–46.0)	< 0.001	***
GMT PRx > 0.35, median % (IQR)	19.5 (14.2–27.9)	26.0 (18.4–35.3)	< 0.001	***
GMT ΔCPPopt < − 5, median % (IQR)	30.9 (23.0–40.2)	34.9 (25.7–44.0)	0.014	*
GMT ΔCPPopt ± 5, median % (IQR)	28.4 (23.4–34.2)	24.4 (20.5–27.9)	< 0.001	***
GMT ΔCPPopt > 5, median % (IQR)	33.1 (25.2–40.5)	33.9 (25.6–43.8)	0.236	

Difference between age groups tested with Mann–Whitney *U*-test

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

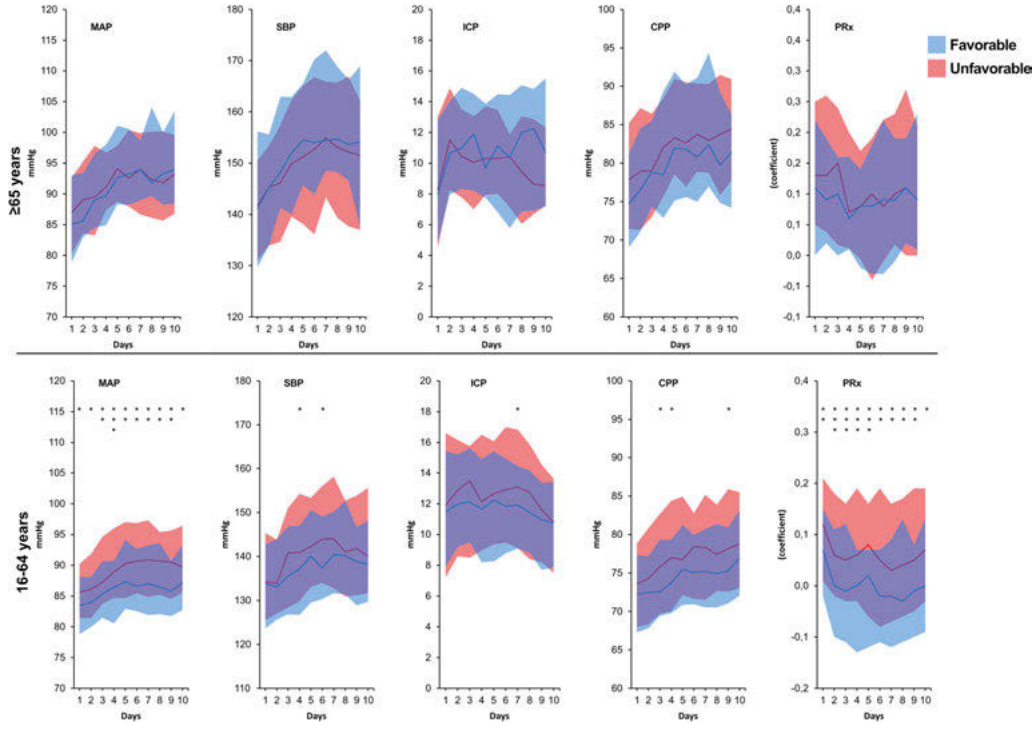

Fig. 1 Temporal daily distribution of MAP, SBP, ICP, CPP, and PRx by outcome and age group. Distribution of patients' daily mean values on group level for each physiological feature with the distribution presented as median (line) and IQR (band). Favorable outcome GOSE 5–8 and unfavorable GOSE 1–4. Difference between favorable and unfavorable tested for each day with Mann–Whitney *U*-test. $*p<0.05$, $**p<0.01$, and $***p<0.001$

differences between favorable and unfavorable outcomes at any day in the old group (Fig. 2). In the young group, patients with unfavorable outcome had significantly higher median of CPPopt almost all days (days 1, 2, 5, 7, and 9) and significantly lower % GMT with ΔCPPopt ± 5 days 1, 4, and 5 (Fig. 2).

The logistic regression analyses for the whole period with favorable outcomes and mortality as dependent variables are presented in Table 3. In the young group, both the univariate and the multivariate analyses showed significantly lower odds ratio (OR)/adjusted odds ratio (AOR) for favorable outcome with increasing Marshall score and increasing % GMT with PRx > 0.25, and significantly higher OR/AOR for favorable outcome with increasing GCS M. Higher ΔCPPopt ± 5 showed significantly higher OR for favorable outcome in the univariate analysis but not in the multivariate analysis. None of the variables showed statistical significance in the elderly group for favorable outcomes, neither in the univariate nor in the multiple regression analysis. In the univariate regression analysis for mortality, the young group had significantly higher OR for mortality with increasing Marshall score, increasing % GMT with PRx > 0.25, and increasing % GMT with ΔCPPopt < − 5 (Table 3). Higher GCS M and higher % GMT with CPPopt ± 5 were significantly associated with lower OR for mortality. In the multiple regression analysis, the young group had a significantly higher AOR for mortality with PRx > 0.25 and a significantly lower AOR with higher GCS M on admission (Table 3). In the old group, significantly higher OR/AOR for mortality was seen for a higher % GMT with PRx > 0.25 in both the univariate and multiple logistic regression analyses but no other significant associations were found (Table 3).

