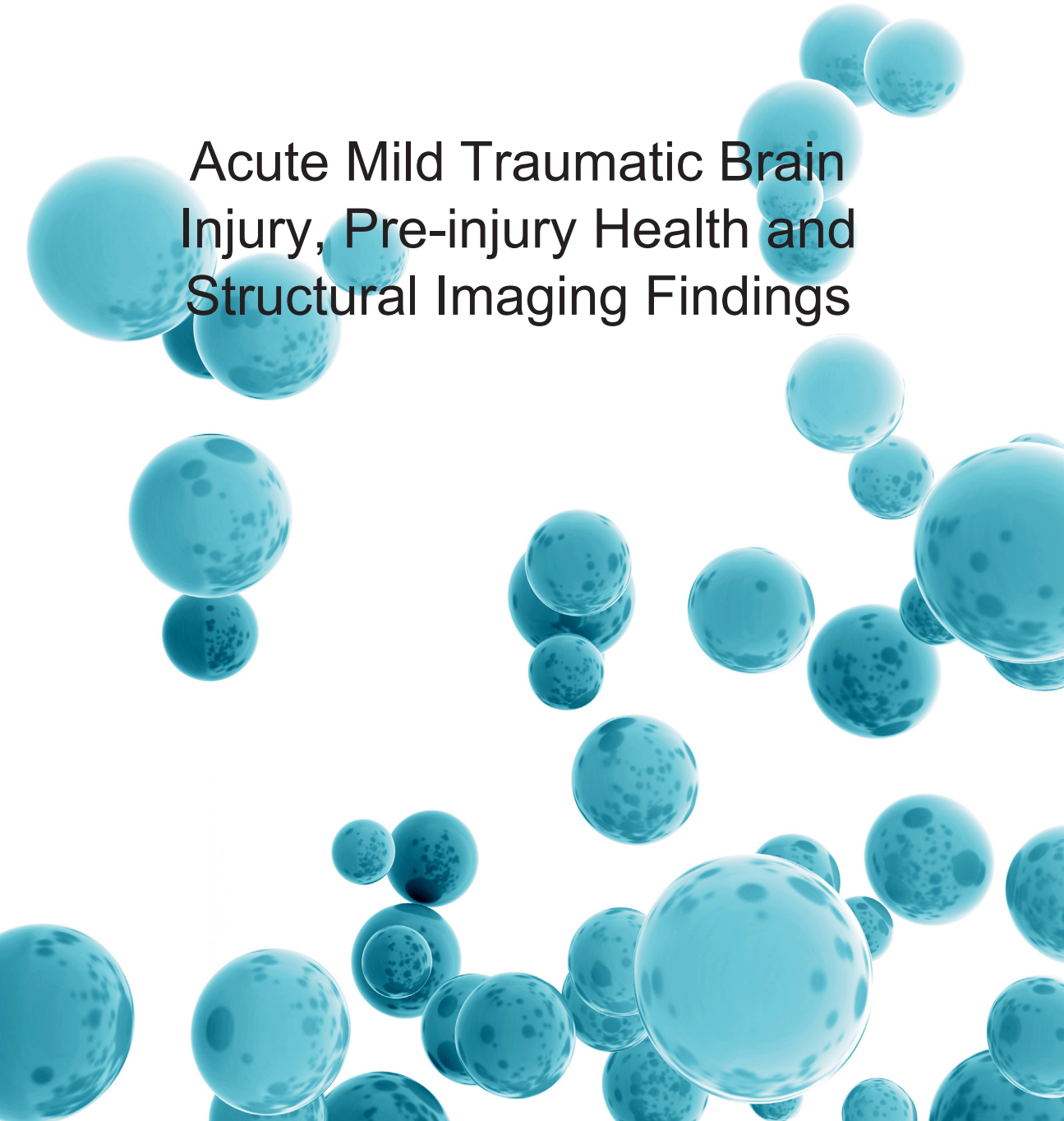
Acta Universitatis Tamperensis 2328

HARRI ISOKUORTTI

# Acute Mild Traumatic Brain Injury, Pre-injury Health and Structural Imaging Findings



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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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ACADEMIC DISSERTATION
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*To my wonderful wife, Elina*

# Contents

# Abstract

Mild traumatic brain injury (MTBI) is a major public health problem. Outcome from MTBI is heterogeneous, largely due to individual pre-injury differences that remain incompletely described or understood. The effects of other characteristics, such as neurodegenerative diseases, brain atrophy, or chronic alcohol abuse on risk for traumatic intracranial lesions are not well known. Moreover, the relative strength of association of individual characteristics, such as age and cause of injury, with CT findings is not well understood. Severe complications (intracranial bleeding, brain edema) are rare after mild brain injury, but their incidence and severity after a normal head CT are not well known. Common Data Elements (CDEs) were developed to systematically document findings and control for heterogeneity in traumatic brain injury (TBI).

The main objective of this thesis was to describe the pre-injury health characteristics as well as the type and location of intracranial abnormalities (both acute and chronic) in patients who sustained head injury (HI) (studies I and II), using the CDE framework in study II. Additionally, the effect of different exclusion criteria on the patient enrollment in MTBI studies was evaluated (study I). The aim of study II was to assess whether certain pre-existing cerebral diseases are associated with greater injury severity. The incidence of delayed complications in acute HI patients after a normal head CT was examined in study III.

The patient pool included all patients who were treated at the emergency department (ED) of the Tampere University Hospital (2010-2012) and who underwent head CT after a HI (N=3,023). Injury-related data and participant-related data (e.g., age, sex, diagnosed diseases, and medications) were collected from hospital records. In study I, the effect of different patient enrollment criteria in MTBI studies was evaluated by selecting a subset of working age adults with no pre-injury medical or mental health problems. Inclusion criteria were: a HI fulfilling the criteria for MTBI, age 18-60 years, and residency within the hospital district. Exclusion criteria were premorbid neurological or psychiatric problems, past TBI or neurosurgical operations, psychoactive medication use, problems with vision or hearing, first language other than Finnish, ED admission after 72 hours from the injury, and/or refusal to participate in the study.

Study III included all HI patients (n=2,444) with a normal head CT. The medical records were reviewed to identify the individuals with a clinically significant complication related to the primary HI within 72 hours of the primary head CT. A repeated head CT, death, or return to the ED were indicative of a possible complication. CT scans were systematically analyzed and coded using the TBI CDE framework. The risk factors for traumatic intracranial abnormalities in MTBIs were quantified by logistic regression modeling.

Of all patients, 1,990 (66%) met the MTBI criteria, 257 (9%) had a more severe TBI, and 776 (26%) had a HI without obvious signs of TBI In these three groups the most common pre-injury diseases were circulatory (39-43%), neurological (24-25%), and psychiatric (26-28%) disorders. Alcohol abuse was present in 18-27%. The most common medications were for cardiovascular (33-37%), central nervous system (21-31%), and blood clotting and anemia indications (22-23%).

Most of the patients who sustained an MTBI had some pre-injury diseases or conditions that could affect clinical outcome. Only 2.5% of the screened patients met all the enrollment criteria. Age, neurological and psychiatric conditions were the most common reasons for exclusion. Pre-existing brain lesions were common in the MTBI patients and the incidence increased with age.

The most common traumatic lesions were subdural hematomas, subarachnoid hemorrhages, and contusions. Every sixth (16%) MTBI patient had an intracranial lesion, compared to 5/6 (86%) in the moderate to severe TBI group. Having a past traumatic lesion was associated with increased risk for an acute traumatic lesion. Lower GCS, male sex, older age, falls, and chronic alcohol abuse were associated with higher risk of acute intracranial lesion in MTBI.

The majority (n=1811, 74%) of the patients with a negative head CT were discharged home. A repeated head CT was performed on 12 (44%) of the returned patients (n=27) and none of the scans revealed an acute lesion. Of the 632 (26%) CT-negative patients admitted to the hospital ward from the ED, a head CT was repeated in 46 (7%) patients and only one patient (0.2%) had a traumatic intracranial lesion. This lesion did not need neurosurgical intervention. The overall complication rate was 0.04% and mortality rate 0%.

The pathological changes seen within the MTBI classification are heterogeneous. By excluding patients with pre-existing conditions, the patients with known risk factors for poor outcome remain poorly studied. This study with unselected HI patients suggests that the probability of delayed life-threatening complications was negligible when the primary CT scan revealed no acute traumatic lesions.

# Tiivistelmä (Abstract in Finnish)

Lievät aivovammat ovat yleisiä ja muodostavat suuren haasteen terveydenhuollolle. Lievän aivovamman toipumisennuste vaihtelee, suurelta osin vammaa edeltävistä yksilöllisistä eroista, jotka tunnetaan puutteellisesti. Muiden erityispiirteiden, kuten neurodegeneratiivisten sairauksien, aivoatrofian tai kroonisen alkoholin liikakäytön, vaikutus traumaattisiin kallonsisäisiin vaurioihin tunnetaan huonosti. Yksilöllisten tekijöiden, kuten iän ja vammamekanismin, sekä tietokonetomografialöydösten välisten yhteyksien suhteellista voimakkuutta ei tunneta. Vakavat komplikaatiot (kallonsisäinen verenvuoto, aivoturvotus) ovat harvinaisia lievän aivovamman jälkeen, mutta niiden ilmaantuvuutta normaalin pään tietokonetomografian (TT) ei tiedetä tarkasti. Common Data Elements (CDE) ovat tutkimustyöhön kehitettyjä vakiomuuttujia, joiden taustalla on pyrkimys dokumentoida tutkimustietoa systemaattisesti ja vakioimaan heterogeenisyyttä aivovammatutkimuksessa.

Väitöskirjan päätavoite oli kuvailla päävammapotilaiden vammaa edeltävää terveydentila sekä kallonsisäisten akuuttien ja kroonisten löydösten tyypit sekä sijainnit (osatyöt I ja II). Osatyössä II käytettiin luokittelussa CDE-viitekehystä. Lisäksi tutkittiin erilaisten sisäänottokriteerien vaikutusta potilasaineistoon (osatyö I). Osatyön II tavoitteena oli selvittää, onko tietyillä aivosairauksilla yhteyttä aivovamman vakavuusasteeseen. Viivästyneiden komplikaatioiden ilmaantuvuutta tutkittiin osatyössä III.

Tutkimusaineisto koostui kaikista TT-kuvatuista päävammapotilaista, joita oli hoidettu Tampereen yliopistollisen sairaalan päivystyspoliklinikalla 2010-2012. Vammaan ja potilaaseen liittyvät tiedot (esim. ikä, sukupuoli, perussairaudet ja lääkitykset) selvitettiin sairauskertomustiedoista. Osatyössä I selvitettiin erilaisten sisäänottokriteerien vaikutusta aivovammatutkimuksessa valikoimalla alaryhmä työikäisiä potilaita, joilla ei ollut vammaa edeltäviä (mielen)terveysongelmia. Sisäänottokriteerit olivat: lievä aivovamma, ikä 18-60 vuotta ja asuminen sairaanhoitopiirin alueella. Poissulkukriteerit olivat vammaa neurologinen tai psykiatrinen sairaus, aikaisempi aivovamma tai neurokirurginen toimenpide, psyykenlääkkeiden käyttö, näkö- tai kuulovamma, jokin muu kieli kuin suomi äidinkielenä, yli 72 tuntia vamman ja päivystyshoidon välillä ja/tai kieltäytyminen tutkimuksesta.

Osatyön III aineiston muodostivat kaikki potilaat, joiden pään TT:ssä ei ollut vammalöydöksiä, riippumatta aivovamman vakavuudesta. Potilasasiakirjat käytiin läpi, jotta mahdolliset pään kuvauksesta 72 tunnin kuluessa ilmaantuvat komplikaatiot havaittaisiin. Komplikaation mahdollisena merkkinä pidettiin uutta pään TT:tä, kuolemaa tai uutta käyntiä päivystyksessä Pään TT-kuvat analysoitiin systemaattisesti CDE-viitekehyksen mukaan. Traumaattisten kallonsisäisten muutosten riskitekijöitä arvioitiin logistisella regressioanalyysillä.

Kaikista potilaista 1 990:lla (66 %) oli lievä aivovamma, 257:llä (89 %) oli vakavampi aivovamma ja 776:lla (26 %) oli päävamma ilman selviä aivovamman merkkejä. Yleisimmät vammaa edeltävät sairaudet olivat sydän- ja verisuonitauteja (39-43 %), neurologisia (24-25 %) ja psykiatrisia (26-28 %) sairauksia. Alkoholin liikakäyttöä oli 18-27 %:lla. Yleisimmät lääkitykset olivat sydän- ja verisuonitauteihin (33,1-36,6%), keskushermostoon (21-31 %) tai veren hyytymiseen tai anemiaan vaikuttavia lääkkeitä (22-23 %).

Suurella osalla lievän aivovamman saavista potilaista on jokin edeltävä sairaus, joka voi vaikuttaa toipumiseen. Vain 2,5% kaikista potilaista täytti kaikki sisäänottokriteerit. Ikä, neurologiset ja psykiatriset sairaudet olivat yleisimmät poissulkusyyt. Krooniset aivomuutokset olivat yleisiä kuvantamislöydöksiä, ja niiden yleisyys kasvoi iän myötä.

Yleisimmät traumaattiset muutokset olivat kovakalvonalaiset verenvuodot, lukinkalvonalaiset verenvuodot ja aivoruhjeet. Joka kuudennella lievän ja viidellä kuudesta vakavamman aivovamman saaneista oli jokin traumaattinen löydös. Vanha traumaattinen aivomuutos oli yhteydessä kasvaneeseen riskiin saada uusi traumaattinen muutos. Matalampi GCS, miessukupuoli, ikä ja krooninen alkoholin liikakäyttö olivat yhteydessä kasvaneeseen riskiin saada traumaattinen aivomuutos lievän aivovamman yhteydessä.

Valtaosa (n=1 811, 74 %) potilaista, joilla ei ollut pään TT:ssä traumaattisia muutoksia, kotiutettiin ja uusi pään TT tehtiin 12:lle päivystykseen palanneelle potilaalle. Näistä yhdelläkään ei ollut aivovammamuutoksia. Osastolle otetuista 632:sta (26 %) potilaasta 46:lle tehtiin uusi pään TT. Yhdellä potilaalla oli traumaattinen kuvantamislöydös. Vamma ei vaatinut neurokirurgista toimenpidettä. Komplikaatioaste oli 0,04 % ja kuolleisuus 0 %.

Lieväksi aivovammaksi luokiteltujen aivovammojen patologiset muutokset ovat vaihtelevia. Poissulkemalla potilaat, joilla on jokin vammaa edeltävä sairaus, toipumiseen vaikuttavat vammaa edeltävät tekijät jäävät puutteellisesti tutkituiksi. Tämän tutkimuksen valikoimattoman potilasaineiston perusteella normaaliksi jäävä pään TT riittää poissulkemaan tulevat komplikaatiot päävamman jälkeen.

# 1 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following three publications.

I Isokuortti H, Iverson GL, Kataja A, Brander A, Öhman J, Luoto TM. Who Gets Head Trauma or Recruited in Mild Traumatic Brain Injury Research? J Neurotrauma. 2016 Jan 15;33(2):232-41.

