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AARO HEINONEN

Delayed Neurosurgical Consequences and Long-term Mortality After Head Injury

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To my lovely wife

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ABSTRACT

Traumatic brain injury (TBI) is a major health problem throughout the world. In addition to the acute effects of TBI, the long-term consequences of TBI are vast. This thesis focuses on two distinct complications of head injury—post-traumatic hydrocephalus (PTH) and chronic subdural hematoma (cSDH)—and on long-term survival and causes of death after head injury.

PTH has been acknowledged as a relatively common complication of head injury, especially for certain types of injuries. The incidence of PTH has varied greatly in prior studies, which is likely explained by differences in the study populations, applied diagnostic criteria, and individual study designs. Especially ventriculomegaly related to brain atrophy is a condition that can be incorrectly interpreted as PTH and thus can raise the incidence of PTH reported. The current literature is lacking research about the incidence of PTH requiring treatment.

cSDH is a frequent neurosurgical condition. The incidence is greatest among the elderly. Priorly, the condition has been considered directly trauma-related, but aging and brain degeneration have recently been highlighted as principal causative factors underlying the condition, and its purely traumatic etiology has been questioned. Although prior trauma is still widely accepted as a risk factor for this condition, little is known about the incidence of cSDH in individuals who have had normal initial head computed tomography (CT) after head injury.

Increased mortality in the acute phase of TBI is well established, and there is good evidence suggesting long-term mortality to be increased as well. While the reasons behind increased acute phase mortality are at least mostly intuitive, factors affecting long-term mortality are not well understood. It is not clear whether the reduced long-term survival of patients with head and brain injuries is due to trauma or some pre-existing factors of these patients.

The first objective of this study was to determine the incidence of surgically treated PTH in a consecutive series of adult patients undergoing acute head CT following head injury (n=1,941). The main outcome variable was specified as surgically treated post-traumatic hydrocephalus to rule out other conditions not requiring treatment.

The second objective was to determine the incidence of surgically treated cSDH in a consecutive series of adult patients with head injuries and normal initial head CTs. Of the 1,941 patients, 1,573 had normal initial head CTs. Patients were retrospectively followed from the hospital's patient medical records up to six months post-injury for the detection of PTH and cSDH.

The third objective was to compare survival and causes of death among patients with head injuries and matched population controls. Ten-year survival and causes of death were compared between a cohort of consecutive adult patients with head injuries (n=1,930) and matched population controls (n=9,605). Controls and mortality data for both patients and controls were obtained from a national registry (Statistics Finland, Tilastokeskus).

The incidence of surgically treated PTH was 0.15% (3 per 1,941) in the whole cohort during the six-month follow-up. The incidence was 0.08% (1 per 1,269) among patients with mild TBI and 1.1% (2 per 187) among those with moderate-to-severe TBI. All the patients who developed PTH were operated on during the initial hospitalization due to the head injury, and hence the incidence of PTH among patients who underwent neurosurgery for acute traumatic intracranial lesions was 2.7% (3 per 111). The three patients with surgically treated PTH had 2-, 5-, and 5-month delays between index injury and shunt surgery.

Two of the 1,573 patients with normal initial head CTs received surgical treatment for cSDH. Consequently, the incidence of surgically treated cSDH after normal initial head CT during the six-month follow-up was 0.13%. Both these patients had initially sustained mild TBIs. One of the two patients was on antithrombotic medication at the time of trauma; hence, the incidence of surgically treated cSDH among patients with antithrombotic medication in patients with normal initial head CT (n=376) was 0.27%. Both patients who developed surgically treated cSDH were elderly women (>70 years); hence, the incidence of cSDH in the age group of over 70 years old (n=506) was 0.40%. The time intervals from trauma to surgical treatment for the cSDH were seven and eight weeks.

After excluding those who died during the first year post-injury, the hazard ratio for death was 1.84 when comparing patients to controls. Death rates were higher among patients for up to five years following injury with a statistically significant difference. Analyses of specific causes of death revealed that unintentional and traumatic causes (9.6 versus 4.4%) and alcohol-related causes (8.4 versus 1.9%) differed significantly between groups, with predominance among patients. When comparing patients with different TBI severities to their matched controls, patients with no documented TBI also had reduced survival and TBI severity was associated

with additional increase in mortality risk. Patient characteristics, and not injury-related factors, were associated with elevated risk for death in a multivariate model containing only patients.

In conclusion, the incidence of surgically treated PTH among patients with traumatic head injuries of all severities was very low but not negligible, especially among patients who had undergone surgery because of the index head injury. The incidence of cSDH requiring treatment after head injury with normal initial head CT was extremely low, even in patients on antithrombotic medication, supporting the notion that routine follow-up imaging after an initial normal head CT is not indicated to exclude the development of cSDH. Long-term survival was reduced in patients with head injuries. A large part of the reduced survival was associated with patient characteristics rather than injury severity-related factors, but TBI severity seemed to have its own additional effect on mortality. Unintentional and traumatic causes, even after excluding the index injuries, and alcohol-related causes of death were more common among patients with head injuries compared to controls.

TIIVISTELMÄ

Traumaattinen aivovamma on merkittävä terveysongelma ympäri maailman. Aivovammaan liittyvien akuuttien ongelmien lisäksi siihen liittyvät pitkäaikaisongelmat ovat laajoja. Tässä väitöskirjassa tutkittiin kahta pään vammaan liittyvää komplikaatioita – vamman jälkeistä hydrokefalusta ja kroonista kovakalvonalaista verenpurkaumaa - sekä pitkäaikaiskuolleisuutta ja kuolemansyitä pään vamman jälkeen.

Vamman jälkeisen hydrokefaluksen on raportoitu olevan suhteellisen yleinen pään vammaan liittyvä komplikaatio, erityisesti tiettyjen vammatyyppien jälkeen. Sen ilmaantuvuus vaihtelee suuresti aiemmin julkaistuissa tutkimuksissa, mikä johtunee tutkimusväestöjen eroavaisuuksista, käytetyistä diagnostisista kriteereistä ja yksittäisten tutkimusasetelmien eroista. Erityisesti aivokammioiden suurentuminen, eli ventrikulomegalia, joka usein liittyy aivojen surkastumiseen, voidaan virheellisesti tulkita vamman jälkeiseksi hydrokefalukseksi, mikä voi nostaa tutkimuksissa raportoituja ilmaantuvuuslukuja. Todellisen, hoitoa vaativan vamman jälkeisen hydrokefaluksen ilmaantuvuudesta pään vamman saaneilla henkilöillä on vähän tietoa.

Krooninen kovakalvonalainen verenpurkauma on yleinen neurokirurginen sairaus, jonka ilmaantuvuus on suurinta iäkkäillä. Aiemmin tilaa on pidetty erityisesti pään vammasta johtuvana, mutta viime aikoina vanheneminen ja siihen liittyvä aivojen surkastuminen on tunnistettu keskeiseksi taustasyyksi. Samalla käsitys puhtaasti vammaan liittyvästä sairaudesta on kyseenalaistettu. Edeltävää pään vammaa pidetään kuitenkin edelleen merkittävänä riskitekijänä. Kroonisen kovakalvonalaisen verenpurkaman ilmaantuvuudesta pään vamman saaneilla potilailla, joilla päivystyksellisesti tehty pään tietokonetomografiakuvaus (TT) on ollut normaali, on vähän tietoa.

Lisääntynyt kuolleisuus heti aivovamman jälkeen on hyvin tunnistettu ja raportoitu aikaisemmissa tutkimuksissa. Lisäksi on näyttöä siitä, että aivovamman saaneilla myös pitkäaikaiskuolleisuus on lisääntynyt. Vaikka syyt korkeaan kuolleisuuteen aivovamman akuutissa vaiheessa ovat ainakin osin intuitiivisia, pitkäaikaiskuolleisuuteen vaikuttavat tekijät tunnetaan huonosti. On epäselvää, onko

lisääntyneen kuolleisuuden taustalla itse vamma vai jotkin potilaaseen liittyvät, vammaan liittymättömät tekijät.

Tutkimuksen ensimmäinen tavoite oli määrittää kirurgisesti hoidetun vamman jälkeisen hydrokefaluksen ilmaantuvuus pään vamman saaneilla aikuispotilailla, jotka kuvattiin päivystyksellisesti pään TT-kuvauksella (n=1 941). Päätulosmuuttujaksi määritettiin kirurgisesti hoidettu vamman jälkeinen hydrokefalus muiden hoitoa vaatimattomien tilojen poissulkemiseksi.

Tutkimuksen toinen tavoite oli määrittää kirurgisesti hoidetun kroonisen kovakalvonalaisen verenpurkauman ilmaantuvuus pään vamman saaneilla aikuispotilailla, joilla päivystyksellisessä pään TT-tutkimuksessa ei todettu akuutteja traumaattisia kallonsisäisiä muutoksia eikä löydöksiä kovakalvonalaisessa tilassa (TT-negatiivinen pään vamma). Kohortin 1 941 potilaasta 1 573 olivat TT-negatiivisia. Potilaita seurattiin takautuvasti sairaalan potilasasiakirjoista vamman jälkeisen hydrokefaluksen ja kroonisen kovakalvonalaisen verenpurkauman havaitsemiseksi kuuteen kuukauteen saakka vammasta.

Kolmas tavoite oli tutkia pään vamman saaneiden potilaiden pitkäaikaiskuolleisuutta. Kuolleisuutta ja kuolemansyitä verrattiin pään vamman saaneiden aikuispotilaiden (n=1 930) ja kaltaistettujen väestöverrokkien (n=9 605) välillä kymmenen vuoden seurannassa. Verrokkikohortti sekä kuolemaa koskevat tiedot potilaille ja verrokeille saatiin kansallisesta kuolemansyytilastosta (Tilastokeskus).

Kirurgisesti hoidetun vamman jälkeisen hydrokefaluksen ilmaantuvuus koko kohortissa oli 0,15 % (3 per 1 941) kuuden kuukauden seurannan aikana. Lievän aivovamman saaneiden keskuudessa ilmaantuvuus oli 0,08 % (1 per 1 269) ja keskivaikean tai vaikean aivovamman saaneiden keskuudessa 1,1 % (2 per 187). Kaikki kolme potilasta, joille kehittyi kirurgisesti hoidettava vamman jälkeinen hydrokefalus, tarvitsivat akuuttia neurokirurgista leikkaushoitoa alkuperäisen pään vamman vuoksi. Akuutissa vaiheessa leikattujen potilaiden vamman jälkeisen hydrokefaluksen ilmaantuvuus oli näin ollen 2,7 % (3 per 111). Vamman jälkeisen hydrokefaluksen vuoksi leikattujen kolmen potilaan aikavälit pään vamman ja leikkaushoidon välillä olivat 2, 5 ja 5 kuukautta.

Kaksi 1 573 TT-negatiivisesta potilaasta hoidettiin kirurgisesti kroonisen kovakalvonalaisen verenpurkauman vuoksi. Näin ollen kirurgisesti hoidetun kroonisen kovakalvonalaisen verenpurkauman ilmaantuvuus potilailla, joilla oli normaali TT-kuva, oli 0,13 % kuuden kuukauden seurannan aikana. Toinen potilaista käytti verenhyytymiseen vaikuttavaa lääkitystä vamman aikana, täten ilmaantuvuus verenhyytymiseen vaikuttavaa lääkitystä käyttävillä potilailla (n=376) oli 0,27 %.

Molemmat potilaat olivat yli 70-vuotta vanhoja ja näin ollen ilmaantuvuus yli 70-vuotiailla (n=506) oli 0,40 %. Kroonisen kovakalvonalaisen verenpurkauman vuoksi leikattujen kahden potilaan aikavälit pään vamman ja leikkaushoidon välillä olivat seitsemän ja kahdeksan viikkoa.

Kun suljettiin pois vamman jälkeisen ensimmäisen vuoden aikana kuolleet, kuoleman riskisuhde oli 1,84 verrattaessa potilaita heidän verrokkeihinsa. Kuolleisuus oli suurempaa potilailla viisi vuotta vamman jälkeen tilastollisesti merkitsevällä erolla. Kuolemansyistä tahattomat ja traumaattiset syyt (9,6 vs. 4,4 %) sekä alkoholiperäiset syyt (8,4 vs. 1,9 %) erosivat merkitsevästi potilaiden ja verrokkien välillä, ja potilailla nämä kuolemansyyt olivat yleisempiä. Kun potilaita verrattiin aivovamman vaikeusasteen mukaan heidän omiin verrokkeihinsa, kuolleisuus oli lisääntynyt myös potilailla, joilla ei todettu aivovammaa ja aivovamman vaikeus lisäsi edelleen kuolemanriskiä. Monimuuttujamallissa, joka sisälsi vain potilaita, potilaan ominaisuuksiin liittyvät muuttujat olivat yhteydessä kohonneeseen kuoleman riskiin, mutta vammaan vaikeuteen liittyvät tekijät eivät.

Yhteenvetona voidaan todeta, että hoitoa vaativan vamman jälkeisen hydrokefaluksen ilmaantuvuus pään vamman saaneilla potilailla vaikuttaa olevan pieni, mutta ei mitätön varsinkaan akuutissa vaiheessa pään vamman takia leikattujen potilaiden joukossa. Kirurgisesti hoidetun kroonisen kovakalvonalaisen verenpurkauman ilmaantuvuus potilailla, joilla vamman jälkeisessä TT-kuvassa ei todettu traumaattisia kallonsisäisiä muutoksia, oli erittäin pieni. Tämä tukee käsitystä, ettei näiden potilaiden rutiininomainen seurantakuvantaminen kroonisen kovakalvonalaisen verenpurkauman osalta ole perusteltua. Kuolleisuus oli suurempaa pään vamman saaneilla potilailla kuin heidän verrokeillaan ja vaikutti liittyvän paljolti potilaan ominaisuuksiin eikä vamman vaikeuteen liittyviin tekijöihin. Aivovamman vaikeudella näytti kuitenkin olevan oma kuolemanriskiä lisäävä vaikutus, kun potilaita verrattiin aivovamman vaikeuden mukaan heidän omiin verrokkeihinsa. Tahattomat ja traumaattiset syyt, myös indeksivammojen poissulkemisen jälkeen, sekä alkoholiperäiset syyt olivat yleisempiä potilaiden kuin verrokkien joukossa.

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ABBREVIATIONS

ASA	Acetylsalicylic acid
cSDH	Chronic subdural hematoma
CDE	Common Data Elements
CNS	Central nervous system
CSF	Cerebrospinal fluid
CI	Confidence interval
CT	Computed tomography
DAI	Diffuse axonal injury
DOAC	Direct oral anticoagulant
EDH	Epidural hematoma
ETV	Endoscopic third ventriculostomy
GCS	Glasgow Coma Scale
GLF	Ground-level fall
HR	Hazard ratio
ICH	Intracerebral hemorrhage
IQR	Interquartile range
LOC	Loss of consciousness
LPS	Lumboperitoneal shunt
MRI	Magnetic resonance imaging
OR	Odds ratio
PTA	Post-traumatic amnesia
PTH	Post-traumatic hydrocephalus
RNA	Ribonucleic acid
SAH	Subarachnoid hemorrhage
SDH	Subdural hematoma
SMR	Standardized mortality ratio
TBI	Traumatic brain injury
VAS	Ventriculoatrial shunt
VPS	Ventriculoperitoneal shunt
WHO	World Health Organization

ORIGINAL PUBLICATIONS

This thesis is based on the following three original publications, which are referred to in the text by their Roman numerals I-III. The publications have been reprinted with the permission of the copyright holders.

I Heinonen A, Rauhala M, Isokuortti H, Kataja A, Nikula M, Öhman J, Iverson GL, Luoto T. Incidence of surgically treated post-traumatic hydrocephalus 6 months following head injury in patients undergoing acute head computed tomography. Acta Neurochir (Wien). 2022 Sep;164(9):2357-2365. doi: 10.1007/s00701-022-05299-3.

II Heinonen A, Rauhala M, Isokuortti H, Raj R, Kataja A, Nikula M, Öhman J, Iverson GL, Luoto T. Incidence of surgically treated chronic subdural hematoma after head injury with normal initial computed tomography. Acta Neurochir (Wien). 2024 Mar 22;166(1):144. doi: 10.1007/s00701-024-06040-y.

III Heinonen A, Rauhala M, Isokuortti H, Raj R, Kataja A, Iverson GL, Huhtala H, Luoto T. Long-Term Mortality of Patients with Head Injuries – A Ten-year Follow-up Study with Population Controls. *Accepted for publication in Neurosurgery.*

The author of this thesis is the first author in all three publications. The first author contributed to each publication as follows.

I Statistical analyses, first manuscript draft, manuscript editing.

II Statistical analyses, first manuscript draft, manuscript editing.

III Study design, data collection, statistical analyses, first manuscript draft, manuscript editing.

1 INTRODUCTION

Traumatic brain injury (TBI) is a major public health problem throughout the world[1]. It is estimated that about half of the world's population will have one or more TBIs over their lifetime[2]. According to population-based studies, 50–60 million people worldwide are affected by a new TBI each year[3]. The great majority of the patients suffer mild TBI[2]. In addition to the acute effects of TBI, the long-term consequences of TBI are vast[4]. This dissertation focuses on two distinct complications of head injury, post-traumatic hydrocephalus (PTH) and chronic subdural hematoma (cSDH), and on long-term mortality after head injury.

PTH is a well-known complication of head injury[5]. The percentage of patients experiencing PTH in trauma cohorts varies greatly, and the broad range can be explained at least partly by differences in study populations and the applied diagnostic criteria for PTH used in different studies. Distinguishing between atrophy-related ventriculomegaly and true hydrocephalus has been especially challenging[6]. The overall occurrence of PTH varies from 0.7 to 51.4%[5], [7], [8], [9], [10] in all cohorts. The occurrence of surgically treated PTH has been reported to be considerably lower[9], [10].

cSDH is a frequently encountered condition across neurosurgical centers[11]. The condition is mainly a disease of the elderly[12]. The overall incidence of cSDH has been reported to range from 1.7 to 20.6/100,000/year[13], [14], [15], whereas reported incidence rates are 46–58/100,000/year in people over 65 years of age[12], [14], [16] and as high as 130/100,000/year in people aged 80 or older[12]. The etiology of cSDH has been a matter of discussion[17], [18]. Recently, aging and brain degeneration with sufficient potential subdural space has been highlighted as the principal causative factor underlying the condition[19]. However, head trauma is still considered to be an important factor in initiating pathological processes of hematoma formation[20]. Regarding this, little is known about the incidence of cSDH after head injuries with normal initial head computed tomography (CT). The prior literature consists mainly of case reports[21], [22], [23], [24], [25].

Increased long-term mortality after TBI has been well-identified in prior studies[26], [27], [28], [29], [30], [31], but the reasons for this finding are not

completely understood. It is thought that individuals who experience head and brain injuries have increased mortality risk at baseline due to pre-existing conditions and lifestyle factors, and that head injury causes an additional increase in mortality risk—a combination of those seen in mortality studies[29]. Additionally, causes of death have been found to differ between individuals with a history of TBI versus their controls without it[26]. Analogously to the decreased survival of TBI patients, it is not clear to what extent this is due to pre-existing conditions and lifestyle factors or the TBI itself. Several studies have reported increased risk for neurologic[26], [27], [29], psychiatric[26], [27], [28], [32], and external[27], [28], [30], [33], [34] causes of death after TBI. Additionally, risk for respiratory[27], [28], [35] (specifically pneumonia[26], [36], [37]) and circulatory[27], [28], [35] causes are reported to be elevated among individuals who have sustained TBIs. A limitation of some prior studies in considering long-term survival is the inclusion of the acute phase in mortality analyses[29], [30]. Inclusion of the acute phase certainly gives evidence of the overall survival after TBI but ignores whether the possible decreased survival is due to the acute effects of the primary trauma or some secondary long-term effects of it. Furthermore, not many studies have examined the difference between index trauma and secondary trauma when death is caused by an external cause. Most prior studies have obtained cause-of-death data from national registries, but this data does not undoubtedly reveal whether traumatic death is due to the index trauma or some secondary trauma irrelevant to the index TBI. Some former studies have acknowledged this problem and viewed death certificates to potentially reclassify death causes to avoid this potential misinterpretation[35], [36].

In this study, we collected and analyzed a cohort of 1,941 consecutive patients with head injuries (18 years and older) who were evaluated and CT-scanned in one Finnish university hospital's emergency department between August 2010 and July 2012. Incidences of surgically treated PTH and cSDH within six months post-injury were studied. Long-term survival and causes of death after head injury were examined at the ten-year follow-up. We compared the survival time and causes of death to those of matched (age, sex, place of residence) population controls. Mortality data was obtained from Statistic Finland (Tilastokeskus).

2 REVIEW OF THE LITERATURE

2.1 Traumatic Head and Brain Injury

2.1.1 Definition and Classification

TBI is broadly defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force[38]. The initial severity of TBI is conventionally classified as mild, moderate, or severe based on the level of consciousness, as measured with the Glasgow Coma Scale (GCS)[2]. The GCS assesses three parameters—eye opening, verbal response, and motor response—with global scores ranging from 3 to 15[39]. Classification by GCS is easy, and it has a strong correlation with morbidity and mortality at the severe end of the TBI spectrum[40]. In addition to the GCS, duration of loss of consciousness (LOC) and post-traumatic amnesia (PTA) are frequently used in severity classifications of TBI[3].

The definition of mild TBI has been a matter of discussion, as many different versions coexist in the literature. The definition recommended by the World Health Organization (WHO) in 2004 to standardize mild TBI research is quite commonly used[3]. By WHOs definition, mild TBI is an acute brain injury resulting from mechanical energy to the head from an external physical force. Criteria for clinical identification include (i) one or more of the following: confusion or disorientation, LOC for 30 minutes or less, PTA for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; and (ii) GCS score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. The definition specifies that these manifestations of mild TBI must not be due to drugs, alcohol, or medications; caused by other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries, or intubation); caused by other problems (e.g., psychological trauma, language barrier, or coexisting medical conditions); or caused by a penetrating craniocerebral injury.[41] The most recent diagnostic criteria for mild TBI were published by the American Congress of Rehabilitation Medicine in 2023[42]. Although principally

similar, these criteria are more detailed compared to the WHO definition and clearly address possible findings from neuroimaging and blood biomarkers among the criteria. This definition also includes the term "suspected" mild TBI, to be used when brain injury is suspected but diagnostic certainty is lowered by the subtlety of the clinical presentation, missing information, or confounding factors.

Moderate-to-severe TBI is defined as GCS under 13, LOC lasting 30 minutes or longer, or PTA 24 hours or greater[43]. Patients can be further classified has having moderate or severe TBI, based on GCS scores of 9 to 12 and 3 to 8, respectively[2]. According to some classifications, patients with LOC of 30 min to 24 h and PTA of 1 to 7 days are considered to have moderate TBI and patients with LOC over 24 h and PTA over 7 days severe[44].

Excluding the note in WHO's definition that mild TBI cannot be caused by a penetrating craniocerebral injury, the aforementioned severity classifications ignore the mechanistic heterogeneity of TBI. From a trivial head bump to a penetrating head injury, there are wide variations in the types and severities of TBIs. A range of pathological changes (e.g., diffuse axonal injury [DAI], contusion, brain swelling, and brain compression by extracerebral hematomas) that contribute in varying degrees to the clinical picture can be present. Classification into penetrating TBI and closed TBI is commonly used as the injury biomechanics are very different and the infection risk in penetrating TBI is higher.[2] Classification can also be done based on imaging (trauma findings or not), and some institutions use the term "mild complicated TBI" for patients who clinically meet the mild classification but have abnormal imaging findings[44].

2.1.2 Pathophysiology and Typical Lesions

2.1.2.1 Pathophysiology Overview

TBI is a heterogenous, dynamic pathophysiological process that starts from the moment of injury (primary effects) and develops over time, with sequalae (secondary effects) potentially seen after many years[45], [46]. Primary effects are caused mainly by two mechanisms: direct mechanical contact and acceleration–deceleration forces[47]. Primary effects of injury include intra-axial contusions, hematomas, parenchymal fractures, and DAI lesions, as well as extra-axial hematomas and bony fractures[45]. Focal injuries result from the direct contact of the trauma, whereas

multifocal injuries (e.g., DAI) result primarily from acceleration–deceleration forces[48]. The primary effects of TBI are considered irreversible[46].