Heatmap interaction analysis of PRx/ΔCPPopt in the elderly showed that the field for favorable outcome had its center around PRx 0 (range − 0.5–0.5) and ΔCPPopt − 10 (range − 20–0) and that the plots were more dispersed than in the younger patients who had a center for favorable outcome around PRx − 0.5 (range − 0.75–0) and ΔCPPopt

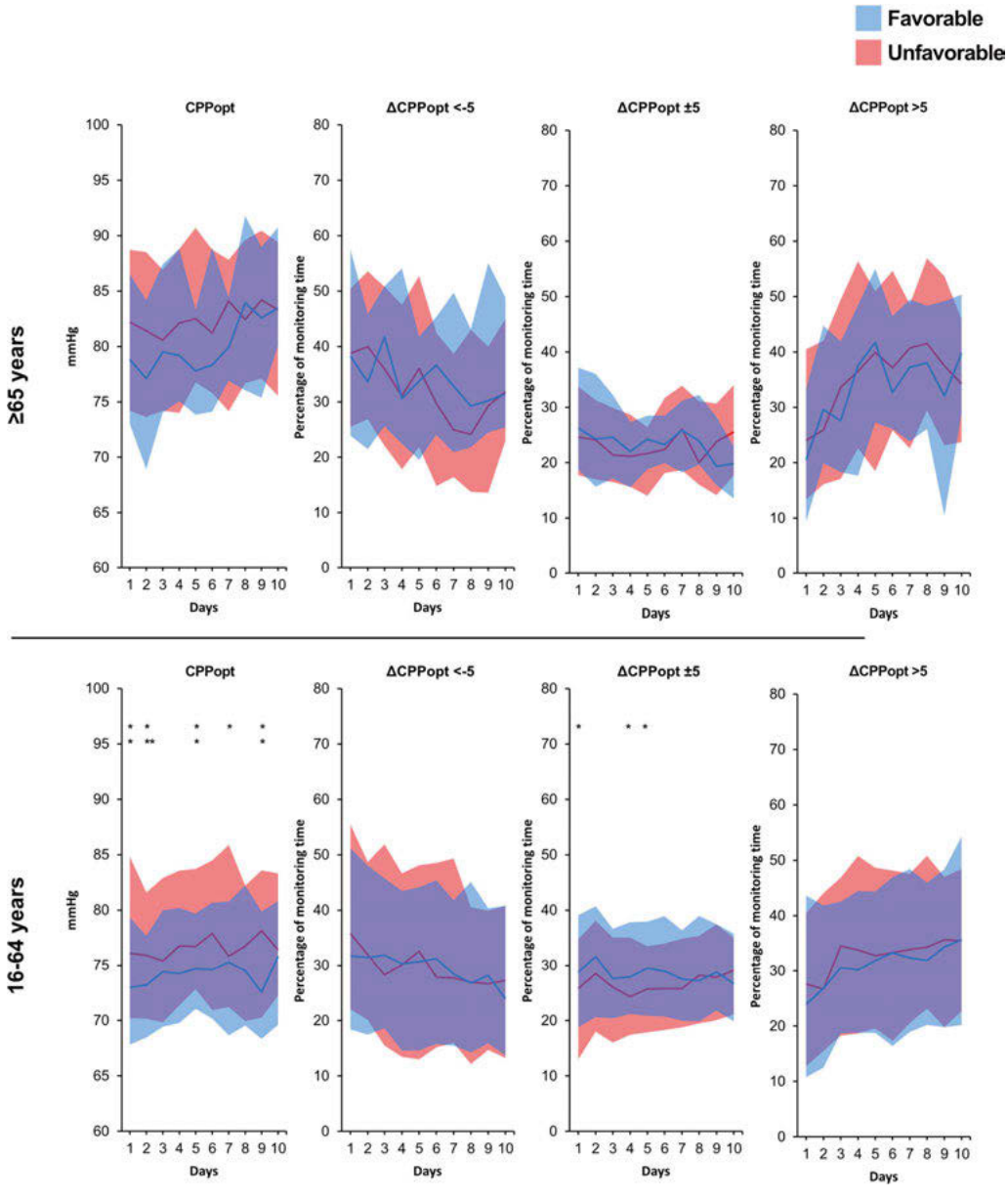

Fig. 2 Temporal daily distribution of CPPopt and ΔCPPopt by outcome and age group. Distribution of patients' daily mean values on group level for CPPopt and mean percentage monitoring time of ΔCPPopt < −5, ΔCPPopt ± 5, and ΔCPPopt > 5 over 10 days with the distribution presented as median (line) and IQR (band). Favorable outcome GOSE 5–8 and unfavorable GOSE 1–4. Difference between favorable and unfavorable tested for each day with Mann–Whitney *U*-test. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