II Isokuortti H, Iverson GL, Kataja A, Brander A, Öhman J, Luoto TM. Characterizing the Type and Location of Intracranial Abnormalities in Mild Traumatic Brain Injury. Journal of Neurosurgery. 2017 (accepted for publication)

III Isokuortti H, Luoto TM, Kataja A, Brander A, Siironen J, Liimatainen S, Iverson GL, Ylinen A, Öhman J. Necessity of monitoring after negative head CT in acute head injury. Injury. 2014 Sep;45(9):1340-4.

The publications are referred to in the text by their Roman numerals. The original publications have been reprinted with the permission of the copyright holders.

# 2 ABBREVIATIONS

| | |
|---|---|
| ACRM | American Congress of Rehabilitation Medicine |
| ATC | Anatomic Therapeutic Classification |
| CDC | Centers for Disease Control and Prevention |
| CDE | Common data elements |
| CNS | Central nervous system |
| CT | Computed tomography |
| DAI | Diffuse axonal injury |
| DTI | Diffusion tensor imaging |
| ED | Emergency department |
| EDH | Epidural hemorrhage |
| EFNS | European Federation of Neurological Societies |
| GFAP | Glial fibrillary acidic protein |
| GCS | Glasgow coma scale |
| GLF | Ground-level fall |
| HI | Head injury |
| ICH | Intracerebral hemorrhage |
| INR | International normalized ratio |
| ICD-10 | International Classification of Diseases, 10th edition |
| LOC | Loss of consciousness |
| MRI | Magnetic resonance imaging |
| MTBI | Mild traumatic brain injury |
| NOAC | Non-vitamin K antagonist oral anticoagulant |
| NICE | National Institute for Health and Clinical Excellence |
| OAC | Oral anticoagulation |
| OR | Odds ratio |
| PCS | Post-concussion syndrome |
| PTA | Post-traumatic amnesia |
| SAH | Subarachnoid hemorrhage |
| SDH | Subdural hemorrhage |
| TBI | Traumatic brain injury |

| | |
|---|---|
| UCHL1 | Ubiquitin C-terminal hydrolase-L1 |
| VKA | Vitamin K antagonist |
| WHO | World Health Organization |

# 3 INTRODUCTION

The prevalence of various diseases and conditions possibly affecting the outcome from mild traumatic brain injury (MTBI) are poorly known. The knowledge on the impact of common diseases (such as neurodegenerative and cardiovascular diseases) on the clinical severity of the TBI and the outcome remains incomplete. MTBI is a common injury and causes many economical, medicolegal and diagnostic challenges. This thesis will increase our knowledge about the risk factors for MTBI and especially complicated MTBI. The role of CT imaging in the acute management of MTBI is another focus of this thesis.

MTBI is a common injury seen in emergency departments (ED), the estimated incidence per year being up to 600/100,000, (Feigin et al., 2013). The burden of TBI varies in rural and urban populations and across ages (Feigin et al., 2013). The true incidence of TBI is widely acknowledged to be even higher than available estimates, because MTBI constitutes from 70 to 90% of all TBIs and only a small proportion of those affected by TBI are admitted to hospital (Cassidy et al., 2004).

In the ED, most important points in the acute care of MTBI are: (i) identification of brain injury; (ii) differential diagnosis between MTBI and more severe intracranial injuries; (iii) early recognition of patients at risk for unfavorable outcome and (iv) patient guidance and possible referral to specialized care (rehabilitation, outpatient clinics). Traditionally, great emphasis has been placed on the radiological findings in the acute phase. Clinically significant structural brain damage is reliably identified by a head CT scan. The role of CT is therefore crucial in the acute management of patients with head injuries (HI).

Certain patient and injury factors have been associated with increased risk of trauma-related intracranial abnormalities after MTBI, including older age (Roozenbeek et al., 2013), pre-existing medical conditions such coagulopathy (Jagoda et al., 2008), alcohol intoxication at the time of injury (Haydel et al., 2000), lower GCS (i.e., 13 or 14 vs. 15) (Undén et al., 2013), and high energy accidents such as motor vehicle accidents and falls from a height (Stiell et al., 2001b). The effects of other characteristics such as neurodegenerative diseases, brain atrophy, or chronic alcohol abuse on risk for traumatic intracranial lesions are not well

known. As well, the relative strength of association of characteristics such as age, socioeconomic status and cause of injury with CT findings is not well understood.

Patients whose TBI is classified as mild and who show radiological evidence of a traumatic intracranial abnormality, have been conceptualized as having a complicated MTBI (Williams et al., 1990). A substantial amount of MTBI patients show acute traumatic intracranial abnormalities detected on CT, with prevalence rates varying from 5% to nearly 40% across studies (Iverson et al., 2012). The common data elements (CDE) were created to systematize data collection and enable data sharing across a wide range of patient and injury variables as without a set of CDE, comparison of findings across studies is difficult (Thurmond et al., 2010). This large-scale initiative provided recommendations on CDE in traumatic brain injury (TBI) across a variety of domains, including neuroimaging. The motivation for creating a CDE database has been to enable the eventual characterization of the natural history and predictive factors in TBI. CDE gives recommendations how to systematically characterize the macrostructural brain lesions in MTBI, both pre-existing and acute.

Delayed intracranial bleeding or brain edema are infrequent but potentially fatal complications of HI that may need neurosurgical care. The key questions are: Who are the patients suffering these complications and is it possible to identify these patients before hospital discharge? Routine hospital observation after a CT-negative HI is conservative, expensive and resource consuming (af Geijerstam and Britton, 2003; A. P. Carlson et al., 2010). Timely identification of patients with a risk of a complication could decrease treatment costs and spare ED resources by reducing unneeded hospital monitoring.

# 4 REVIEW OF THE LITERATURE

## 4.1 Definitions

In this thesis, traumatic brain injury (TBI) is defined as an acute brain injury caused by an external traumatic, direct or indirect, biomechanical force to the head. The diagnosis of TBI is based on four clinical signs, of which at least one should be present as a direct result of the traumatic force: (i) loss of consciousness (LOC), (ii) loss of memory i.e. post-traumatic amnesia (PTA), (iii) alteration in mental status, and/or (iv) focal neurological deficits (Borg et al., 2004; Giza et al., 2013; Harmon et al., 2013; McCrory et al., 2013; Menon et al., 2010; Signoretti et al., 2011).

Numerous international diagnostic criteria exist for mild TBI (MTBI) (Carroll et al., 2004a; CDC, 2003; Giza et al., 2013; Harmon et al., 2013; Kay et al., 1993; McCrory et al., 2013; VA/ DoD, 2009a; Vos et al., 2012). The most notable and used criteria are published by (i) the World Health Organization's Collaborating Centre for Neurotrauma Task Force on MTBI (Carroll et al., 2004a) (hereafter "WHO criteria"), (ii) American Congress of Rehabilitation Medicine (ACRM) (Kay et al., 1993), (iii) European Federation of Neurological Societies (EFNS) (Vos et al., 2012), and (iv) Centers for Disease Control and Prevention (CDC) (CDC, 2003). The aforementioned clinical signs that define TBI form the framework of the different criteria: (i) LOC of any length, (ii) memory loss concerning events before or after the injury (post-traumatic amnesia, PTA), (iii) focal neurological signs and symptoms, and (iv) any alteration in mental state. In some of the definitions, acute neuroimaging findings are included in the criteria. Some criteria consider a TBI with an intracranial lesion at least moderate TBI. These criteria are very similar and only differ to a detail. Aforementioned criteria are summarized in Table 1.

In the literature, the mild traumatic brain injury (MTBI) is often referred to as concussion, especially in the sport medicine literature. The terms concussion and MTBI are often used interchangeably. No international consensus exists on the definition of concussion. American Academy of Neurology (AAN) 2013 concussion guideline (Giza et al., 2013) defines concussion as a "pathophysiologic disturbance in neurologic function characterized by clinical symptoms induced by biomechanical forces, occurring with or without loss of consciousness. Standard structural neuroimaging is normal, and symptoms typically resolve over time." The AAN guidelines acknowledge the absence of a consensus definition and that concussion is frequently included in the category of MTBI (Giza et al., 2013). Moreover, sports concussion also has been suggested as a distinct subcategory of MTBI (Harmon et al., 2013; Levin and Diaz-Arrastia, 2015; McCrory et al., 2013).

The word "concussion" is derived from the Latin "concutera" ("to shake violently") or "concussus" ("action of striking together"). MTBI is more common term in civilian and military studies. In Europe (including Finland), the Latin term commotio (cerebri) is sometimes used in medical context (McCrory et al., 2013). Concussion is often deemed as the mildest form of MTBI. In this thesis, the term MTBI is used.

**Table 1.** Summary of the most used MTBI criteria

| | ACRM | CDC | EFNS | WHO |
|---|---|---|---|---|
| Loss of consciousness | < 30 minutes | < 30 minutes | < 30 minutes | < 30 minutes |
| Post-traumatic amnesia | < 24 hours | < 24 hours | < 1 hour | < 24 hours |
| Disorientation or confusion | Yes | Yes | Not defined | Yes |
| Neurological deficit | Transient or permanent | Yes (nature not specified) | No | Transient |
| Glasgow coma scale | 13-15 | 13-15 | 13-15 | 13-15 |
| Traumatic lesion seen in CT or MRI | Yes or no | Yes or no | No | Yes or no |
| Neurosurgical intervention | No | No | No | No |

## 4.2 Pathophysiology

TBI causes wide disruption in the function of the brain. Biomechanical stretching and shearing of neurons' cell membranes initiate a complex series of changes within the brain. This pathophysiological process is often called "the neurometabolic cascade" (Figure 1). The disruption of the neurochemical homeostasis results in temporal or persisting abnormal brain function

(Barkhoudarian et al., 2011; Blennow et al., 2012; Giza and Hovda, 2014; Prins et al., 2013).

The nature and the direction of the force define the magnitude of pathological processes in the brain. MTBI neuropathology contains a broad range of different pathological changes from temporary ionic imbalance to diffuse axonal injury and even focal lesions (Iverson et al., 2012; Taber and Hurley, 2013). Changes are mostly functional and not structural in MTBI. Conventional imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) are able to visualize gross structural but not functional brain damage in MTBI.

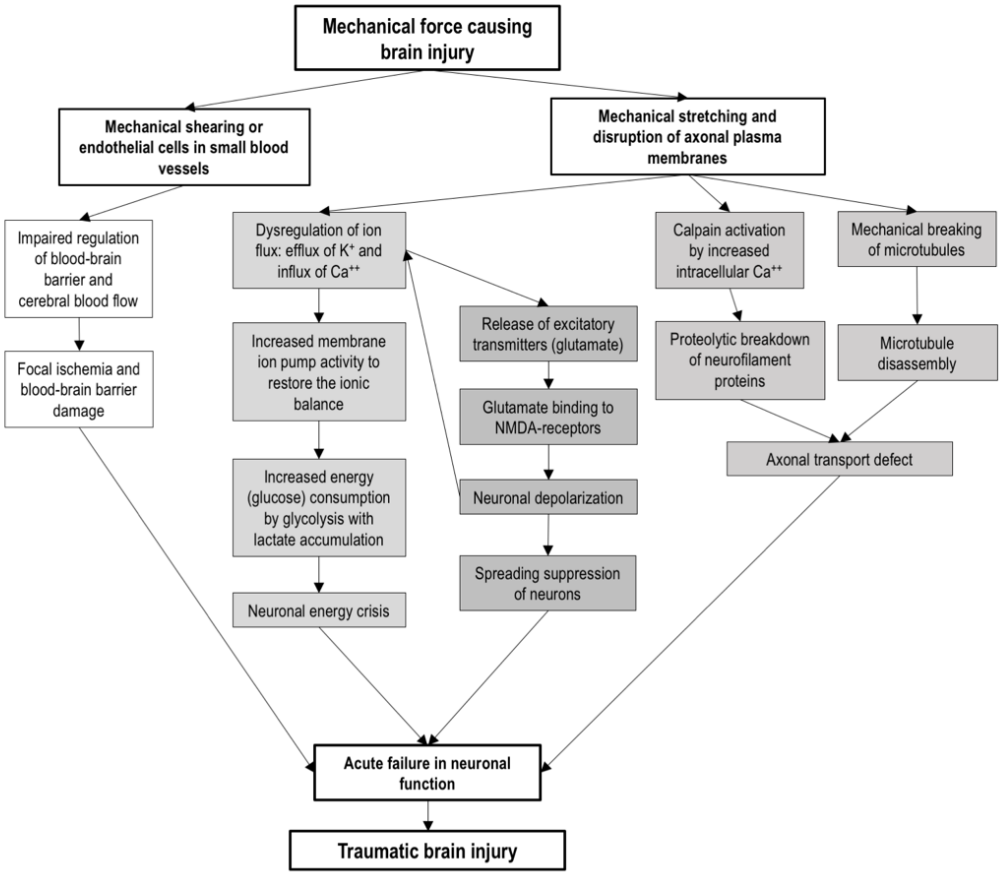


**Figure 1.** Molecular pathophysiology of mild traumatic brain injury, adapted from (Blennow et al., 2012)

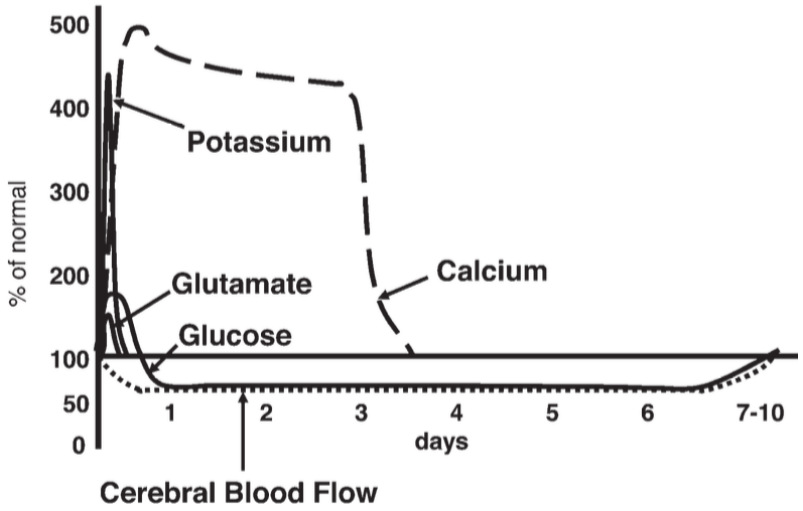


**Figure 2.** Time course of the neurometabolic cascade of concussion: influx of $K^+$, glutamate-induced hypermetabolism and efflux of $Ca^{2+}$ (Giza and Hovda, 2014). Reprinted with permission from Oxford University Press.