The secondary effects of TBI are a diverse group of conditions caused by a series of pathophysiological reactions resulting from the initial injury. Secondary effects are associated with trauma-induced neurochemical alterations causing changes in cerebral blood flow, blood–brain barrier function, cerebral metabolism, ion homeostasis, and direct neurotoxic effects[48]. Secondary effects include brain swelling and edema, brain herniation syndromes, cranial nerve deficits, ischemia, inflammation, and infarction[45]. Hypoxia, cerebral hypoperfusion, and metabolic stress aggravate the secondary effects of TBI, and thus the acute management of TBI is targeted to prevent them[49]. Apoptotic mechanisms contribute to the overall pathology of TBI[46]. There is evidence that DAI causes neurodegeneration after TBI[50]. Neuronal loss over time may be a consequence of axonal trauma leading to progressive Wallerian degeneration[51] and/or proteinopathies[52]. Loss of neurons and abnormal proteinaceous accumulation are associated with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease[46]. This connection might explain the predisposition to neurodegenerative diseases after TBI seen in many studies[26], [27], [29]. Delayed effects of TBI include complications such as PTH[5] and cSDH[18], which are covered in detail later in the literature review.

2.1.2.2 Extra-axial Lesions

Extra-axial hematomas occur within the skull space but outside the brain parenchyma and are further classified into subarachnoid hemorrhage (SAH), subdural hematoma (SDH), epidural hematoma (EDH), and intraventricular hemorrhage[40], [53]. SAH is the most common extra-axial hemorrhage, followed by SDH and EDH, respectively[45]. SAH occurs within the subarachnoid space between the pia and the arachnoid mater[45]. It commonly occurs at the site of impact (coup) or opposite the site of impact (countercoup)[40]. SAH might result from direct laceration of the small cortical vessels, redistribution of intraventricular hemorrhage, or direct extension from cortical hematoma[54].

In turn, SDH occurs between the dura and arachnoid mater[40]. It is caused by a tearing of a surface or bridging vessel[55]. SDH can occur at either the coup or countercoup site, although the latter is more common[54]. The typical appearance in radiological examinations is a crescentic collection over the cerebral convexity. SDH can cross suture lines but not dural attachments[45]. SDH is commonly further divided into acute, subacute, and chronic based on the temporal profile of the

condition[56]. Chronic SDH is covered in detail later in the literature review. In addition, traumatic subdural collections include subdural hygroma caused by traumatic tears in the arachnoid membrane and resulting in cerebrospinal fluid accumulation in the subdural space[40]. It can develop into chronic SDH with time[57].

EDH occurs between the inner table of the skull and the superficial layer of the dura, and the typical shape seen in radiological examinations is lenticular. EDH does not typically cross suture lines as the superficial layer of the dura is tightly attached to the skull along the sutures[40]. EDH classically arises from the middle meningeal artery but can also be due to injury to other meningeal artery or venous structures[58]. EDH is almost always associated with an overlying skull fracture and typically occurs at the coup site[54].

Intraventricular hemorrhage can originate from trauma to subependymal veins, extension from an intraparenchymal hematoma, or retrograde redistribution from the subarachnoid space[40]. The prevalence of traumatic intraventricular hemorrhage in patients with TBI ranges from 0.4 to 22%, and higher rates are associated with more severe injuries[59]. Poor outcome is associated with intraventricular hemorrhage, although this is thought to be due to associated lesions rather than the presence of intraventricular hemorrhage alone[60].

2.1.2.3 Intra-axial Lesions

In contrast to extra-axial lesions, which are external to the brain parenchyma, intra-axial lesions occur within the brain substance. Brain contusions are the most common of the intra-axial lesions[45]. Contusions are hemorrhagic lesions of the brain parenchyma resulting from the impact of the brain against the osseous confines of the calvarium and/or the rigid falx cerebri and tentorium cerebelli[45]. They typically occur at characteristic locations at the coup and countercoup sites. The most common locations for brain contusions are the inferior frontal lobes and anterior–inferior temporal lobes, which may be due to the ridged morphology of the inner table of the skull.[40] Intracerebral hemorrhage (ICH) is differentiated from contusion as it predominantly consists of a collection of homogenous blood[61]. ICH occurs from injury to intraparenchymal arteries or veins. Typical sites include the fronto-temporal white matter and basal ganglia.[62] Differentiation of ICH from hemorrhagic contusion and DAI can be challenging, and some overlap between these entities is common[61], [62].

Diffuse axonal injury (DAI) is a frequent pathologic finding of severe head injury[63]. As well, it is a key feature of pathology following mild TBI[64]. DAI is caused by acceleration–deceleration forces occurring in a linear or rotational manner, which strain different parts of the brain apart and result in axonal injury and rupture[63]. Differences in tissue consistency and the degree of fixation between brain tissues account for the mechanism and location of DAI injury[63]. DAI lesions are most typically seen at white–gray matter junctions and in deep centroaxial white matter such as the corpus callosum, periventricular and hippocampal regions, cerebral peduncles, brachium conjunctivum, superior colliculi, and deep reticular formation[63].

2.1.3 Epidemiology

Traumatic brain injury (TBI) is a major public health problem throughout the world[1]. It is estimated that about half of the world's population will have one or more TBIs over their lifetime[2]. According to population-based studies, 50–60 million people worldwide are affected by a new TBI each year[3]. In the European Union, it is estimated that 1.5 million people are hospitalized and 57,000 people die due to TBI annually[65]. In the United States, there were approximately 64,000 TBI-related deaths in 2020[29]. A cross-sectional analysis across the European Union estimated that 259 years of life were lost (quantifies the number of years of life lost because a person dies prematurely due to a disease or injury) per 100,000 persons due to TBI in 2013. Extrapolated to the whole population of the European Union, the study suggested that about 1.3 million years of life were lost attributable to TBI in 2013[66]. The financial impacts of TBI are also vast, as estimates indicate the annual worldwide economic burden of TBI to be 400 billion US dollars, comprising about 0.5% of the gross world product[67].

Brazinova et al. reported the annual incidence of TBI (all severities) in Europe to range from 47.3 to 849 per 100,000 in their living systematic review in 2021[68]. They found no notable change in mean incidence rate compared to the previous systematic review of TBI incidence in Europe published by Tagliaferri et al. in 2006[69]. A review of population-based studies in the United States published in 2003 reported the annual incidence of TBI to be 180 to 250 per 100,000[70]. A population-based study from New Zealand published in 2013 reported a considerably higher total TBI incidence of 790 per 100,000 person-years[71]. The great majority of the patients suffer from mild TBI[2]. Although the percentages of

patients with different TBI severities vary between study populations, it is estimated that mild TBI accounts for 80–90% of all cases of TBI in both civilian and military populations[72].

The highest incidence rates are observed among young children, young adults, and older adults[73]. According to the surveillance report published by the Centers for Disease Control and Prevention, rates of TBI-related emergency department visits in the United States were highest among those aged ≥75 years (1,682/100,000), 0–4 years (1,612/100,000), and 15–24 years (1,010/100,000) in 2014[74]. Epidemiological studies of TBI consistently report higher incidences among men[75]. Brazinova et al. reported the proportion of males in TBI incidence studies to range from 55 to 80%[68]. The predominance is often explained by the higher propensity of men to be involved in physical altercations, military service, and contact sports—activities that pose a risk for injury[75]. More frequent use of alcohol among men likely increases the male predominance[76], [77]. The proportion of men seems to decease with age[78].

Leading causes of TBI include unintentional falls, being unintentionally struck by or against an object, motor vehicle injuries, and intentional self-harm[29], [74], [79]. During 2014 in the United States, the three most common mechanisms of injury were unintentional falls, being unintentionally struck by or against an object, and motor vehicle injuries, accounting for 48%, 17%, and 13%, respectively, of all TBI-related emergency department visits[74]. The highest proportion of fall-related TBIs are seen in young children and in the elderly, whereas motor vehicle and traffic injuries are highest among young adults[73]. A changing pattern of injury mechanisms over time has been observed: the number of TBIs occurring in traffic accidents has reduced and, conversely, the contribution of falls has become relatively grater in recent studies[68], [80]. These changes may relate to improved road infrastructure and traffic discipline that could explain declining traffic-related TBI incidence, as well as the demographic trend of population aging[68].

Estimates of TBI incidence are susceptible to diagnostic and selection biases[81]. Differences in applied diagnostic criteria and study samples pose a risk of biases. There is good evidence that, in many studies, the incidence of TBI is underestimated as only a small portion of cases are admitted to the hospital[81]. Additionally, it is possible that milder forms of TBI are under-diagnosed when a patient is admitted to the hospital with multiple traumas or other injuries in addition to TBI[68]. The predominance of men may still be an underestimation as men are likely more reluctant to seek medical attention after injuries[82]. Moreover, there is evidence that the proportion of females affected by TBI might be underestimated due to failure to

report or seek medical attention for injuries resulting from intimate partner violence, but this observation needs further validation[75].

2.1.4 Diagnosis and Imaging

TBI is suspected based on patient history and possible signs and symptoms of TBI. Imaging is integral to the management of patients with TBIs as it can provide rapid assessment of primary damage, reveal potentially preventable secondary effects of trauma, and provide markers that may help to predict outcome[45]. Computed tomography (CT) and magnetic resonance imaging (MRI) are the principal imaging modalities[54], [61].

Head CT is the primary imaging modality for initial assessment in patients who are suspected to suffer from TBI. It rapidly shows if there are space-occupying lesions that are feasible surgical candidates[2]. In addition, CT readily identifies the progression of hemorrhage and signs of secondary injury relevant to neurocritical care, such as cerebral swelling, herniation, and hydrocephalus[54]. CT also has a high sensitivity for detecting bony fractures[40]. In turn, CT has worse diagnostic sensitivity for certain types of lesions, including cortical contusions and nonhemorrahagic traumatic axonal injuries, in contrast to MRI[54]. DAI can be suspected from CT by the presence of tiny hyperdense foci that represent the microhemorrhages that often accompany axonal damage[45]. However, CT's overall sensitivity for DAI is poor, and MRI should be performed if DAI is suspected[45].

MRI detects lesions that may explain clinical symptoms that remain unresolved after initial CT[45]. It provides greater sensitivity than CT for parenchymal lesions, especially in the posterior fossa, brain stem, and superficial cortical areas[2]. Special MRI sequences, diffusion tensor imaging and susceptibility-weighted imaging, are particularly sensitive for the detection of DAI[2]. However, the use of MRI is limited by access, feasibility with patient monitoring and potential instability, long acquisition time, and degradation by motion artifacts[45]. In the future, MRI might become more useful in the acute setting as imaging times become shorter[83]. Special fast MRI protocols have already been proven to be feasible alternatives to CT in acute settings for pediatric populations[84], [85].

Blood biomarkers have been extensively studied as a novel diagnostic method for TBI. However, due to the heterogenous nature of TBI etiology, lesion types, and clinical course, current biomarkers have several limitations in the clinical setting[86]. Several different molecules corresponding to different pathologic processes have

been studied[86]. Neuron-specific enolase and ubiquitin C-terminal hydrolase-L1 are neuronal cytoplasmic enzymes, and extracellular presentation of these enzymes indicates neuron cell injury[87]. S100B protein and glial fibrillary acidic protein are indicators of glial cell injury, and neurofilament proteins, myelin basic protein, and tau protein indicate axonal injury[86]. In addition, inflammation-mediated biomarkers[88], extracellular vesicles[89], and microRNA[90] are being studied for the detection and prognostic evaluation of TBI. To date, S100B is the only biomarker with a role in clinical decision making. The Scandinavian Neurotrauma Committee include this biomarker in their guidelines for initial management of minimal, mild, and moderate head injuries to assess the need for CT[91].

2.2 Post-traumatic Hydrocephalus

2.2.1 Pathophysiology

Head injury can cause a disruption to the normal dynamic balance between cerebrospinal fluid (CSF) production and absorption, resulting in hydrocephalus by different mechanisms. As with other types of hydrocephalus, PTH can be roughly categorized as communicating or non-communicating (obstructive) to characterize the etiology and type of the condition. In communicating hydrocephalus, the flow of CSF is free between the different parts of ventricular system, whereas in non-communicating hydrocephalus the CSF flow is blocked from passing between the ventricles or exiting the ventricular system.[92]

According to the traditional hypothesis, CSF is produced by the ependymal cells and the choroid plexuses in the ventricles; it circulates between the ventricles, cisterns, and subarachnoid space and drains into the venous system by arachnoid granulations[93]. Recent studies have challenged this traditional view, stating that CSF is mainly produced and reabsorbed by bidirectional fluid exchange across the walls of blood capillaries in the central nervous system (CNS)[94]. Recent studies have also suggested that CSF dynamics are affected by pulsatile movements derived from cardiac and respiratory pressure pulsations throughout the brain that increase the fluid interchange among interstitial space, blood, and CSF[93]. Earlier evidence has suggested that CSF absorption is pressure-dependent, as arachnoid granulations appear to function as unidirectional valves draining the CSF[95]. Astrocytes, aquaporins, and other membrane transporters might have important roles in the

maintenance of CSF homeostasis as well[96]. To conclude, there is evidence that CSF dynamics are much more complex than was previously suggested with the concept of unidirectional CSF flow.

Obstructive PTH, involving disruption of normal CSF dynamics, can result from obstructive effects caused by traumatic intraventricular hemorrhage, subarachnoid hemorrhage, or space-occupying lesions with associated mass effect[97]. Communicating PTH, on the other hand, can be explained by adhesions and scars resulting from trauma, which consequently reduce intracranial compliance and cause obstruction of the basal cisterns[98].

2.2.2 Incidence

The percentages of patients experiencing PTH in trauma cohorts varies greatly. The broad range can be at least partly explained by differences in study populations and the applied diagnostic criteria for PTH used in different studies. To date, no universal criteria for PTH have been established[99]. Ventriculomegaly after severe TBI is a relatively common finding[9]. Distinguishing true PTH from atrophy (e.g., hydrocephalus *ex vacuo*) can be challenging[100]. The overall occurrence of PTH varies from 0.7 to 51.4%[5], [7], [8], [9], [10] in all cohorts, whereas the incidence of ventriculomegaly after head injury has been reported to be as high as 30–86%[101]. A recent Taiwanese study with a large retrospective cohort (n=23,775) reported a PTH incidence of 0.48% for patients without traumatic SAH and 1.98% for patients with traumatic SAH[7]. That study included patients with all TBI severities. The occurrence of surgically treated PTH after more severe head injury is reported to be 3.5[10]–11%[9]. The percentages of patients experiencing PTH after decompressive craniectomy due to head injury is 26–30% in previous studies[102], [103], [104].

2.2.3 Risk Factors

The main risk factors for PTH are decompressive craniectomy[105], [106] and SAH[7]. Regarding decompressive craniectomy, proximity of the craniotomy to the skull midline[8], [107], delayed cranioplasty[93], and the presence of subdural hygroma after craniectomy[108] might be additional predisposing factors for PTH. Decompressive craniectomy transforms the cranial vault from a closed compartment to an open system, resulting in the loss of pulsatile CSF dynamics. This disruption of pressure-dependent CSF absorption has been highlighted as one of the

mechanisms responsible for decompressive craniectomy's being a risk factor for PTH[93], [109]. Inflammation-mediated scars and adhesions related to intracranial hemorrhages, trauma, and meningitis can explain the predisposition to PTH[98], [110]. Other possible risk factors for PTH are increased age and younger age, longer duration of coma post-injury, CSF infection, and intraventricular hemorrhage[8], [9], [106], [111].

2.2.4 Clinical Presentation

Clinical signs and symptoms of PTH include headache, nausea, cognitive dysfunction, ataxia, obtundation, and the tetrad of psychomotor retardation, memory loss, gait trouble, and urinary incontinence[112], [113]. Atypical symptoms such as emotional disorder have been reported as well[113]. The clinical signs and symptoms of PTH can overlap with those of the primary injury, which can make the recognition of PTH difficult[7]. A classic clinical feature for suspecting PTH is poor improvement or stagnation of recovery from the primary head injury [7], [92].

2.2.5 Diagnosis and Imaging

Various criteria for PTH diagnosis have been suggested but no universal criteria have been established[99]. In the clinical setting, PTH is diagnosed based on the combination of clinical signs and symptoms of PTH, as well as radiological findings of ventricular enlargement occurring within a reasonable period of time post-injury[114].

The main imaging modalities for PTH are CT and MRI[115]. Both modalities reliably show the typical manifestation, as well as the prerequisite for PTH, the progressive ventricular enlargement[115]. Evan's Index (the ratio of maximum width of the frontal horns of the lateral ventricles to maximal internal diameter of the skull at the same level) is used to evaluate ventricular enlargement. Values above 0.3 are considered abnormally large. Other typical signs of hydrocephalus are enlargement of the frontal angle of the lateral ventricle, enlargement of the temporal horn, and rounding of the third ventricle.[116]

New examination methods might help improve the diagnosis of PTH when the diagnosis is unclear based on clinical assessment and routine radiological findings. Future applications of diffusion tensor imaging might be useful in distinguishing true hydrocephalus from ventriculomegaly[6]. Additionally, studies of CSF

dynamics[100], [117], [118] have shown that parameters such as resistance to CSF outflow and pulse amplitude of intracranial pressure might be useful in selecting patients with PTH who may benefit from ventriculoperitoneal shunting[6]. Blood-based biomarkers (e.g., S100B)[119] also show promise for predicting the development of PTH. Chen et al.[120] have introduced a risk-scoring system based on clinical characteristics to predict PTH after TBI, with promising results.

2.2.6 Management and Treatment

The principal treatment for PTH is CSF diversion by shunt surgery[121]. Techniques for this include ventriculoperitoneal shunt (VPS), ventriculoatrial shunt (VAS), and lumboperitoneal shunt (LPS), among which VPS remains the primary treatment option for most cases[116], [121]. An additional treatment option is endoscopic third ventriculostomy (ETV)[116]. Selection of the optimal technique is based on patient characteristics and the type of hydrocephalus[116]. Early recognition of PTH is essential in the follow-up of patients with TBI, as CSF diversion has been shown to improve outcomes during rehabilitation[97], [122].

VPS is a technique in which excess CSF is drained from the lateral ventricles into the peritoneal cavity[116]. When diverting the CSF to the peritoneal cavity is contraindicated, alternative shunting spaces can be used[123]. In VAS technique, the distal end of the shunt is placed into the right atrium and the proximal placement is the same as in VPN[124]. In LPS technique, the excess CSF is diverted from the spinal canal in the lumbar region of the spine into the peritoneal cavity[125]. Predicting whether a patient will benefit from CSF diversion is not always clear[101]. Studies on CSF dynamics[6], [100], [117], [118], [126] have shown that parameters such as resistance to CSF outflow and pulse amplitude of intracranial pressure might be useful in selecting patients with PTH who may benefit from ventriculoperitoneal shunting. Wang et al. introduced a scoring system with high sensitivity that could predict shunt responsiveness in PTH patients with consciousness disturbance[127]. This might be a useful method to estimate the benefit of shunt surgery in such patients.

In the future, ETV might be a useful treatment option for PTH, even though this intervention has been contraindicated for PTH in the past[128], [129]. In ETV, CSF drainage into the basal cisterns is permitted in an endoscopic procedure during which an opening is made in the floor of the third ventricle[130]. In obstructive hydrocephalus, the goal of this treatment is to bypass the obstruction, and there is

recent evidence that ETV might be a favorable treatment option in communicating hydrocephalus as well. It is hypothesized that, by working as an "internal shunt," it may restore intracranial compliance by reducing CSF stagnation in the ventricular system[98], [121].

Drug therapy is not commonly used for the management of PTH. Available drug therapies are limited for short-term management. Medications that have been considered with the goal of reducing intracranial pressure include dehydrating agents (mannitol), diuretics (furosemide, acetazolamide), and corticosteroids (dexamethasone)[116].

2.3 Chronic Subdural Hematoma

2.3.1 Pathophysiology

There remain uncertainties relating to the etiology of cSDH. In 1857, Virchow[17] described the condition as "pachymeningitis hemorrhagica chronica interna," and at that time this inflammation theory was widely accepted. Subsequently, a traumatic etiology[18] has been emphasized. In particular, trauma to the bridging veins of the cerebral cortex was believed to be the origin of bleeding. More complex etiology has been proposed in recent years, although prior trauma has still been considered the main causative factor[20]. cSDH is hypothesized to form in part by an inflammatory process originating from trauma to the dural border cells. Inflammatory cells attempt to repair the border cell damage but instead cause membrane and blood vessel formation in the affected subdural region. These fragile and permeable neovessels bleed, resulting in fluid accumulation in the subdural space. The fluid accumulation maintains the inflammatory processes and further promotes the growth of the hematoma, which eventually causes the clinical signs and symptoms of cSDH.[131] Spontaneous *de novo* formation with no preceding trauma has been identified, challenging the purely traumatic etiology of cSDH[19]. Moreover, cSDH can modulate from subdural hygroma or acute subdural hematoma[19]. Recently, aging and brain degeneration with sufficient potential subdural space have been highlighted as principal causative factors underlying the condition[19].

2.3.2 Incidence

The incidence of cSDH is shown to increase drastically with age[12]. The overall incidence of cSDH has been reported to range from 1.7 to 20.6/100,000/year[13], [14], [15]. The reported incidence rates are 46–58/100,000/year in people over 65 years of age[12], [14], [16] and 130/100,000/year in people aged 80 or older[12].

An increasing trend in the incidence of cSDH has been observed[132]. Presumably, the incidence has risen because some of the main risk factors of cSDH, including increased age and use of antithrombotic medications, have become more prevalent[12]. Additionally, increased availability of CT scanners and improved awareness of the condition itself have been hypothesized as factors contributing to the increased incidence[133].

There is limited research on the development of cSDH after head traumas with normal initial CT scans. The only study examining consecutive CT-scanned patients after head trauma has been published recently by a Japanese group. Karibe et al. examined cSDH formation after mild head trauma in elderly (>65 years) Japanese patients. Among patients with normal initial CT scans (n=322), surgically treated cSDH was diagnosed in 4.3% of patients at more than one month after injury[24]. The rest of the current literature on the development of cSDH after normal initial CT scan consists of case reports. Chia et al. reported a case of an 84-year-old man with a normal initial CT scan after minor head injury, who developed symptomatic cSDH after two months[21]. The patient was not on antithrombotic medication at the time of injury. Deitch et al. reported on two patients with normal initial CT scans after minor head injuries and the development of cSDH after several weeks[22]. Their use of antithrombotic medication was not documented. Snoye et al. published a case report of three patients suffering minor head injuries with normal initial head CT scans, who developed cSDH in a mean time of seven weeks[23]. Their use of antithrombotic medication was not documented. Kim et al. published a case report of an 82-year-old man with normal initial CT and MRI scans after a mild head injury, who was diagnosed with a cSDH after five weeks[25]. The patient was not on antithrombotic medication at the time of injury.

In conclusion, the overall incidence of cSDH is well-reported. However, a literature gap exists in this specific group of patients with normal initial CT scans after head injury.

2.3.3 Risk Factors

cSDH mainly affects the elderly, whereas its incidence among younger adults is minute[134]. This difference is usually explained by age-related brain degeneration and consequent atrophy, which widen the subdural space and allow formation of the subdural collection[19], [135]. In addition, the more prevalent use of antithrombotic medication and the propensity to falling among the elderly have been introduced as potential contributing factors[12].

In addition to atrophy, head trauma is considered another major risk factor for cSDH[136]. In traumatic cSDH, trauma to the dural border cells is considered the starting point of hematoma formation[131]. Preceding head traumas have been reported in 57–76% of cSDH patients[137]. Even minor head injury is considered a risk factor for cSDH[138].

Male gender has been consistently reported as a risk factor for cSDH[132]. cSDH affects predominantly males, with a 3:1 male-to-female ratio across all age groups[138]. Causes for this predominance might be related to the predisposition to head traumas[137] and more frequent chronic alcohol consumption among men[12]. Gender differences in cranial size and morphology[139] and the vasoprotective effects of estrogen in women[140] have been proposed as potential factors explaining the male predominance as well.

Medications affecting blood clotting[141] and other coagulopathic states[136] have been identified as major risk factors for cSDH. A large Danish case-control study with 10,010 cases compared the risk of cSDH for different antithrombotic medications[141]. The adjusted odds ratios (ORs) with confidence intervals (CIs) for different antithrombotics were reported as follows: acetylsalicylic acid (ASA; adjusted OR 1.24; 95% CI 1.15–1.33), clopidogrel (adjusted OR 1.87; 95% CI 1.57–2.24), a direct oral anticoagulant (DOAC; adjusted OR 1.73; 95% CI 1.31–2.28), and warfarin (adjusted OR 3.69; 95% CI, 3.38–4.03). The risk for cSDH was highest when a combination of warfarin and antiplatelet drug was used (warfarin and ASA [adjusted OR 4.00; 95% CI 3.40–4.70], warfarin and clopidogrel [adjusted OR 7.93; 95% CI 4.49–14.02]). An association between cSDH and antithrombotic medication has been reported in the absence of trauma as well[142], [143]. In addition to antithrombotic medication, coagulation disorders have been identified as factors increasing the risk for cSDH[137]. Medical conditions affecting blood coagulation include renal dialysis, sepsis, and hepatic failure[137].