Table 3 Logistic regression analysis (whole 10 days period) with favorable and mortality as dependent

Variable	16–64 years							
	Univariate logistic regression				Multiple logistic regression			
	OR	95% CI	*p*		AOR	95% CI	*p*	
Favorable model[c]								
Sex (male)	1.005	0.599–1.686	0.985		1.134	0.628–2.046	0.676	
GCS M on admission	1.852	1.499–2.288	< 0.001	***	1.914	1.484–2.467	< 0.001	***
Marshall score	0.763	0.655–0.889	< 0.001	***	0.809	0.679–0.964	0.018	*
PRX > 0.25 (%GMT)	0.964	0.948–0.98	< 0.001	***	0.973	0.953–0.993	0.009	**
ΔCPPopt < − 5 (%GMT)	0.995	0.979–1.011	0.520		1.211	0.854–1.718	0.282	
ΔCPPopt ± 5 (%GMT)	1.048	1.016–1.082	0.003	**	1.287	0.866–1.912	0.213	
ΔCPPopt > 5 (%GMT)	0.987	0.968–1.005	0.164		1.184	0.835–1.679	0.343	
Mortality model[d]								
Sex (male)	0.783	0.33–1.86	0.580		0.830	0.292–2.358	0.726	
GCS M on admission	0.648	0.514–0.818	< 0.001	*	0.784	0.562–0.995	0.046	*
Marshall score	1.313	1.048–1.645	0.018	*	1.243	0.949–1.627	0.114	
PRX > 0.25 (%GMT)	1.057	1.035–1.08	< 0.001	***	1.029	1.000–1.058	0.046	*
ΔCPPopt < − 5 (%GMT)	1.040	1.013–1.067	0.003	**	1.118	0.715–1.750	0.625	
ΔCPPopt ± 5 (%GMT)	0.915	0.865–0.969	0.002	**	1.066	0.643–1.768	0.803	
ΔCPPopt > 5 (%GMT)	0.980	0.949–1.012	0.221		1.107	0.707–1.733	0.658	
Variable	≥ 65 years							
	Univariate logistic regression				Multiple logistic regression			
	OR	95% CI	*p*		AOR	95% CI	*p*	
Favorable model[c]								
Sex (male)	0.616	0.234–1.624	0.328		0.858	0.302–2.439	0.774	
GCS M on admission	1.186	0.864–1.629	0.292		1.158	0.823–1.630	0.401	
Marshall score	0.949	0.763–1.18	0.636		0.958	0.758–1.212	0.721	
PRX > 0.25 (%GMT)	0.983	0.96–1.006	0.148		0.986	0.960–1.013	0.300	
ΔCPPopt < − 5 (%GMT)	1.001	0.978–1.025	0.932		0.905	0.535–1.533	0.711	
ΔCPPopt ± 5 (%GMT)	1.024	0.972–1.079	0.364		0.907	0.496–1.658	0.751	
ΔCPPopt > 5 (%GMT)	0.991	0.965–1.018	0.502		0.897	0.529–1.520	0.685	
Mortality model[d]								
Sex (male)	0.968	0.364–2.575	0.948		1.084	0.357–3.292	0.887	
GCS M on admission	0.822	0.605–1.115	0.208		0.879	0.616–1.254	0.477	
Marshall score	1.196	0.944–1.515	0.137		1.159	0.888–1.513	0.278	
PRX > 0.25 (%GMT)	1.044	1.017–1.071	0.001	**	1.035	1.005–1.066	0.023	*
ΔCPPopt < − 5 (%GMT)	1.015	0.991–1.041	0.227		1.117	0.637.1.961	0.699	
ΔCPPopt ± 5 (%GMT)	0.983	0.93–1.038	0.535		1.127	0.594–2.140	0.714	
ΔCPPopt > 5 (%GMT)	0.986	0.959–1.015	0.343		1.108	0.630–1.947	0.722	

Univariate logistic regression analyses for variables from each age group with favorable or mortality as dependent. For each age group multiple regression analyses were made for favorable outcome and mortality taking all variables into account. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

[c] 16–64 years: Nagelkerke R square = 0.254. ≥ 65 years; Nagelkerke R square = 0.049

[d] 16–64 years: Nagelkerke R Square = 0.176. ≥ 65 years; Nagelkerke R square = 0.135

closer to zero (range − 10–10 (Fig. 3). The density plots showed almost the same center in both age groups (marginally lower PRx center in the younger) but with a wider field in the elderly group (Fig. 3). In the PRx/CPP interaction heatmap, the elderly showed a more dispersed field for favorable outcome compared to the young group (Fig. 4). In the old group, the field of favorable outcome mostly fitted in between PRx − 0.5 and 0.5 and CPP between 60 and 80 in contrast to the younger group where the field had a more distinct center at approximately PRx − 0.3 (range