External force initiates the pathological changes in MTBI. Rapid stretch forces break the integrity of the cellular membrane of the neurons (Farkas et al., 2006). Subsequently, a flux of ions, consisting mainly of an inward flow of calcium ions and outward flow of potassium ions, occurs (Katayama et al., 1990). This leads to an increase of release of excitatory neurotransmitters, especially glutamate. Glutamate binds to N-methyl-D-aspartate (NMDA) receptors and this creates advancing depolarization, which eventually causes an influx of $Ca^{2+}$ ions (Faden et al., 1989). Cellular ionic imbalance distorts normal glucose metabolism (Katayama et al., 1990; Kawamata et al., 1992). This trauma-induced hypermetabolism reflects the effort of cells to restore normal ionic balance, which is disrupted by pathological ionic flows through ion channels. Neuronal glucose consumption increases, which in turn diminishes energy stores, and causes calcium influx into mitochondria (Giza and Hovda, 2014). Impaired oxidative metabolism, anaerobic glycolysis, lactate production, and reactive oxygen species cause acidosis and edema. The This all causes neuronal dysfunction that is thought to reflect to the acute symptoms of TBI (Blennow et al., 2012). The disrupted state can last for days (Giza and Hovda, 2014). The temporal changes of the neurometabolic cascade are presented in Figure 2.

## 4.3 Epidemiology

The annual incidence of TBI is estimated to be 47-618 per 100,000 (Cassidy et al., 2004; Feigin et al., 2013; Koskinen and Alaranta, 2008; Leibson et al., 2011; Numminen, 2011; Pérez et al., 2012; Rickels et al., 2010; Thurman et al., 1999). In Finland, the annual incidence of TBI is estimated to be 101-221 per 100,000 (Koskinen and Alaranta, 2008; Numminen, 2011). There is large variation in the incidence numbers mainly because the methods of TBI case determination and the diagnostic criteria are different in the studies. Moreover, these numbers are limited to TBI patients treated in hospitals (Cassidy et al., 2004; Numminen, 2011). Precise "real life" population-based incidence numbers are difficult to acquire and thus such data is scarce (Feigin et al., 2013). The real-life incidence of TBI is widely acknowledged to be higher than current estimates (Cassidy et al., 2004; Hyder et al., 2007), because 70–90% of all TBIs are mild (Cassidy et al., 2004) with only a small proportion of those affected by TBI being admitted to hospital (Bazarian et al., 2009; Cassidy et al., 2004; Ribbers, 2007).

Distribution of MTBI incidence is bimodal with peaks at age groups of 15-24 years and over 65 years. (Gordon et al., 2006). Incidence of MTBI is greater within males than in females (Gordon et al., 2006; Laker, 2011). The most common causes of MTBI are falls and motor-vehicle accidents (Cassidy et al., 2004; Feigin et al., 2013). Elderly population aged 75 years and older have the highest rates of TBI-related hospitalization and death (Thompson et al., 2006). A ground-level fall (GLF) is a common cause of TBI, especially among the elderly. In the rural settings, transport accidents are the major cause of TBI (Feigin et al. 2013). The risk of ground level falls resulting in TBI increases in older adults (Hartholt et al., 2011; Pöyry et al., 2013). GLF-related head injuries (HI) are often not seen in the ED unless other injuries, such as wounds or fractures are present. Likewise, "low falls" from as high as 6 meters are sometimes regarded as mild injuries unless clear orthopedic or neurological injuries are seen (Helling et al., 1999). Even a low-energy trauma, however, can cause serious damage, particularly intracranial injuries (Helling et al., 1999; Sarani et al., 2009; Spaniolas et al., 2010).

MTBI is in general an injury with a good outcome. In the acute phase of the injury, the probability of having a potentially fatal intracranial hemorrhage which needs instant neurosurgery is minute (approximately 1% of all cases) (af Geijerstam and Britton, 2003) and the overall mortality is even lower (circa 0.1%). Common subjective symptoms (e.g. headache, fatigue, dizziness) after MTBI may not be caused by brain injury per se, but they can cause persistent problems in some

patients. Those with more initial complaints and psychological distress tend to recover slower (Cassidy et al., 2014).

## 4.4 Diagnosis of Mild Traumatic Brain Injury

In the ED, patients with a suspected HI should be considered as having a TBI, unless the clinical examination, history, or imaging studies show otherwise. Patients with a possible TBI require immediate assessment in order to identify those at risk of a more severe TBI. In the ED, a careful but focused history and physical examination are the first and most important steps in the assessment of TBI. A thorough approach to a TBI improves diagnostic precision, assists in decision-making in acute imaging, helps in outcome assessment and may prevent medicolegal problems.

Excessive costs can be limited by making clear and quick ED discharge policies and reducing ineffective imaging studies (Haydel, 2012; Jagoda, 2010; Jagoda et al., 2008; McCrea et al., 2009; Menon et al., 2010; Powell et al., 2008; Vos et al., 2012). Multiple pre- and post-injury factors should be taken into account, as they can distract, resemble, and/or hide the signs and symptoms of MTBI and alter the clinical picture of TBI.

Although this clinical examination might be compromised by intoxication with alcohol, recreational or prescribed drugs in a significant portion of patients with MTBI (Stiell and Perry, 2014), at least two current guidelines for acute head CT scanning (Canadian CT Head Rule and New Orleans Criteria) (Haydel et al., 2000; Stiell et al., 2001b) are still applicable (Stiell and Perry, 2014). Brain imaging in the ED can show acute lesions requiring observation or surgical procedures. Imaging studies are not affected by the effects of intoxication and therefore can aid diagnosis and differentiate MTBI from more severe injuries.

### 4.4.1 Assessment of Consciousness

The Glasgow coma scale (GCS) is a scale tool used to assess the level of consciousness of a person. The scale dates back to 1974 (Teasdale and Jennett, 1974). It was originally aimed for assessment of HI patients, but nowadays it is commonly used as a universal tool to evaluate the level of consciousness. The scale consists of assessing three types of reaction (primarily to a verbal command and if

no response is seen, to a painful stimulus): (i) eye opening response, (ii) verbal response, and (iii) motor response. Each of these three parts are individually scored according to the best response and the resulting points give a patient score between 3 (indicating deep unconsciousness) and 15 (normal consciousness). The first version of GCS was a 14-point scale, missing the motor response "abnormal flexion". Currently, the revised 15-point scale is used. The scoring of GCS is shown in Table 2. A GCS score of 13 to 15 points after 30 minutes from the injury is considered an MTBI (Carroll et al., 2004a; CDC, 2003; Kay et al., 1993; VA/ DoD, 2009a; Vos et al., 2012).

GCS is a robust tool, which gives an approximation of the initial severity of TBI. Even in MTBI the likelihood of a more severe injury increases as the GCS score decreases. GCS scores below 15 are associated with an increased risk for intracranial injury (Pandor et al., 2012). In various studies the incidences of traumatic intracranial abnormalities stratified by GCS score are as follows: 13 points: 28-51%, 14 points: 12-52%, 15 points: 6-34% (Borczuk, 1995; Jeret et al., 1993; Livingston et al., 1991; Ono et al., 2007; Saboori et al., 2007; Stein and Ross, 1992; Stiell et al., 2005; Thiruppathy and Muthukumar, 2004).

The use of GCS is not entirely unproblematic. The inter-rater reliability of the GCS is only moderate. The scoring appears to differ according to the professional background of the health care provider (Zuercher et al., 2009). There is less variability with high GCS scores (Zuercher et al., 2009). Reliable use of GCS requires training (Rowley and Fielding, 1991). Trained personnel tend to apply the GCS better, although interpretation of intermediate scores on the GCS is considered difficult even for emergency physicians (Menegazzi et al., 1993). Simplification of the GCS score has been suggested after documenting poor inter-rater reliability in TBI (Gill et al., 2005). Other causes than TBI may lower the GCS score, such as drugs, alcohol (Lange et al., 2010a), medications (e.g., sedatives), other injuries (e.g., bodily injuries, facial injuries,), intubation, and pre-existing diseases (e.g., neurodegenerative diseases) (Kanich et al., 2002).

The GCS requires a verbal response and as many unconscious patients are intubated, the verbal component cannot be tested. Some clinicians use the lowest possible score; others extrapolate the verbal response based on other neurological findings. The GCS does not detect abnormal brainstem reflexes, changing breathing patterns or the need for mechanical ventilation. Attempts have been made to modify the GCS, but these have not become clinical practice (Wijdicks et al., 2005). GCS has proven to be useful in the acute phase of TBI, but it performs suboptimally while the observation of the patient lasts over the most acute phase

(eg. in the intensive care unit). Newer coma scales, eg. FOUR (Full Outline of Unresponsiveness) score has numerous advantages in monitoring the state of consciousness: ability to recognize a locked-in syndrome, possible vegetative state, uncal herniation and further characterize the severity of the comatose state in patients with the lowest GCS score (Wijdicks et al., 2005).

**Table 2.** Glasgow coma scale (Teasdale and Jennett, 1974, 1976)

| **Best eye opening response (E)** | | **Best verbal response (V)** | | **Best motor response (M)** | |
|---|---|---|---|---|---|
| Spontaneous | 4 | Oriented, normal conversation | 5 | Follows commands | 6 |
| To verbal stimuli | 3 | Confused, answers questions | 4 | Localizes painful stimuli | 5 |
| To painful stimuli | 2 | Inappropriate | 3 | Withdraws from painful stimuli | 4 |
| None | 1 | Incomprehensible | 2 | Abnormal flexion, decorticate posture | 3 |
| | | None | 1 | Abnormal extension, decerebrate posture | 2 |
| | | | | None | 1 |

E+V+M=3-15 points total, 15 being fully conscious and 3 being deeply unconscious

#### 4.4.1.1 Loss of Consciousness

LOC is the time of unresponsive state caused by TBI (Blyth and Bazarian, 2010). A Glasgow Coma Scale (GCS) score of under nine is universally regarded as unconsciousness (Teasdale and Jennett, 1974). In MTBI, the period of LOC must be 30 minutes or less (Carroll et al., 2004a), even though LOC for longer than a couple of minutes is considered rare in MTBI.

The mechanism of unconsciousness following a TBI is incompletely known. The localization of dysfunction following concussion has been attributed to an injury-induced deactivation of brain stem regions (Hayes et al., 1984). Several other mechanisms have been suggested for the unconsciousness that happens in MTBI, including the reticular, pontine-cholinergic system, centripetal, and convulsive hypotheses (Blyth and Bazarian, 2010; Shaw, 2002). LOC is thought to be caused by the temporal impairment in one or more parts of the ascending reticular

activating system, which is located in the central pons, midbrain, hypothalamus, and thalamus (Olson and Graffagnino, 2005; Shaw, 2002).

External acceleration-deceleration forces stretch brain tissue disrupting its normal function. In the more severe TBI, diffuse axonal injuries are considered to cause prolonged unconsciousness and comatose states. (Shaw, 2002) There is some evidence that LOC in participants with even MTBI is associated with injury to white matter tracts detected by DTI (Levin et al., 2016).

### 4.4.2 Post-traumatic Amnesia

No uniform definition for PTA exists. It can be defined as a disorder of episodic memory for personally experienced events and information. It is a temporary state of confusion, disorientation, and memory impairment caused by a HI (Friedland and Swash, 2016; King et al., 1997; Menon et al., 2010). The pathophysiology and the clinical picture of PTA are incompletely known (Marshman et al., 2013). PTA may result from direct injury, edema, ischemia, and/or perfusion changes in the temporal lobes and the hippocampus (Ahmed et al., 2000; Metting et al., 2010; Zola-Morgan et al., 1986).

Autobiographical memory, however, is not continuous, not even in normal individuals. Instead, it is episodic, and any account of a remembered event in normal individuals will feature both detailed recollections and gaps (The British Psychological Society, 2008). Most studies of PTA, especially the seminal early studies, have been made in patients with a relatively severe TBI. Levin et al (Levin et al., 1979) defined PTA as a period following a TBI with loss of consciousness during which there is confusion, amnesia for ongoing events and often a behavioral disturbance. Russell and Smith (Russell and A. Smith, 1961) considered that the end of PTA was most easily defined as the point at which the patient could give a clear, consecutive account of what was happening around them.

#### 4.4.2.1 Altered Mental State

The altered mental state (confusion and loss of orientation) is commonly included in the definition of PTA, even though some MTBI criteria consider it a separate entity (Tate et al., 2000). The confused state seen in PTA resembles in many features an acute delirium (Marshman et al., 2013). Spatial and temporal disorientation are often seen. Additionally, speech deficits (e.g. meaninglessness

and rambling) are seen (Daniel et al., 1987; Schnider et al., 1996; Tate et al., 2000; Tittle and Burgess, 2011). The mechanisms causing disorientation are thought to be the incapability to store new information and increased confusion of temporal memory traces from different events (Daniel et al., 1987; Schnider et al., 1996). Anatomically, the dysfunctioning brain parts are thought to be in the basal forebrain and medial orbitofrontal regions (Schnider et al., 1996).

#### 4.4.2.2 Measurement of PTA

Usually, the length of PTA is defined as the time between TBI and the return of normal function of anterograde memory and orientation (Jacobs et al., 2012; Marshman et al., 2013). In clinical practice, PTA can be assessed prospectively and retrospectively. In the prospective measurement of PTA, scales such as the Westmead PTA Scale (WPTAS) and the Galveston Orientation and Amnesia Test (GOAT) are often recommended.

Lack of consensus on the definition of the end of PTA is generally acknowledged in studies of MTBI (King et al., 1997; Levin et al., 1979). The prominence of additional neurobehavioral manifestations including confusion, sleep-wake cycle disturbance, motor agitation, affective lability, aggressive behavior and abnormalities in thought processes (Nakase-Thompson et al., 2009) has given rise to the concept that the term "post-traumatic confusional state" should replace "PTA". The most prominent features of PTA are disorientation and anterograde amnesia that may be with or without confusion, behavioral disturbances, agitation, stupor, attention deficits, delirium, and retrograde amnesia (RA) (Marshman et al., 2013; Tittle and Burgess, 2011). The majority of diagnostic criteria classify TBI as mild, when the PTA lasts less than 24 hours (Carroll et al., 2004a).

Much of the literature on outcome after TBI, especially that related to retrospective assessment, has focused on the length of PTA, assessed by the return of the normal continuous memory, and not by resolution of the post-traumatic confusional state. The latter, however, can only be accurately assessed prospectively. Since the disruption of categorical memory and the confusional state are closely associated in the acute stage of TBI, it is difficult to address prospectively or retrospectively any distinction between the two (Tate et al., 2006). Tate et al (Tate et al., 2000) found that recognition memory reached criterion before orientation to place and to time. They also stated that there was variability in determining the end of PTA according to the scale used for the assessment.

Nonetheless, there was a close correlation between the recovery of orientation and return of memory. In this context, it is perhaps relevant to remember that people admitted to hospital even without brain damage often do not know the date or day of the week.

Assessment of PTA retrospectively is considerably less reliable. It involves asking the individual to recall their first memory after the injury. It is required that the clinician specifically asks the patient to describe their personal recall of events and not what they have subsequently learnt (Ruff et al., 2009). In practice, the learnt things and the memories for events occurred after brain injury is very hard to distinguish, to both the clinician and the patient.