Another widely accepted risk factor for cSDH is chronic alcohol consumption[137], which induces brain atrophy and coagulation dysfunction and increases the risk of head trauma[136].

2.3.4 Clinical Presentation

cSDH can cause various symptoms, and symptom onset and progression can vary from days to weeks[138]. Frequently reported symptoms of cSDH include gait disturbance and recurrent falls, limb weakness, speech impairment, cognitive dysfunction, acute confusion, vomiting, and headaches[134], [144]. Occasionally, presentation can mimic stroke or rapidly progressive dementia, inspiring the name the "great imitator"[138]. Patients with cSDH usually present with a good level of consciousness[145], although cSDH may lead to alterations in mental status and even unconsciousness[146].

The clinical presentation of cSDH is affected by age[147]. Symptoms of increased intracranial pressure (e.g., headache, papilledema, and vomiting) are reported more among younger adults, whereas hemispheric symptoms (e.g., motor and sensory symptoms) are more frequent among older adults[147]. These differences in symptoms are likely explained by age-related brain atrophy[134]. In older patients, atrophy allows hematomas to grow sufficiently large to cause external compression of the hemisphere, resulting in sensorimotor symptoms without necessarily causing increased intracranial pressure. In younger patients with no brain atrophy, smaller hematomas can cause symptoms of increased intracranial pressure before neurological deficits occur[134], [147].

2.3.5 Diagnosis and Imaging

cSDH is suspected based on the patient's history and the possible neurological signs and symptoms of the condition. The main diagnostic tool for cSDH is head CT[18]. A primarily hypodense crescentic collection along the convexity of skull is seen in CT and can be accompanied with isodense and hyperdense components[138]. Secondary signs of cSDH include midline displacement, decreased ventricle size, ipsilateral ventricle compression, contralateral ventricle dilatation, and cortical sulci effacement[148].

Isodense subdural hematoma may pose a diagnostic challenge. Medial displacement of the gray–white matter interface and failure of the convexity sulci to

reach the inner table of the skull might help to diagnose the condition in these cases[138]. MRI is not routinely used for the detection of cSDH and is usually performed when other conditions are suspected[138]. Subdural pathologies that may mimic subdural hematoma include lymphoma, metastasis, sarcoma, and infectious and autoimmune pathologies. MRI is indicated if one these conditions is suspected[149].

2.3.6 Management and Treatment

The natural history of cSDH is not fully understood[150]. While cSDH can resolve spontaneously[151], no clear clinical or radiological signs have been identified to indicate whether it will resolve spontaneously or not[150]. Conservative treatment can be applied for patients with no or minor symptoms, through careful observation[152]. For symptomatic patients or hematomas exerting significant mass effects, surgical evacuation is the mainstay of management[138].

Burr hole craniostomy with subsequent draining is the most frequently used surgical technique for cSDH[152]. For a minority of cases, craniotomy or twist drill craniostomy is performed[153]. The size of the skull opening varies between techniques. The diameter of the opening is usually less than 5 mm for twist drill craniostomy and 5–30 mm for burr hole craniostomy, while craniotomy involves larger openings[144]. Twist drill craniostomy can be performed bedside, thus it represents a treatment option for patients at high surgical risk[154]. In a meta-analysis of 34,829 patients, the twist drill and burr hole craniostomy techniques were found to have no significant differences in mortality, morbidity, cure, or recurrence rates[133]. In the same study, craniotomy was associated with higher complication rates but was superior to minimally invasive techniques in the management of recurrences. Surgical treatment of symptomatic cSDH results in rapid improvement of symptoms and produces favorable outcomes in over 80% of the patients[138].

Middle meningeal artery embolization has emerged as an effective treatment for cSDH[155]. By preventing the blood supply to the neomembranes from the middle meningeal artery, the repetitive cycle of bleeding and inflammation can be stopped[155]. It has shown promise as a viable primary treatment option, a complementary treatment to surgical intervention, and a rescue therapy for recurrent hematomas[156]. In Finland, this treatment option is currently mainly preserved for management of recurring recurrences[157].

Conservative treatment includes the so-called "wait and watch" or "wait and scan" management practices of cSDH in patients with no or minor symptoms[150]. Drug therapies have been attempted to develop based on the identified roles of inflammation and angiogenesis in cSDH development. Corticosteroids[158], etizolam (a benzodiazepine analog that antagonizes platelet-activating factor receptors)[159], tranexamic acid[160], angiotensin-converting enzyme[161], and atorvastatin[162] have been studied as potential drugs, alone or adjuvant to surgery, in the treatment of cSDH. Given the lack of evidence, none of these therapies have been established in clinical practice. Recent randomized controlled trials did not show promise for the use of corticosteroids[163], [164] or angiotensin-converting enzyme (perindopril)[165] in the management of cSDH.

Correction of coagulopathy and thrombopathy is crucial for amending the conservative treatment or to reduce the risk of bleeding during operative intervention and to minimize recurrence[166]. Correction includes cessation of antithrombotic medication and possible additional therapy, depending on the medication in use and the time available for correction[138].

2.4 Mortality After Traumatic Brain Injury

2.4.1 Acute Phase Mortality

TBI is the leading cause of injury-related deaths in the developed countries[167]. Considering all traumas, much of the injury-related mortality occurs in the acute phases[168]. This is true with TBI as well, as it is well established that mortality in the acute phases (hours to months) of TBI is substantially increased[29].

Mortality increases significantly with trauma severity. In a study of 8,717 patients, patients were divided into four groups by trauma severity (moderate, serious, severe, critical). In-hospital mortality was 1.3% among patients with moderate TBI and 5.7%, 8.7%, and 52.0% among patients with serious, severe, and critical TBI, respectively[79]. Similar associations between TBI severity and decreased acute phase survival have been reported in other studies[169]. In the previous study, mortality also varied by the cause of injury: over half of the subjects (51.2%, 86 of 168) with gunshot wounds died in the hospital, as compared with 10.9% (304 of 2,782) of subjects involved in motor vehicle crashes, 13.2% (381 of 2,888) of subjects experiencing falls, and 4.1% (33 of 798) of subjects with blows to the head[79]. This

is likely explained by associations with certain trauma mechanisms and trauma severity. Additional risk factors that are recognized for acute phase mortality are the presence of comorbidities and older age[169] as well as concomitant trauma and treatment received[170].

To exclude the acute effects of TBI on mortality, some studies have examined the acute and long-term phases separately, with varying time cut-off points from six months to two years to distinguish these two phases[28], [33], [35], [171], [172]. No distinct explanations have been provided for the use of these specific time points in the referred studies.

2.4.2 Long-term Mortality

2.4.2.1 Excess Mortality

Increased long-term mortality after TBI has been well-identified in prior studies, but the reasons for this finding are not completely understood. It is thought that individuals who experience head and brain injuries have increased mortality risk at baseline and that head and brain injuries cause an additional increase in mortality risk—a combination of those seen in mortality studies.[29] Additionally, decreased long-term survival has been acknowledged across trauma patients, not just among individuals who have experienced head injuries[168]. As long-term mortality risk is elevated even in patients with mild head injuries, it has been suggested that factors other than the traumatic injury, such as pre-existing conditions and lifestyle factors, may be causal factors for both TBI and cause of death in many cases[31]. For example, substance abuse or neurodegenerative condition can pose a risk for TBI and later cause death by a mechanism irrelevant to the TBI. A limitation of some of the previous research is the inclusion of the acute phase (hours to months) of TBI in the survival analyses[29]. This is important to notice as the majority of deaths occur in the acute phases of injuries[168]. Inclusion of the acute phase certainly gives evidence about the overall survival after TBI but ignores whether the possible decreased survival is due to the acute effects of the primary trauma or to some secondary long-term effects of it.

A population-based study from the United States published in 2010 by Ventura et al. compared mortality of their cohort of 18,998 TBI patients (all severities) to population mortality rates. The observed risk of death among TBI patients was 2.5 times the expected risk of those in the general population, and the reduction in life

expectancy was around six years. The median follow-up time was 4.4 years and the excess in mortality lessened as time from the injury increased. For those who survived one year after trauma, the excess in mortality dropped to less than twice the expected risk (standardized mortality ratio [SMR] 1.7, 95% CI 1.6–1.9)[26]. A recent study published in 2023 by Elser et al. examined mortality after head injury in a cohort setting of 2,402 cases and 10,635 controls. In addition to the cases recruited based on data from emergency department visits and inpatient hospitalizations, they included patients with self-reported head injuries, although most cases were diagnosed by a health care professional (only 12% of all cases were identified via self-report alone). The hazard ratio (HR) for all-cause mortality among individuals with head injuries was 2.0 (95% CI, 1.9–2.1) compared with those with no head injury. They found a dose-dependent association with head injury frequency (one head injury: HR, 1.7 [95% CI, 1.6–1.8]; two or more head injuries: HR, 2.1 [95% CI, 1.9–2.4]) and severity (mild: HR, 2.2 [95% CI, 2.0–2.3]; moderate, severe, or penetrating: HR, 2.9 [95% CI, 2.6–3.2]). Median follow-up time was 27 years (interquartile range [IQR] 18-31), though follow-up started from enrollment in the study, not from the time of injury. Among individuals with head injuries, the median time from enrollment to first injury was 17 years (IQR, 7.5–23).[29] Elser et al. did not exclude the acute phase from the analyses.

A study performed in the UK and published in 2011 by McMillan et al. (cohort of 767 TBIs admitted to hospital) found substantially elevated death rates compared to the general population and other-injury controls (7- and 1.6-fold, respectively) one year after trauma[28]. Rates were attenuated after one year but remained markedly elevated during rest of the follow-up (13 years), with 2.3- and 1.4-fold death rates compared to general population and other-injury controls, respectively. McMillan et al. did not find association between head injury severity and survival beyond the first year after injury: even in individuals with mild TBI, the death rate was more than twice as high as in community controls[28].

Vaaramo et al. (2015) found that even patients with minimal head injury without TBI (737 head injuries, from which 323 were without TBI) were at increased risk for both death from all causes (HR 2.0, 95% CI 1.6–2.6) and intentional or unintentional traumatic death (HR 4.0, 95% CI 2.2–7.3), as compared with general population controls in a case-control study with 15-year follow-up[30]. The results suggest that much of the increased mortality risk could result from pre-existing factors rather than trivial head injury. A limitation to this study was that the researchers could not compare head trauma subjects and controls in terms of lifestyle factors or

comorbidities, as they lacked this information among controls. Additionally, the acute phase was not excluded in this study.

A population-based study of 1,448 TBIs (164 moderate-to-severe and 1,284 mild) by Brown et al. (2004) did not find increased mortality after mild or moderate-to-severe TBI among those who survived six months after trauma, although there was a significant reduction in long-term survival when the first six months were included[173]. Another study published by Brown et al. (2014) examined mortality in a population-based cohort study with special control group[171]. The cohort included 1,257 TBIs, and the mean follow-up was 11 years. Brown et al. compared mortality of the cases to matched population controls and a special subgroup of cases with accompanying non-head injuries (n=221) to control participants with similar non-head injuries. The comparison was performed in two time frames: from baseline to six months and from six months to the study's end. An increased mortality risk was found in individuals with TBI compared with matched population controls in both time frames (HRs for risk of death 11 [95% CI 2.9–41] and 1.4 [95% CI 1.1–2.2], respectively). Among individuals with accompanying non-head injury, the risk for death was elevated in the acute phase but not statistically significantly after six months (HR 7.1 [95% CI 3.1–16] and 1.05 [95% CI 0.80–1.4], respectively). A limitation to this study was the relatively small size of the subgroup. The study highlights that much of the increased mortality occurs in the acute phases after trauma and that pre-existing factors may explain much of the increased long-term mortality of TBI patients.[171] In a sequel study, the authors stated that TBI is associated with higher mortality rates only during the first six months after injury, and that the increased risk for death is due to external causes. The conclusion was based on the fact that deaths due to external causes accounted for the greatest proportion of case deaths and were significantly greater than for matched controls. Further, when the special subgroup of cases with accompanying non-head injuries was compared with their controls, the proportion of deaths due to external causes was significantly different from the referents only during the first six months after injury[34].

Groswasser et al. (2018) reported the survival of patients with mild TBI to be similar to the general population for those who survived two years post-injury, whereas life expectancy was shorter among patients with moderate or severe TBI[172]. This study was greatly limited by its size, having 279 individuals of whom only 32 died during the follow-up. Instead, in a large population-based Swedish study published by Fazel et. al in 2014 (n=218,300), mortality risk after TBI remained substantially increased after six months. Among all severities, for those who survived

six months, odds of mortality were 3.2 (95% CI 3.0–3.4) compared to matched general population controls (adjusted for sociodemographic confounders) and 2.6 (95% CI 2.3–2.8) compared to unaffected siblings. Among individuals with mild TBI (concussion), rates were 2.2 (95% CI 2.1–2.3) for men and 2.0 (95% CI 1.8–2.1) for women when compared to population controls. They concluded that TBI is associated with substantially increased long-term mortality, even after adjustment for sociodemographic and familial factors[33].

Sercy et al. (2020) studied associations with mortality in mild TBI patients to examine whether their increased mortality was due to pre-existing conditions and lifestyle factors or the injury itself[31]. In their study of 964 mild TBI patients and 5,567 minimally injured controls, they found mild TBI to be a strong risk factor for death, even after adjusting for comorbidities. In adjusted survival analyses of patients with mild TBI, they found that only increasing age and three comorbidities—cardiovascular, neurological, and respiratory—were independently associated with increased mortality. They concluded that rather than clinical characteristics of the injury, the presence of pre-existing conditions in conjunction with experiencing mild TBI may be the cause behind increased mortality. This study included patients who were discharged after the initial hospitalization. Patients who were discharged to a hospice, nursing home, or skilled nursing facility were excluded because of the likelihood that cause of death in these patients was unrelated to their most recent hospital admission.

In addition to the aforementioned risk factors—trauma severity[26], [29], [33] and recurrent head traumas[29], [32]—other risk factors for increased long-term mortality have been proposed. Older age[26], [27], [36], [174], [175], which is a strong natural risk factor for death, has been reported as a risk factor for increased mortality among individuals who have experienced TBI. As for the general population, male sex is associated with increased mortality[27], [36]. Associations have been found between post-traumatic epilepsy and reduced survival[174], [176]. As former studies have found strong associations between the severity of TBI and post-traumatic epilepsy, it is hypothesized that TBI severity might be behind this finding[177]. Pre-existing conditions are associated dose-dependently with increased risk for mortality[26], [169]. Poor rehabilitation outcome[36] and poor vocational outcome[175] are associated with increased mortality. Overall, poor functional status has been found to decrease long-term survival in prior studies[27], [35], [178], [179]. Ventura et al. found associations with lower-income neighborhood and metropolitan residence and increased mortality in specific age groups[26]. Other factors that have been studied include alcohol use, time since injury, year of injury, communication

and cognitive function, education, and maladaptive behaviors. The causal relationships between various factors can be complicated, and the strengths of the associations can vary substantially depending on what other factors are considered in the analysis.[36]

To conclude, individuals experiencing TBI seem to be at elevated risk of premature death. Adjusting for confounding factors lessens the risk but does not remove it totally. Increased mortality reduces over time but remains elevated even years after trauma in many studies. Similar findings have been reported across studies with different cohorts (population-based[26], [33] and other TBI cohorts[29], [30], [31]), different controls (population controls[26], non-head injury controls[28], family members[33]), and different statistical analyses (reduced life expectancy by years[26], odds ratios[33] and hazard ratios[29], [30], [31] for death, and standardized mortality ratios[26], [27]). However, not all studies have reported similar increased long-term mortality after TBI[172], [173]. Additionally, the reasons behind the increased mortality rates remain poorly understood, especially among individuals who have sustained only minor head injuries.

2.4.2.2 Causes of Death

Causes of death have been found to differ between individuals with history of TBI versus their controls without it[29]. What remains unclear are the reasons behind this finding. Analogously to the decreased survival of patients with TBI, it is not clear whether this is due to pre-existing conditions and lifestyle factors or the TBI itself. A limitation of many of the previous studies, regarding long-term mortality, is that index traumas—the traumas for which individuals were recruited in these studies—have been included in the mortality analyses[29], [30]. For example, when a cohort of severe traumas is studied, it is no surprise that injury-related causes of death are overrepresented compared to their non-injured controls. To eliminate this effect, some studies have examined the acute phase and the rest of the follow-up separately. Fazel[33] and Brown[171] used a cut-off value of six months, McMillan[28] and Shavelle[35] one year, and Groswasser[172] two years post-injury to distinguish these different phases. However, these studies did not report any detailed evidence for why these cut-off values were chosen. Additionally, most prior studies have obtained cause-of-death data from national registries and therefore use data that does not undoubtedly reveal whether traumatic death is due to the index trauma or some secondary trauma irrelevant to the index TBI. Some past studies have acknowledged this problem and examined death certificates to potentially reclassify death causes to

avoid this potential misinterpretation[35], [36]. Relevant prior literature concerning causes of death after head injury is referred next in this chapter.

Several studies that have examined causes of death after TBI have included all TBI severities in their analyses. Ventura et al. (2010) found that deaths among TBI patients (n=18,998, all severities) were significantly greater than expected for almost all specific causes of death. Notable increases were seen in deaths caused by mental or behavioral disorders (SMR 4.7, 95% CI 3.3–6.7) and nervous system disease (SMR 3.3, 95% CI 2.5–4.5) when comparing the causes of deaths to those of the general population. The follow-up began after discharge from acute care hospitalization, and mean follow-up time was 4.4 years[26]. The authors state that study design did not allow interpretation of causality between TBI and cause of death and that the mechanism by which TBI might exacerbate deaths caused by existing mental or behavioral and neurologic disorders could not be determined in this analysis. Elser et al. (2023; n=2,402, all severities) found neurologic and unintentional, and traumatic causes of death more frequent among patients with TBI compared to the general population. Neurodegenerative diseases comprised a greater proportion of overall deaths among individuals with head injury (14%) versus those without (6.6%), and a greater proportion of deaths were due to all neurologic causes among individuals with head injury (62%) versus those without (51%). A limitation of this study is that it did not exclude the acute phase from the mortality analyses[29]. In Fazel's population-based study (2014) of 218,300 patients with TBI who survived six months after trauma (all severities included), patients with TBI were found to be at increased risk for external causes of death (injuries, suicide, assault) compared to their controls[33]. Odds of premature mortality in patients with both TBI and psychiatric comorbidity, specifically substance abuse and depression, were substantially elevated, ranging from 8 to 24. Pre-existing psychiatric diagnoses appeared to have stronger effects on odds of mortality than post-TBI diagnoses[33]. TBI was found to an independent risk factor for premature mortality as well.

Likewise, Pentland et al. (2005) reported a higher frequency of suicides compared to reported rates in the general population, but no matched comparison was performed in their study of 1,871 hospital admitted TBI (16% of TBI were coded as moderate-to-severe)[180]. Esterov et al. (2021; n=1,257, all severities) reported that proportions of deaths only differed for external causes, while no significant differences were seen between groups in any other causes of death when patients with TBI were compared to general population controls[34]. Differences were seen when deaths were compared over the whole study period (mean follow-up time of 11 years) and when the analysis was restricted to those who survived the first six

months. When TBI patients with accompanying non-head injuries were compared to non-head injury controls of similar severity, this was only true when whole study period was included, and no significant difference was seen among patients who survived the first six months. The relatively small portion of participants with moderate-to-severe TBI (8%) was hypothesized to explain the finding that causes of death only differed for external causes. In this cohort, increased overall risk of death only existed in the first six months after injury.

McMillan et al. (2011) compared causes of death between 767 head injuries admitted to the hospital (all severities, percentages not reported) and non-head injury and community controls, who were followed up to 13 years[28]. The frequency of death in the head injury group was significantly higher than for community controls for circulatory, respiratory, digestive, mental or behavioral, and external causes and was higher in the non-head injury group than in community controls for external causes. Death from self-harm was not different between groups at 13 years after injury. Regarding causes of death, the acute phases were not excluded, although survival time after head injury was examined for two separate time intervals.

The prior literature also contains studies that have analyzed causes of death after more severe forms of TBI solely. In a study of 1,678 TBI patients who received inpatient rehabilitation and survived the first year after injury, Harrison-Felix et al. (2009) found death causes of pneumonia (especially aspiration pneumonia), suicide, digestive, and seizure to be markedly increased compared to the general population[36]. Persons with TBI were almost 50 times more likely to die of aspiration pneumonia and about four times more likely to die of pneumonia. A similar result for increased risk to die of pneumonia[68] was reported by the same author in a study of TBI patients who likewise received inpatient rehabilitation[37].

Ventura et al. (2010) reported SMRs of 3.3 (95% CI 2.1–5.0) for pneumonia and 3.4 (95% CI 1.7–6.6) for aspiration pneumonia among TBIs of all severities. However, almost all specific causes of death were significantly greater than expected based on mortality rates for the general population in this study[26]. Shavelle et al. (2001) studied causes of deaths in patients with long-term mental disability after a TBI (n=2,320). Disability after TBI suggests that these patients had suffered more severe TBI, even though severity classification was not reported in the analyses. SMRs for causes of deaths compared to those expected of the general population were calculated. SMRs were markedly elevated for choking or suffocation (29, 95% CI 12–53) and seizures (24, 95% CI 12–42). Significantly increased but less striking risks were seen for respiratory (9.7, 95% CI 5.6–15) and circulatory causes (3.3, 95% CI 2.2–4.9) and, a bit surprisingly, for urinary and kidney disease-caused deaths (15,

95% CI 5.5–33). Cancer, digestive, and external causes of death (other than choking or suffocation) were not significantly elevated. Risk for pneumonia-caused death was not specifically addressed in this study.[35]

Baguley et al. (2012) reported higher death rates after severe TBI (n=2,545) compared to those expected in the general population for several individual causes of death. Rates were elevated for mental and behavioral disorders (SMR 5.4, 95% CI 2.4–9.6), nervous system diseases (SMR 6.4, 95% 3.4–10), circulatory diseases (SMR 2.6, 95% CI 1.9–3.4), respiratory diseases (SMR 10, 95% CI 7.5–13), digestive diseases (SMR 5.2, 95% CI 2.9–8.3), and external causes (SMR 5.2, 95% CI 3.9–6.7). The study cohort consisted of individuals who had experienced severe TBI and been discharged from an inpatient rehabilitation facility. Individuals were followed up to 16 years post-injury[27].

Few studies have examined cause-specific mortality specifically among milder head injuries. A study by McMillan et al. (2014; 2,428 mild head injuries) compared causes of death after mild head injury to other-injury controls and community controls[32]. Death rates were higher in mild head injury and other-injury groups compared to community controls for all causes except neoplasm. The mild head injury group had more frequent deaths than other-injury controls for digestive and mental or behavioral causes. No significant differences were seen in neurological causes nor in self-harm or other external causes between groups. Acute phases after head injury were not excluded from the analyses.

In a study of 964 mild TBI patients and 5,567 minimally injured hospital controls by Sercy et al. (2020), only diseases related to the appendix, digestive system, liver, or gallbladder as cause of death were found statistically different between cases and controls (10% vs 4%, P=0.018) five years after hospital discharge. This slightly surprising finding is probably not explained by alcohol consumption, as analyses examining alcohol-related liver disease as cause of death revealed no significant difference between cases and controls. This study included patients who were discharged after the initial hospitalization. Patients who were discharged to hospice, nursing home, or skilled nursing facilities were excluded because of the likelihood that their causes of death were unrelated to their most recent hospital admission[31]. Vaaramo et al. (2015) found patients with TBIs (mild to severe) to be at increased risk for future traumatic death as compared to population controls matched by age, sex, and residence. This was true with head injury patients without TBI as well, suggesting that pre-existing factors might have had notable effects on the mortality of these patients. This study did not exclude acute phases after head injury from the mortality analyses[30].