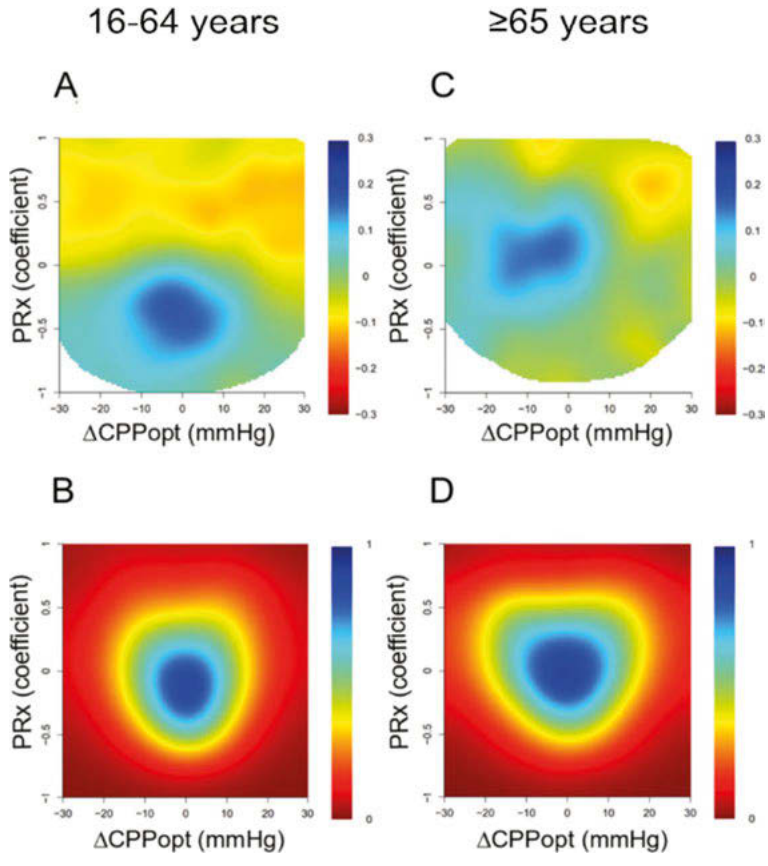

Fig. 3 Combined effect of PRx and ΔCPPopt on clinical outcome. The figure illustrates the combined association of the percentage of monitoring time (% GMT) for absolute PRx and ΔCPPopt values with GOSE (**A** and **C**) and density plots with the data frequency of certain PRx and ΔCPPopt combinations (**B** and **D**). The % GMT for the concurrent combination of PRx and ΔCPPopt during the 10 days was calculated and correlated with GOSE. The jet color range denotes the value of the correlation coefficients, where blue color indicates favorable and red color indicates unfavorable outcome. Pixels with less than five patients with 5 min of monitoring with a certain combination of PRx and CPP were colored as white

PRx − 0.7–0.4) and CPP 65 (range CPP 50–80). The density plots had approximately the same center of PRx in both groups, but the elderly group has more values in the higher CPP range than the young (Fig. 4).

Discussion

In this single-center study, we analyzed monitoring data from 129 elderly TBI patients (≥ 65 years) and compared the results with 342 younger TBI patients (16–64 years), with particular interest in CPA. All patients were treated during the same period according to the same protocol. The cerebrovascular indices were calculated in retrospect in order to evaluate the potential of using PRx and CPPopt for guidance of CPP treatment in the elderly. Our concern was that older patients may differ, especially since we found in our previous study that the elderly spent more time with higher CPP and higher systolic blood pressure (SBP) but seemed to benefit from this in contrast to the young adults [16].

In this study, the elderly proved to have higher median values of PRx, which is in accordance with the findings by Czonyka et al. [6]. We observed also that the median CPPopt was higher in the elderly. Furthermore, the elderly spent a higher % GMT with higher PRx values and a higher % GMT with CPP outside ΔCPPopt ± 5 (Table 2). These findings were also consistent with the density plots (Fig. 3). It appears convincing that elderly TBI patients have worse CPA and spend less time where the CPA works best in comparison to younger patients. The reasons for the age differences probably depend on multiple factors, e.g., different dominating types of brain injury, co-existing cardio- and cerebrovascular diseases, and medication. In order to evaluate the potential of using PRx and CPPopt for individualized treatment of CPP in the elderly, analysis of the impact on outcome may give insights.