#### 4.4.2.3 Psychogenic Amnesia and PTA

The clinical distinction between organic and psychogenic amnesia can be difficult, for example, in an assessment made some time after the injury (Jones et al., 2007). PTA and dissociation occurring in post-traumatic stress disorder (PTSD) or acute stress disorder (ASD) can mimic each other. It is not always true to assume that if a patient cannot remember the details of the injury this would indicate PTA and TBI. Amnesia could also result from a psychological dissociation. It has been debated that patients suffering TBI with PTA, could not be capable of having PTSD. The recognized contemporary position, however, is that a patient may develop PTSD after TBI, perhaps especially so in the case of MTBI (Jones et al., 2007). In a meta-analysis, Carlson et al (K. F. Carlson et al., 2011) found that PTSD and TBI occur often simultaneously.

### 4.4.3 Focal Neurological Signs

Even MTBI can cause focal neurological symptoms. It can impair sensory (vision, hearing, tactile), language, or motor functions (Coello et al., 2010; Haydel, 2012). The most frequent symptoms are post-traumatic seizures, anosmia/hyposmia, visual field deficits/diplopia, aphasia, and balance disturbance (Carroll et al., 2004a). Anatomic location of the central nervous system (CNS) injury defines the symptoms (e.g. contusion of the motor cortex results in contralateral motor weakness).

### 4.4.4 Medical History

The relevant medical history is an integral part of the evaluation of a patient with an MTBI. MTBI is a difficult injury to diagnose, because the diagnosis is often hindered by the lack of obvious injuries on CT or conventional MRI and usually is based solely on clinical sign and symptoms. Hence, the information gathered from the medical records and a clinical interview forms the base of the diagnosis. The assessment of HI patients should include history of pre-existing diseases and regular medication, as they are significant for several reasons.

Certain pre-existing medical conditions (e.g., coagulopathies), previous neurosurgery (e.g., cerebral shunt) or medication (e.g., antithrombotic agents), increase the risk of having an intracranial hemorrhage (National Institute for Health and Clinical Excellence, 2007; Undén et al., 2013). Pre-injury health problems may alter the clinical picture of acute MTBI, and interfere with the identification and assessment of the injury (Haydel, 2012; Jagoda, 2010; Menon et al., 2010). Pre-injury health status, especially mental health, has a strong effect on MTBI outcome (Gould et al., 2011; Lange et al., 2010b; Ponsford et al., 2012; 2000; Silverberg et al., 2015; Silverberg and Iverson, 2011). The use of OAC in MTBI patients is well-known risk factor for intracranial bleeding (Cohen et al., 2006; Pieracci et al., 2007). The effect of anticoagulants should be always considered in the acute assessment of MTBI. A cerebral shunt and coagulation disorders are regarded as risk factors for traumatic intracranial hemorrhage (Undén et al., 2013).

Psychiatric and neurological conditions and diseases may resemble the symptoms of MTBI (Menon et al., 2010; Ruff et al., 2009). For instance, patients with acute MTBI typically express the symptoms of affective (e.g., depression) and stress-related disorders (e.g., anxiety), particularly during the first days after the injury. It is difficult to distinguish acute post-MTBI symptoms from underlying mental health problems (Iverson and Lange, 2003; King, 1996; Reuben et al., 2014). Both occasional and long-term alcohol and drug abuse should also be noted because they make TBI identification and outcome. Alcohol abuse is also associated with an increased risk for intracranial hemorrhage (Haydel et al., 2000). Acute alcohol intoxication is also associated with lower GCS score and a higher hospital admission rate (Scheenen et al., 2016).

Numerous coexisting neurological diseases can mimic the acute symptoms of MTBI. Neurodegenerative diseases (e.g. Alzheimer's disease) cause memory problems that are often present in the acute phase of an MTBI (Markowitsch and

Staniloiu, 2012). Previous HI may increase the risk for worse outcome and should be seen as a possible confounding factor in the acute assessment (Dams-O'Connor et al., 2013; Silverberg et al., 2013). Different types of medication such as sedatives (e.g., benzodiazepines), analgesics (e.g., opioids), and antiemetics (e.g., dopamine antagonists) can have an effect on MTBI symptoms and affect the initial assessment. Trauma patients even without HI experience similar post-traumatic symptoms (fatigue, dizziness, poor concentration, memory problems, headache and irritability) as MTBI patients (Meares et al., 2008; 2011). The role of other injuries should be considered when treating HI patients. On the other hand, a chance exists that trauma patients without TBI, are incorrectly diagnosed with an MTBI based on the cognitive and psychological symptoms they are experiencing in the acute phase.

### 4.4.5 Injury-related Information

It is important to distinguish HI from TBI. Head injury is a trauma of any part of the head (including wounds, facial or dental injuries, fractures). Both injuries occur often in combination but isolated head injuries without brain injury are more common. In most cases, a HI occurs without TBI, but a TBI can occur without any direct or visible injury to the skull or head (Ruff, 2005).

Injury-related information, such as mechanism of injury and clinical presentation of the symptoms in the field (LOC, GCS, PTA, mental status), are crucial in the MTBI diagnostics for two main reasons. The diagnosis is often based on eyewitness and patient interviews. The dangerousness of the mechanism of injury should be evaluated as high-energy trauma increases the probability of having a TBI. Dangerous mechanism of injury includes ejection from a motor vehicle, a pedestrian struck, and a fall from a height of more than 90 cm or 5 stairs (Jagoda et al., 2008)

Different kinds of trauma can cause TBI: direct force or a blast exposure (VA/ DoD, 2009b). Also rotational or acceleration- deceleration forces to the head without direct impact to the head can result in TBI (Kay et al., 1993). Another way of categorizing TBI is dividing it into closed and penetrating. HI is defined penetrating if the skull and dura are perforated by sharp objects and closed if not.

### 4.4.6 Neurologic Examination

Symptoms of MTBI in the acute phase can be categorized into physical, cognitive, emotional, and sleep problems (Harmon et al., 2013), but these symptoms are not specific for MTBI. A thorough neurological examination includes assessing the motor and sensory function, including the cranial nerve function, balance and coordination, evaluating the level of consciousness, mental status (especially cognition) and noting other acute symptoms (e.g. headache, nausea).

Any focal neurological deficit after HI should be thought as possible sign of TBI. Focal neurological symptoms are associated with increased risk of intracranial lesions in TBI (Mower et al., 2005; National Institute for Health and Clinical Excellence, 2007; Vos et al., 2012). It must be noted, however, that a normal neurological examination does not entirely exclude the possibility of a significant TBI (Vilke et al., 2000).

The most common cranial nerve deficits are within olfactory, facial, and oculomotor nerves (Coello et al., 2010). Pupillary reflexes indicate both underlying pathology and severity of injury and should be monitored serially (Hoffmann et al., 2012). The pupillary abnormalities in MTBI patients are most probably caused by other etiologies (e.g., substance abuse, physiological anisocoria) as oculomotor palsy caused by uncal herniation is a sign of a severe increase in intracranial pressure (Haydel, 2012).

The level of consciousness is evaluated by using the GCS (Teasdale and Jennett, 1974). Monitoring the level of consciousness is started at site of injury when the patient is reached. After a HI, neurological deterioration should be regarded as a sign of a potentially fatal intracranial lesion and the patient requires an instant head CT scan. According to numerous CT decision rules (Haydel et al., 2000; National Institute for Health and Clinical Excellence, 2007; Smits et al., 2007; Stein et al., 2009; Stiell et al., 2001a; Undén et al., 2013) an immediate head CT is recommended for those with a GCS score of 14 or lower. Amnesia, vomiting, and/or severe (and often worsening) headache are also considered as risk factors for an acute traumatic intracranial lesion in some guidelines (Haydel et al., 2000; Mower et al., 2005; Stiell et al., 2001b; Vos et al., 2012).

Some studies suggest that memory tests could be utilized to predict post-concussive symptoms (Bazarian and Atabaki, 2001; Faux et al., 2010; Sheedy et al., 2009). Basic cognitive testing in the ED extends the focus of care from the detection of intracranial lesion to a more patient-focused approach, addressing the cognitive symptoms that patients tend to experience. High symptom burden,

especially of psychological stress symptoms, is associated with an increased risk for persistent post-concussion symptoms (Ponsford et al., 2012; 2000; Silverberg et al., 2015).

### 4.4.7 Physical Examination

MTBI is a common co-occurring injury and patients may have different extracranial injuries, from skin lacerations to spinal, axial bony, thoracic, and abdominal injuries. Concurrent cervical spine injuries are common in TBI (Budisin et al., 2016). Clinically relevant cervical spinal injuries can be excluded (Michaleff et al., 2012) with a proper physical examination done according to the Canadian C-spine rule (Stiell et al., 2001c) or National Emergency X-Radiography Utilization Study (NEXUS) (Hoffman et al., 2000).

Visible depression is a clear sign of skull fracture. Signs of skull base fractures include hemotympanum, periorbital ecchymosis ("raccoon eyes" or "panda eyes"), mastoid ecchymosis (Battle's sign), cerebrospinal fluid rhinorrhea and otorrhea (Haydel, 2012). Suspicion of skull fractures indicates the need of emergency head CT (Haydel et al., 2000; Mower et al., 2005; National Institute for Health and Clinical Excellence, 2007; Stiell et al., 2001b; Undén et al., 2013; Vos et al., 2002).

## 4.5 Neuroimaging

Soon after the introduction of CT in 1974, head CT became the central component in the acute assessment and diagnosis of TBI. MRI is another imaging modality that is in regular use, commonly in the subacute phase. More developed and promising neuroimaging techniques include more sophisticated MRI techniques, such as diffusion tensor imaging (DTI) and functional MRI (fMRI). DTI and fMRI are currently used mainly for research purposes.

### 4.5.1 Traumatic Intracranial Lesions

HI can cause multiple different macroscopic, permanent traumatic changes, which can be visualized by MRI or CT. These lesions include traumatic intracerebral hemorrhage (ICH), subdural hemorrhage (SDH), epidural hemorrhage (EDH),

subarachnoid hemorrhage (SAH), intraventricular hemorrhage, contusion, diffuse axonal injury (DAI), and secondarily brain edema and ischemia. Skull and facial bone fractures are often associated with intracranial injuries (Coles, 2007; Pappachan and Alexander, 2006).

Focal cerebral contusions, traumatic subdural hemorrhages (SDH) and subarachnoid hemorrhages (SAH) are commonest and the most important traumatic lesions in moderate to severe TBI patients (Maas et al., 2008; Raj et al., 2014) as well as in MTBI patients (Haydel et al., 2000; Stiell et al., 2001b). The incidence and clinical impact of aforementioned lesions differs greatly according to the severity of the injury. Even within the MTBI patients, the rate of acute CT-positive intracranial lesions varies greatly, between 4.7% and 38.9% (Iverson et al., 2000; Stiell et al., 2005). Only about 1% of these lesions in MTBI patients need neurosurgery (Ibañez et al., 2004; Smits et al., 2005; Stiell et al., 2001b). Different studies have reported wide range of acute lesions detected with conventional MRI in MTBI, from 0 to 43%(Hofman et al., 2001; Hughes et al., 2004; Kurca et al., 2006; Mittl et al., 1994; Uchino et al., 2001; Voller et al., 1999; Yuh et al., 2013). The presence of traumatic lesions is noted differently in diagnostic criteria for MTBI (Table 1).

### 4.5.2 Computed Tomography

Cranial CT scan is the neuroimaging modality of choice in the emergency room, as it can readily identify the small subset of patients who require prompt neurosurgery. Depending on the applied MTBI criteria, the incidence of acute CT-positive intracranial lesions ranges from 4.7% to 38.9% in individual studies (Borczuk, 1995; Iverson et al., 2000; Jeret et al., 1993; Livingston et al., 1991; S. G. Moran et al., 1994; Ono et al., 2007; Saboori et al., 2007; Stein and Ross, 1992; Stiell et al., 2005; Thiruppathy and Muthukumar, 2004). Contusions, SAHs, and SDHs are the most important CT-positive lesions in MTBI population (Haydel et al., 2000; Stiell et al., 2001a) and only about 1% of these patients need neurosurgery (Fabbri et al., 2005; Ibañez et al., 2004; Smits et al., 2005; Stiell et al., 2001b).

Since 2000, several guidelines have been published and validated to guide decision making in CT imaging (Haydel et al., 2000; Ingebrigtsen et al., 2000; Jagoda et al., 2008; Mower et al., 2005; National Institute for Health and Clinical Excellence, 2007; Smits et al., 2007; Stiell et al., 2001b; Undén et al., 2013; Vos et al., 2012; 2002). These guidelines are reliable tools in predicting the need for

neurosurgical procedures and clinically important TBI on CT. Guidelines are recommended for ED management, decision rules reduce unnecessary head CT scans, optimize the use of hospital resources, and improve cost-effectiveness (Jagoda et al., 2008; Morton and Korley, 2012; Stein et al., 2009; 2006; Stiell et al., 2005) The newest of the guidelines is the "Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries in adults" (Undén et al., 2013).

Observation for 6–8 hours in hospital setting can probably be used as an alternative to CT scans in patients without altered mental status or signs of skull fracture (Norlund et al., 2006). Absence of risk factors and worsening symptoms are factors that guide the decision between a head CT scan and observation. Home observation is recommended as a possibility for patients with a normal mental status and neurological examination, and the availability of a companion (National Institute for Health and Clinical Excellence, 2007).

#### 4.5.2.1 Delayed Intracranial Hemorrhage

After a negative CT, the most-feared complication is clinical deterioration from a delayed development of a significant intracranial lesion. Delayed intracranial hemorrhage or brain edema are infrequent but recognized dangerous complications of HI that may need neurosurgical care (af Geijerstam and Britton, 2003; A. P. Carlson et al., 2010). Delayed diagnosis can occur either through misdiagnosis of intracranial hemorrhage existing immediately after injury or true delayed hemorrhage. In the literature, these patients have been regarded as patients who "talked and died" (Rose et al., 1977). However, this concept dates back to the 1970s, when CT imaging was not yet widely available.

The probability of severe complications after a negative CT is minimal (3 out of 62,000 patients in a review study, ~0.005%), when GCS score is 15 and neurological examination is normal on initial presentation (af Geijerstam and Britton, 2005). However, GCS scores below 15 are associated with an increased risk for intracranial injury (Pandor et al., 2012).

The most important questions are: Who are the patients suffering these complications and is it possible to identify these patients before hospital discharge? Routine hospital monitoring after a CT-negative HI is conservative, expensive and resource consuming (af Geijerstam and Britton, 2003; A. P. Carlson et al., 2010). Timely identification of patients with a risk of a complication could decrease

treatment costs and spare ED resources by reducing unnecessary hospital observation. In the past, a large proportion of MTBI patients were hospitalized for observation because of a history of loss of consciousness or amnesia and discharged with a diagnosis of brain concussion within a few days after the injury. Within the last decades, this policy has been questioned as CT scan is increasingly used (af Geijerstam et al., 2000). Table 3 summarizes the studies on delayed complications following a normal head CT scan.

There are multiple possible reasons for a delayed bleeding (Hamilton et al., 2010). Disturbed cerebral autoregulation may reduce the brain's capacity to optimally regulate cerebral blood flow (CBF). Impaired autoregulation of CBF may lead to persistent bleeding of smaller contusions. Other potential causes of delayed intracranial hemorrhage include blood coagulation disorders or medication affecting the coagulation. Venous bleeding is slower in nature than arterial bleeding. Venous injuries are thought to show signs of high intracranial pressure later than arterial bleeding.