The mechanisms behind the increased risk for certain causes of death after TBI are currently poorly understood. Neuropathological changes and their possible effects on functional outcome and lifestyle have been proposed as underlying cause[181]. TBI is caused by brain damage resulting in loss of neurons, astrocytic gliosis, and microglial activation, which all culminate in complex neurological disorders[46]. Even in mild TBI, cellular metabolism is disturbed and microstructural damage occurs, resulting in both biochemical and vascular autoregulation abnormalities[46]. There is growing evidence that repeated mild TBI may have great cumulative effects on brain function, leading to neuropsychological disabilities, and that it significantly increases the risk of developing neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease[182]. Hence, it is likely that some degree of the elevated risk for certain causes of death is due to traumatic neuropathological alterations. Several of the aforementioned studies reported increased risk for neurologic conditions as the cause of death after TBI[26], [27], [29]. More severe forms of TBI predispose affected individuals to a variety of health problems that could explain the risk for certain causes of death that are not directly linked to TBI. Changes in physical activity after TBI can lead to more sedentary lifestyle[183], [184], which could result in increased risk for a variety of metabolic and cardiovascular diseases. As well, poor functional status could partially explain the increased risk for respiratory causes such as pneumonia. The effects of pre-existing conditions and lifestyle factors on the causes of death seen in mortality analyses are also debated. It is possible that pre-existing conditions predispose individuals to head injury and that the same underlying pre-existing conditions are seen as causes of death in mortality analysis[31]. For instance, a neurodegenerative condition such as Parkinson's disease can pose a risk for TBI and later be lethal for the affected person. The same is true for lifestyle factors such as risk-taking behavior. Individuals taking more risks in terms of their own health are more prone to TBI[185]. An individual could have been recruited into a TBI mortality study for one trauma and die during follow-up after sustaining a subsequent trauma. Traumatic causes seen in mortality analysis as the cause of death could be partly affected by the same risk-taking behavior, rather than the prior head injury for which the individual was recruited into the study.

To conclude, several specific causes of death after TBI seem to be overrepresented compared to controls. Some of them are more intuitive than others. Methodological problems occur, and further studies are required for better understanding and treatment of patients with TBIs.

3 AIMS OF THE STUDY

The specific aims were:

1. To determine the incidence of surgically treated post-traumatic hydrocephalus within six months of head injury and to examine the time interval between the trauma and the manifestation of post-traumatic hydrocephalus in a cohort of adult patients with head injuries. (Study I)

2. To determine the incidence of surgically treated chronic subdural hematoma within six months of head injury in patients with normal initial head computed tomography in a cohort of adult patients with head injuries. (Study II)

3. To examine and compare ten-year survival and causes of death between a cohort of adult patients with head injuries and their matched population controls. (Study III)

4 MATERIALS AND METHODS

4.1 Study Design and Ethical Aspects

This thesis is part of the Tampere Traumatic Head and Brain Injury Study and was conducted at Tampere University Hospital (Tampere, Finland). The original study included all consecutive patients with head injuries who were treated and CT-scanned at the Tampere University Hospital's emergency department between August 2010 and July 2012. These patients were retrospectively evaluated using the hospital's patient records. A total of 3,023 head injuries in 2,908 patients were identified in the primary sample. A six-month follow-up period for the development of PTH and cSDH was included for secondary data collection. Survival and causes of death were compared between patients and matched population controls over a period of ten years. Mortality data for patients and controls was obtained from a national registry maintained by Statistics Finland (Tilastokeskus).

This study was conducted following the principles outlined in the Declaration of Helsinki. The study was approved by the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland (ethical code R10027). All data was collected retrospectively without contacting the patients; therefore, no written informed consent was obtained or required.

4.2 Study Population

This study focused on adult (18 years or older) patients who were residents of the Pirkanmaa region at the time of injury and who were clinically evaluated and scanned with head CT at the Tampere University Hospital's emergency department within 48 hours (≤48h) after head injury. Patients who had suffered more than one head injury during the study period were included only once in the study sample, with the initial head injury as the index injury. A total of 1,941 adult patients undergoing acute head CT following injury were identified.

The Pirkanmaa region is a geographically well-defined area, with both rural and urban areas, that holds one of Finland's five university hospitals with neurosurgical

service (Tampere University Hospital, Tampere, Finland). During the study period, Pirkanmaa had 490,000 residents, comprising nine percent of the total population of Finland (5.4 million) at the time. In addition to Tampere University Hospital, there is one other local hospital with a CT scanner used for patients with head injuries in the Pirkanmaa region. However, most of the head trauma patients, and all the patients requiring neurosurgical care, are evaluated at the Tampere University Hospital.

Mortality data for patients and controls (community control subjects) was obtained from a national registry maintained by Statistics Finland (Tilastokeskus). Patient control matching (1:5) was conducted by age, gender, and place of residence (municipality) during the year of injury. The control subjects needed to have been alive at the date of injury for their corresponding patient. They could not be included in the study as both a patient and a control, and the control subjects were unique, meaning they could not serve as a control for more than one patient. From the 1,941 patients, eight had invalid Finnish personal identity codes and three were without a place of residence. As a result, a total of 1,930 patients were included in the mortality analyses. Five controls were requested for each patient. Not all five controls meeting the prerequisites were found for each patient, hence a total of 9,605 controls were obtained. All deaths occurring within 3,650 days (ten years) post-injury were obtained from the registry.

4.3 Data Collection

4.3.1 Primary Data Collection

Detailed and structured data collection was performed using the hospital's patient medical records. Variables collected included demographics, antithrombotic medication (including anticoagulants and antiplatelets), injury-related information, clinical TBI indices, emergency head CT findings (acute traumatic lesions), and acute neurosurgery due to TBI. Minimal criteria for TBI were based on WHO's definition[41]. GCS scores of <13 after 30 minutes post-injury, PTAs greater than 24 hours, and/or LOCs over 30 minutes were coded as moderate-to-severe TBIs. A considerable number of patients had missing GCS scores. These patients were coded based on clinical findings and examinations, as reported in the patient medical records. Not all the patients had documented clinical signs of TBI but were likely

CT-scanned because of age, antithrombotic medication, or concern about the mechanism of injury based on the judgment of the on-call physician. Referral criteria for acute head CT were based on former Scandinavian guidelines for the initial management of minimal, mild, and moderate head injuries[186]. Two neuroradiologists examined all the head CT scans. Study data was collected before the National Institution of Neurological Disorders and Stroke Common Data Elements (CDEs)[187] for TBI imaging were established. However, all CDEs possible with non-contrast structural CT were included[188].

4.3.2 Post-traumatic Hydrocephalus

A thorough review of records for neurological signs and symptoms of hydrocephalus was conducted for all patients having radiological suspicion of hydrocephalus/ventriculomegaly in their patient medical records within six months of injury. The diagnosis of PTH was based on clinical and radiological signs of the condition. The outcome of interest was specified as surgically treated post-traumatic hydrocephalus to rule out conditions not requiring treatment, such as post-traumatic ventriculomegaly resulting from secondary atrophy. Additionally, clinical evidence of shunt responsiveness (i.e., improvement in preoperative PTH signs and symptoms) was required. Patients with other apparent causes of hydrocephalus (e.g., normal pressure hydrocephalus diagnosis prior to injury and obstructive hydrocephalus due to posterior fossa lesions) were considered to have non-traumatic hydrocephalus.

4.3.3 Chronic Subdural Hematoma

As with the documentation of PTH, a careful review of records was conducted for the cohort to document the possible development of cSDH within six months of injury. To examine the development of cSDH after normal initial head CT, the patients were divided into two groups: CT-positive and CT-negative. A patient was regarded CT-positive if there were any signs of acute traumatic intracranial pathology on initial head CT. Because the aim of this study was to examine the development of cSDH (and eventual surgical treatment) after normal initial head CT, patients with any kind of subdural collection on initial head CT were regarded as CT-positive. Consequently, patients with no signs of acute traumatic intracranial pathology or any type of subdural collection on initial head CT were regarded as CT-negative. CT-

negative patients may have had other lesions or abnormalities on the initial head CT (e.g., lesions of vascular etiology). The outcome of interest was specified as surgical treatment of cSDH. In the absence of strict universal criteria, we used the following definition for cSDH: a predominantly hypodense blood collection in the subdural space on head CT (or MRI). No structural follow-up was conducted, and patients were CT scanned only if neurological symptoms emerged. Hence, surgical treatment of cSDH was the most reliable outcome measurement available.

4.3.4 Mortality Data and Death Certificates

Data about deaths, causes of death, and conditions of death were obtained from a national causes-of-death database maintained by Statistics Finland (Tilastokeskus). The database includes all individuals who have died in Finland or abroad since 1971, have Finnish personal identity codes, and have had their deaths recorded in the Finnish Population Information System maintained by the Digital and Population Data Service Agency. The obtained variables included year of death, date of death, statistical underlying cause of death (based on the International Classification of Diseases, Tenth Revision [ICD-10]), over-time harmonized 54-class statistical underlying cause of death, immediate cause of death, first-to-fourth contributing cause of death, whether or not the cause of death was alcohol-related, location and type of accident for trauma-related deaths, and main external cause of injury or poisoning leading to the statistical underlying cause of death for accidental and violent deaths.

To examine the causal connection between head injury and death, we reviewed all death certificates of patients who were coded as having died of external causes. Particularly, we wanted to examine whether the patients who had traumatic causes of death died from the index trauma for which they were included into the study or some secondary trauma occurring during follow-up. Death certificates were obtained from Statistics Finland (Tilastokeskus). For confidentiality reasons, the death certificates for controls were not granted.

4.4 Statistical Analyses

IBM SPSS Statistics for Mac (version 27 and 29, IBM Corp.) was used for data analyses. Descriptive statistics (frequency [n], percentage, mean, median,

interquartile range [IQR]) were used to describe variable characteristics. A chi-squared test was used to test statistical differences between category variables. The independent samples t-test was used to test statistical differences in the means of two groups. Hazard ratios (HRs) for death were calculated using the Cox proportional hazard ratio model. The proportional hazard assumptions were checked using Schoenfeld residuals and were not violated. In the multivariate model, included variables were selected based on the prior literature. Cumulative survival was visualized using Kaplan–Meier survival curves. P-values of <0.05 were considered statistically significant. Confidence intervals (CIs) were calculated with 95% confidence levels. In mortality analyses comparing patients and controls, patient groups were only compared to groups containing their individually matched controls. For analyses of cSDH incidence, Blaker's binomial CIs (95% confidence level) were calculated with R (version 4.3.2).

5 RESULTS

5.1 Study Sample

A total of 1,941 adult patients undergoing acute head CT following injury were identified. The whole cohort was included in analyses of incidences of PTH (Study I, Section 5.2) and cSDH (Study II, Section 5.3). In the mortality analyses (Study III, Section 5.4), 11 patients were excluded due to patient characteristics that prevented patient control matching, leaving a total of 1,930 patients. Five controls were requested for each patient. Not all five controls meeting the prerequisites were found for each patient; hence, a total of 9,605 controls were obtained. Given the differences in study samples, cohorts are described individually later in this section.

5.2 Post-traumatic Hydrocephalus

5.2.1 Cohort Overview

A flowchart of the study sample is provided in **Figure 1**. The cohort included 1,941 patients with a median age of 59 years. Of the 1,941 patients, 1,122 (58%) were men. The most common mechanism of injury was a ground-level fall (GLF) in 1,016 (52%) patients. Alcohol intoxication was reported for 567 (29%) patients, and 494 (26%) patients were on antithrombotic medication at the time of injury. Loss of consciousness was documented in 417 (22%) patients and amnesia in 510 (26%) patients. GCS scores were not reported for a third of the patients (n=663, 34%). Among patients with reported GCS scores, the scores were distributed as follows: 57% (n=1,100) arrived at the emergency department with GCS scores of 13–15, 5.0% (n=97) with GCS scores of 9–12, and 4.2% (n=81) with GCS scores of 3–8. Most of the patients, 1,269 (65%), had mild TBI. Moderate-to-severe TBI was reported for 187 (9.6%) patients, and 485 (25%) patients did not have evidence of TBI in their records. The most frequent acute traumatic lesions on head CT at admission were subdural hematoma (acute and/or chronic) in 254 (13%) patients

and subarachnoid hemorrhage in 216 (11%). Emergency trauma neurosurgery was performed on 111 (5.7%) patients. Characteristics of the study cohort are summarized in **Table 1**.

5.2.2 Incidence of Post-traumatic Hydrocephalus

Only three patients were diagnosed and surgically treated for clinically and radiologically diagnosed PTH during the six-month follow-up period. Ventriculoperitoneal shunts were placed for all these patients. The three patients were reported to benefit from the shunts, but there was no systematic follow-up after PTH diagnosis and surgical treatment. A positive response to shunt surgery was identified based on the information reviewed in the patient records. If there was consistent clinical improvement after the shunt operation and no other distinct cause for it, the patient was considered to have benefited from the shunt. As a result, the incidence of surgically treated PTH in our cohort was 0.15%. One of the surgically treated PTH patients had a mild TBI, and thus the incidence of PTH among mild TBI patients was 0.08 % (1 per 1,269). Two of the three patients had moderate TBI, so the incidence of PTH among moderate-to-severe TBI patients was 1.1% (2 per 187). All the surgically treated PTH cases underwent acute neurosurgery due to the index head trauma. The incidence of surgically treated PTH among patients undergoing acute neurosurgery was 2.7% (3 per 111).

Of the three patients with PTH, two were men aged 56 and 87 years and one was a 62-year-old woman. Both men sustained a moderate TBI and the woman sustained a mild TBI. GLF was the injury mechanism for all three patients. The 87-year-old man was on antithrombotic medication (warfarin) at the time of trauma. Alcohol intoxication was reported for the 56-year-old man and for the 62-year-old woman. Acute traumatic lesions were seen in all three patients: contusions and acute SDH in all patients and SAH in the two male patients. All three patients underwent acute neurosurgery during initial admission. The 56-year-old man underwent evacuation of intracranial contusion hemorrhage and SDH through craniotomy. An acute SDH craniotomy was performed on the 87-year-old man. An emergency trepanation and evacuation of a subdural hygroma was performed on the woman. The surgically treated PTH patients had 2-, 5-, and 5-month delays between the index injury and the shunt surgery. A detailed description of all patients with surgically treated PTH within six months of injury is presented in **Table 2**. Due to the small number of cases (n=3), group analyses on possible PTH risk factors were not performed.

5.2.3 Other Hydrocephalus After Head Injury

Two patients among our cohort of 1,941 patients experienced acute hydrocephalus secondary to severe TBI, and their initial CT scans revealed enlarged ventricles. These two patients underwent acute neurosurgery because of their severe TBIs and initially had very poor prognoses. During the initial hospital admission, both patients died due to complications related to the severe TBI. The active treatment of hydrocephalus in these moribund cases had been considered disadvantageous, and no surgical interventions for hydrocephalus were performed.

In addition, 10 patients with non-traumatic hydrocephalus who underwent neurosurgery were identified either on the first head CT or during the follow-up period. These hydrocephalus cases were categorized as obstructive hydrocephalus (n=4) or communicating hydrocephalus (n=6). The etiologies for obstructive hydrocephalus cases were hemangioblastoma, cerebellar infarct, aqueduct stenosis, and cervical spinal cord injury with vertebral dissection and basilar infarct. The communicating hydrocephalus cases were due to normal-pressure hydrocephalus (n=4), spontaneous SAH (n=1), or non-specific etiology (n=1). The six patients with communicating hydrocephalus had pre-existing symptoms and enlarged ventricles before or at the time of head trauma. These findings are presented schematically in **Figure 1**.

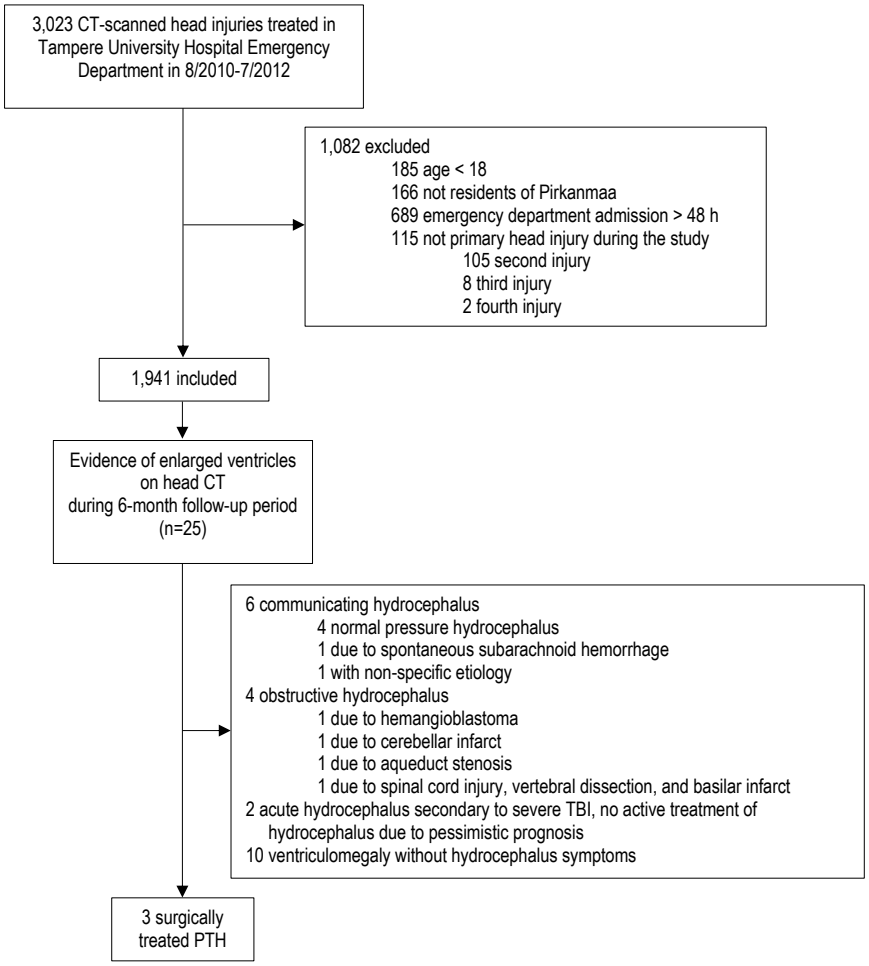

Figure 1. A flowchart of the study sample (Study I). CT=computed tomography, TBI=traumatic brain injury, PTH=post-traumatic hydrocephalus.

Table 1. Characteristics of the study cohort (Study I; n=1,941).

Variable		
Age median, years (IQR)	58.7 (39.1-58.7)	
	n	**%**
Men	1,122	57.8
Cause of injury		
Ground-level fall	1,016	52.3
Motor vehicle accident	261	13.4
Fall from a height	215	11.1
Traffic accident as pedestrian or bicyclist	116	6.0
Other	333	17.2
Alcohol intoxication	567	29.2
Antithrombotic medication	494	25.5
Loss of consciousness	417	21.5
Amnesia	510	26.3
Glasgow Coma Scale		
13-15 points	1,100	56.7
9-12 points	97	5.0
3-8 points	81	4.2
Unknown	663	34.2
Traumatic brain injury severity		
No traumatic brain injury	485	25.0
Mild	1,269	65.4
Moderate-to-severe	187	9.6
Acute traumatic lesion on head CT-scan		
Subdural hematoma (acute and/or chronic)	254	13.1
Subarachnoid hemorrhage	216	11.1
Contusion	152	7.8
Intraventricular hemorrhage	54	2.8
Epidural hematoma	14	0.7
Diffuse axonal injury	7	0.4
Emergency neurosurgery due to acute traumatic brain injury	111	5.7
Decompressive craniectomy	14	0.7
Shunted post-traumatic hydrocephalus within 6 months post-injury	3	0.15

Notes: IQR=interquartile range; CT=computed tomography.

Table 2. Detailed description of patients with post-traumatic hydrocephalus within six months after injury (n=3).

Patient	Injury mechanism	TBI severity	CT findings	Acute neurosurgery	Hydrocephalus symptoms	Shunt surgery; delay since injury	Hydrocephalus etiology	Clinical improvement after shunt placement
Woman, Age 62	Fall	Mild	Contusion, acute SDH, subdural hygroma	TRP, evacuation of subdural hygroma	Headache, nausea, vertigo	VP, 2 months	PTH	Yes
Man, Age 56	Fall	Moderate	Skull fracture, SAH, Contusion, acute SDH	CRT, evacuation of ICH and SDH	Disorientation, slowed down	VP, 5 months	PTH	Yes
Man, Age 87	Fall	Moderate	SAH, Contusion, acute SDH	CRT, evacuation of acute SDH	General malaise	VP, 5 months	PTH	Yes

Notes: All mechanisms of injury were ground-level falls. TBI=traumatic brain injury; CT=computed tomography; SAH=subarachnoid hemorrhage; SDH=subdural hemorrhage; CRT=craniotomy; ICH=intracerebral hemorrhage; PTH=post-traumatic hydrocephalus; TRP=burr hole trepanation; VP=ventriculo-peritoneal.

5.3 Chronic Subdural Hematoma

5.3.1 Cohort Overview

The cohort included all 1,941 patients who were included in the study and in the analyses of PTH and cSDH. The demographics of the whole cohort are described in Section 5.2.1 and presented in detail in **Table 3,** with slight variations to the reported data in **Table 1**. Regarding cSDH, a flowchart of the study sample is provided in **Figure 2**. Initial head CT showed acute traumatic intracranial pathology and/or subdural fluid collection (CT-positive) in 368 (19%) patients. Consequently, 1,573 (81%) patients had normal initial head CT in relation to the trauma (CT-negative): they had no signs of acute traumatic intracranial pathology or any type of subdural collection on initial head CT. Due to specific interest in studying patients with genuinely normal initial head CTs, a small number of cases with ambiguous subdural fluid collection were reclassified for analysis of cSDH.

5.3.2 CT-positive Group

Initial head CT showed acute traumatic intracranial pathology and/or subdural fluid collection (CT-positive) in 368 (19%) patients. In the CT-positive group, the most frequent acute traumatic lesion on head CT was subdural hematoma, of which 227 (90%) were acute and 25 (10%) subacute or chronic. As subdural hygromas have no unified clinical or radiological criteria, these lesions were included in the subacute or chronic subdural hematoma group. Only 38 (17%) of all acute SDH patients received acute surgical treatment for the condition. Of the 38 patients who received surgical treatment for acute SDH, three (7.9%) later underwent surgery for cSDH. Of the 189 conservatively treated acute SDHs, nine patients (4.8%) underwent later surgery for cSDH. These findings are presented schematically in **Figure 2**.

5.3.3 CT-negative Group

One thousand, five hundred seventy-three (81%) patients had normal initial head CT in relation to the trauma (CT-negative): they had no signs of acute traumatic intracranial pathology or any type of subdural collection on initial head CT. The CT-negative group included 81% of the cohort. The demographics of the CT-negative

group were similar to the characteristics of the entire cohort, with the exception that there were markedly fewer patients with moderate-to-severe TBI in the CT-negative group. Characteristics of the patients with normal initial head CT are summarized in detail in **Table 4**.

Only six patients were diagnosed with cSDH after normal initial head CT scans during the six-month follow-up period. Two of the six patients received surgical evacuation of the hematoma (trepanation), while the rest were treated conservatively. Therefore, the incidence of surgically treated cSDH after normal initial head CT during six-month follow-up was 0.13% (95% CI 0.023–0.45). Both patients suffered initially from mild TBI. Therefore, the incidence among patients with mild TBI was 0.19% (95% CI 0.034–0.67). None of the patients with moderate-to-severe TBI (n=29) or no TBI (n=483) were diagnosed with cSDH during the follow-up period. One of the two patients was on antithrombotic medication (warfarin) at the time of trauma; hence, the incidence among patients on antithrombotic medication (n=376, 24%) was 0.27% (95% CI 0.014–1.5). In addition to these two cases, one patient (female, aged 75 years) developed a subdural hygroma which was treated via trepanation shortly (ten days) after trauma. Consequently, of the 1,573 patients with CT-negative head injuries, three were surgically treated for subdural fluid collection. Due to the small number of cases that underwent surgery (n=2), statistical analyses of possible risk factors for surgically treated cSDH were not performed.

Both patients who developed surgically treated cSDH were elderly women, aged 77 and 78 years. Hence, the incidence of cSDH in the age group of over-70 years old (n=506) was 0.40% (95% CI 0.070–1.4). Ground-level fall was the injury mechanism for both. Both had bilateral cSDHs. The time intervals from trauma to trepanation for the cSDH were seven and eight weeks. The characteristics of the two patients with surgically treated cSDH are described in detail in **Table 5**.

Table 3. Characteristics of the study cohort (Study II; n=1,941).