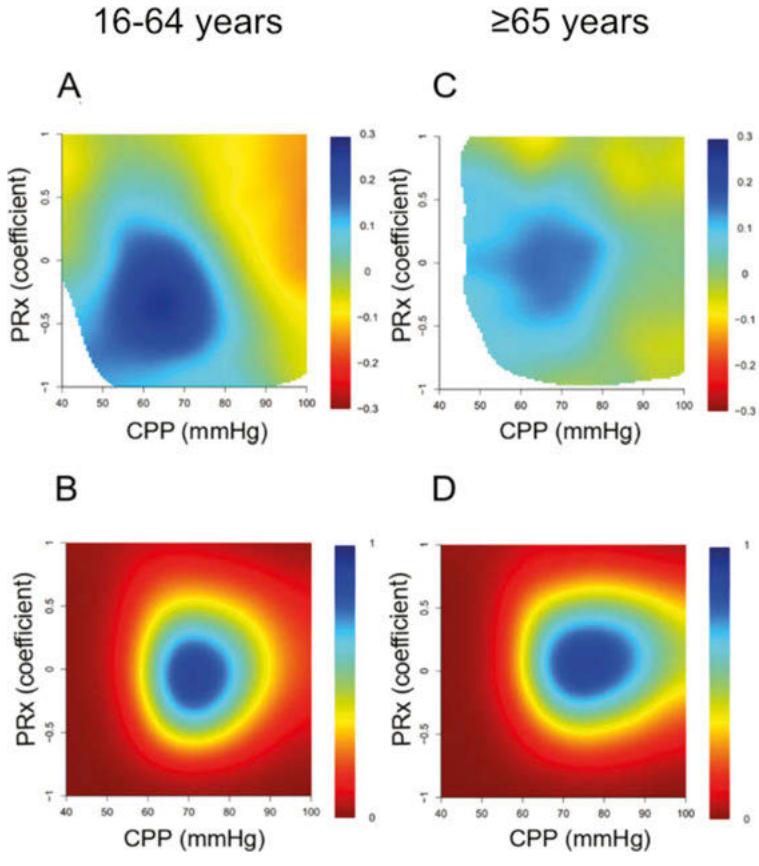

Fig. 4 Combined effect of PRx and CPP on clinical outcome. The figure illustrates the combined association of the percentage of monitoring time (% GMT) for absolute PRx and CPP values with GOSE (**A** and **C**) and density plots with the data frequency of certain PRx and CPP combinations (**B** and **D**). The % GMT for the concurrent combination of PRx and CPP during the 10 days was calculated and correlated with GOSE. The jet color range denotes the value of the correlation coefficients, where blue color indicates favorable and red color indicates unfavorable outcome. Pixels with less than five patients with 5 min of monitoring with a certain combination of PRx and CPP were colored as white

When the temporal patterns during the whole study period of 10 days were analyzed for the monitoring parameters by outcome (Fig. 1), old patients with unfavorable outcomes tended to have lower MAP days 8–10, lower SBP days 3–10, and higher PRx days 0–5. A different picture was found for the young group where PRx and MAP were significantly higher in patients with unfavorable outcomes during the whole study period. Looking at mean CPPopt and ΔCPPopt, no significant correlations with outcome were found in the elderly (Fig. 2). In the young group on the other hand, high mean CPPopt was significantly related to worse outcome half of the days (days 1, 2, 5, 7, and 9) and high % GMT with ΔCPPopt ± 5 was significantly related to favorable outcome (day 1, 4, and 5). The overall impression was thus that median CPP and proportion of time with CPP close to CPPopt, above CPPopt, or below CPPopt exert a greater impact on outcome in patients who are young and that those factors are less important in the elderly.

Looking at the logistic regression analysis of the whole monitoring period, poor cerebrovascular reactivity (high PRx) proved consistently to be associated with unfavorable outcome and mortality in the young group, both in the univariate and multivariate analyses (Table 3). Furthermore, in the young group large % GMT with ΔCPPopt ± 5 was significantly related to favorable outcome in the univariate analysis although no independent influence on outcome was found in the multivariate analysis. Regarding mortality, large % GMT with ΔCPPopt < − 5 and small % GMT with ΔCPPopt ± 5 were significantly associated to mortality in the univariate analysis of the young group, although no significant associations were found in the multivariate analysis. In the old group, the only significant finding was that CPA was associated to mortality both in the univariate and multivariate analyses Detailed interpretation of the differences found between the young and old groups is difficult but may probably to some extent be explained by the observed differences in physiological monitoring features. However, the results

indicate that cerebrovascular reactivity and deviations from CPPopt play a more important role for the clinical course in younger patients than in the elderly.

Another way of studying the significance of CPA and deviations from CPPopt is to visualize the interactions of PRx with CPP and ΔCPPopt, respectively, by generation of heatmaps. The heatmaps also indicated that cerebrovascular reactivity and small ΔCPPopt are more important in the young group. In the PRx/CPPopt heatmap, the elderly showed that the field for favorable outcome had its center around PRx 0 and was ranging between both functioning and impaired CPA (PRx range − 0.5–0.5) and that the center of ΔCPPopt was at − 10 (ranging between − 20 and 0), and the plots were more dispersed than in the younger patients who had the center for favorable outcome at around PRx − 0.5 with a field within functioning CPA (PRx range − 0.75–0) and the center of ΔCPPopt closer to zero (range − 10–10 (Fig. 3).

More studies of CPA in the elderly are warranted to substantiate our findings. Many questions remain to be answered that require multicenter studies with a large number of elderly patients, e.g., the impact of injury type and cardiovascular status. Careful consideration is always needed before the implementation of new treatment strategies, and we believe our results highlight that management principles that originate from younger TBI patients cannot be directly generalized to the elderly. Hence, before introducing CPA-guided CPP management in the elderly, more knowledge regarding CPA must be gathered from observational studies. The introduction of non-standardized CPA-guided management should be avoided in order not to bias the observational studies. At present our findings only indicate that it may be beneficial with relatively high blood pressure and high CPP in the elderly.