The use of oral anticoagulants (OAC) in MTBI patients is an independent risk factor for intracranial hemorrhagic complications (Cohen et al., 2006; Pieracci et al., 2007). The risk of secondary deterioration after a normal CT is <0.1% (af Geijerstam and Britton, 2005; de Boussard et al., 2006). Whether OAC use is a risk factor for delayed bleeding in MTBI patients after an initially normal CT scan is unclear. There are case reports showing a subdural hematoma in few patients between 9 and 72 hours (Engelen et al., 2009; Itshayek et al., 2006), but larger studies have shown partly conflicting results. In different studies, the risk of delayed intracranial hemorrhage in patients with OAC has been between 0-7.2% (Kaen et al., 2010; Menditto et al., 2012a; Nishijima et al., 2012; Peck et al., 2011; Reynolds et al., 2003; Schoonman et al., 2014). The time of possible deterioration is virtually impossible to predict, as it can be anything from hours to almost a month (Schoonman et al., 2014). In these studies, OAC was a vitamin K antagonist (VKA), usually a coumarin, such as warfarin.

Because of the increasing use of anticoagulation medication, clinicians are wary of the risk of delayed intracranial bleeding in the presence of minor HI. Although European guidelines suggest a period of observation and repeat imaging (Vos et al., 2012), trauma centers worldwide have developed heterogeneous protocols for managing such patients (Rendell, 2014). Some evidence exists that HI symptoms and GCS can be used to predict acute poor outcome in anticoagulated HI patients. INR seems not to predict poor outcome in patients taking VKA and with a GCS of 15. Patients with GCS of 15 and no symptoms have a low risk (2.7%) of poor

outcome regardless of INR. These findings suggest that use of CT scanning in low-risk anticoagulated patients may be of limited value (Mason et al., 2017). The likelihood of having an intracranial traumatic lesion increases as INR rises (Claudia et al., 2011).

In general population there are few studies about the incidence and time pattern of delayed, intracranial complications in MTBI patients as well as about the reliability of an early CT scan without abnormalities with regard to delayed complications (de Boussard et al., 2006). Nevertheless, there are some convincing studies about the reliability of an early CT scan. CT has been confirmed to be non-inferior to observation in hospital (af Geijerstam et al., 2006). The large-scale studies on the early discharge after a normal head CT scan have concentrated exclusively on mildest part of the MTBI, meaning that the patients have GCS of 15 (af Geijerstam and Britton, 2005; de Boussard et al., 2006).

A recent systematic review states that in most situations, a repeat CT scan in the ED is not necessary if the first scan is normal, even in anticoagulated patients. However, special attention may be required for patients with serious mechanism of injury, patients showing signs of neurologic deterioration, and patients presenting with excessive anticoagulation or receiving antiplatelet medication (Chauny et al., 2016).

Most patients with MTBI could be discharged early without any in-hospital observation, if the CT was normal, and there were no other reasons for admission. Still many patients are both receiving a CT and observed. Such overlapping treatment decisions consumes resources ineffectively (Norlund et al., 2006). There are multiple reasons for this kind of practice. One simple reason is that clinical practice often changes slowly (Grol and Grimshaw, 2003). The routine observation after MTBI has been in use for decades, and medical staff has been accustomed to it.

**Table 3.** Summary of studies on delayed complications after initial negative head CT scan

| Study | Year | n | Age | GCS | Follow-up | Injury progression | Comments |
|---|---|---|---|---|---|---|---|
| Schoonman et al. | 2014 | 211 | All | 13-15 | Up to 28 days | 5/211 new lesions on follow-up scan, 2 had an operation and 1 died after operation | Only patients on anticoagulation medication |
| Docimo et al. | 2014 | 168 | >18 | 3-15 | No | 2/168, no interventions | Only patients on anticoagulation or antiplatelet medication |
| Menditto et al. | 2012 | 87 | >13 | 14-15 | Up to 30 days | 5/87 new lesions on follow-up scan, 1 showed neurological deterioration, 1 had neurosurgery. | Only patients on anticoagulation medication. Unclear if patient requiring neurosurgery had neurological deterioration. |
| Peck et al. | 2011 | 424 | >14 | N/A | Until discharge | 4/424 new lesions on follow-up scan, all minor changes and no effect on treatment | Only patients on anticoagulation or antiplatelet medication |
| Dalbayrak et al. | 2011 | 112 | All | >7 | Chart review | Initially normal CT n=21, 6/21 new lesions on follow-up scan, all 6 had neurosurgery | Unclear if patients treated surgically had neurological deterioration. Not a consecutive series. |
| Kaen et al. | 2010 | 137 | >16 | 14-15 | Until discharge | 2/137 new lesions on follow-up scan, none had neurological deterioration or neurosurgery | Only patients on anticoagulation medication |
| Tauber et al. | 2009 | 100 | >64 | 15 | Until discharge | 4/100 new lesions on follow-up scan, 1 died and 1 had neurosurgery due to ICH progression | Only patients with low-dose acetylsalicylic acid (100 mg/day) |
| Türedi et al. | 2008 | 120 | All | 13-15 | No | 3/120 new lesions on follow-up scan, no intervention needed | Only patients with “high risk” MTBI (GCS 14-15 and LOC, PTA, vomiting, suspected skull fracture, polytrauma, headache, asymmetric pupils, focal signs, seizures or anticoagulant/coagulopathy) |
| Itshayek et al. | 2006 | 4 | 65-86 | 15 | GOS up to 26 months | A case series of 4 patients with minimal HI (GCS 15, no LOC/amnesia) all showed delayed subdural hemorrhage after 9 hours to 3 days post-trauma. | Only patients on anticoagulation or antiplatelet medication |
| Livingston et al. | 2000 | 2152 | >15 | 14-15 | 4-8 hours, 20 hours and at discharge | 19/1664 new lesions on follow-up scan, of whom 2 were treated in an intensive care unit, no surgical interventions needed | - |
| Nagy et al. | 1999 | 1131 | All | 15 | Short-term hospital follow-up | No neurologic deterioration after initial negative head CT | - |

N/A: not available

### 4.5.3 Magnetic Resonance Imaging

CT is the most used imaging modality in the evaluation of MTBI but many studies have shown that conventional MRI has superior sensitivity compared to CT in identification of certain acute lesions, including hemorrhagic axonal injury and small contusions. The incidence of acute lesions detected with conventional MRI in MTBI ranges from 0% to 43% (Hofman et al., 2001; Hughes et al., 2004; Kurca et al., 2006; Mittl et al., 1994; Uchino et al., 2001; Voller et al., 1999; Yuh et al., 2013). The large difference in the rates comes from the variance in the applied imaging sequences and the MTBI diagnostic criteria. Also, the timing of the imaging affects the findings as conventional MRI loses some of its usefulness in showing intracranial damage within weeks post-injury (Brandstack et al., 2006; Orrison et al., 1994; Provenzale, 2007). The results on the relationship between MRI-positive traumatic lesions and long-term outcome of MTBI are conflicting, which has limited the more extensive use of conventional MRI (H. Lee et al., 2008; Yuh et al., 2014). Despite its high sensitivity, routine use of brain MRI in acute MTBI is rare because of the higher costs and limited availability. Currently MRI is mostly used in the clinical management of subacute MTBI with persistent symptoms.

In the TBI Common Data Elements, the recommended MRI sequences include: (i) 3D T1-weighted, (ii) 3D T2-weighted, (iii) T2-weighted fast spin echo, (iv) T2-weighted fluid-attenuated inversion-recovery (FLAIR), (v) diffusion weighted echo planar imaging, (vi) 3D susceptibility weighted imaging (SWI), and (vii) 2D gradient-echo (Duhaime et al., 2010). The SWI sequence is the most sensitive in detecting hemorrhagic lesions (Yuh et al., 2014).

The limitations of the imaging possibilities have led to the development of more advanced neuroimaging techniques that are promising in improving diagnostics in MTBI. Diffusion tensor imaging (DTI) is a technique used to quantify white matter integrity in the brain. DTI is sensitive to subtle changes in white matter fiber tracts and is capable of revealing microstructural axonal injuries (Basser et al., 1994; Pierpaoli and Basser, 1996). Each of the four major DTI analysis methods (histogram analysis, voxelwise analysis, region-of-interest [ROI] analysis, and tractography) has strengths and weaknesses. Many studies have shown group differences in DTI parameters between MTBI patients and controls (A. Gardner et al., 2012; Shenton et al., 2012; Yuh et al., 2014). DTI is nowadays commonly used in MTBI research, but the results have not been uniform in terms of predicting the outcome from MTBI (Panenka et al., 2015).

In functional MRI (fMRI), the blood oxygen level dependent (BOLD) effect is used: when brain activity increases locally, flow of oxygenated blood to that region also increases. This change can be detected with specialized MRI sequences. Two main types of fMRI exist: task-based fMRI and resting state fMRI (rs-fMRI). In the rs-fMRI, the spontaneous changes in the BOLD signal in resting patients are recorded, reflecting the functional connectivity of different brain regions. There are only few rs-fMRI studies of strictly MTBI to date and the results are inconsistent (Yuh et al., 2014). In their current states, DTI or fMRI are not used regularly in clinical practice.

## 4.6 Common Data Elements in Neuroradiology of TBI

The motivation for creating the Common Data Elements (CDE) for TBI has been to enable the detailed characterization of the natural history and predictive factors in TBI. The approaches to the characterization of TBI severity and outcome have changed little in more than three decades. Even today, the clinical classification of TBI patients into categories of mild, moderate, and severe is largely based on GCS (Teasdale and Jennett, 1974). During the last decade, working groups have developed consensus-based recommendations for harmonization of data across clinical trial sites with an emphasis on demographics, clinical care, genetic and proteomic biomarkers, neuroimaging, and a battery of outcome measures suitable for use across the spectrum of TBI (Yue et al., 2013)

The CDE were created to systematize data collection and enable data sharing across a wide range of patient and injury variables as without a set of CDE, comparison of findings across studies is difficult (Thurmond et al., 2010). This large-scale data harmonization initiative provided recommendations across a variety of domains, including neuroimaging. Recommendations for TBI-related imaging were formulated by a multidisciplinary expert panel through an iterative scientific review process.

Neuroimaging makes it possible to visualize and categorize the location, nature, and degree of damage in TBI. The utility of modern neuroimaging in triaging patients for acute interventions and determining prognosis is well known. The CDE set for neuroimaging aims for structuring how patients entering clinical trials will be classified, stratified, and treated (Duhaime et al., 2010).

**Table 4.** Overview of the Common Data Elements in TBI imaging (CT/MRI)

| **Technical information** | **Findings** |
|---|---|
| Study date and time | Skull fracture |
| Imaging modality | Epidural hematoma |
| Imaging scanner strength (if MRI) | Extra-axial hematoma |
| Imaging scanner manufacturer, model, software | Acute/chronic/mixed density subdural hematoma |
| Imaging sequence | Subarachnoid hemorrhage |
| | Vascular dissection |
| | Traumatic aneurysm |
| | Venous sinus injury |
| | Midline shift supratentorial |
| | Cisternal compression |
| | Fourth ventricle shift or effacement |
| | Contusion |
| | Intraventricular hemorrhage |
| | Diffuse axonal injury |
| | Penetrating injury |
| | Edema/brain swelling |
| | Ischemia or infarction or hypoxic-ischemic injury |
| | Brain atrophy or encephalomalacia |

## 4.7 Biomarkers of Brain Injury

The development and research of biomarkers stem from the need for an objective, prognostic, and cost-efficient tools to recognize and grade TBI. The goal has been to develop biomarkers to aid in the early identification and diagnosis, as well as to predict patient outcomes. Biomarkers in the blood, saliva, urine, and cerebrospinal fluid are being investigated (Zetterberg et al., 2013). Most of the studies are on serum biomarkers (Papa et al., 2013). In recent times, the most studied blood biomarkers have been glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCHL1) (Levin and Diaz-Arrastia, 2015). Thus far, protein 100B (S100B) is the only blood-based biomarker that has been included in an TBI guideline (Undén et al., 2013). The blood levels of S100B rise in polytrauma, reducing its usefulness when extracranial trauma is present (Thelin et al., 2016; Pelinka et al., 2003). Despite the scientific progress, further validation is needed regarding the use of biomarkers in TBI management. With the heterogeneity of pathological mechanisms implicated in MTBI, development of a panel of

biomarkers might be required to achieve sufficient sensitivity and specificity for broad clinical application (Diaz-Arrastia et al., 2014).

## 4.8 Outcome of Mild Traumatic Brain Injury

The typical clinical course of MTBI is the clearing of confusion within the first 24 hours (Levin and Diaz-Arrastia, 2015). Most patients recover from an MTBI within days or weeks (Dean et al., 2011; McHugh et al., 2006). A substantial body of evidence suggests that MTBI-related neuropsychological deficits are present during the first two weeks after an MTBI. However, it is not clear when these deficits resolve, and there is evidence from studies conducted over the last decade that some objectively measured cognitive deficits can last up to 12 months (Carroll et al., 2014). Pre-injury neuropsychiatric disorders are strongly related to the persistence of symptoms for 3 months or longer after MTBI (Meares et al., 2011; Ponsford et al., 2011). Athletes seem to recover more rapidly than the general population from an MTBI. Differences in the LOC, comorbidities, and pre-injury disorders have led to a suggestion that sports concussion might be a distinct type of MTBI (Levin and Diaz-Arrastia, 2015). In comparison with patients with MTBI presenting to emergency rooms, post-concussion symptoms in 80–90% of adult athletes typically resolve within 7–10 days after their first concussion (McCrory et al., 2013).

Common subjective symptoms after MTBI are not necessarily caused by brain injury per se (Korley et al., 2017), and the term ”post-traumatic symptoms” has been proposed to replace post-concussion symptoms (Cassidy et al., 2014). However, there is some evidence that certain symptom aspects (sadness and fatigue) might be more common in patients 3 months after MTBI than in trauma controls (Ponsford et al., 2011). These symptoms may be associated with disability (Dams-O'Connor et al., 2013). MTBI symptoms may reduce the ability to work and unemployment at 3 months could be as high as a third of patients (Boake et al., 2005). However, unemployment status of MTBI patients at 3–6 months is similar compared to general trauma patients (Boake et al., 2005; Ponsford et al., 2011).

Initial impairment of memory, slow information processing, and executive dysfunction are common findings on neuropsychological tests within the first 2 weeks after injury (Carroll et al., 2014). Whereas cognitive recovery by 3 months has been documented in prospective, longitudinal studies (Ponsford et al., 2011),

confirmatory research is needed to characterize the time course and identify any persistent cognitive deficit that is attributable to MTBI (Carroll et al., 2014). Cognitive deficits affecting attention, processing speed, and memory are frequently present during the first week to a month (Carroll et al., 2014). Despite favorable recovery in a majority of patients, there is a subgroup comprising 15-20% of the patients with MTBI (depending on case definition, follow-up interval, outcome measure, and comparison group) which might be left with residual deficits or symptoms that impair their ability to fulfill their work, school, or family responsibilities (Carroll et al., 2014; Cassidy et al., 2014). However, post-concussive symptoms such as fatigue are nonspecific (Kristman et al., 2014) and the normal variability in scores that occurs in healthy persons across a series of cognitive tests could be misattributed to MTBI (Carroll et al., 2014). The evidence that cognitive deficits last longer than 6 months is weak (Carroll et al., 2014). Functional long-term problems after MTBI are often complex and many biopsychosocial factors are involved in the recovery (Silverberg and Iverson, 2011). Early recognition of patients at increased risk for prolonged symptoms is important, as an early intervention may prevent the regularly occurring symptoms during the first days and weeks from eliciting secondary long lasting symptoms (Ponsford et al., 2002).