Variable		
Age median, years (IQR)	58.7 (39.1-78.5)	
	n	**%**
Men	1,122	57.8
Cause of injury		
Ground-level fall	1,016	52.3
Motor vehicle accident	261	13.4
Fall from a height	215	11.1
Traffic accident as pedestrian or bicyclist	116	6.0
Other	333	17.2
Alcohol intoxication	567	29.2
Antithrombotic medication	494	25.5
Loss of consciousness	417	21.5
Amnesia	510	26.3
Glasgow Coma Scale		
13-15 points	1,100	56.7
9-12 points	97	5.0
3-8 points	81	4.2
Unknown	663	34.2
Traumatic brain injury severity		
No documented clinical signs of traumatic brain injury	485	25.0
Mild	1,269	65.4
Moderate-to-severe	187	9.6
CT-positive head injury	368	19.0
Subdural hematoma (acute)	227	11.7
Subdural hematoma (subacute or chronic)	25	1.3
Subarachnoid hemorrhage	216	11.1
Contusion	152	7.8
Cerebral edema	14	0.7
Epidural hematoma	14	0.7
Diffuse axonal injury	7	0.4
CT-negative head injury	1,573	81.0

Notes: IQR=interquartile range; CT=computed tomography.

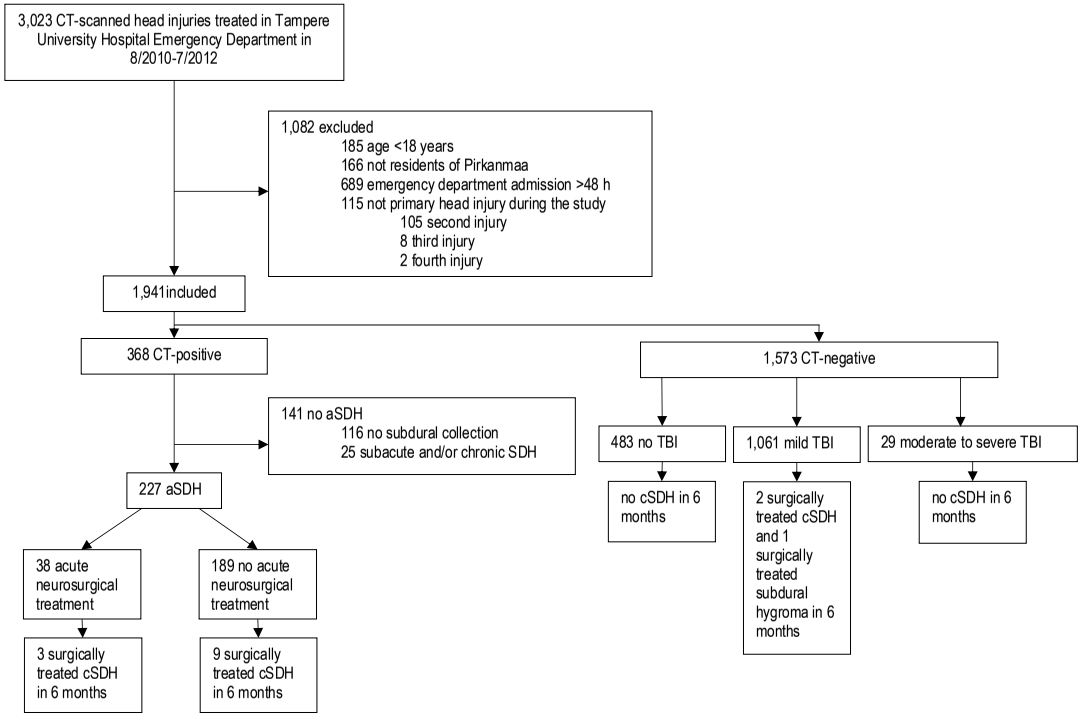

Figure 2. A flowchart of the study sample (Study II). CT=computed tomography; aSDH=acute subdural hematoma; cSDH=chronic subdural hematoma; h=hours; TBI=traumatic brain injury.

Table 4. Characteristics of the patients with normal initial head computed tomography (n=1,573).

Variable		
Age median, years (IQR)	56.2 (36.7-77.2)	
	n	**%**
Men	887	56.4
Cause of injury		
Ground-level fall	804	51.1
Motor vehicle accident	240	15.3
Fall from a height	169	10.7
Traffic accident as pedestrian or bicyclist	84	5.3
Other	276	17.5
Alcohol intoxication	455	28.9
Antithrombotic medication	376	23.9
Loss of consciousness	295	18.8
Amnesia	407	25.9
Glasgow Coma Scale		
13-15 points	938	59.6
9-12 points	55	3.5
3-8 points	24	1.5
Unknown	556	35.3
Traumatic brain injury severity		
No documented clinical signs of traumatic brain injury	483	30.7
Mild	1,061	67.5
Moderate-to-severe	29	1.8
Chronic subdural hematoma within 6 months post-injury	6	0.38
Surgically treated chronic subdural hematoma	2	0.13

Notes: IQR=interquartile range.

Table 5. Detailed description of the two patients with surgically treated chronic subdural hematoma after normal initial head computed tomography within six months post-injury (n=2).

Patient	Injury mechanism	TBI severity	Antithrombotic medication at the time of trauma	cSDH trepanation, time since injury	cSDH side	cSDH symptoms
Woman, Age 78	GLF	Mild	Warfarin	8 weeks	Bilateral	Postural instability, Vertigo, Aphasia, Fatigue
Woman, Age 77	GLF	Mild	No	7 weeks	Bilateral	Postural instability

Notes: GLF=ground-level fall; TBI=traumatic brain injury; cSDH=chronic subdural hematoma.

5.4 Mortality

5.4.1 Cohort Overview

The cohort included 1,930 patients with head injuries and 9,605 matched population controls. The demographics and clinical characteristics of the patients with head injuries are presented in **Table 6.** Data is presented for all patients (n=1,930) and separately for those who survived less than one year after injury (n=259) and for those who survived more than one year (n=1,671). Of those who survived more than one year, 969 (58%) were men. The median age of this group was 55 years. Most of these patients had pre-existing conditions (n=1,256, 75%). Moderate-to-severe TBI was diagnosed in 115 (6.9%) of the patients, and acute traumatic lesion on head CT was present in 272 (16%) of the patients in this group. Those who survived less than one year were considerably older and had more pre-existing conditions than those who survived more than one year. They also sustained more serious injuries.

5.4.2 Mortality

Among all patients and controls, 821 (43%) of the patients and 2,458 (26%) of the controls (P<0.001) died during the ten-year follow-up period. Their mean ages at time of death were 76.8 and 85.6 years (P<0.001) among patients and controls, and the mean survival times after injury were 7.2 and 8.7 years (P<0.001) among patients and controls, respectively. The HR for death was 2.00 (P<0.001) when comparing patients to controls. Cumulative survival of all patients and controls is visualized with Kaplan–Meier curves in **Figure 3A**. A rapid decline in the survival of patients with head injuries is seen during the first year following injury.

Of the patients who survived more than one year and their controls who survived more than one year, 562 (34%) of the patients and 1,668 (20%) of the controls (P<0.001) died during the follow-up. The mean ages at time of death were 77.5 and 84.1 years (P<0.001) among patients and controls, and the mean survival times after injury were 8.2 and 9.0 years (P<0.001) among patients and controls, respectively. The HR for death was 1.84 (P<0.001) when comparing patients to controls. Proportions of deaths by year in patients and controls are presented in **Figure 4.** Deaths occurred at an increased rate of more than twofold in patients compared to

controls at the start of the follow-up and then decreased to close to the control rate toward the end of the follow-up period. Deaths occurred at a greater rate among patients during the whole follow-up period. The difference was statistically significant for up to five years post-injury, as illustrated by no overlapping CIs up to that point. Cumulative survival of this group of patients and controls is visualized with Kaplan–Meier curves in **Figure 3B.**

5.4.3 Causes of Death

5.4.3.1 Underlying Cause of Death

Underlying causes of death during the first year are presented in **Table 7**. The excess mortality among patients is explained by unintentional and traumatic causes. Among patients who survived more than one year and their controls who survived more than one year, the three most common causes of death were cardiovascular, neurologic, and neoplasms. Together these causes comprised 82% of all deaths during the follow-up period. Of these, cardiovascular causes (35 vs 39%, P=0.045) and neoplasms (11.2 vs 17.2%, P <0.001) were more common among controls, with statistically significant differences. No statistically significant difference in neurologic causes was found. Among the other specific causes of death, only unintentional and traumatic causes (9.6 vs 4.4%, P<0.001) and alcohol-related causes (8.4 vs 1.9%, P<0.001) differed statistically significantly between groups, with greater proportions among patients with head injuries. These findings are presented in detail in **Table 8.**

To examine the possible causal connection between head injury and death, we reviewed death certificates for all patients who were coded as having died of external causes. Among patients who survived more than one year, only two died of primary head injuries. None of the patients in this group died from other primary external causes (i.e., related to injuries that occurred at same time as the index head injury). In one patient who was coded as having died of an event-related external cause, the causality between primary trauma and death was not discernable from the death certificate. These findings are presented in **Table 9**. After excluding these three patients, unintentional and traumatic causes were still overrepresented among patients (9.1 vs 4.4%, P<0.001) with almost the same proportion (now 9.1 versus prior 9.6%).

5.4.3.2 Immediate Cause of Death

Immediate causes of death were reported for only 37% of all deaths during the ten-year follow-up period. Of those patients who survived more than one year and their controls who survived more than one year, immediate causes were reported for 36.3% (204 of 562) and 36.1% (602 of 1 668) of all deaths, respectively. The immediate cause-of-death distribution differed statistically significantly between groups (P=0.031). In analyses of specific causes among those who had immediate cause of death reported, only aspiration pneumonia (11 of all 204 deaths in patients [5.4%] versus 14 of all 602 deaths in controls [2.3%], P=0.029) and epileptic cause (2 of all 204 deaths in patients [1.0%] versus 0 of all 602 deaths in controls [0%], P=0.015) differed statistically significantly between patients and controls.

5.4.4 Factors Associated with Decreased Survival

Associations between patient demographics and injury characteristics with survival in patients who survived more than one year post-injury are presented in **Table 10**. In a multivariate model, age, male sex, pre-existing conditions, chronic alcohol use, and regular substance abuse were significantly independently associated with decreased survival. Regarding injury characteristics, neither clinical TBI severity nor CT positivity were associated with decreased survival.

5.4.5 Comparison of Subgroups of Patients to Their Matched Controls

When comparing patients with different TBI severities to their controls, HRs for death were 1.73 (P<0.001, 95% CI 1.40–2.14), 1.84 (P<0.001, 95% CI 1.64–2.06), and 2.47 (P<0.001, 95% CI 1.65–3.71), among patients with no documented TBI, mild TBI, and moderate-to-severe TBI, respectively. The number of individuals in each severity group can be seen in **Table 6**. When comparing patients with no pre-existing conditions and no alcohol or substance abuse (n=295) to their controls, no significant differences in survival was found (HR 0.89, P=0.710, 95% CI 0.51–1.59). Subgroup analyses were made among patients who survived more than one year and their controls who survived more than one year.

Table 6. Demographics and clinical characteristics of patients with head injuries (Study III).

	All patients n=1,930		Survived less than one year n=259		Survived more than one year n=1,671	
Age median, years (IQR)	58.9 (39.2–78.5)		80.9 (67.3–87.3)		54.8 (37.0–74.3)	
	n	%	n	%	n	%
Men	1,113	57.7	144	55.6	969	58.0
Pre-existing condition	1,496	77.5	240	92.7	1,256	75.2
No	335	17.4	7	2.7	328	19.6
Unknown	99	5.1	12	4.6	87	5.2
Cardiovascular	811	42.0	187	72.2	624	37.3
No	1,020	52.8	60	23.2	960	57.5
Unknown	99	5.1	12	4.6	87	5.2
Mental, behavioral	541	28.0	56	21.6	485	29.0
No	1,310	67.9	195	75.3	1,115	66.7
Unknown	79	4.1	8	3.1	71	4.2
Neurological	475	24.6	101	39.0	374	22.4
No	1,357	70.3	146	56.4	1,211	72.5
Unknown	98	5.1	12	4.6	86	5.1
Endocrine, nutritional, metabolic	360	18.7	73	28.2	287	17.2
No	1,471	76.2	174	67.2	1,297	77.6
Unknown	99	5.1	12	4.6	87	5.2
Respiratory	188	9.7	34	13.1	154	9.2
No	1,643	85.1	213	82.2	1,430	85.6
Unknown	99	5.1	12	4.6	87	5.2
Neoplasm	117	6.1	40	15.4	77	4.6
No	1,714	88.8	207	79.9	1,507	90.2
Unknown	99	5.1	12	4.6	87	5.2
Chronic detrimental alcohol use	399	20.7	48	18.5	351	21.0
Regular substance abuse	81	4.2	5	1.9	76	4.5
Regular medication	1,054	54.6	189	73.0	865	51.8
No	457	23.7	21	8.1	436	26.1
Unknown	419	21.7	49	18.9	370	22.1
Antithrombotic medication in use at time of injury	494	25.6	127	49.0	367	22.0
Cause of injury						
Ground-level fall	1,013	52.5	197	76.1	816	48.8
Motor vehicle accident	259	13.4	14	5.4	245	14.7
Fall from a height	213	11.0	19	7.3	194	11.6
Violence-related accident	144	7.5	5	1.9	139	8.3
Traffic accident as a pedestrian or bicyclist	116	6.0	5	1.9	111	6.6
Other	185	9.6	19	7.3	166	9.9
Alcohol intoxication at time of trauma	566	29.3	38	14.7	528	31.6
Narcotics use at time of trauma	21	1.1	3	1.2	18	1.1
Glasgow Coma Scale score at emergency department						
13-15	1,093	56.6	96	37.1	997	59.7
9-12	96	5.0	23	8.9	73	4.4
3-8	81	4.2	41	15.8	40	2.4
Unknown	660	34.2	99	38.2	561	33.6
Loss of consciousness	412	21.3	53	20.5	359	21.5
No/Unknown	1,518	78.7	206	79.5	1,312	78.5
Traumatic brain injury severity						
No documented traumatic brain injury	482	25.0	50	19.3	432	25.9
Mild	1,261	65.3	137	52.9	1,124	67.3
Moderate-to-severe	187	9.7	72	27.8	115	6.9
Acute traumatic lesion on head CT	385	19.9	113	43.6	272	16.3
Subdural hematoma	253	13.1	89	34.4	164	9.8
Subarachnoid hematoma	215	11.1	75	29.0	140	8.4
Contusion	152	7.9	40	15.4	112	6.7
Epidural hematoma	14	0.7	2	0.8	12	0.7
Diffuse axonal injury	7	0.4	1	0.4	6	0.4
Acute neurosurgery	111	5.8	33	12.7	78	4.7
Discharge disposition						
Home	737	38.2	23	8.9	714	42.7
Hospital ward	648	33.6	70	27.0	578	34.6
Primary care ward	438	22.7	98	37.8	340	20.3
Other facility	52	2.7	13	5.0	39	2.3
Died in emergency department	55	2.8	55	21.2	0	0.0

Notes: IQR=interquartile range; CT=computed tomography. If not otherwise stated, there were no participants with missing data regarding each variable.

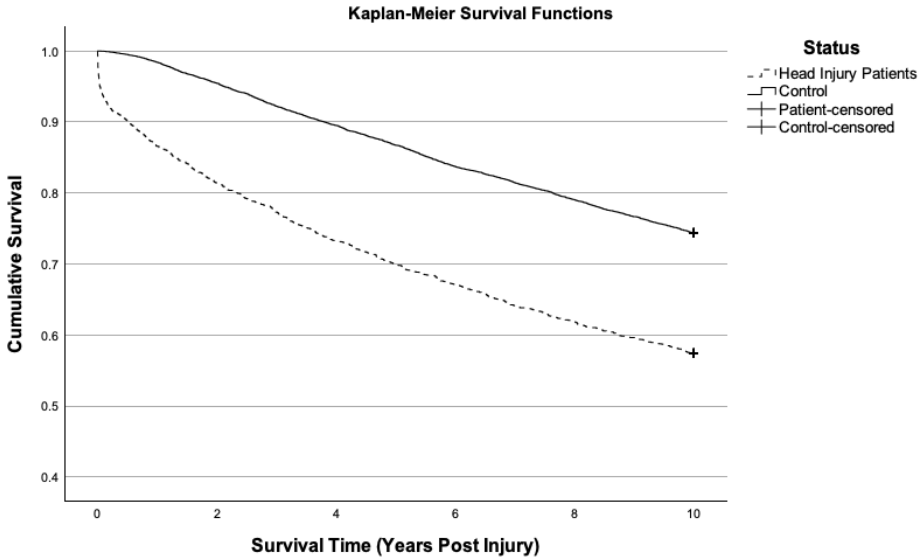

Figure 3A. Cumulative survival in all patients with head injuries (n=1,930) and controls (n=9,605) during the ten-year follow-up period. P-value <0.001 for Log Rank marked statistically significant difference between distributions.

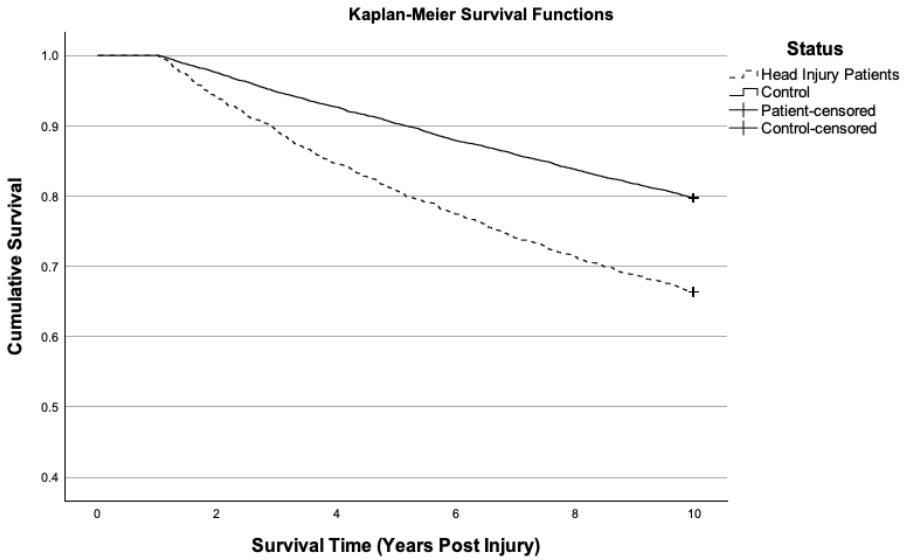

Figure 3B. Cumulative survival in patients with head injuries who survived more than one year (n=1,671) and their controls who survived more than one year (n=8,230) during the ten-year follow-up period. P-value <0.001 for Log Rank marked statistically significant difference between distributions.

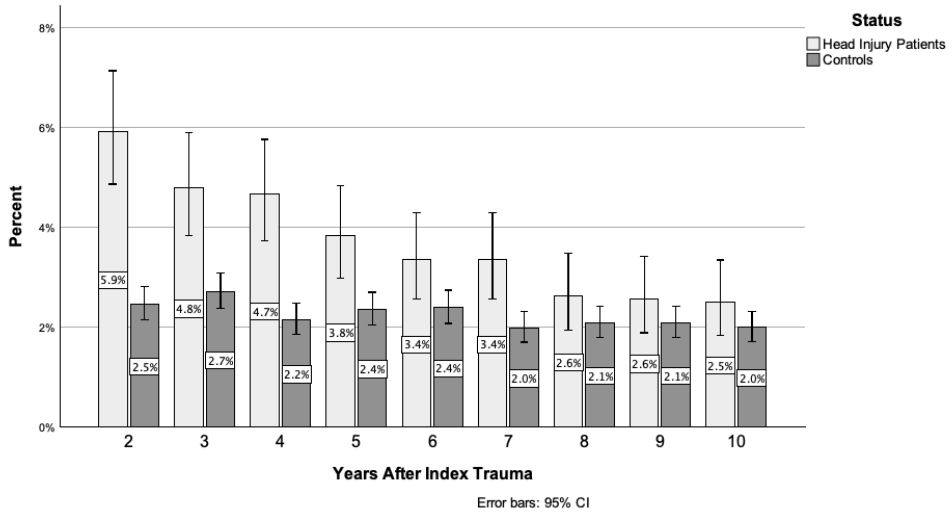

Figure 4. Yearly proportions (%) of deaths in patients with head injuries who survived more than one year (n=1,671) and their matched controls who survived more than one year (n=8,230). CI=confidence interval.

Table 7. Underlying causes of death in patients with head injuries and their community control subjects during the first year.

	Patients with head injuries n=1,930		**Controls n=9,605**		**P-value**
	n	**%**	**n**	**%**	
All-cause deaths	259	13.4	152	1.6	**<0.001**
	n	**%**	**n**	**%**	
Cardiovascular	92	35.5	62	40.8	0.287
Neurologic	21	8.1	51	33.6	**<0.001**
Neoplasm	26	10	19	12.5	0.440
Unintentional, traumatic	90	34.7	5	3.3	**<0.001**
Alcohol related	14	5.4	5	3.3	0.324
Respiratory	5	1.9	2	1.3	0.642
Gastrointestinal, urinary, sex organ related	5	1.9	6	3.9	0.221
Endocrine, nutritional, metabolic	1	0.4	0	0	0.443
Infectious	3	1.2	0	0	0.183
Other	2	0.8	2	1.3	0.558

Notes: P-values for the differences in proportions were calculated using Chi-square tests. Bolding highlights any P-value below 0.05, which was considered statistically significant.

Table 8. Underlying causes of death in patients with head injuries who survived more than one year post-injury and their community control subjects who survived more than one year, within the ten year follow-up period.

	Patients with head injuries n=1,671		Controls n=8,230		P -value
	n	**%**	**n**	**%**	
All-cause deaths	562	33.6	1,668	20.3	**<0.001**
	n	**%**	**n**	**%**	
Cardiovascular	195	34.7	658	39.4	**0.045**
Neurologic	155	27.6	478	28.7	0.624
Neoplasm	63	11.2	287	17.2	**<0.001**
Unintentional, traumatic	54	9.6	74	4.4	**<0.001**
Alcohol related	47	8.4	31	1.9	**<0.001**
Respiratory	16	2.8	48	2.9	0.970
Gastrointestinal, urinary, sex organ related	15	2.7	47	2.8	0.853
Endocrine, nutritional, metabolic	5	0.9	16	1.0	0.883
Infectious	3	0.5	13	0.8	0.551
Other	9	1.6	16	1.0	0.211

Notes: P-values for the differences in proportions were calculated using Chi-square tests. Bolding highlights any P-value below 0.05, which was considered statistically significant.

Table 9. Distribution of all unintentional and traumatic causes of death (n=144) among patients with head injuries, between those who survived less than one year and those who survived more than one year.

	Survival less than one year n=90		Survival more than one year n=54	
Cause of death	**n**	**%**	**n**	**%**
Primary head injury	67	74.7	2	3.7
Other primary external cause	13	14.4	0	0
Future head injury	3	3.3	15	27.8
Other future external cause	7	7.8	36	66.7
Causality not trackable	0	0	1	1.9

Table 10. Associations with death in patients with head injuries who survived more than one year (n=1,671).

	Univariate			Multivariate		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Patient demographics						
Age (years)	**1.072**	**1.066-1.078**	**<0.001**	**1.082**	**1.074-1.090**	**<0.001**
Sex (male)	**0.654**	**0.554-0.772**	**<0.001**	**1.308**	**1.083-1.580**	**0.005**
Pre-existing condition	**9.780**	**6.113-15.647**	**<0.001**	**2.459**	**1.517-3.989**	**<0.001**
Mental or behavioral disorder	0.897	0.745-1.080	0.251	1.234	0.962-1.584	0.098
Chronic alcohol use	1.007	0.822-1.233	0.949	**1.664**	**1.239-2.234**	**<0.001**
Regular substance abuse	**0.450**	**0.260-0.780**	**0.004**	**2.312**	**1.256-4.255**	**0.007**
TBI characteristics						
TBI severity						
No documented TBI	Reference		**<0.001**	Reference		0.887
Mild TBI	**1.480**	**1.204-1.820**	**<0.001**	1.049	0.846-1.300	0.662
Moderate-to-severe TBI	1.104	0.753-1.619	0.611	1.000	0.643-1.556	0.998
CT-positive head injury	**1.476**	**1.204-1.808**	**<0.001**	1.059	0.843-1.331	0.662

Notes: TBI=traumatic brain injury, CT=computed tomography, HR=Hazard Ratio, CI=confidence interval, P=P-value. Bold indicates statistically significant results.

6 DISCUSSION

6.1 Summary of the Key Findings

For this thesis, we evaluated the incidence of two distinct complications of head injury—PTH and cSDH—and studied long-term survival and causes of death after head injury. Our study comprised a large consecutive series of CT-scanned head injuries from one university hospital's emergency department (n=1,941). First, we examined the incidence of surgically treated PTH. Second, we examined the incidence of surgically treated cSDH after normal initial CT scan. Third, we compared long-term survival and causes of death between our cohort of patients with head injuries and matched population controls.