There are some limitations of the study that need to be considered. The study was retrospective, although data were prospectively collected. The results must be validated in other centers since this was a single-center study, and generalization of the results to other centers needs to be done with caution. It should also be mentioned that there is a referral selection bias, especially for the elderly since patients with more severe injuries and/or significant comorbidity considered not possible to treat were not accepted. The effect of a treatment bias must also be considered. The policy was that thiopental coma treatment and/or decompressive craniectomy should be initiated more restrictively in the elderly. This was also true in reality. The selection bias and treatment bias may have influenced the results, but these circumstances are what we have to deal with in reality. Furthermore, there were multiple comparisons but since this was an observational study we did not adjust for that. The fact that CPPopt was only possible to calculate in slightly above 50% of the GMT is a weakness of the concept, although this finding did not differ substantially between the age groups. Using the multi-window method described by Liu and colleagues [17] may have improved the CPPopt yield but since most earlier studies of CPPopt are based on the original 4-h window we preferred to use that.

In conclusion, the results of this study show that the elderly have higher PRx (worse autoregulation) and higher CPPopt; that high PRx influences outcome negatively in elderly patients but to a lesser extent than in the younger patients; and that more time spent close to CPPopt is associated with favorable outcome in younger patients but not in the elderly. Thus, CPA-guided therapy seems less promising in the elderly. Accordingly, the differences found for the elderly need to be considered when studies of CPPopt-guided therapy are designed since the inclusion of elderly patients may confound the results, and power analysis may be misled.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00701-024-05956-9.

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Declarations

Research involving human participants and animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

The study was approved by the Local ethical review board.

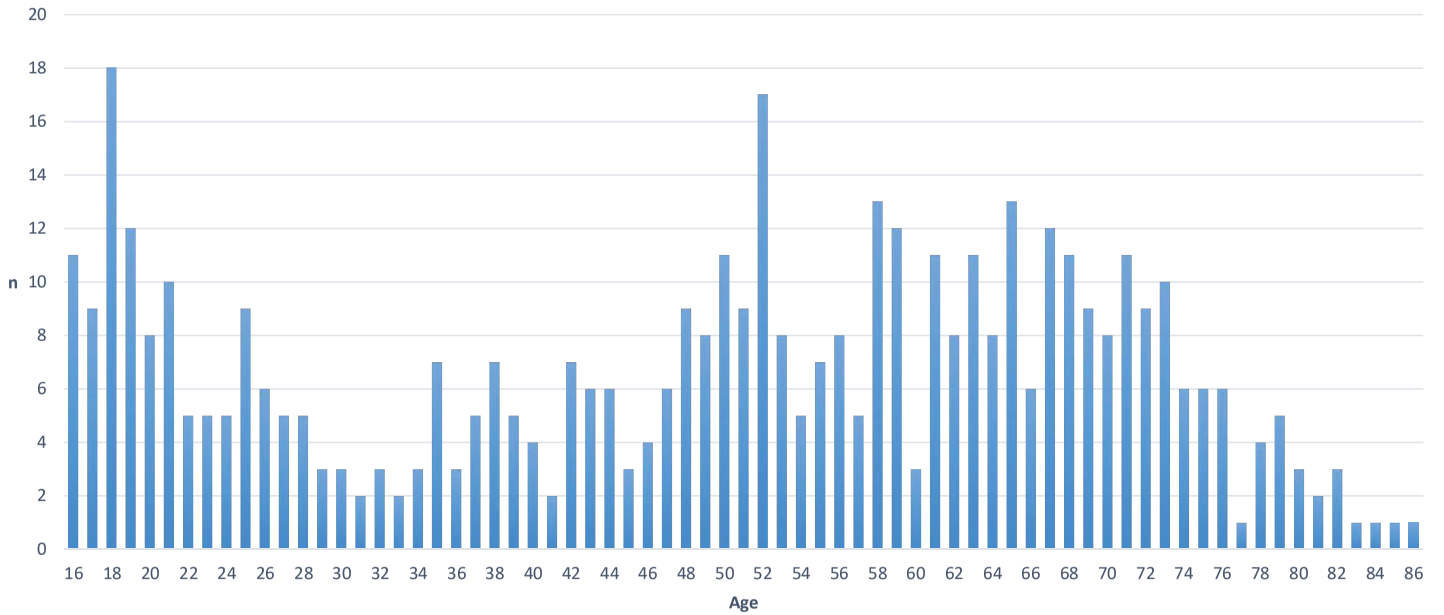
Informed consent Informed consent was obtained from individual participants or their relatives if the participant did not have the decision-making capacity for informed consent.

Conflict of interest The authors declare no competing interests.