Unfortunately, the early outcome prediction in MTBI has turned out to be a challenge (Carroll et al., 2014; 2004b). TBI severity indicators (PTA, LOC, GCS scores or neuroimaging findings) do not offer much help in MTBI outcome prognostication (Hughes et al., 2004; Iverson et al., 2012; Jacobs et al., 2010; Lange et al., 2012; Nolin and Heroux, 2006; Stulemeijer et al., 2008; Wäljas et al., 2013; 2014). Pre-injury health status, especially mental health, has a strong effect on MTBI outcome (Gould et al., 2011; Lange et al., 2010b; Ponsford et al., 2012; 2000; Silverberg et al., 2014; Silverberg and Iverson, 2011).

There is some evidence, that MRI could have a role in the prediction of outcome in patients with GCS scores of 13–15 (Yuh et al., 2013). The International Collaboration on Mild Traumatic Brain Injury Prognosis (Carroll et al., 2014) has identified positive CT findings as an indicator of poor outcome, regardless of surgical relevance, but the evidence is still weak.

# 5 AIMS OF THE STUDY

The aim of this dissertation was to investigate the association between pre-injury health status and previous imaging findings in MTBI as well as to examine the ability of non-contrast head CT scanning to exclude delayed intracranial complications. Specific aims were the following:

- to provide a comprehensive description of the pre-injury health characteristics of patients sustaining a HI and to describe how different exclusion criteria affect the patient enrollment in MTBI studies (study I).
- to describe the type and location of intracranial abnormalities (both acute and chronic) of patients who sustained MTBI and underwent computed tomography, using the CDE framework (study II).
- to evaluate whether certain pre-existing cerebral diseases are associated with more severe TBI (study II).
- to evaluate the incidence of delayed complications in acute HI patients after a normal head CT (study III).

# 6 MATERIAL AND METHODS

## 6.1 Study Design and Setting

This thesis is part of the larger research program, the Tampere Traumatic Head and Brain Injury Study. One part of the program has been recruiting a study sample of working aged adults with no pre-injury health problems by screening acute HI patients. (Luoto et al., 2014; 2013). The initial patient pool for the studies consisted of all patients (n=3,023) with HI who underwent head computed tomography (CT) at the Tampere University Hospital ED between August 2010 and July 2012. Ethics approval for the study was obtained from the ethical committee of Pirkanmaa Hospital District, Finland (code R10027).

The ED of Tampere University Hospital provides health services for Pirkanmaa Hospital District that is a joint municipal authority of 22 municipalities with a catchment area of 470,000 residents. All acute life-threatening neurosurgical conditions within the hospital district are treated at the Tampere University Hospital. The study patients form a consecutive community-based sample of the Finnish population. The whole patient pool represents the entire severity spectrum of HI from minimal to severe, including TBI and non-TBI HI patients who were all CT scanned.

MTBI and TBI in general were defined according to the WHO criteria (Carroll et al., 2004a). TBI was defined as an acute brain injury resulting from mechanical energy to the head from external physical forces. Definition of TBI requires the presence of at least one of the following: PTA or LOC of any duration, posttraumatic disorientation or confusion, or focal neurological abnormality.

MTBI criteria proposed by the WHO Collaborating Centre Task Force on MTBI states: "MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) one or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare.

These manifestations of MTBI must not be due to drugs, alcohol, 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 penetrating craniocerebral injury."

## 6.2 Data Collection

In study I, the initial patient pool consisted of all consecutive acute HI patients undergoing head CT (N=3,023). Applying various inclusion and exclusion criteria, a "pure" MTBI subgroup was formed, which comprised of previously healthy working-age patients who were living in the area of the hospital district and had Finnish as their first language. The exclusion and inclusion criteria were formed to investigate the effect of various study criteria on the patient population. The final screened population has been studied in detail in further studies (Holli-Helenius et al., 2014; Ilvesmäki et al., 2014; Losoi et al., 2016; 2015; 2014; Luoto et al., 2014; 2013; 2015; Silverberg et al., 2014)

The enrollment protocol had three inclusion criteria and nine exclusion criteria. Inclusion criteria were: (i) a HI fulfilling the WHO criteria for MTBI (ii) age between 18 and 60 years, and (iii) residency within the hospital district. Exclusion criteria were (i) premorbid neurological problems (brain tumor, neurodegenerative disease, cerebrovascular or demyelinating disease, cerebral palsy, white matter lesions, epilepsy), (ii) prior psychiatric developmental disorders (chronic alcohol or substance abuse; mood, somatoform, personality, or anxiety disorders; schizophrenia spectrum and other psychotic disorders; or developmental disorders such as attention-deficit hyperactivity disorder), (iii) past TBI (a previous HI meeting at least MTBI criteria), (iv) regular psychoactive medication use, (v) neurosurgery (any intracranial surgery or endovascular procedure for the index injury or a previous injury), (vi) major problems with vision or hearing [better ear hearing level 0.5–4 kHz $\geq$ 40 dB or visual acuity 0.3 (decimal) or less with glasses], (vii) first language other than Finnish, (viii) a time interval between injury and ED admission over 72 hours, and/or (ix) declined to participate in the study.

The information about medication use and pre-existing diseases were obtained by a chart review of the hospital records. The medication used by the patients was categorized by the Anatomical Therapeutic Chemical (ATC) classification system. The preinjury medical conditions were classified by the 10th revision of the

International Statistical Classification of Diseases and Related Health Problems (ICD-10). Alcohol abuse was classified as diagnoses F10.1 (Alcohol abuse, i.e. the use of alcoholic beverages to excess, either on individual occasions ["binge drinking"] or as a regular practice) or F10.2 (Alcohol dependence).

The most common causes for exclusion were: (i) age criteria not met (n=1,552, 51.3%), (ii) MTBI criteria not met (n=1,033, 34.2%), (iii) psychiatric problems (n=915, 30.3%) and/or (iv) neurological problems (n=770, 25.5%). Some patients fulfilled multiple criteria, causing significant overlap in the causes of exclusion.

Hospital records data included subject- and injury-related data, and clinical information from the ED. Subject-related data included age, gender, and health history including medication use, chronic alcohol and/or drug abuse, and possible prior brain injuries. The mechanisms of injury and time intervals (from injury to ED admission to CT and to ED discharge) were recorded. Clinical variables were GCS in the ED, witnessed LOC, seizures, disorientation, and retrograde and/or anterograde amnesia (PTA). The on-call ED physicians identified amnesia during an interview by asking questions about pre- and post-injury events, and noted only the presence or absence of amnesia, not the exact duration of amnesia. The study protocol used no structured forms to measure amnesia. Discharge data included four categories: home, hospital ward, local health center, or death.

To identify patients with delayed intracranial complications in the study III, the hospital records of the study patients were reviewed. A repeated head CT in the hospital ward, death, or return to the ED within 72 hours from the first admission were considered as a possible complication. Routine clinical practice determined the decisions on repeated head CT in the hospital ward. The reasons for repeated imaging were patient monitoring, prolongation or worsening of the HI-related symptoms, decline in general condition and new HI during admission. Detailed data collection was performed on the medical records of the patients with possible complications. The data collection consisted of the reason for the ED return visit, information related to a repeated head CT, and discharge data. Hospital records were the source of causes of death. In case the cause of death was not revealed in the hospital records, the source was the Statistics Finland (Helsinki, Finland), which holds the national registry on death certificates.

### 6.2.1 Neuroimaging

In the ED, an emergency non-contrast head CT scan was performed as per the 2000 Scandinavian guideline (Ingebrigtsen et al., 2000) to all patients with a 64-row CT scanner (Lightspeed VCT; GE, Wisconsin). The guideline recommends that after HI adult patients with any of the following should undergo a head CT: (i) GCS 3-13, (ii) LOC, (iii) focal neurological deficits, (iv) therapeutic anticoagulation or hemophilia, (v) clinical signs of depressed skull fracture or skull base fracture, (vi) posttraumatic seizures, (vii) shunt-treated hydrocephalus or (iix) multiple injuries.

In a non-on-call setting, two blinded neuroradiologists separately analyzed and systematically coded all CT scans using a structured data collection form. Acute traumatic intracranial lesions included subdural hematoma and effusion (SDH), epidural hematoma and effusion (EDH), diffuse axonal injury (DAI) lesions, edema, compression of the cerebrospinal fluid spaces, midline shift, contusions, pneumocephalus, skull fracture, and traumatic subarachnoid hemorrhage. Traumatic lesions, acute ischemic lesions, non-traumatic hemorrhage and tumors were recorded by type, anatomical location and site.

Pre-existing findings included ischemic lesions, chronic post-traumatic lesions, microangiopathy/small vessel ischemic disease, general atrophy, and intracranial tumors. Either characteristic periventricular or subcortical patchy low-density areas in cerebral white matter defined ischemic small vessel disease. CDEs for TBI imaging were established after the data collection of this thesis. However, the data collection form included all CDEs possible with non-contrast structural CT scan (Haacke et al., 2010).

## 6.3 Statistical Analyzes

The normal distribution of the variables was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. In study I, Mann-Whitney U tests were computed for continuous variables and Pearson $\chi^2$ tests for categorical variables. Normally distributed variables are reported as mean ± SD, and non-normally distributed variables as median + interquartile range.

In study II, MTBI and moderate to severe TBI groups, as well as subgroups with versus without acute intracranial abnormalities were compared with $\chi^2$ test for proportions and t-test for group mean differences. Unconditional logistic

regression modeling was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of acute intracranial abnormalities while controlling for multiple confounders (demographic, clinical variables, and pre-existing imaging features).

The statistical significance level was set at 5% for all analyses. IBM SPSS Statistics versions 20.0-22.0 for OS X (IBM Corp. Armonk, NY, USA) were used to perform the analyses.

# 7 RESULTS

## 7.1 Health Problems and Pre-existing Diseases

The health problems and conditions of the whole study population and subgroups are illustrated in Table 5. The number of older adults, stratified by age groups, were the following: 60-69 years = 393 (13.0%), 70-79 years= 373 (12.3%), 80-89 years = 487 (16.1%), and 90+ years = 125 (4.1%). The most common diseases in all subgroups were diseases of the circulatory system (39.4-43.2%), particularly in those over the age of 60 years (71.9%). Different diseases of the nervous system occurred in approximately every fourth (23.7-25.2%), and again the rate was highest in patients over the age of 60 years (36.1%). Previous brain injuries were present in 10.3 to 11.7%. Mental and behavioral disorders occurred in approximately one fourth (25.8-27.5%). Chronic detrimental alcohol abuse was present in 18.4 to 26.8%, and an affective disorder during the past 12 months was present in 9.5 to 11.1% of the patients. Endocrine, nutritional, and metabolic diseases were present in approximately 1 in 5 people (17.9-19.1%). Pre-existing diseases and disorders of the musculoskeletal system and connective tissue occurred in 8.2 to 12.4% of the patients.

Combinations of health problems and diseases were also investigated to illustrate the prevalence of having one or more health conditions that might influence MTBI outcome. Combinations of health problems within the subgroups are presented in Table 6. About half of the patients had either diseases of the circulatory system or mental and behavioral disorders (43.6-46.9%). Two-thirds had mental and behavioral disorders, diseases of the nervous and circulatory system and endocrine, nutritional, or metabolic diseases (66.5-69.4%).

**Table 5.** Health problems and diseases in the cohort.

| | Total Sample* N=3,023 | | MTBI n=1,990 | | Moderate to severe TBI n=257 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Diseases of the circulatory system | 1,192 | 39.4 | 808 | 40.6 | 111 | 43.2 |
| Diseases of the respiratory system | 277 | 9.2 | 183 | 9.2 | 21 | 8.2 |
| Mental and behavioral disorders | 780 | 25.8 | 548 | 27.5 | 70 | 27.2 |
| Chronic detrimental alcohol use (during the last two years) | 557 | 18.4 | 405 | 20.4 | 69 | 26.8 |
| Regular substance abuse (during the last two years) | 108 | 3.6 | 76 | 3.8 | 6 | 2.3 |
| Schizophrenia, schizotypal, or delusional disorder | 52 | 1.7 | 35 | 1.8 | 4 | 1.6 |
| Affective disorder (during the last year) | 312 | 10.3 | 220 | 11.1 | 24 | 9.3 |
| Neurotic, stress-related, and somatoform disorder | 39 | 1.3 | 31 | 1.6 | 0 | 0 |
| Adulthood personality disorder or disturbance of conduct | 47 | 1.6 | 31 | 1.6 | 1 | 0.4 |
| Mental retardation | 19 | 0.6 | 13 | 0.7 | 0 | 0 |
| Mental developmental disorder | 15 | 0.5 | 10 | 0.5 | 1 | 0.4 |
| Diseases of the nervous system | 717 | 23.7 | 502 | 25.2 | 61 | 23.7 |
| Brain tumor** | 26 | 0.9 | 21 | 1.1 | 1 | 0.4 |
| Degenerative disease | 250 | 8.3 | 177 | 8.9 | 21 | 8.2 |
| Demyelinating disease | 7 | 0.2 | 5 | 0.3 | 0 | 0 |
| Stroke or a transient cerebral ischemic attack | 301 | 10 | 227 | 11.4 | 16 | 6.2 |
| Cerebral palsy | 8 | 0.3 | 5 | 0.3 | 1 | 0.4 |
| Cerebral atrophy and/or white matter lesions more than related to age | 205 | 6.8 | 151 | 7.6 | 10 | 3.9 |
| Epilepsy | 137 | 4.5 | 97 | 4.9 | 11 | 4.3 |
| Prior brain injury | 311 | 10.3 | 231 | 11.6 | 30 | 11.7 |
| Endocrine, nutritional, and metabolic diseases | 566 | 18.7 | 381 | 19.1 | 46 | 17.9 |
| Diseases of the digestive system | 212 | 7 | 142 | 7.1 | 18 | 7.0 |
| Diseases of the genitourinary system | 184 | 6.1 | 118 | 5.9 | 15 | 5.8 |
| Diseases of the musculoskeletal system and connective tissue | 365 | 12.1 | 247 | 12.4 | 21 | 8.2 |
| Certain infectious and parasitic diseases | 82 | 2.7 | 56 | 2.8 | 7 | 2.7 |
| Neoplasms | 169 | 5.6 | 113 | 5.7 | 15 | 5.8 |
| Diseases of the blood | 67 | 2.2 | 44 | 2.2 | 6 | 2.3 |
| Diseases of the eye and adnexa | 120 | 4 | 85 | 4.3 | 9 | 3.5 |
| Diseases of the ear and mastoid process | 43 | 1.4 | 25 | 1.3 | 4 | 1.6 |
| Diseases of the skin and subcutaneous tissue | 69 | 2.3 | 48 | 2.4 | 7 | 2.7 |
| Pregnancy, childbirth, and the puerperium | 0 | 0 | 0 | 0 | 0 | 0 |
| Certain conditions originating in the perinatal period | 0 | 0 | 0 | 0 | 0 | 0 |
| Congenital malformations. deformations and chromosomal abnormalities | 12 | 0.4 | 10 | 0.5 | 1 | 0.4 |