The incidence of surgically treated PTH was 0.15% (3 per 1,941) in the whole cohort during the six-month follow-up. Incidence was 0.08% (1 per 1,269) among patients with mild TBI and 1.1% (2 per 187) among those with moderate-to-severe TBI. The incidence of PTH among patients who underwent neurosurgery for acute traumatic intracranial lesions was 2.7% (3 per 111). Our three patients with PTH underwent ventriculoperitoneal shunt surgery within two-to-five months of injury.

Two (n=2) of the 1,573 CT-negative patients received surgical treatment for cSDH. Consequently, the incidence of surgically treated cSDH after normal initial head CT during the six-month follow-up was 0.13%. One of the two patients was on antithrombotic medication at the time of trauma; hence, the incidence of surgically treated cSDH among patients with antithrombotic medication in CT-negative patients (n=376) was 0.27%. Both patients who developed surgically treated cSDH were elderly women (>70 years); hence, the incidence of cSDH in the age group of over-70 years old (n=506) was 0.40%.

Long-term survival was reduced in patients with head injuries compared to their matched population controls in our ten-year follow-up study. Excluding those who died during the first year post-injury, the HR for death was 1.84 when comparing patients to controls. Death rates were higher among patients up to five years post-injury. Analyses of specific causes of death revealed that unintentional and traumatic causes (9.6 vs 4.4%) and alcohol-related causes (8.4 vs 1.9%) differed significantly between groups, with greater proportions among patients with head injuries. When

comparing patients with different TBI severities to their controls, also patients with no documented TBI had reduced survival, and TBI severity was associated with additional increase in mortality risk. In multivariate analysis containing only patients, patient characteristics rather than injury-related factors were associated with elevated risk for death: age, male sex, pre-existing conditions, chronic alcohol use, and regular substance abuse were significantly associated with decreased survival.

6.1.1 Incidence of Post-traumatic Hydrocephalus

The incidence of surgically treated PTH among our cohort of 1,941 patients undergoing acute head CT was 0.15%. The incidence was 0.08% among patients with mild TBI and 1.1% among patients with moderate-to-severe TBI. All three patients who developed PTH underwent acute neurosurgery for intracranial bleeding due to the index injury. The incidence of surgically treated PTH among patients undergoing acute neurosurgery was 2.7%. No patients who did not undergo acute neurosurgery due to head trauma developed surgically treated PTH. Our three PTH patients underwent ventriculoperitoneal shunt surgery within two-to-five months following injury.

The literature on PTH is limited. In our study, PTH incidence was lower than previously reported. Earlier studies show percentages of patients experiencing PTH ranging from 0.7 to 51.4%[5], [7], [8], [9], [10]. A recent Taiwanese study with a large retrospective cohort (n=23,775) reported PTH incidences of 0.48% for patients without traumatic SAH and 1.98% for patients with traumatic SAH[7]. That study included patients with all TBI severities. PTH occurrence was highest during the first three months after head trauma, but the exact time from injury to PTH occurrence was not reported. Wettervik et al.[10] reported that 3.5% of patients with TBI treated in a neurointensive care unit (n=836) experienced PTH.

We found three studies that describe the temporal profile of PTH. Mazzini et al.[9] studied 140 patients with severe TBIs, with the mean time from injury to shunt surgery being 55 days (45% experienced PTH). Kammersgaard et al.[99] had a similar result: among 444 patients with severe TBIs, more than 75% of cases that developed PTH did so within eight weeks (56 days) from the index injury (14% had PTH in that study). Wetterwik et al.[10] reported a median time of 5 months from injury to shunt surgery in a cohort of 836 patients treated in neurointensive care (3.5% experienced PTH).

The percentages of people with PTH vary widely across studies for several reasons, such as differences in sample size and in inclusion and exclusion criteria. Selection bias can occur when subgroups of patients with varying prevalences of PTH-predisposing factors are studied. There are several guidelines on the use of head CT for patients with acute head injury[91], [189], [190]. In clinical practice, patients are scanned if certain risk factors for traumatic intracranial lesions are evident. Of course, not all patients with minor head injuries are imaged. We excluded patients with head trauma who were not scanned during the first 48 hours after injury. Consequently, PTH incidence among all patients presenting to the emergency department following head injury is probably even lower than in our study.

It is important to note that the applied diagnostic criteria for PTH differ between studies[8]. PTH diagnosis is generally based on clinical presentation and radiological findings[7], [106]. A more reliable diagnosis is established with the inclusion of shunt responsiveness in the diagnostic criteria[92]. Additionally, register studies may include other types of treated hydrocephalus, separate from PTH, after head trauma. Ventriculomegaly after severe TBI is a relatively common finding[9]. Difficulty distinguishing PTH from atrophy, especially in patients with ambiguous clinical presentation, has led to a search for new diagnostic methods[6], [100], [118], [119]. To date, no universal criteria for PTH have been established[99]. Our study was based on patients with PTH who benefited from shunt surgery, and non-traumatic hydrocephalus cases were excluded by careful evaluation of medical records and head CT scans. Another factor that complicated comparing our results to previous studies was the use of term "incidence" in the prior literature. Not all studies we examined reported clearly whether they reported true incidence or only the percentage or number of patients experiencing PTH in a trauma cohort.

We were not able to conduct statistical analyses to examine pre-operative and perioperative risk factors for surgically treated PTH, given that there were only three cases. Interestingly, however, all our head trauma patients who developed surgically treated PTH underwent acute neurosurgery for intracranial bleeding. In the previous literature, increased age, intraventricular hemorrhage, subarachnoid hemorrhage, cerebrospinal fluid infection, decompressive craniectomy, and the presence of subdural hygroma have been reported to predispose patients to PTH[8], [106], [108], [191], [192]. All three of our patients who developed surgically treated PTH had at least one of these risk factors: SAH, subdural hygroma, or increased age. None of the patients in our cohort who underwent decompressive craniectomy (n=14) developed PTH in the six-month follow-up period, although this surgery is considered an independent risk factor for PTH[8], [120], [191], [193]. The

percentages of patients experiencing PTH after decompressive craniectomy due to a head injury are 26–30% in previous studies[102], [103], [104].

6.1.2 Incidence of Chronic Subdural Hematoma

The incidence of surgically treated cSDH after head injury in adults with normal initial head CT was 0.13% in our cohort during the six-month follow-up. The incidence of surgically treated cSDH among patients with antithrombotic medication was 0.27% and 0.40% among patients over 70 years old.

The prevalence of abnormal initial CT scan after mild head injury has been reported to range from 6.9–29%[194], [195], [196] in the prior literature. In our cohort, 19% had acute intracranial pathology or any type of subdural fluid collection present in the initial CT scan.

The overall incidence of cSDH is well-reported in the prior literature. The annual incidence of cSDH in an adult population was 18/100,000 in a study performed in the same region as ours[12]. The incidence was very low in patients under 60 years of age but was significantly higher in older age groups. The incidence was highest in people aged 80 years or older (130/100,000/year), in which it nearly tripled within the study period of 25 years (1990 to 2015).

Instead, little is known about the development of cSDH in patients with head injuries who have normal initial head CT scans. The only study examining consecutive CT-scanned patients after head trauma has been published recently by a Japanese group. Karibe et al. examined cSDH formation after mild head trauma in elderly (>65 years) Japanese patients. Surgically treated cSDH was diagnosed in 4.3% of patients with normal initial CT scans (n=322) at more than one month after injury[24]. In this study, antithrombotic medication did not increase the risk for cSDH, although antithrombotic medications were not discontinued or counteracted.

Additionally, a few case reports on this topic have been published. Chia et al. reported a case of an 84-year-old man with a normal initial CT scan after minor head injury who developed symptomatic cSDH after two months[21]. The patient was not on antithrombotic medication at the time of injury. Deitch et al. reported that two patients with normal initial CT scans after minor head injury developed cSDH after several weeks; their use of antithrombotic medication was not documented[22]. Snoye et al. published a case report of three patients suffering minor head injuries with normal initial head CT scans who developed cSDH in a mean time of seven weeks; their use of antithrombotic medication was not documented[23]. Kim et al.

published a case report of an 82-year-old man with normal initial CT and MRI scans after a mild head injury, who was diagnosed with a cSDH after five weeks[25]. The patient was not on antithrombotic medication at the time of injury.

Our study had a notably lower incidence rate of surgically treated cSDH compared to the results published by Karibe et al. The lower incidence rate could be related to the nature of our cohort. The mean age among CT-negative patients in our study was 56 years, while Karibe et al. reported a considerably higher mean age of 82 years for the whole cohort. The incidence of cSDH has been shown to increase steeply with age[12]. Therefore, the large difference in the mean ages of our samples might partly explain the notable difference in cSDH incidences. In our study, both patients with surgically treated cSDH were elderly women aged 77 and 78 years. The incidence of cSDH in the age group of over 70 years old was 0.40%, which is still considerably lower than the incidence reported by Karibe et al. Another factor that might have affected the incidences in our studies was the different follow-up practices. Karibe at al. screened all patients with head CT scans one month post-injury for the detection of cSDH and followed the patients for up to 12 months for the detection of symptomatic cSDH, while there was no structural follow-up in our study. Although the main outcome result in our study was the surgical treatment of cSDH, an outcome that should be present in all patients with symptomatic cSDH, some cSDH cases might have been undiagnosed.

The use of antithrombotic medication has been considered as a primary reason for the increasing incidence of cSDH in the elderly[12]. The incidence of surgically treated cSDH among patients with antithrombotic medication was 0.27% in all CT-negative patients. Overall, the risk for delayed intracranial hemorrhage after head trauma seems to be low based on the prior literature. A recent meta-analysis studied delayed intracranial hemorrhage in patients on DOACs (n=1,263) and warfarin (n=1,788). Delayed intracranial hemorrhage was reported in 2.4% of patients on DOAC and 2.3% of patients on warfarin after blunt head trauma[197]. In this meta-analysis, the duration of the follow-up periods varied, with the maximum being just one month. Ghenoweth et al. reported an intracranial hemorrhage incidence of 0.4% for patients without any antithrombotic medication after blunt head trauma in a follow-up period of two weeks[198]. While our study focused purely on the development of cSDH, these studies examined all intracranial hemorrhages and had very short follow-up periods in relation to development of cSDH. Our study supports the idea that head trauma patients with normal initial head CT do not require routine follow-up CT. The risk for symptomatic cSDH among patients with antithrombotic medication seems to be very low as well.

There remain uncertainties relating to the etiology of cSDH. In 1857, Virchow[17] described the condition as "pachymeningitis hemorrhagica chronica interna," and this inflammation theory was widely accepted at the time. Subsequently, a traumatic etiology[18] has been emphasized. Recently, aging and brain degeneration[19] have been highlighted as principal causative factors underlying the condition. Although we cannot draw conclusions based on our results about the etiology, the extremely small incidence in our study partly questions the purely traumatic etiology of cSDH.

6.1.3 Mortality and Causes of Death

Long-term survival was reduced in patients with head injuries compared to their matched population controls in this ten-year follow-up study. After excluding those who died during the first year post-injury, the HR for death was 1.84 when comparing patients to controls. Death rates were higher among patients up to five years post-injury. Analyses of specific causes of death revealed that unintentional and traumatic causes (9.6 versus 4.4%) and alcohol-related causes (8.4 versus 1.9%) differed significantly between groups, with greater proportions among patients with head injuries. When comparing patients with different TBI severities to their controls, patients with no documented TBI had reduced survival and TBI severity was associated with additional increase in mortality risk. In a multivariate analysis containing only patients, patient characteristics rather than injury-related factors were associated with elevated risk for death: age, male sex, pre-existing conditions, chronic alcohol use, and regular substance abuse were significantly associated with decreased survival.

Increased long-term mortality after TBI has been reported in prior studies[26], [28], [29], [30], [31], [33]. It is thought that individuals who experience head and brain injuries have increased mortality risk at baseline, prior to injury, and that head injury causes an additional increase in mortality risk[29]. Furthermore, reduced long-term survival has been reported for trauma patients in general, not just for patients with head and brain injuries[168]. Because long-term mortality risk has been reported to be elevated even in patients with mild head injuries, it has been suggested that factors other than the traumatic injury could be the causal factors for both TBI and cause of death in many cases[31]. After excluding those who died during the first year post-injury, the HR for death was 1.84 when comparing patients to controls in our study.

Similar mortality figures of about twofold have been reported by other studies[26], [28], [29], [33].

Causes of death have been found to differ between individuals with a history of TBI versus their controls without it[29], [32]. Similar to the decreased survival of TBI patients, it is not clear whether this is due to pre-existing conditions and lifestyle factors or the TBI itself. A limitation of many previous studies examining long-term mortality is that index traumas—the traumas that result in individuals being recruited in these studies—are included in the mortality analyses[29], [30], [32]. In our study, analyses of specific causes of death revealed that unintentional and traumatic causes (9.6 versus 4.4%) and alcohol-related causes (8.4 versus 1.9%) differed significantly between groups, with greater proportions among patients with head injuries, among those who survived more than one year. After excluding patients coded as having died from the index injury, unintentional and traumatic causes were still overrepresented among patients (9.1 versus 4.4%, $P<0.001$), with almost the same degree of proportional difference. Several other studies have found patients with head injuries to be at greater risk for death from traumatic and external causes compared to controls, both in settings that have included the acute phase[28], [29], [30], [34] and in those that have excluded it[33], [34]. Overrepresentation in alcohol-related causes of death has also been reported[180].

In our analysis of immediate causes of death between patients and controls who survived more than year, only aspiration pneumonia and epileptic causes differed statistically significantly between patients and controls, with overrepresentation among patients. Pneumonia[26], [36], [37], specifically aspiration pneumonia[26], [36], and respiratory causes in general[27], [28], [35], as well as epileptic cause[35], [36], have been reported to be overrepresented as causes of death in patients with head injuries in other studies as well. Most past studies that have found pneumonia and epileptic causes to be overrepresented have studied only patients with more severe forms of TBI.

Much of the reduced survival among patients with head injuries might be due to factors not directly related to brain injury. First, compared to controls, patients with no documented TBIs had reduced survival as well. Similar findings have been reported in the past[30], [33]. Second, underlying causes of death differed only among unintentional and traumatic and alcohol-related causes, suggesting consequences of lifestyle factors. Other studies have reported similar results[28], [29], [30], [33], [34], [180]. Third, patient characteristics rather than injury-related factors were associated with elevated risk for death in our multivariate model. Similar associations with decreased survival and patient demographics have been published

in other studies regarding older age[26], [27], [31], [36], [174], [175], male sex[27], [29], [36], and presence of pre-existing conditions[26], [29], [31], [169]. However, in subgroup analyses comparing patients to their matched controls, TBI severity was associated with increased mortality risk, suggesting that TBI might have its own effect on mortality. Adjusting for confounding factors other than age, sex, and place of residence was not possible when comparing patients to controls due to the methodological limitations of the present study. In studies that have had information about the demographics and characteristics of controls, and which have therefore been able to adjust for confounding factors, traumatic brain injury has still been found to be an independent risk factor for reduced survival[31], [33].

6.2 Strengths and Limitations

Our study represents an extensive retrospective series of consecutive head injury patients from one geographically well-defined area. All patients were evaluated and scanned in the emergency department of one university hospital. All initial head CT scans were evaluated by two neuroradiologists. Considering the development of cSDH, rigorous analysis of the head CT scans was performed to examine only patients with genuinely normal head CT regarding the primary trauma: CT-negative patients had no signs of acute traumatic intracranial pathology or any type of subdural collection on initial head CT. Although our study was not population-based, it reflects the incidence of surgically treated PTH and cSDH in head trauma patients in Pirkanmaa, Finland. These results are comparable to those of populations similar to Finland, with an aging population and GLF as the main causes of TBI[199].

Considering the mortality analyses, strengths of our study include its large sample size, extensive data relating to patient demographics and injury characteristics, and accurate mortality data. Our relatively large sample enabled greater statistical power compared to studies with smaller samples. Detailed data collection of patient demographics and injury characteristics was possible because all patients with head injuries were identified from the records of a single university hospital. Comparison of mortality was accurate in part because mortality data were obtained from one source. An additional strength of this study is that we reviewed the death certificates of all patients who were coded as having died of external causes to ensure that index traumas were not incorrectly interpreted as secondary traumatic causes of death caused by new traumas occurring during the follow-up.

Our study has several limitations. Due to the retrospective design, not all desired data was available. CT-scanning practice might have influenced the composition of our cohort because only CT-scanned patients were recruited to the study. However, our sample included a significant number of patients who were scanned without clear clinical signs of TBI documented in their medical records. The sample likely captures the full severity spectrum of head injuries treated in a university hospital's emergency department.

The very low numbers of cases with surgically treated PTH and cSDH increase the uncertainty of the results. Hence, generalization of these results to a larger scale is challenging. Studies with larger patient cohorts are needed to validate the results. The lack of a systematic follow-up for the detection of PTH and cSDH means that some cases of PTH and cSDH could have been missed. The patients were followed up at different time points post-injury on a purely clinical basis. Most patients were evaluated by a neurosurgeon only if neurosurgically treatable problems were suspected. Therefore, this follow-up practice might have increased the probability of missing PTH and cSDH cases. This is particularly true for patients with mild or no symptoms. However, we estimate the rate of missed cases to be low because patients with head and brain injuries, their family members, and their healthcare professionals are instructed to contact the neurosurgical department if new worrisome signs or symptoms emerge after injury. Another limitation of our study is that the number of cases was too small for PTH and cSDH risk factor analyses or meaningful measurements of the temporal profiles of PTH or cSDH, and thus we could not address all our *a priori* research questions. This study did not analyze the development of cSDH among patients with subdural hygromas on their initial CT scans due to the lack of univocal criteria for subdural hygromas. This is an interesting research question and should be specifically addressed in future studies.

Regarding the mortality analyses, several limitations exist. Due to confidentiality reasons, data relating to the demographics and characteristics of the controls were not possible to obtain. This meant that it was only possible to conduct analyses of factors associated with decreased survival among patients. The use of population controls, versus hospital controls, might have overestimated the association between head injury and mortality because individuals admitted to the hospital for any reason are likely at increased risk for reduced survival compared to the general population. Additionally, most of the patient data was collected retrospectively from hospital records, and hence some relevant information was missing (e.g., admission GCS). This may have biased our estimation of the relationship between injury characteristics and mortality findings.

6.3 Directions for Future Research

Given the very low incidences of PTH and cSDH observed in our study, similar studies with larger patient cohorts are needed to replicate and validate the results. Additionally, larger cohorts are needed, with enough cases with the primary outcome (PTH and cSDH) to examine risk factors, temporal development, and optimal treatment modalities.

New examination methods might help improve the diagnosis of PTH when the diagnosis is unclear based on clinical assessment and routine radiological findings. Future applications of diffusion tensor imaging might be useful in distinguishing true hydrocephalus from ventriculomegaly[6]. Additionally, studies on CSF dynamics[100], [117], [118] have shown that parameters such as resistance to CSF outflow and pulse amplitude of intracranial pressure might be useful in selecting patients with PTH who may benefit from ventriculoperitoneal shunting. Blood-based biomarkers (e.g., S100B)[119] also show promise for predicting the development of PTH. Chen et al.[120] have introduced a risk-scoring system based on clinical characteristics for predicting PTH after TBI, with promising results. Endoscopic third ventriculostomy might be a useful treatment option for PTH, even though this intervention has been considered contraindicated for PTH in the past[128], [129]. Uniform diagnostic criteria for PTH in future studies would facilitate better comparison of scientific findings.

Epidemiological studies of populations with verified head traumas and case-control matching with patients without trauma could provide more information about traumatic versus non-traumatic etiologies of cSDH. Given the very low incidence of cSDH observed in our study, future studies with larger patient cohorts are needed to validate the results and study the risk factors for the condition. A prospective study design including structural follow-up for the development cSDH, as in Karibe et al.'s study[24], should be considered when planning future research.

The effects of traumatic head and brain injury on mortality need further research. Sufficiently large samples are needed to identify the potentially very minor effects of head and brain injury on mortality. The use of hospital or other trauma controls could facilitate better adjustment for confounding factors. Follow-up time needs to be sufficiently long to allow for the possible development of head and brain injury-related conditions. Subgroup analyses among different trauma types and severities are vitally important given the heterogenous etiology of head and brain injury.

7 CONCLUSIONS

The main outcomes of the thesis can be summarized as follows:

1. The incidence of surgically treated post-traumatic hydrocephalus among patients with traumatic head injuries of all severities was very low but not negligible, especially among patients who had undergone surgery because of the index head injury.

2. The incidence of surgically treated chronic subdural hematoma after normal initial head computed tomography, among patients with traumatic head injuries, was extremely low. The low incidence of surgically treated chronic subdural hematoma, even in patients on antithrombotic medication, supports the notion that routine follow-up imaging after normal initial head computed tomography is not indicated to exclude the development of chronic subdural hematoma.

3. Long-term survival was reduced in patients with traumatic head injuries. A large part of the reduced survival was associated with patient characteristics rather than injury severity-related factors, but traumatic brain injury severity seemed to have its own additional effect on mortality. Unintentional and traumatic causes, even after excluding the index injuries, and alcohol-related causes of death were more common among patients with head injuries compared to controls.

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PUBLICATIONS

PUBLICATION I

Incidence of surgically treated post-traumatic hydrocephalus 6 months following head injury in patients undergoing acute head computed tomography

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ORIGINAL ARTICLE - CSF CIRCULATION

Incidence of surgically treated post-traumatic hydrocephalus 6 months following head injury in patients undergoing acute head computed tomography

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Abstract

Background Post-traumatic hydrocephalus (PTH) is a well-known complication of head injury. The percentage of patients experiencing PTH in trauma cohorts (0.7–51.4%) varies greatly in the prior literature depending on the study population and applied diagnostic criteria. The objective was to determine the incidence of surgically treated PTH in a consecutive series of patients undergoing acute head computed tomography (CT) following injury.

Methods All patients ($N=2908$) with head injuries who underwent head CT and were treated at the Tampere University Hospital's Emergency Department (August 2010–July 2012) were retrospectively evaluated from patient medical records. This study focused on adults (18 years or older) who were residents of the Pirkanmaa region at the time of injury and were clinically evaluated and scanned with head CT at the Tampere University Hospital's emergency department within 48 h after injury ($n=1941$). A thorough review of records for neurological signs and symptoms of hydrocephalus was conducted for all patients having a radiological suspicion of hydrocephalus. The diagnosis of PTH was based on clinical and radiological signs of the condition within 6 months following injury. The main outcome was surgical treatment for PTH. Clinical evidence of shunt responsiveness was required to confirm the diagnosis of PTH.

Results The incidence of surgically treated PTH was 0.15% ($n=3$). Incidence was 0.08% among patients with mild traumatic brain injury (TBI) and 1.1% among those with moderate to severe TBI. All the patients who developed PTH underwent neurosurgery during the initial hospitalization due to the head injury. The incidence of PTH among patients who underwent neurosurgery for acute traumatic intracranial lesions was 2.7%.

Conclusion The overall incidence of surgically treated PTH was extremely low (0.15%) in our cohort. Analyses of risk factors and the evaluation of temporal profiles could not be undertaken due to the extremely small number of cases.

Keywords Post-traumatic hydrocephalus · Traumatic brain injury · Ventriculoperitoneal shunt · Neurosurgery

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Introduction

Traumatic brain injury (TBI) is a significant cause of both mortality and morbidity [8]. Post-traumatic hydrocephalus (PTH) is a well-known complication of TBI [31]. PTH signs and symptoms (e.g., headache, nausea, cognitive dysfunction, ataxia, obtundation, a tetrad of psychomotor retardation, memory loss, gait trouble, and urinary incontinence [1, 33]) overlap with the signs and symptoms of the primary injury, which makes the condition difficult to diagnose in some cases [11]. A classic clinical feature to suspect PTH after TBI is poor improvement or stagnation of recovery [11, 32]. Early recognition of PTH is essential in the follow-up of patients with TBIs, as cerebrospinal fluid diversion (ventricular shunting) has been shown to improve outcome during rehabilitation [27, 41].