References

1. Aries MJH, Czosnyka M, Budohoski KP et al (2012) Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury*. Crit Care Med 40(8):2456–2463
2. Batson C, Stein KY, Gomez A, Sainbhi AS, Froese L, Alizadeh A, Mathieu F, Zeiler FA (2022) Intracranial pressure–derived cerebrovascular reactivity indices, chronological age, and biological sex in traumatic brain injury: a scoping review. Neurotrauma Rep 3(1):44–56
3. Becker P, Ward JD, Young HF (1977) The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg 4:12
4. Bowers SA, Marshall LF (1980) Outcome in 200 consecutive cases of severe head injury treated in San Diego County: a prospective analysis. Neurosurgery 6(3):237–242
5. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD (1997) Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 41(1):11–19
6. Czosnyka M, Balestreri M, Steiner L, Smielewski P, Hutchinson PJ, Matta B, Pickard JD (2005) Age, intracranial pressure, autoregulation, and outcome after brain trauma. J Neurosurg 102(3):450–454
7. Dams-O'Connor K, Cuthbert JP, Whyte J, Corrigan JD, Faul M, Harrison-Felix C (2013) Traumatic brain injury among older adults at level I and II trauma centers. J Neurotrauma 30(24):2001–2013
8. Depreitere B, Meyfroidt G, Roosen G, Ceuppens J, Grandas FG (2012) Traumatic brain injury in the elderly: a significant phenomenon. In: Schuhmann MU, Czosnyka M (eds) Intracranial pressure and brain monitoring XIV. Springer, Vienna, pp 289–294
9. Elf K, Nilsson P, Enblad P (2002) Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care*. Crit Care Med 30(9):2129–2134
10. Hawley C, Sakr M, Scapinello S, Salvo J, Wrenn P (2017) Traumatic brain injuries in older adults—6 years of data for one UK trauma centre: retrospective analysis of prospectively collected data. Emerg Med J 34(8):509–516
11. Howells T, Piper I, Souter M, Miller J, Jones P (1995) Design of a research database for the study of secondary insults following head injury. J Neurotrauma 12:471–472
12. Hukkelhoven CWPM, Steyerberg EW, Rampen AJJ, Farace E, Habbema JDF, Marshall LF, Murray GD, Maas AIR (2003) Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg 99(4):666–673
13. Iaccarino C, Carretta A, Nicolosi F, Morselli C (2018) Epidemiology of severe traumatic brain injury. J Neurosurg Sci 62(5):8
14. Lenell S, Nyholm L, Lewén A, Enblad P (2015) Updated periodic evaluation of standardized neurointensive care shows that it is possible to maintain a high level of favorable outcome even with increasing mean age. Acta Neurochir 157(3):417–425
15. Lenell S, Nyholm L, Lewén A, Enblad P (2019) Clinical outcome and prognostic factors in elderly traumatic brain injury patients receiving neurointensive care. Acta Neurochir 161(6):1243–1254
16. Lenell S, Lewén A, Howells T, Enblad P (2022) Neurointensive care of traumatic brain injury in the elderly—age-specific secondary insult levels and optimal physiological levels to target need to be defined. Acta Neurochir (Wien) 164(1):117–128
17. Liu X, Donnelly J, Czosnyka M et al (2017) Cerebrovascular pressure reactivity monitoring using wavelet analysis in traumatic brain injury patients: a retrospective study. PLoS Med 14(7):e1002348
18. Majdan M, Plancikova D, Brazinova A, Rusnak M, Nieboer D, Feigin V, Maas A (2016) Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. Lancet Public Health 1(2):e76–e83
19. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part II: acute and chronic barbiturate administration in the management of head injury. J Neurosurg 50(1):26–30
20. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part I: the significance of intracranial pressure monitoring. J Neurosurg 50(1):20–25
21 Marshall LF, Marshall SB, Klauber MR, van Berkum Clark M, Eisenberg HM, Jane JA, Luerssen TG, Marmarou A, Foulkes MA (1991) A new classification of head injury based on computerized tomography. J Neurosurg 75(Supplement):S14–S20
22. Mulcahy LT, O'Halloran PJ, O'Rourke C, Corr P, Nolan D, O'Brien DP (2020) Traumatic brain injury in the Republic of Ireland twenty-five years on: a comparison of two cohorts from a neurosurgical unit. Brain Inj 34(12):1610–1617
23. Nyholm L, Howells T, Enblad P, Lewén A (2013) Introduction of the Uppsala Traumatic Brain Injury register for regular surveillance of patient characteristics and neurointensive care management including secondary insult quantification and clinical outcome. Upsala J Med Sci 118(3):169–180
24. Petkus V, Krakauskaitė S, Preikšaitis A, Ročka S, Chomskis R, Ragauskas A (2016) Association between the outcome of traumatic brain injury patients and cerebrovascular autoregulation, cerebral perfusion pressure, age, and injury grades. Medicina 52(1):46–53
25. Petkus V, Preiksaitis A, Krakauskaite S, Zubaviciute E, Rocka S, Rastenyte D, Vosylius S, Ragauskas A (2017) Benefit on optimal cerebral perfusion pressure targeted treatment for traumatic brain injury patients. J Crit Care 41:49–55
26. Petkus V, Preiksaitis A, Chaleckas E et al (2020) Optimal cerebral perfusion pressure: targeted treatment for severe traumatic brain injury. J Neurotrauma 37(2):389–396
27. Steyerberg EW, Wiegers E, Sewalt C et al (2019) Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. Lancet Neurol 18(10):923–934
28. Stocchetti N, Paternò R, Citerio G, Beretta L, Colombo A (2012) Traumatic brain injury in an aging population. J Neurotrauma 29(6):1119–1125
29. Svedung Wettervik TM, Hånell A, Howells T, Lewén A, Enblad P (2023) Autoregulatory management in traumatic brain injury: the role of absolute PRx-values and CPPopt curve shape. J Neurotrauma 40(21–22):2341–2352. https://doi.org/10.1089/neu.2023.0017
30. Tas J, Beqiri E, van Kaam RC et al (2021) Targeting autoregulation-guided cerebral perfusion pressure after traumatic brain injury (COGiTATE): a feasibility randomized controlled clinical trial. J Neurotrauma 38(20):2790–2800
31. Teasdale GM, Pettigrew LEL, Wilson JTL, Murray G, Jennett B (1998) Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow outcome scale. J Neurotrauma 15(8):587–597
32. Wilson JTL, Pettigrew LEL, Teasdale GM (1998) Structured interviews for the Glasgow outcome scale and the extended Glasgow outcome scale: guidelines for their use. J Neurotrauma 15(8):573–585
33. Zeiler FA, Ercole A, Cabeleira M, Zoerle T, Stocchetti N, Menon DK, Smielewski P, Czosnyka M (2019) Univariate comparison of performance of different cerebrovascular reactivity indices for outcome association in adult TBI: a CENTER-TBI study. Acta Neurochir (Wien) 161(6):1217–1227
34. Zeiler FA, Ercole A, Cabeleira M et al (2021) Patient-specific ICP epidemiologic thresholds in adult traumatic brain injury: a CENTER-TBI validation study. J Neurosurg Anesthesiol 33(1):28–38