*Total sample included all HI patients, who had a head CT scan, i.e. MTBI, more severe TBI and head injury without brain injury

**Parenchymal tumor of any size or superficial tumor of over 10mm

**Table 6.** Combinations of health problems

| | Total Sample* N=3,023 | | MTBI n=1,990 | | Moderate to severe TBI n=257 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Mental and behavioral disorders OR diseases of the nervous system | 1,324 | 43.8 | 934 | 46.9 | 112 | 43.6 |
| Diseases of the circulatory system OR endocrine, nutritional, or metabolic diseases | 1,349 | 44.6 | 916 | 46.0 | 116 | 45.1 |
| Mental and behavioral disorders OR diseases of the nervous system OR diseases of the circulatory system OR endocrine, nutritional, or metabolic diseases | 2,014 | 66.6 | 1,381 | 69.4 | 171 | 66.5 |
| Mental and behavioral disorders OR diseases of the nervous system OR diseases of the circulatory system OR endocrine, nutritional, or metabolic diseases OR diseases of the musculoskeletal system and connective tissue | 2,078 | 68.7 | 1,420 | 71.4 | 172 | 66.9 |

*Total sample included all HI patients, who had a head CT scan, i.e. MTBI, more severe TBI and head injury without brain injury

**Table 7.** Medication use in the cohort.

| | Total Sample* N=3,023 | | MTBI n=1,990 | | Moderate to severe TBI n=257 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Regular medication | 1,582 | 52.3 | 1,088 | 54.7 | 117 | 45.5 |
| Cardiovascular medication | 1,051 | 34.8 | 729 | 36.6 | 85 | 33.1 |
| Medication affecting blood clotting and anemia | 651 | 21.5 | 436 | 21.9 | 58 | 22.6 |
| Central nervous system medication | 870 | 28.8 | 612 | 30.8 | 55 | 21.4 |
| Antimicrobial medication | 73 | 2.4 | 46 | 2.3 | 7 | 2.7 |
| Analgesic medication | 352 | 11.6 | 243 | 12.2 | 26 | 10.1 |
| Pulmonary medication | 200 | 6.6 | 134 | 6.7 | 14 | 5.4 |
| Gastrointestinal medication | 398 | 13.2 | 275 | 13.8 | 33 | 12.8 |
| Hormones and contraceptives | 297 | 9.8 | 203 | 10.2 | 16 | 6.2 |
| Sexual and urinary organ medication | 157 | 5.2 | 105 | 5.3 | 17 | 6.6 |
| Diabetes medication | 258 | 8.5 | 171 | 8.6 | 22 | 8.6 |
| Cancer medication/immune system modulators | 47 | 1.6 | 33 | 1.7 | 3 | 1.2 |
| Bone tissue medication | 47 | 1.6 | 36 | 1.8 | 2 | 0.8 |
| Dermatological medication | 18 | 0.6 | 14 | 0.7 | 1 | 0.4 |
| Ophthalmological medication | 81 | 2.7 | 57 | 2.9 | 2 | 0.8 |
| Otological medication | 0 | 0 | 0 | 0 | 0 | 0 |
| Muscle relaxants | 4 | 0.1 | 3 | 0.2 | 0 | 0 |
| Vitamins and minerals | 378 | 12.5 | 267 | 13.4 | 26 | 10.1 |

*Total sample included all HI patients, who had a head CT scan, i.e. MTBI, more severe TBI and head injury without brain injury

The medication use of the cohort is presented in Table 7. About half of the patients had one or more regular medication (45.5-54.7%). The most common medication was cardiovascular medication, used by over third of the patients (33.1-36.9%). Medication affecting blood clotting and anemia was used by over a fifth of the patients (21.5-22.6%). About every fourth of the patients (21.4-30.8%) was using central nervous system medication.

## 7.2 Effect of Exclusion Criteria on Patient Enrollment

The effect of applying the different exclusion and inclusion criteria on the sample size in the study process is shown in Table 8. The number of patients with co-occurring exclusion criteria is presented in Table 9 (i.e., the frequency and percentage of participants who met more than one exclusion criteria). Only 75 out of 3,023 (2.5%) of the screened patients met all the inclusion criteria. Of all the patients, 1,990 (65.2%) fulfilled the MTBI criteria, the rest having a more severe TBI (n=257, 8.5%) or a HI without clear signs of brain injury (n=776, 25.7%). Patients with MTBI were divided in two groups: excluded MTBI sample (n=1,915) and enrolled MTBI sample (n=75). The enrolled MTBI sample comprised the patients who met all the study criteria after applying the inclusion and exclusion criteria. The most common reasons for exclusion were age, not a MTBI, premorbid neurological problems, and premorbid psychiatric problems. More than every fourth had neurological (n=770, 25.5%) or psychiatric (n=915, 30.3%) disorders, and over half had either of these or both (n=1,066, 55.7%) in the excluded MTBI group.

**Table 8.** Application of exclusion criteria to the study cohort

| **Exclusion criterion** | **n** | **%** |
|---|---|---|
| Not a mild TBI | 1,033 | 34.2 |
| Older than 60 years | 1,378 | 45.6 |
| Younger than 18 years | 185 | 6.1 |
| Psychiatric problem | 915 | 30.3 |
| Neurological problem | 770 | 25.5 |
| Psychoactive medication | 835 | 27.6 |
| >72 hours from injury to arrival in ED | 506 | 16.7 |
| Past TBI | 311 | 10.3 |
| Previous neurosurgery | 168 | 5.6 |
| Not a resident of the hospital district | 166 | 5.5 |
| First language not Finnish | 72 | 2.4 |
| Problems with hearing or vision | 47 | 1.6 |
| Declined to participate | 105 | 3.5 |
| **Total enrolled (out of 3,023) after applying the above criteria** | **75** | **2.5** |

**Table 9.** Coexistence of the inclusion and exclusion criteria N (%)

| | Not a mild TBI | Age criteria not met | Psychiatric Problem | Neurological Problem | Psychoactive Medication | Past TBI | Not a resident of the hospital district | First language not Finnish | >72 Hours from Injury to Arrival in ED | Previous Neurosurgery | Problems with Hearing or Vision | Declined to Participate |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Not a mild TBI | 1,033 (34.2) | 460 (15.2) | 263 (8.7) | 212 (7.0) | 247 (8.2) | 80 (2.6) | 72 (2.4) | 22 (0.7) | 144 (4.8) | 98 (3.2) | 17 (0.6) | 7 (0.2) |
| Age criteria not met | | 1,552 (51.3) | 295 (9.8) | 605 (20.0) | 505 (16.7) | 97 (3.2) | 54 (1.8) | 8 (0.3) | 274 (9.1) | 79 (2.6) | 38 (1.3) | 0 |
| Psychiatric Problem | | | 916 (30.3) | 194 (6.4) | 415 (13.7) | 155 (5.1) | 22 (0.7) | 8 (0.3) | 130 (4.3) | 63 (2.1) | 8 (0.3) | 1 (0.03) |
| Neurological Problem | | | | 771 (25.5) | 403 (13.3) | 89 (2.9) | 17 (0.6) | 3 (0.1) | 134 (4.4) | 66 (2.2) | 14 (0.5) | 0 |
| Psychoactive Medication | | | | | 835 (27.6) | 89 (2.9) | 13 (0.4) | 3 (0.1) | 167 (5.5) | 50 (1.7) | 18 (0.6) | 1 (0.03) |
| Past TBI | | | | | | 311 (10.3) | 5 (0.2) | 6 (0.2) | 27 (0.9) | 50 (1.7) | 1 (0.03) | 2 (0.07) |
| Not a Resident of the Hospital District | | | | | | | 166 (5.5) | 12 (0.4) | 9 (0.3) | 15 (0.5) | 0 | 0 |
| First Language Not Finnish | | | | | | | | 72 (2.4) | 13 (0.4) | 2 (0.1) | 1 (0.03) | 0 |
| >72 Hours from Injury to Arrival in ED | | | | | | | | | 506 (16.7) | 22 (0.7) | 9 (0.3) | 0 |
| Previous Neurosurgery | | | | | | | | | | 168 (5.6) | 3 (0.1) | 0 |
| Problems with Hearing or Vision | | | | | | | | | | | 47 (1.6) | 0 |
| Declined to Participate | | | | | | | | | | | | 105 (3.5) |

Statistical comparisons were performed between excluded MTBI sample and enrolled MTBI sample in relation to injury-related and clinical variables. The comparisons are presented in Tables 10-13. Enrolled patients were younger, were admitted in less time and had CT imaging performed faster. LOC and PTA information was recorded more comprehensively in the enrolled sample. Ground-level falls were more common in the excluded sample, whereas car, bicycle, motorcycle and sports accidents were more common in the enrolled sample. Mandibular and parietal impacts were more common in the enrolled sample. Enrolled patients were discharged home more often. Information about alcohol intoxication was recorded more thoroughly and the intoxication was rarer in the enrolled. Pre-existing diseases and regular medication were more common in the excluded sample.

**Table 10.** Comparison of age and time intervals between the enrolled and excluded samples

| | Enrolled MTBI n = 75 | Excluded MTBI n = 1,915 | p-value |
|---|---|---|---|
| | **Median (25-75%)** | **Median (25-75%)** | |
| **Age, years** | 36.6 (27.5-47.6) | 60.1 (35.9-78.4) | <0.001 |
| **Time intervals, hours** | | | |
| From injury to ED admission | 1.6 (1.0-3.5) | 4.8 (1.4-46.5) | <0.001 |
| From injury to primary head CT | 3.0 (2.0-5.8) | 6.8 (2.8-48.8) | <0.001 |
| From ED admission to primary head CT | 1.0 (0.6-1.6) | 1.1 (0.6-1.9) | NS |
| From primary head CT to hospital discharge | 7.6 (2.2-37.3) | 6.6 (2.3-28.2) | |
| Hospital stay | 9.3 (3.7-38.7) | 9.0 (3.9-30.6) | |

**Table 11.** Comparison injury severity indices and time before CT imaging between the enrolled and excluded samples

| | Enrolled MTBI n=75 | | Excluded MTBI n=1,915 | | p-value |
|---|---|---|---|---|---|
| **Loss of consciousness** | | | | | |
| Yes | 28 | 37.3 | 434 | 22.7 | <0.001 |
| No | 21 | 28 | 363 | 19 | |
| Not witnessed / Unknown | 26 | 34.7 | 1,118 | 58.4 | |
| **Amnesia** | | | | | |
| Yes | 59 | 78.7 | 578 | 30.2 | <0.001 |
| No | 16 | 21.3 | 422 | 22 | |
| Unknown | 0 | 0 | 915 | 47.8 | |
| **Glasgow Coma Scale** | | | | | |
| 15 points | 63 | 84 | 1,049 | 54.8 | <0.001 |
| 14 points | 3 | 4 | 83 | 4.3 | |
| 13 points | 0 | 0 | 25 | 1.3 | |
| N/A | 9 | 12 | 745 | 38.9 | |
| **Time before CT imaging** | | | | | |
| CT within 24 hours post-injury | 68 | 90.7 | 1,287 | 67.2 | <0.001 |
| CT within 48 hours post-injury | 72 | 96 | 1,431 | 74.7 | <0.001 |

**Table 12.** Comparison of gender, injury-related data and follow-up between the enrolled and excluded samples

| | Enrolled MTBI n=75 | | Excluded MTBI n=1,915 | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Gender** | | | | | NS |
| Men | 45 | 60 | 1,086 | 56.7 | |
| Women | 30 | 40 | 829 | 43.3 | |
| **Mechanism of injury** | | | | | |
| Ground-level falls | 10 | 13.3 | 1,077 | 56.2 | <0.001 |
| Falls from a height | 12 | 16 | 204 | 10.7 | NS |
| Car accidents | 12 | 16 | 132 | 6.9 | 0.003 |
| Violence-related injuries | 5 | 6.7 | 158 | 8.3 | NS |
| Other | 7 | 9.3 | 123 | 6.4 | NS |
| Bicycle accidents | 11 | 14.7 | 85 | 4.4 | <0.001 |
| Unknown | 0 | 0 | 45 | 2.3 | NS |
| Sports | 13 | 17.3 | 40 | 2.1 | <0.001 |
| Motorcycle accidents | 5 | 6.7 | 29 | 1.5 | 0.001 |
| Traffic accidents as a pedestrian | 0 | 0 | 22 | 1.1 | NS |
| Moped accidents | 0 | 0 | 22 | 1.1 | NS |
| **Location of direct head impact** | | | | | <0.001 |
| Maxillary | 12 | 16 | 254 | 13.3 | NS |
| Mandibular | 11 | 14.7 | 56 | 2.9 | <0.001 |
| Frontal | 15 | 15 | 325 | 17.0 | NS |
| Temporal | 11 | 14.7 | 274 | 14.3 | NS |
| Parietal | 12 | 16.0 | 140 | 7.3 | 0.005 |
| Occipital | 26 | 34.7 | 757 | 39.5 | NS |
| Unknown | 21 | 28 | 721 | 37.7 | NS |
| **Location of follow-up treatment** | | | | | |
| Home | 52 | 69.3 | 765 | 39.9 | |
| Health center | 1 | 1.3 | 488 | 25.5 | <0.001 |
| Other health care facility | 0 | 0 | 68 | 3.6 | |
| Hospital | 22 | 29.3 | 577 | 30.1 | |
| Death | 0 | 0 | 17 | 0.9 | |
| **Alcohol intoxication** | | | | | |
| Yes | 10 | 13.3 | 510 | 26.6 | <0.001 |
| No | 65 | 86.7 | 761 | 39.7 | |
| Unknown | 0 | 0 | 644 | 33.6 | |