PTH diagnosis is generally based on a combination of clinical signs, symptoms, and radiological findings [11, 13, 18]. Various criteria for PTH diagnosis have been suggested, but no universal criteria have been established [25]. The percentage of patients experiencing PTH in trauma cohorts varies broadly from 0.7 to 51.4% [2, 4, 11, 31, 42]. The broad range is largely explained by the differences in the study population, applied diagnostic criteria, and the individual study designs [4]. A recent Taiwanese study with a large retrospective cohort ($n = 23{,}775$) reported a very low incidence of PTH, only 0.48 to 1.98% [11]. In that study, PTH incidence peaked within three months after injury. Those patients with subarachnoid hemorrhage (SAH) had a threefold risk of developing PTH compared to patients with no SAH during the 2-year follow-up period. Earlier studies with lower numbers of cases ($n = 139$–444) are inconsistent regarding SAH as a risk factor for PTH [24, 25, 38]. Also, decompressive craniectomy [13, 17] and the presence of subdural hygroma after craniectomy [29] seem to increase the risk for PTH. In craniectomy, the proximity of the craniotomy to the skull midline [4, 43] might increase the risk as well. Other possible risk factors for PTH increased age, cerebrospinal fluid infection, and intraventricular hemorrhage [4, 13]. Inflammation-mediated adhesions related to intracranial hemorrhages can explain the predisposition to PTH [36]. In children, PTH incidence also varies greatly depending on study population and applied diagnostic criteria. However, pediatric PTH incidence is suspected to be lower compared to adults [16, 35, 40]. Similar to adults, severe TBI, decompressive craniectomy, and SAH have been reported to increase the risk for PTH in children [9, 40]. Additionally, unique pediatric PTH risk factors include young age, electrolyte disorder, and weight loss [7, 9, 35].

As a relatively rare condition with signs and symptoms that are sometimes elusive or difficult to differentiate from the primary injury, PTH remains a diagnostic challenge. The literature regarding PTH is limited. It has been shown that the treatment of PTH is beneficial [41]. The objective of this study was to determine the incidence of surgically treated PTH within 6 months from head injury in a series of consecutive adult patients undergoing acute head CT following injury. A specific interest was to document the time interval between the injury and the manifestation of PTH. We also aimed to determine if there are any identifiable pre- or peri-injury risk factors for surgically treated PTH.

Methods and materials

Material and ethics

This study is a part of the Tampere Traumatic Head and Brain Injury Study. All consecutive patients with head injuries who underwent acute CT, treated at the Tampere University Hospital's Emergency Department between August 2010 and July 2012, were retrospectively evaluated from hospital's patient records. There was a total of 3023 head injuries in 2908 patients during this 2-year period. Data collection included a 6-month follow-up period for PTH. The length of the follow-up period was based on the most likely occurrence time of PTH reported in prior studies [11, 19, 25, 31, 42].

This study focused on adult (18 years or older) patients who were residents of the Pirkanmaa region at the time of injury and were clinically evaluated and scanned with head CT at the Tampere University Hospital's emergency department within 48 h ($\leq$48 h) after head injury. Patients who had suffered more than one head injury during the study period were included once in the study sample with the initial head injury as the index injury. A total of 1941 adult patients undergoing acute head CT following injury were identified. A flowchart of the study sample is provided in Fig. 1.

The Pirkanmaa region is a geographically well-defined area with both rural and urban areas that holds one of Finland's five university hospitals with a neurosurgical service (Tampere University Hospital, Tampere, Finland). During the study period, Pirkanmaa had 490,000 residents, which comprised 9% of the total population of Finland (5.4 million) at the time. In addition to Tampere University Hospital, there is one local hospital with a CT scanner used for patients with head injuries in the Pirkanmaa region. However, most of the head trauma patients, and all the patients requiring neurosurgical care, are evaluated at the Tampere University Hospital.

The study was approved by the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland (ethical

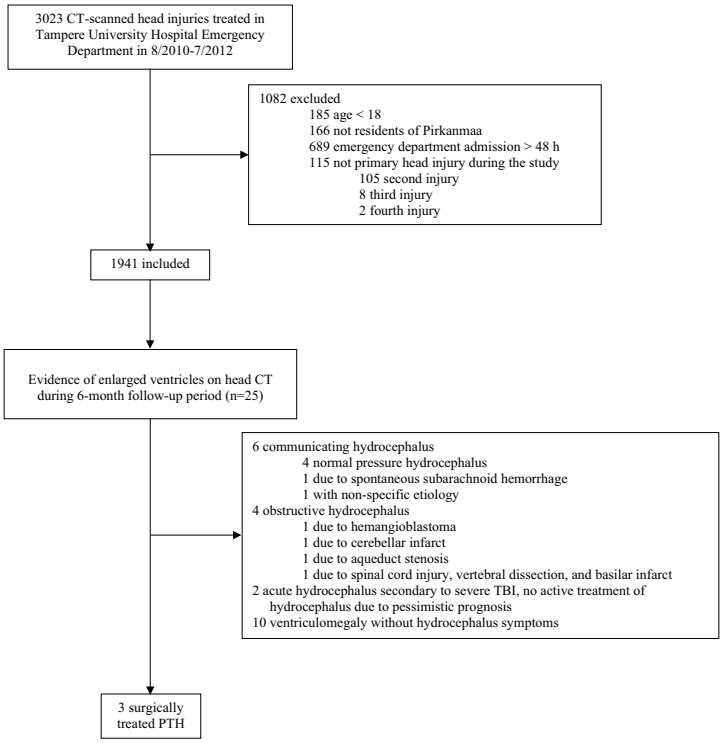

Fig. 1 Study profile. *CT* computed tomography, *TBI* traumatic brain injury, *PTH* post-traumatic hydrocephalus

code: R10027). All data was collected retrospectively without contacting the patients; therefore, no written informed consent was obtained or required.

Data collection

A detailed and structured data collection was performed from the medical records. Two neuroradiologists examined all the head CT scans. Study data were collected before the National Institution of Neurological Disorders and Stroke Common Data Elements (CDEs) [15] for TBI imaging were established. However, all CDEs possible with non-contrast structural CT were included [23]. Variables collected included demographics, antithrombotic medication (including anticoagulants and antiplatelets), injury-related information, clinical TBI indices, emergency head CT findings (acute traumatic lesions), acute neurosurgery due to TBI, and follow-up findings in relation to PTH. Minimal criteria for TBI were based on the World Health Organization's (WHO) definition [10]. Cases with Glasgow Coma Scale (GCS) score < 13 after 30-min postinjury, post-traumatic amnesia more than 24 h, and/or loss of consciousness more than 30 min were coded as moderate to severe TBI. There was a considerable number of patients with missing GCS scores. Based on other clinical findings and examinations reported in the patient medical records, and the lack of reported low GCS or other sign of more severe TBI, these patients were coded as having a mild TBI or no TBI.

A thorough review of records for neurological signs and symptoms of hydrocephalus was conducted for all patients having a radiological suspicion of hydrocephalus/ventriculomegaly. The diagnosis of PTH was based on clinical and radiological signs of the condition. The main outcome variable was specified as *surgically treated post-traumatic hydrocephalus* to rule out conditions not requiring treatment, such as post-traumatic ventriculomegaly resulting from secondary atrophy. Additionally, clinical evidence of shunt responsiveness (i.e., improvement in preoperative PTH signs and symptoms) was required. Patients with other apparent causes for hydrocephalus (e.g., normal pressure hydrocephalus diagnosis prior to injury and obstructive hydrocephalus

due to posterior fossa lesions) were considered to have non-traumatic hydrocephalus.

Statistical analysis

IBM SPSS Statistics for Windows (version 27, IBM Corp.) was used for data analyses. We used Kolmogorov–Smirnov test to examine variable distribution. Descriptive statistics (frequency, percentage, median, interquartile range (IQR)) were used to describe variable characteristics.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Characteristics of the cohort

The cohort included 1941 patients with the median age of 59 years. Of the 1941 patients, 1122 (58%) were men. The most common mechanism of injury was a ground-level fall (GLF) in 1016 (52%) patients. Alcohol intoxication was reported for 567 (29%) patients and 494 (26%) patients were on antithrombotic medication at the time of injury. Loss of consciousness was documented in 417 (22%) patients and amnesia in 510 (26%) patients. GCS scores were not reported for a third of the patients ($n = 663$, 34%). Among patients with reported GCS scores, the scores were distributed as follows: 57% ($n = 1100$) arrived at the emergency department with a GCS score of 13–15, 5.0% ($n = 97$) of patients with a GCS score of 9–12, and 4.2% ($n = 81$) of patients with a GCS score of 3–8. The majority of the patients, 1269 (65%), had a mild TBI. Moderate to severe TBI was reported for 187 (9.6%) patients, and 485 (25%) patients did not have evidence of TBI in their records. The most frequent acute traumatic lesions on admission head CT were a subdural hematoma (acute and/or chronic) in 254 (13%) patients and subarachnoid hemorrhage in 216 (11%). Emergency trauma neurosurgery was performed on 111 (5.7%) patients. Characteristics of the study cohort are summarized in Table 1.

Post-traumatic hydrocephalus

Only three patients were diagnosed and surgically treated for clinically and radiologically diagnosed PTH during the 6-month follow-up period. A ventriculoperitoneal shunt was placed in all of these patients. The three patients were reported to benefit from the shunt, but there was no systematic follow-up after the PTH diagnosis and surgical treatment. A positive response to shunt surgery was based on the information reviewed from the patient records. If there was consistent clinical improvement after the shunt operation and no other distinct cause for it, the patient was considered to benefit from the shunt. As a result, the incidence of surgically treated PTH in our cohort was 0.15% (Table 1). One of the surgically treated PTH patients had a mild TBI, and thus, the incidence of PTH among mild TBI patients was 0.08% (1 per 1269). Two of the three patients had a moderate TBI, and the incidence of PTH among moderate to severe TBI patients was 1.1% (2 per 187). All the surgically treated PTH cases underwent acute neurosurgery due to the index head trauma. The incidence of surgically treated PTH among patients undergoing acute neurosurgery was 2.7% (3 per 111).

Of the three patients with PTH, two were men aged 56 and 87 years, and one was a 62-year-old woman. Both men sustained a moderate TBI and the woman sustained a mild TBI. GLF was the injury mechanism for all three patients. The 87-year-old man was on antithrombotic medication (warfarin) at the time of trauma. Alcohol intoxication was reported for the 56-year-old man and for the 62-year-old woman. Acute traumatic lesions were seen in all three patients: contusions and acute subdural hematoma (SDH) in all patients and SAH in two patients (both of the men). All three patients underwent acute neurosurgery during the initial admission. The 56-year-old man underwent evacuation of intracranial contusion hemorrhage and SDH through craniotomy. An acute SDH craniotomy was performed on the 87-year-old man. An emergency trepanation and evacuation of a subdural hygroma were performed on the woman. The surgically treated PTH patients had 2, 5, and 5 months of delay between the index injury and the shunt surgery. A detailed description of all patients with surgically treated PTH within 6 months after injury is presented in Table 2. Due to the small number of cases ($n = 3$), group analyses on possible PTH risk factors were not performed.

Other hydrocephalus after head trauma

Two patients among our cohort of 1941 patients experienced acute hydrocephalus secondary to severe TBI, and their initial CT scan revealed enlarged ventricles. These two patients underwent acute neurosurgery because of their severe TBI, and they initially had a very poor prognosis. During the initial hospital admission, both of these patients died due to complications related to the severe TBI. The active treatment of hydrocephalus in these moribund cases was considered

Table 1 Characteristics of the study cohort ($n=1941$)

Variable		
Age median, years (IQR)	58.7 (39.1–58.7)	
	n	%
Men	1122	57.8
Cause of injury		
Ground-level fall	1016	52.3
Motor vehicle accident	261	13.4
Fall from a height	215	11.1
Traffic accident as pedestrian or bicyclist	116	6.0
Other	333	17.2
Alcohol intoxication	567	29.2
Antithrombotic medication	494	25.5
Loss of consciousness	417	21.5
Amnesia	510	26.3
Glasgow Coma Scale		
13–15 points	1100	56.7
9–12 points	97	5.0
3–8 point	81	4.2
Unknown	663	34.2
Traumatic brain injury severity		
No traumatic brain injury	485	25.0
Mild	1269	65.4
Moderate to severe	187	9.6
Acute traumatic lesion on head CT-scan		
Subdural hematoma (acute and/or chronic)	254	13.1
Subarachnoid hemorrhage	216	11.1
Contusion	152	7.8
Intraventricular hemorrhage	54	2.8
Epidural hematoma	14	0.7
Diffuse axonal injury	7	0.4
Emergency neurosurgery due to acute traumatic brain injury	111	5.7
Decompressive craniectomy	14	0.7
Shunted post-traumatic hydrocephalus within 6-month post-injury	3	0.15

IQR, interquartile range; *CT*, computed tomography

as disadvantageous and no surgical interventions for hydrocephalus were performed.

In addition, 10 cases of non-traumatic hydrocephalus who underwent neurosurgery were recognized either on the first head CT or during the follow-up period. These hydrocephalus cases were categorized as obstructive hydrocephalus ($n=4$) and communicating hydrocephalus ($n=6$). The etiologies for obstructive hydrocephalus cases were hemangioblastoma, cerebellar infarct, aqueduct stenosis, and cervical spinal cord injury with vertebral dissection and basilar infarct. The communicating hydrocephalus cases were due to normal pressure hydrocephalus ($n=4$), spontaneous SAH, and one with a non-specific etiology. The six patients with communicating hydrocephalus had pre-existing symptoms and enlarged ventricles before or at the time of head trauma.

Discussion

Summary of the key findings

The incidence of surgically treated PTH among our cohort of 1941 patients undergoing acute head CT was 0.15%. The incidence was 0.08% among patients with mild TBI and 1.1% among patients with moderate to severe TBI. All three patients who developed PTH underwent acute neurosurgery for intracranial bleeding due to the index injury. The incidence of surgically treated PTH among patients undergoing acute neurosurgery was 2.7%. No patients who did not undergo acute neurosurgery due to head trauma developed surgically treated PTH. Our three PTH patients underwent ventriculoperitoneal shunt surgery within 2 to 5 months following injury.

Table 2 Detailed description of patients with post-traumatic hydrocephalus within six months after injury ($n=3$)

Patient	Injury mechanism	TBI severity	CT findings	Acute neurosurgery	Hydrocephalus symptoms	Shunt surgery; delay since injury	Hydrocephalus etiology	Clinical improvement after shunt placement
Woman, age 62	Fall	Mild	Contusion, acute SDH, subdural hygroma	TRP, evacuation of subdural hygroma	Headache, nausea, vertigo	VP, 2 months	PTH	Yes
Man, age 56	Fall	Moderate	Skull fracture, SAH, contusion, acute SDH	CRT, evacuation of ICH and SDH	Disorientation, slowed down	VP, 5 months	PTH	Yes
Man, age 87	Fall	Moderate	SAH, contusion, acute SDH	CRT, evacuation of acute SDH	General malaise	VP, 5 months	PTH	Yes

All mechanisms of injury were ground-level falls. *TBI*, traumatic brain injury; *CT*, computed tomography; *SAH*, subarachnoid hemorrhage; *SDH*, subdural hemorrhage; *CRT*, craniotomy; *ICH*, intracerebral hemorrhage; *PTH*, post-traumatic hydrocephalus; *TRP*, burr hole trepanation; *VP*, ventriculo-peritoneal

Comparison of the current findings to prior literature

The literature on PTH is limited. In our study, PTH incidence was lower than previously reported. Earlier studies show percentages of patients experiencing PTH ranging from 0.7 to 51.4% [2, 4, 11, 31, 42]. A recent Taiwanese study with a large retrospective cohort ($n=23,775$) reported PTH incidence of 0.48% for patients without traumatic SAH and 1.98% for patients with traumatic SAH [11]. In that study, patients with all severities of TBI were included. PTH occurrence was the highest during the first 3 months after head trauma, but the exact time from injury to PTH occurrence was not reported. Wettervik et al. [42] reported that 3.5% experienced PTH among patients treated in neurointensive care unit ($n=836$).

We found three studies that described the temporal profile of PTH. Mazzini et al. [31] studied 140 patients with severe TBIs, with the mean time from injury to shunt surgery being 55 days (45% experienced PTH). Kammersgaard et al. [25] had a similar result. Among 444 patients with severe TBIs, more than 75% of cases that developed PTH, PTH occurred within 8 weeks (56 days) from the index injury (14% had PTH in that study). Wetterwik et al. [42] reported a median time of 5 months from injury to shunt surgery in a cohort of 836 patients treated in neurointensive care (3.5% experienced PTH).

The percentages of people with PTH, across studies, varies widely for several reasons, such as differences in sample sizes and in inclusion and exclusion criteria. Selection bias can occur when subgroups of patients with varying prevalence of factors predisposing to PTH are studied. There are several guidelines on the use of head CT for patients with acute head injury [20, 37, 39]. In clinical practice, patients are scanned if certain risk factors for traumatic intracranial lesions are evident. Of course, not all patients with a minor head injury are imaged. We excluded patients with head trauma who were not scanned during the first 48 h after injury. Consequently, PTH incidence among all patients presenting to the emergency department following head injury is probably even lower than in our study.

It is important to note that the applied diagnostic criteria for PTH differs between studies [4]. PTH diagnosis is generally based on clinical presentation and radiological findings [11, 13]. A more reliable diagnosis is established with inclusion of shunt responsiveness into the diagnostic criteria [32]. Additionally, register studies may include other types of treated hydrocephalus after head trauma separate from PTH. Ventriculomegaly after severe TBI is a relatively common finding [31]. Difficulty distinguishing PTH from atrophy, especially in patients with ambiguous clinical presentation, has led to a search for new diagnostic methods [28, 30, 34, 44]. To date, no universal criteria for PTH have been established [25]. Our study was based on patients with PTH who benefited from shunt surgery and non-traumatic hydrocephalus cases were excluded by careful evaluation of medical records and head CT scans. Another factor that complicated comparing our results to previous studies was the use of term "incidence" in the prior literature. Not all studies we examined reported clearly whether they reported true incidence or only the percentage or number of patients experiencing PTH in a trauma cohort.

We were not able to conduct statistical analyses to examine pre-operative and perioperative risk factors for surgically treated PTH given there were only three cases. Interestingly, however, all our head trauma patients, who developed surgically treated PTH, underwent acute neurosurgery for intracranial bleeding. In the previous literature, increased

age, intraventricular hemorrhage, subarachnoid hemorrhage, cerebrospinal fluid infection, decompressive craniectomy, and the presence of subdural hygroma have been reported to predispose to PTH [4, 13, 24, 29, 38]. All of our three patients who developed surgically treated PTH had at least one of these aforementioned risk factors: SAH, subdural hygroma, or increased age. None of the patients in our cohort who underwent decompressive craniectomy ($n = 14$) developed PTH in the 6-month follow-up period, although this surgery is considered an independent risk factor for PTH [4, 12, 22, 24]. The percentages of patients experiencing PTH after decompressive craniectomy due to a head injury are 26–30% in previous studies [5, 21, 26].

Strengths and limitations

Our study represents an extensive retrospective series of consecutive patients from one geographically well-defined area. All the patients were evaluated and scanned in the emergency department of one university hospital. Although our study was not population-based, it reflects the incidence of surgically treated PTH in head trauma patients in Pirkanmaa, Finland. The results are generalizable for populations similar to Finland, with an aging population and GLF as the main cause of TBI [8].

Our study has several limitations. Due to the retrospective design, not all desired data were available. The lack of a systematic long-term follow-up protocol for all of our TBI patients means that some cases of PTH could have been missed. The patients were followed up at different time points postinjury on a purely clinical basis. The majority of patients were evaluated by a neurosurgeon only if neurosurgically treatable problems were suspected. Therefore, this follow-up practice might have increased the probability of missing PTH cases. However, we estimate the rate of missed cases to be low because TBI patients, family members, and healthcare professional are informed to contact the neurosurgical department if new worrisome signs or symptoms emerge after TBI. In addition, no routine outpatient clinic follow-up was performed with the PTH patients. Another limitation of our study is that the number of cases was too small for PTH risk factor analyses or meaningful measurements of the temporal profile of PTH development, and thus, we could not address all our a priori research questions.

Directions for future research

New examination methods might help improve the diagnosis of PTH, when the diagnosis is unclear based on clinical assessment and routine radiological findings. Future applications of diffusion tensor imaging might be useful in distinguishing true hydrocephalus from ventriculomegaly [34]. Additionally, studies on cerebrospinal fluid (CSF) dynamics [3, 28, 30] have shown that parameters such as resistance to CSF outflow and pulse amplitude of intracranial pressure might be useful in selecting patients with PTH who may benefit from ventriculoperitoneal shunting [34]. Blood-based biomarkers (e.g., S100B) [44] also show promise for predicting the development of PTH. Chen et al. [12] introduced a risk scoring system based on clinical characteristics to predict PTH after TBI with promising results. Endoscopic third ventriculostomy might be a useful treatment option for PTH, even though this intervention has been considered contraindicated for PTH in the past [6, 14].

Literature about PTH is relatively scarce. Uniform diagnostic criteria for PTH in future studies would facilitate better comparison of scientific findings. More studies with larger patient cohorts are needed to have sufficient number of cases with the primary outcome (PTH) to examine risk factors, temporal development, and optimal treatment modalities. Studies on CSF pressure dynamics and newer imaging modalities might lead to improved diagnostic accuracy in unclear cases.

Conclusions

The incidence of surgically treated PTH in our cohort was extremely low (overall 0.15%, mild TBI 0.08%, moderate-severe TBI 1.1%). Analyses of risk factors and the evaluation of temporal profiles could not be undertaken due to the extremely small number of cases.

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Author contribution Study design: TL, JÖ, MR; data collection: TL, MN, AK; statistical analyses: AH; first manuscript draft: AH; manuscript editing: AH, MR, TL, GI, HI; pre-submission manuscript approval: AH, MR, TL, GI, HI, AK, MN, JÖ.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability The code and analyses used are available from the corresponding author upon reasonable request.

Declarations

Ethics approval The study was approved by the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland (ethical code: R10027). All data was collected retrospectively without contacting the patients, therefore no written informed consent was obtained or required.

Conflict of interest Grant Iverson, Ph.D., serves as a scientific advisor for NanoDX®, Sway Operations, LLC, and Highmark, Inc. He has a clinical and consulting practice in forensic neuropsychology, including expert testimony, involving individuals who have sustained mild TBIs. He has received past research funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He acknowledges unrestricted philanthropic support from ImPACT Applications, Inc., the Mooney-Reed Charitable Foundation, the National Rugby League, and the Spaulding Research Institute. None of the above entities was involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. Teemu Luoto has received speaker's fees from Orion Corporation, Novartis Finland, and the Finnish Medical Society Duodecim. Teemu Luoto has also accepted research grants from the Finnish Brain Foundation sr, the Emil Aaltonen Foundation sr, the Maire Taponen Foundation, the Science Fund of the City of Tampere, and the Finnish Medical Society Duodecim. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comments This is a well-written study on the risk of post-traumatic hydrocephalus in well-characterized population based epidemiological cohort with appropriate follow-up. This kind of study is difficult to conduct outside of Scandinavia. The surprisingly low number of HC after unselected TBI describes the rarity of this complication after mild/moderate TBI. Noteworthy, the risk is non-existing in patients not requiring neurosurgical intervention on primary admission.

Ville Leinonen.

Finland.

The authors report on the incidence of post-traumatic hydrocephalus (PTH) in a population within a well-defined geographical area. The records of adult patients who underwent an acute CT scan for head injury at their institution's emergency department between August 2010 and June 2012 were evaluated. Within the first six months, only three developed PTH and required a VP shunt; all demonstrated subsequent clinical improvement. All three had required a neurosurgical procedure in the acute phase. The authors emphasize the rarity of PTH.

The introduction and discussion present a concise but comprehensive overview of the literature on this issue, and explain the rationale for the study. The well-demarcated population base is a major strength of the study, and give it an epidemiological context. Although a significant proportion of patients did not have a recorded GCS at the time of the acute episode, the authors argue that there was enough clinical data on their records to confirm no or mild brain injury in these patients. They reassure the reader that it was unlikely that any patient with PTH would have been missed in this relatively small community neurosurgical service. It is unfortunate that a full analysis of the associations with TBI will require larger population studies.

This is a useful and valuable study. Although PTH is rare, it reminds neurosurgeons and all health care workers that PTH may be difficult to identify after traumatic brain injury but remains a reversible cause of failure to progress and respond to rehabilitation.

Kristian Aquilina.

London,UK.

PUBLICATION
II

Incidence of surgically treated chronic subdural hematoma after head injury with normal initial computed tomography

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ORIGINAL ARTICLE

Incidence of surgically treated chronic subdural hematoma after head injury with normal initial computed tomography

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Abstract

Purpose The objective was to determine the incidence of surgically treated chronic subdural hematoma (cSDH) within six months after head trauma in a consecutive series of head injury patients with a normal initial computed tomography (CT).