Online Resource 1. Age distribution



Online Resource 2 Number of patients with monitoring data for each physiological feature and age group by day.

Day		1	2	3	4	5	6	7	8	9	10
MAP, n (%)	16-64 years	329 (96.2)	326 (95.3)	317 (92.7)	310 (90.6)	297 (86.8)	274 (80.1)	268 (78.4)	254 (74.3)	234 (68.4)	211 (61.7)
	≥65 years	127 (98.4)	124 (96.1)	121 (93.8)	114 (88.4)	108 (83.7)	98 (76.0)	92 (71.3)	81 (62.8)	77 (59.7)	69 (53.5)
BPs, n (%)	16-64 years	329 (96.2)	326 (95.3)	318 (93.0)	310 (90.6)	297 (86.8)	274 (80.1)	268 (78.4)	254 (74.3)	234 (68.4)	211 (61.7)
	≥65 years	127 (98.4)	124 (96.1)	121 (93.8)	114 (88.4)	108 (83.7)	98 (76.0)	92 (71.3)	81 (62.8)	77 (59.7)	69 (53.5)
ICP, n (%)	16-64 years	306 (89.5)	314 (91.8)	307 (89.8)	298 (87.1)	288 (84.2)	263 (76.9)	243 (71.1)	231 (67.5)	212 (62.0)	192 (56.1)
	≥65years	112 (86.8)	115 (89.1)	114 (88.4)	103 (79.8)	93 (72.1)	87 (67.4)	74 (57.4)	63 (48.8)	57 (44.2)	47 (36.4)
CPP, n (%)	16-64 years	307 (89.8)	313 (91.5)	306 (89.5)	296 (86.5)	285 (83.3)	260 (76.0)	242 (70.8)	227 (66.4)	209 (61.1)	188 (55.0)
	≥65 years	112 (86.8)	114 (88.4)	113 (87.6)	102 (79.1)	93 (72.1)	86 (66.7)	74 (57.4)	62 (48.1)	57 (44.2)	47 (36.4)
CPPopt, n (%)	16-64 years	287 (83.9)	306 (89.5)	297 (86.8)	290 (84.8)	275 (80.4)	254 (74.3)	237 (69.3)	224 (65.5)	201 (58.8)	181 (52.9)
	≥65 years	103 (79.8)	108 (83.7)	109 (84.5)	99 (76.7)	88 (68.2)	83(64.3)	71 (55.0)	61 (47.3)	55 (42.6)	47 (36.4)
PRx, n (%)	16-64 years	301 (88.0)	310 (90.6)	302 (88.3)	291 (85.1)	279 (81.6)	256 (74.9)	237 (69.3)	223 (65.2)	204 (59.6)	181 (52.9)
	≥65 years	109 (84.5)	112 (86.8)	111 (86.0)	99 (76.7)	89 (69.0)	83 (64.3)	72 (55.8)	61 (47.3)	57 (44.2)	47 (36.4)