Methods A total of 1941 adult patients with head injuries who underwent head CT within 48 h after injury and were treated at the Tampere University Hospital's emergency department were retrospectively evaluated from medical records (median age = 59 years, IQR = 39–79 years, males = 58%, patients using antithrombotic medication = 26%). Patients with no signs of acute traumatic intracranial pathology or any type of subdural collection on initial head CT were regarded as *CT negative* ($n = 1573$, 81%).

Results Two ($n = 2$) of the 1573 *CT negative* patients received surgical treatment for cSDH. Consequently, the incidence of surgically treated cSDH after a normal initial head CT during a six-month follow-up was 0.13%. Both patients sustained mild traumatic brain injuries initially. One of the two patients was on antithrombotic medication (warfarin) at the time of trauma, hence incidence of surgically treated cSDH among patients with antithrombotic medication in *CT negative* patients ($n = 376$, 23.9%) was 0.27%. Additionally, within *CT negative* patients, one subdural hygroma was operated shortly after trauma.

Conclusion The extremely low incidence of surgically treated cSDH after a normal initial head CT, even in patients on antithrombotic medication, supports the notion that routine follow-up imaging after an initial normal head CT is not indicated to exclude the development of cSDH. Additionally, our findings support the concept of cSDH not being a purely head trauma-related disease.

Keywords Chronic subdural hematoma · Computed tomography · CT negative · Head injury

Study performed at Tampere University Hospital.

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Introduction

Chronic subdural hematoma (cSDH) is a frequent neurosurgical condition [26]. The incidence of cSDH is highest in the elderly, with reported incidence rates of 46–58/100,000/year in people over 65 years of age [1, 13, 29]. The incidence has risen presumably because some of the main risk factors of cSDH, including increased age and use of antithrombotic medications, have become more prevalent [29]. Historically, the condition was considered directly trauma related [25]. Especially trauma of the bridging veins of the cerebral cortex was believed to be the origin of bleeding. More complex etiology has been proposed in recent years, although prior trauma has still been considered the main causative factor [14]. cSDH is hypothesized to form in part by an inflammatory process originating from trauma to dural border cells. Inflammatory cells attempt to repair the border cell

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damage—but instead cause membrane and blood vessel formation to the affected subdural region. These fragile and permeable neovessels bleed and result in fluid accumulation to subdural space. The fluid accumulation maintains the inflammatory processes and further promotes the growth of the hematoma which eventually causes the clinical signs and symptoms of cSDH [10]. Spontaneous de novo formation with no preceding trauma has been characterized as well [24]. In addition to trauma, increased age [1, 11], and the use of antithrombotic medication (including anticoagulants and antiplatelets) [2, 6, 7, 12, 30], another risk factor for cSDH is alcohol misuse [25]. Additionally, subdural hygroma, an accumulation of cerebrospinal fluid in the subdural space, has been proposed as an etiologic factor for cSDH [22, 27, 32]. Surgical evacuation of subdural hematoma via burr hole accompanied with subsequent draining remains the primary treatment option for symptomatic patients[33].

There is limited research on the development of cSDH after head traumas with normal initial computed tomography (CT) scans. The prior literature consists mainly of case reports [5, 20]. The objective of this study was to determine the incidence of surgically treated cSDH within six months from a head injury in a series of consecutive adult patients with normal initial head CT scans. Additionally, we aimed to determine if there are any identifiable pre- or peri-injury risk factors for surgically treated cSDH after head injuries with normal initial CT scans.

Methods and materials

Material and ethics

This study is a part of the Tampere Traumatic Head and Brain Injury Study. All consecutive patients with head injuries who were treated and CT scanned at the Tampere University Hospital's emergency department, between August 2010 and July 2012, were retrospectively evaluated from the hospital's patient records. A total of 3023 head injuries in 2908 patients were identified. A six-month follow-up period for the development of cSDH was included in the data collection.

This study focused on adult (18 years or older) patients who were residents of the Pirkanmaa region at the time of injury and were clinically evaluated and scanned with head CT at the Tampere University Hospital's emergency department within 48 h ($\leq$48 h) after head injury. Patients who had suffered more than one head injury during the study period were included only once in the study sample with the initial head injury as the index injury. A total of 1941 adult patients undergoing acute head CT following injury were identified. A flowchart of the study sample is provided in Fig. 1.

The Pirkanmaa region is a geographically well-defined area with both rural and urban areas that holds one of Finland's five university hospitals with a neurosurgical service (Tampere University Hospital, Tampere, Finland). During the study period, Pirkanmaa had 490,000 residents, which comprised 9% of the total population of Finland (5.4 million) at the time. In addition to Tampere University Hospital, there is one local hospital with a CT scanner used for patients with head injuries in the Pirkanmaa region. However, most of the head trauma patients, and all the patients requiring neurosurgical care, are evaluated at the Tampere University Hospital.

The study was approved by the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland (ethical code: R10027). All data was collected retrospectively without contacting the patients, therefore no written informed consent was obtained or required.

Data collection

A detailed and structured data collection was performed from the patient's medical records. Variables collected included demographics, antithrombotic medication (including anticoagulants and antiplatelets), injury-related information, clinical TBI indices, emergency head CT findings (acute traumatic lesions), acute neurosurgery due to TBI, and follow-up findings in relation to cSDH. Minimal criteria for TBI were based on the World Health Organization's (WHO) definition [3]. Cases with a Glasgow Coma Scale (GCS) score < 13 after 30 min post-injury, post-traumatic amnesia greater than 24 h, and/or loss of consciousness more than 30 min were coded as moderate to severe TBI. There was a considerable number of patients with missing GCS scores. These patients were coded based on clinical findings and examinations reported in the patient's medical records. Not all the patients had documented clinical signs of TBI but were likely CT scanned because of age, antithrombotic medication, or concern about the mechanism of injury based on the judgment of the on-call physician. Referral criteria for acute head CT were based on the former Scandinavian guidelines for the initial management of minimal, mild, and moderate head injuries [16]. Two neuroradiologists examined all the head CT scans. Study data was collected before the National Institute of Neurological Disorders and Stroke and Common Data Elements (CDEs) [9] for traumatic brain injury (TBI) imaging were established. However, all CDEs possible with non-contrast structural CT were included [17].

All patients were CT scanned within 48 h ($\leq$48 h) after head injury and divided into two groups: *CT positive* and *CT negative*. A patient was regarded *CT positive* if there were any signs of acute traumatic intracranial pathology on initial head CT. Because the aim of this study was to examine the development of cSDH (and eventual surgical treatment)

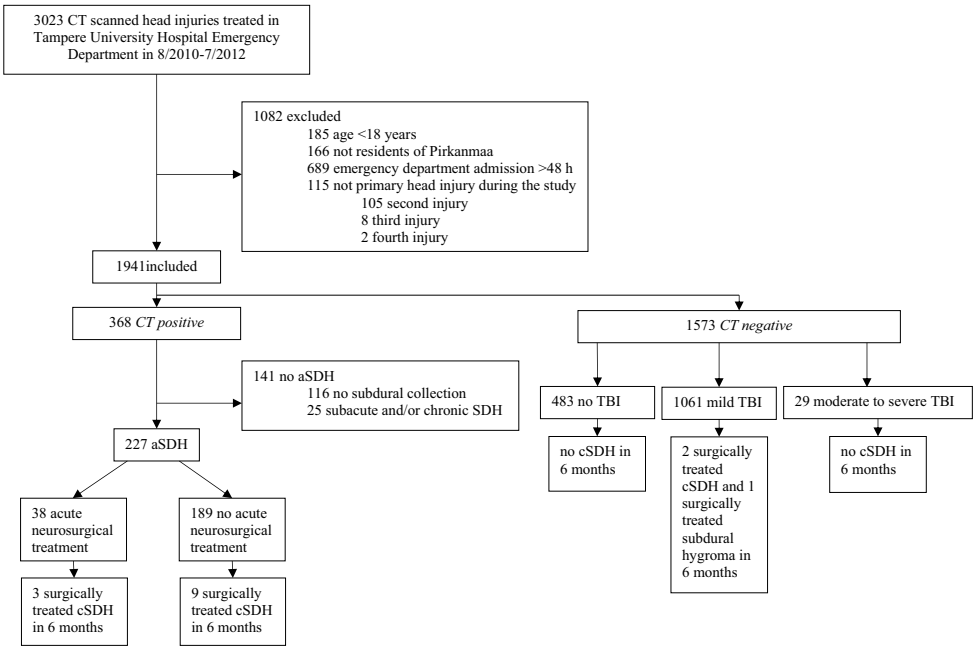

Fig. 1 A flowchart of the study sample

after normal initial head CT, the patients with any kind of subdural collection on initial head CT were regarded as *CT positive*. Consequently, patients with no signs of acute traumatic intracranial pathology or any type of subdural collection on initial head CT were regarded as *CT negative*. CT negative patients may have had other lesions or abnormalities on the initial head CT (e.g., lesions of vascular etiology).

The main outcome variable was defined as *surgical treatment of cSDH*. In the absence of strict universal criteria, we used the following definition for cSDH: a predominantly hypodense blood collection in the subdural space on head CT (or on magnetic resonance imaging (MRI)). No structural follow-up was conducted, and patients were CT scanned only if neurological symptoms emerged. Hence, surgical treatment of cSDH was the most reliable outcome measurement available.

Statistical analysis

IBM SPSS Statistics for Windows (version 29, IBM Corp.) was used for data analyses. Descriptive statistics (frequency, percentage, median, interquartile range (IQR)) were used to describe variable characteristics. Blaker's binomial confidence intervals (CI) (95% confidence level) were calculated with R (version 4.3.2).

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Characteristics of the cohort

The cohort included 1941 patients with a median age of 59 years. Of the 1941 patients, 1122 (58%) were men. The most common mechanism of injury was ground-level fall in 1016 (52%) patients. Alcohol intoxication was reported for 567 (29%) patients, and 494 (26%) patients were on antithrombotic medication at the time of injury. Most of the patients, 1269 (65%), had a mild TBI. Moderate to severe TBI was reported for 187 (9.6%) patients, and 485 (25%) patients did not have clinical signs of TBI documented in

their records. Characteristics of the study cohort are summarized in detail in Table 1.

Initial head CT showed acute traumatic intracranial pathology and/or any subdural fluid collection (*CT positive*) in 368 (19%) patients. Consequently, 1573 (81%) patients had normal initial head CT in relation to the trauma (*CT negative*)—they had no signs of acute traumatic intracranial pathology or any type of subdural collection on initial head CT.

CT positive group

In the *CT-positive* group, the most frequent acute traumatic lesion on the head CT was a subdural hematoma, from which 227 (90%) were acute and 25 (10%) subacute or chronic. As subdural hygromas have no unified clinical or radiological criteria, these lesions were included in the subacute or chronic subdural hematoma group. Only 38 (17%) of all acute subdural hematoma (aSDH) patients received acute surgical treatment for the condition. From the 38 patients who received surgical treatment for aSDH, three (7.9%) underwent a future surgery for cSDH. Of the 189 conservatively treated aSDH, nine patients (4.8%) underwent future surgery for cSDH. These findings are presented schematically in Fig. 1.

Table 1 Characteristics of the study cohort ($n = 1941$)

Variable		
Age median, years (IQR)	58.7 (39.1–78.5)	
	n	%
Men	1122	57.8
Cause of injury		
Ground-level fall	1016	52.3
Motor vehicle accident	261	13.4
Fall from a height	215	11.1
Traffic accident as pedestrian or bicyclist	116	6.0
Other	333	17.2
Alcohol intoxication	567	29.2
Antithrombotic medication	494	25.5
Loss of consciousness	417	21.5
Amnesia	510	26.3
Glasgow Coma Scale		
13–15 points	1100	56.7
9–12 points	97	5.0
3–8 points	81	4.2
Unknown	663	34.2
Traumatic brain injury severity		
No documented clinical signs of traumatic brain injury	485	25.0
Mild	1269	65.4
Moderate to severe	187	9.6
CT positive head injury	368	19.0
Subdural hematoma (acute)	227	11.7
Subdural hematoma (subacute or chronic)	25	1.3
Subarachnoid hemorrhage	216	11.1
Contusion	152	7.8
Cerebral edema	14	0.7
Epidural hematoma	14	0.7
Diffuse axonal injury	7	0.4
CT negative head injury	1573	81.0

IQR interquartile range, *CT* computed tomography

CT negative group

The *CT negative* group included 81% of the cohort. The demographics of the *CT negative* group were similar to the characteristics of the entire cohort with the exception that there were markedly fewer patients with moderate to severe TBI in the *CT negative* group. Characteristics of the patients with normal initial head CT are summarized in detail in Table 2.

Chronic subdural hematoma after normal initial computed tomography

Only six patients were diagnosed with cSDH after a normal initial head CT scan during the six-month follow-up period. Two of the six patients received surgical evacuation of the hematoma (trepanation) while the rest were treated conservatively. Therefore, the incidence of surgically treated cSDH after a normal initial head CT during a six-month follow-up was 0.13% (95% CI 0.023–0.45). Both patients suffered initially from a mild TBI. Therefore, the incidence among patients with mild TBI was 0.19% (95% CI 0.034–0.67). None of the patients with moderate to severe TBI ($n = 29$) or patients with no TBI ($n = 483$) were diagnosed with cSDH during the follow-up period. One of the two patients was on antithrombotic medication (warfarin) at the time of trauma; hence, the incidence among patients on antithrombotic medication ($n = 376$, 24%) was 0.27% (95% CI 0.014–1.5). In addition to these two cases, one patient (a woman, aged 75 years) developed a subdural hygroma which was treated via trepanation shortly after trauma (ten days). Consequently, of the 1573 patients with *CT negative* head injuries, three were surgically treated for subdural fluid collection. Due to the small number of cases that underwent surgery ($n = 2$), statistical analyses on possible risk factors for surgically treated cSDH were not performed.

Both patients who developed surgically treated cSDH were elderly women, aged 77 and 78 years. Hence, the incidence of cSDH in the age group of over 70 years old ($n = 506$) was 0.40% (95% CI 0.070–1.4). Ground-level fall was the injury mechanism for both. Both had bilateral cSDHs. Time intervals from trauma to trepanation for the cSDH were seven and eight weeks. The characteristics of

Table 2 Characteristics of the patients with normal initial head computed tomography ($n = 1573$)

Variable		
Age median, years (IQR)	56.2 (36.7–77.2)	
	n	%
Men	887	56.4
Cause of injury		
Ground-level fall	804	51.1
Motor vehicle accident	240	15.3
Fall from a height	169	10.7
Traffic accident as pedestrian or bicyclist	84	5.3
Other	276	17.5
Alcohol intoxication	455	28.9
Antithrombotic medication	376	23.9
Loss of consciousness	295	18.8
Amnesia	407	25.9
Glasgow Coma Scale		
13–15 points	938	59.6
9–12 points	55	3.5
3–8 points	24	1.5
Unknown	556	35.3
Traumatic brain injury severity		
No documented clinical signs of traumatic brain injury	483	30.7
Mild	1061	67.5
Moderate to severe	29	1.8
Chronic subdural hematoma within 6 months post-injury	6	0.38
Surgically treated chronic subdural hematoma	2	0.13

IQR interquartile range

the two patients with surgically treated cSDH are described in detail in Table 3.

Discussion

Summary of the key findings

The incidence of surgically treated cSDH after head injuries in adults with normal initial head CT during six-month follow-up was 0.13% in our cohort. The incidence of surgically treated cSDH among patients with antithrombotic medication was 0.27% and 0.40% among patients over 70 years old.

Comparison of the current findings to prior literature

The prevalence of abnormal initial CT scan after a mild head injury has been reported to range from 6.9 to 29% [15, 18, 21] in the prior literature. In our cohort, 19% had acute intracranial pathology or any type of subdural fluid collection present in the initial CT scan.

The overall incidence of cSDH is well reported in the prior literature. The annual incidence of cSDH in an adult population was 18/100,000 in a study performed in the same region as ours [29]. The incidence was very low in patients under 60 years of age but was significantly higher in

Table 3 Detailed description of the two patients with surgically treated chronic subdural hematoma after normal initial head computed tomography within six months post-injury ($n = 2$)

Patient	Injury mechanism	TBI severity	Antithrombotic medication at the time of trauma	cSDH trepanation, time since injury	cSDH side	cSDH symptoms
Woman, age 78	GLF	Mild	Warfarin	8 weeks	Bilateral	Postural instability, vertigo, aphasia, fatigue
Woman, age 77	GLF	Mild	No	7 weeks	Bilateral	Postural instability

GLF ground-level fall, *TBI* traumatic brain injury, *cSDH* chronic subdural hematoma

older age groups. The incidence was highest in people aged 80 years or older (130/100,000/year), in which it nearly tripled within the study period of 25 years from 1990 to 2015.

Instead, little is known about the development of cSDH in patients with head injuries who have normal initial head CT scans. The only study looking at consecutive CT-scanned patients after head trauma has been published recently by a Japanese group. Karibe et al. examined cSDH formation after mild head trauma in elderly (> 65 years) Japanese patients. Among patients with normal initial CT scans ($n = 322$), surgically treated cSDH was diagnosed in 4.3% of patients at more than one month after injury [19]. In this study, antithrombotic medication did not increase the risk for cSDH although antithrombotic medications were not discontinued or counteracted.

Additionally, a few case reports on this topic have been published. Chia et al. reported a case of an 84-year-old man with a normal initial CT scan after a minor head injury who developed a symptomatic cSDH after two months [5]. The patient was not on antithrombotic medication at the time of injury. Deitch et al. reported on two patients with normal initial CT scans after minor head injury and the development of cSDH after several weeks[8]. The use of antithrombotic medication was not documented. Snoye et al. published a case report of three patients suffering a minor head injury with normal initial head CT scans and the development of cSDH in a mean time of seven weeks[31]. The use of antithrombotic medication was not documented. Kim et al. published a case report of an 82-year-old man with normal initial CT and MRI scans after a mild head injury who was diagnosed with a cSDH after five weeks [20]. The patient was not on antithrombotic medication at the time of injury.

Our study had a notably lower incidence rate of surgically treated cSDH compared to the results published by Karibe et al. The lower incidence rate could be related to the nature of our cohort. The mean age among *CT negative* patients in our study was 56 years, while Karibe et al. reported a considerably higher mean age of 82 years for the whole cohort. The incidence of cSDH has been shown to increase steeply with age [29]. Therefore, the large difference in the mean ages of our samples might partly explain the notable difference in cSDH incidences. In our study, both patients with a surgically treated cSDH were elderly women, aged 77 and 78 years. The incidence of cSDH in the age group of over 70 years old was 0.40%, still considerably lower than the incidence reported by Karibe et al. Another factor that might have affected to the incidences of our studies was the different follow-up practices. Karibe et al. screened all patients with head CT scans one-month post-injury for the detection of cSDH and followed the patients up to 12 months for the detection of symptomatic cSDH, while there was no structural follow-up in our study. Although the main outcome result in our study was the surgical treatment of cSDH, an outcome that should be present with all patients with symptomatic cSDH, some cSDH cases might have been undiagnosed.

The use of antithrombotic medication has been considered one of the primary reasons for the increasing incidence of cSDH in the elderly [29]. The incidence of surgically treated cSDH among patients with antithrombotic medication was 0.27% in all *CT negative* patients. Overall, the risk for delayed intracranial hemorrhage after head trauma seems to be low based on the prior literature. A recent meta-analysis studied delayed intracranial hemorrhage with patients on direct oral anticoagulants (DOAC) ($n = 1263$) and warfarin ($n = 1788$). Delayed intracranial hemorrhage was reported in 2.4% of the patients on DOAC and in 2.3% on warfarin after blunt head trauma [28]. In this meta-analysis, the duration of the follow-up periods varied, with the maximum being just one month. Ghenoweth et al. reported an intracranial hemorrhage incidence of 0.4% for patients without any antithrombotic medication after blunt head trauma in a follow-up period of two weeks [4]. These studies examined all intracranial hemorrhages, while our study focused purely on the development of cSDH, and those studies had very short follow-up periods in relation to the development of cSDH. Our study supports the idea that head trauma patients with normal initial head CT do not require routine follow-up CT. The risk for symptomatic cSDH among patients with antithrombotic medication seems to be very low as well.

There remain uncertainties relating to the etiology of cSDH. In 1857, Virchow [23] described the condition as "pachymeningitis hemorrhagica chronica interna", and at that time, this inflammation theory was widely accepted. Subsequently, a traumatic etiology [25] has been emphasized. Recently aging and brain degeneration [24] have been highlighted as principal causative factors underlying the condition. Although we cannot draw conclusions based on our results about the etiology, the extremely small incidence in our study partly questions the purely traumatic etiology of cSDH.

Strengths and limitations

To our knowledge, no similar study has been performed previously. Rigorous analysis of the head CT scans was performed to examine only patients with genuinely normal head CT regarding the primary trauma. All the initial head CT scans were evaluated by two neuroradiologists. *CT negative* patients had no signs of acute traumatic intracranial pathology or any type of subdural collection on initial head CT.

Our retrospective patient cohort represents an extensive series of consecutive patients from one geographically well-defined area. All patients were evaluated in the emergency department of one university hospital. Our study was not population-based, though it reflects the incidence of

surgically treated cSDH in head trauma patients in Pirkanmaa, Finland. Our cohort was relatively large with 1573 *CT negative* head injuries.

Our study has several limitations. Due to the retrospective design, not all desired data was available. CT scanning practice might have influenced to the composition of our cohort because only CT-scanned patients were recruited to the study. However, our sample included a significant number of patients who were scanned without clear clinical signs of TBI documented in their medical records. The sample likely captures the full severity spectrum of head injuries treated in a university hospital's emergency department. Additionally, there was no systematic follow-up protocol for the development of cSDH. Most of the cSDH-suspected patients were evaluated by a neurosurgeon and CT scanned only if signs or symptoms of a neurologically treatable condition emerged. Although patients, family members, and health care professionals are informed to contact the neurosurgical department if new worrisome signs or symptoms emerge, some cSDH cases might have been undiagnosed. This is particularly true for patients with only mild or no symptoms. Hence, the main outcome variable was specified as surgically treated cSDH because these patients were most reliably identified. Further, our study was limited by the sample size. The very low number of cases with the outcome of interest increases the uncertainty of the results. Hence, generalization of these results to a larger scale is challenging. Studies with larger patient cohorts are needed to validate the results. Additionally, we were not able to conduct group analyses on possible risk factors for surgically treated cSDH due to the small number of cases. This study did not analyze the development of cSDH among patients with subdural hygromas on the initial CT scans due to the lack of univocal criteria for subdural hygromas. This is an interesting research question and should be specifically assessed in future studies.

Directions for future research

Similar studies with larger patient cohorts are needed to replicate or validate the results. Epidemiological studies on populations with verified head traumas and case–control matching with patients without trauma could provide interesting information about traumatic vs. non-traumatic etiologies of cSDH.

Conclusions

The incidence of surgically treated cSDH after head injury in people with normal initial head CTs during a six-month follow-up was minute (0.13%) in our cohort. The extremely low incidence of surgically treated cSDH after a normal initial head CT, even in patients on antithrombotic medication, supports the notion that routine follow-up imaging after an initial normal head CT is not indicated to exclude the development of cSDH. Additionally, our findings support the concept of cSDH not being a purely head trauma-related disease.

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Author contribution Study design: TL, MR; data collection: MN; statistical analyses: AH; first manuscript draft: AH; manuscript editing: AH, MR, GI, TL. All authors reviewed and approved the final version of the manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability The code and analyses used are available from the corresponding author upon reasonable request.

Declarations

Ethics approval The study was approved by the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland (ethical code: R10027). All data was collected retrospectively without contacting the patients, therefore no written informed consent was obtained or required.

Conflict of interest Aaro Heinonen has accepted research grants from the Maire Taponen Foundation. Grant Iverson, Ph.D. serves as a scientific advisor for NanoDX®, Sway Operations, LLC, and Highmark, Inc. He has a clinical and consulting practice in forensic neuropsychology, including expert testimony, involving individuals who have sustained mild TBIs. He has received past research funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He acknowledges unrestricted philanthropic support from ImPACT Applications, Inc., the Mooney-Reed Charitable Foundation, the National Rugby League, and the Schoen Adams Research Institute at Spaulding Rehabilitation. None of the above entities were involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. Teemu Luoto has received speaker's fees from Orion Corporation, Novartis Finland, and the Finnish Medical Society Duodecim. Teemu Luoto has also accepted research grants from the Finnish Brain Foundation sr, the Emil Aaltonen Foundation sr, the Maire Taponen Foundation, the Science Fund of the City of Tampere, the Finnish Medical Society Duodecim, and the Academy of Finland (Terveyden tutkimuksen toimikunta #349758). The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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PUBLICATION III

Long-term mortality of patients with head injuries – a ten-year follow-up study with population controls

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