N/A Not applicable
NS Non-significant

**Table 13.** Comparison between the enrolled and excluded samples, diseases and medications

| | Enrolled MTBI n = 75 | | Excluded MTBI n = 1,915 | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Diagnosed disease / medical condition** | | | | | |
| Diseases of the circulatory system | 8 | 10.7 | 800 | 41.8 | <0.001 |
| Diseases of the respiratory system | 8 | 10.7 | 175 | 9.2 | NS |
| Mental and behavioral disorders | 0 | 0 | 548 | 28.6 | <0.001 |
| Diseases of the nervous system | 3 | 4 | 499 | 26.1 | <0.001 |
| Endocrine, nutritional and metabolic diseases | 7 | 9.3 | 374 | 19.5 | 0.01 |
| Diseases of the digestive system | 2 | 2.7 | 140 | 7.1 | 0.045 |
| Diseases of the genitourinary system | 1 | 1.3 | 117 | 6.1 | 0.034 |
| Diseases of the musculoskeletal system and connective tissue | 7 | 9.3 | 240 | 12.5 | NS |
| Certain infectious and parasitic diseases | 0 | 0 | 56 | 2.9 | NS |
| Neoplasms | 1 | 1.3 | 112 | 5.8 | 0.038 |
| Diseases of the blood | 0 | 0 | 44 | 2.3 | NS |
| Diseases of the eye and adnexa | 0 | 0 | 85 | 4.5 | 0.027 |
| Diseases of the ear and mastoid process | 1 | 1.3 | 24 | 1.3 | NS |
| Diseases of the skin and subcutaneous tissue | 0 | 0 | 48 | 2.5 | NS |
| Pregnancy, childbirth and the puerperium | 0 | 0 | 0 | 0 | N/A |
| Certain conditions originating in the perinatal period | 0 | 0 | 0 | 0 | |
| Congenital malformations, deformations, and chromosomal abnormalities | 1 | 1.3 | 9 | 0.5 | NS |
| **Medications** | | | | | |
| Cardiovascular medication | 8 | 10.7 | 721 | 37.7 | <0.001 |
| Medication affecting blood clotting and anemia | 0 | 0 | 436 | 22.8 | <0.001 |
| Central nervous system medication | 0 | 0 | 612 | 32 | <0.001 |
| Microbe medication | 0 | 0 | 46 | 2.4 | <0.001 |
| Analgesic medication | 1 | 1.3 | 242 | 12.6 | <0.001 |
| Pulmonary medication | 4 | 4 | 131 | 6.8 | <0.001 |
| Gastrointestinal medication | 0 | 0 | 275 | 14.4 | <0.001 |
| Hormones and contraceptives | 7 | 9.3 | 196 | 10.2 | <0.001 |
| Sexual and urinary organ medication | 0 | 0 | 105 | 5.5 | <0.001 |
| Diabetes medication | 1 | 1.3 | 170 | 8.9 | <0.001 |
| Cancer medication, immune system modulators | 1 | 1.3 | 32 | 1.7 | <0.001 |
| Bone tissue medication | 0 | 0 | 36 | 1.9 | <0.001 |
| Dermatological medication | 0 | 0 | 14 | 0.7 | <0.001 |
| Ophthalmological medication | 0 | 0 | 57 | 3 | <0.001 |
| Otological medication | 0 | 0 | 0 | 0 | N/A |
| Muscle relaxants | 0 | 0 | 3 | 0.2 | <0.001 |
| Vitamins and minerals | 2 | 2.7 | 265 | 13.8 | <0.001 |
| **Computed Tomography (CT)** | | | | | |
| CT-Positive, Trauma-Related | 7 | 9.3 | 383 | 20 | 0.022 |
| CT-Positive, Trauma-Related, No Pre-Existing Findings | 7 | 9.3 | 238 | 12.4 | NS |
| CT-Positive, Pre-Existing Findings, No Trauma-Related Findings | 0 | 0 | 572 | 29.9 | <0.001 |

N/A Not applicable
NS Non-significant

## 7.3 Type and Location of Intracranial Abnormalities in MTBI

Demographic and clinical characteristics of the injury severity groups are presented in Table 14. The patients were categorized into three injury severity groups:

(i) the suspected MTBI group included all patients who underwent CT scan, but whose injury was milder than moderate or severe TBI,

(ii) the confirmed MTBI group included all patients who underwent CT scan, but whose TBI was milder than moderate or severe TBI and excluded those whose HI was not a MTBI, and

(iii) the moderate to severe TBI group included all TBI patients whose TBI was more severe than a MTBI.

The rates of trauma-related intracranial abnormalities were 11.6%, 16.1%, and 85.6% in the suspected and confirmed MTBI group, confirmed MTBI subgroup, and moderate-severe TBI group, respectively. All of the acute lesions in the "suspected MTBI" group are from patients in the "confirmed MTBI" group. Within the suspected and confirmed MTBI group, the rates of those with complicated MTBIs stratified by GCS scores were as follows: 15=10.1%, 14=36.1%, 13=48.1% and in those whose GCS was not available=11.5%. Within the confirmed MTBI subgroup, the rates of those with complicated MTBIs stratified by GCS scores were as follows: 15=14.2%, 14=40.7%, and 13=52.0% and in those whose GCS was not available=15.2%.

Specific CT findings stratified by the injury severity groups are presented in Table 15. In the total MTBI group, the rates of specific abnormalities were as follows: subdural hematoma=8.4%, subarachnoid hemorrhage=5.0%, and contusion=3.9% (see Table 2). Of the 142 contusions (in 109 patients), 52.8% were frontal and 39.4% were temporal in location. Of the 495 subdural hematomas (in 232 patients), 38.8% were frontal, 21.8% were temporal, 22.0% were parietal, and only 7.5% were occipital. For comparison, in the moderate to severe TBI group, the rates of specific abnormalities were as follows: subdural hematoma=63.0%, subarachnoid hemorrhage=55.6%, and contusion=43.6% (see Table 15). Of the 150 contusions (in 112 patients), 50.0% were frontal and 40.0% were temporal in location. Of the 439 subdural hematomas (in 162 patients), 32.1% were frontal, 24.8% were temporal, 21.0% were parietal, and only 9.8% were occipital.

**Table 14.** Demographic and clinical characteristics, stratified by injury severity (study II)

| | Suspected MTBI | | Confirmed MTBI | | Moderate to severe TBI | |
|---|---|---|---|---|---|---|
| | (n=2,766) | | (n=1,990) | | (n=257) | |
| **Variable** | **Median (25-75%)** | | **Median (25-75%)** | | **Median (25-75%)** | |
| **Age, years** | 56.4 (34.2-77.1) | | 58.4 (34.7-77.8) | | 57.5 (40.0-74.9) | |
| **Time intervals, hours** | | | | | | |
| Injury to ED admission | 4.5 (1.4-45.0) | | 4.5 (1.4-40.4) | | 2.5 (1.0-8.9) | |
| Injury to head CT | 6.5 (2.6-47.7) | | 6.5 (2.6-44.8) | | 4.3 (1.8-11.2) | |
| ED admission to head CT | 1.0 (0.6-1.8) | | 1.0 (0.6-1.9) | | 0.7 (0.4-1.2) | |
| Head CT to discharge | 6.0 (2.2-27.6) | | 6.6 (2.3-28.4) | | 88.1 (19.9-196.1) | |
| Hospital stay | 8.2 (3.8-29.1) | | 9.0 (3.9-31.2) | | 89.5 (22.1-197.6) | |
| **Gender** | **n** | **%** | **n** | **%** | **n** | **%** |
| Male | 1,542 | 55.1 | 1,131 | 56.8 | 181 | 70.4 |
| Female | 1,242 | 44.9 | 859 | 43.2 | 76 | 29.6 |
| **CT within 24 hours** | 1,865 | 67.4 | 1,355 | 68.1 | 218 | 84.8 |
| **CT within 48 hours** | 2,076 | 75.1 | 1,503 | 75.5 | 235 | 91.4 |
| **Cause of injury** | | | | | | |
| Motor vehicle accident | 275 | 9.9 | 200 | 10.1 | 23 | 8.9 |
| Traffic accident as pedestrian or bicyclist | 145 | 5.2 | 118 | 5.9 | 22 | 8.6 |
| Fall from a height | 304 | 11.0 | 216 | 10.9 | 33 | 12.8 |
| Ground-level fall | 1,454 | 52.6 | 1,087 | 54.6 | 130 | 50.6 |
| Other | 535 | 19.3 | 324 | 16.3 | 29 | 11.3 |
| **Follow-up treatment** | | | | | | |
| Home | 1,215 | 43.9 | 813 | 41.3 | 28 | 7.6 |
| Health center | 628 | 22.7 | 489 | 24.6 | 28 | 10.9 |
| Other health care facility | 87 | 3.1 | 68 | 3.4 | 4 | 1.6 |
| Hospital | 809 | 29.2 | 599 | 30.1 | 172 | 66.9 |
| Death | 27 | 1.0 | 17 | 0.9 | 41 | 16.0 |
| **Alcohol intoxication** | | | | | | |
| Yes | 660 | 23.9 | 520 | 26.1 | 81 | 31.5 |
| No | 1,151 | 41.6 | 826 | 41.5 | 92 | 35.8 |
| Unknown | 955 | 34.5 | 644 | 32.4 | 84 | 32.7 |
| **Loss of consciousness** | | | | | | |
| Yes | 481 | 17.4 | 462 | 23.2 | 103 | 40.1 |
| No | 764 | 27.6 | 384 | 19.3 | 25 | 9.7 |
| Not witnessed / Unknown | 1,521 | 55.0 | 1,144 | 57.5 | 129 | 50.2 |
| **Amnesia** | | | | | | |
| Yes | 646 | 23.4 | 637 | 32.0 | 38 | 14.8 |
| No | 916 | 33.1 | 438 | 22.0 | 16 | 6.2 |
| Unknown | 1,204 | 43.5 | 915 | 46.0 | 203 | 79.0 |
| **Glasgow Coma Scale** | | | | | | |
| 13-15 points | 1,682 | 60.8 | 1,223 | 61.5 | 34 | 13.2 |
| 9-12 points | 67 | 2.4 | 13 | 0.7 | 75 | 29.2 |
| 3-8 points | 25 | 0.9 | 2 | 0.1 | 83 | 32.3 |
| N/A | 992 | 35.9 | 752 | 37.8 | 65 | 25.3 |
| **CT** | | | | | | |
| Traumatic Intracranial Abnormality | 320 | 11.6 | 320 | 16.1 | 220 | 85.6 |
| Pre-Existing Abnormality | 941 | 34.0 | 717 | 36.0 | 44 | 17.1 |

**Table 15.** Acute and pre-existing lesions in head CT

| | Suspected MTBI (n=2,766) | | Confirmed MTBI (n=1,990) | | Moderate-severe TBI (n=257) | |
|---|---|---|---|---|---|---|
| **Abnormality/Location** | **f** | **%** | **f** | **%** | **f** | **%** |
| Epidural Hematoma* | 6 | 0.2 | 6 | 0.3 | 15 | 5.8 |
| Subdural Hematoma* | 232 | 8.4 | 232 | 11.7 | 162 | 63.0 |
| Frontal | 192 | 6.9 | 192 | 9.6 | 141 | 54.9 |
| Temporal | 108 | 3.9 | 108 | 5.4 | 109 | 42.4 |
| Parietal | 109 | 3.9 | 109 | 5.5 | 92 | 35.8 |
| Occipital | 37 | 1.3 | 37 | 1.9 | 43 | 16.7 |
| Cerebellar | 3 | 0.1 | 3 | 0.2 | 3 | 1.2 |
| Tentorial | 46 | 1.7 | 46 | 2.3 | 51 | 19.8 |
| Subarachnoid Hemorrhage* | 139 | 5.0 | 139 | 7.0 | 143 | 55.6 |
| Intraventricular* | 33 | 1.2 | 33 | 1.7 | 53 | 20.6 |
| Basal Cisterns | 24 | 0.9 | 24 | 1.2 | 36 | 14.0 |
| Convexity Sulci | 113 | 4.1 | 113 | 5.7 | 124 | 48.2 |
| Contusion* | 109 | 3.9 | 109 | 5.5 | 112 | 43.6 |
| Frontal | 75 | 2.7 | 75 | 3.8 | 75 | 29.2 |
| Temporal | 56 | 2.0 | 56 | 2.8 | 60 | 23.3 |
| Parietal | 6 | 0.2 | 6 | 0.3 | 3 | 1.2 |
| Occipital | 1 | 0.04 | 1 | 0.1 | 2 | 0.8 |
| Cerebellar | 2 | 0.1 | 2 | 0.1 | 8 | 3.1 |
| Brainstem | 2 | 0.1 | 2 | 0.1 | 2 | 0.8 |
| Diffuse Axonal Injury* | 5 | 0.2 | 5 | 0.3 | 9 | 3.5 |
| Cerebrospinal Fluid Space Compression* | 35 | 1.3 | 35 | 1.8 | 75 | 29.2 |
| Ventricles* | 22 | 0.8 | 22 | 1.1 | 58 | 22.6 |
| Basal Cisterns* | 5 | 0.2 | 5 | 0.3 | 41 | 16.0 |
| Convexity Sulci | 22 | 0.8 | 22 | 1.1 | 61 | 23.7 |
| Fractures | 168 | 6.1 | 142 | 7.1 | 112 | 43.6 |
| Skull Fractures* | 76 | 2.7 | 75 | 3.8 | 95 | 37.0 |
| Facial Fractures | 103 | 3.7 | 78 | 3.9 | 44 | 17.1 |
| Pneumocephalus | 10 | 0.4 | 10 | 0.5 | 20 | 7.8 |
| Hydrocephalus | 8 | 0.3 | 6 | 0.3 | 6 | 2.3 |
| Non-Traumatic Hemorrhage | 16 | 0.6 | 13 | 0.7 | 16 | 6.2 |
| Acute Ischemia* | 24 | 0.9 | 17 | 0.9 | 4 | 1.6 |
| Midline Shift* | 45 | 1.6 | 44 | 2.2 | 89 | 34.6 |
| Diffuse edema* | 2 | 0.1 | 1 | 0.1 | 15 | 5.8 |
| Pre-Existing, Post-Traumatic Lesions | 77 | 2.8 | 62 | 3.1 | 5 | 1.9 |
| Pre-Existing, Ischemic Lesions | 198 | 7.2 | 159 | 8.0 | 6 | 2.3 |
| Microangiopathy/Small Vessel Ischemic Disease | 581 | 21.0 | 441 | 22.2 | 26 | 10.1 |
| Generalized Atrophy* | 495 | 17.9 | 377 | 18.9 | 25 | 9.7 |
| Tumors | 21 | 0.8 | 17 | 0.9 | 1 | 0.4 |
| **Summary** | | | | | | |
| Any Traumatic Intracranial Abnormality | 320 | 11.6 | 320 | 16.1 | 220 | 85.6 |
| More than One Traumatic Intracranial Abnormality | 128 | 4.6 | 128 | 6.4 | 144 | 56.0 |
| Any Pre-Existing Abnormality | 941 | 34.0 | 717 | 36.0 | 44 | 17.1 |
| More than One Pre-Existing Abnormality | 518 | 18.7 | 400 | 20.1 | 27 | 10.5 |
| Any Traumatic Intracranial AND Pre-Existing Abnormality | 146 | 5.3 | 133 | 6.7 | 37 | 14.4 |
| Any Traumatic Intracranial OR Pre-Existing Abnormality | 1,212 | 43.8 | 904 | 45.2 | 227 | 88.3 |

* Imaging findings included in the neuroimaging CDE

The total MTBI group included those with a suspected MTBI (n=2,766). The subgroup with complicated MTBIs was older (66.7 ±19.9 years) than those with uncomplicated MTBIs (55.3 ±24.2 years, $p<0.001$), and men were significantly more likely to have complicated MTBIs than women were (12.8% vs. 10.1%, $\chi^2=4.99$, $p=0.026$). Within the complicated MTBI group, the mechanisms of injury were as follows: ground-level fall=66.3%, fall from a height=10.3%, traffic accident as pedestrian or bicyclist=7.5% and motor vehicle accident=2.2%. Adults aged 55 years and older who were injured in a ground-level fall had a greater incidence of trauma-related abnormalities than younger adults injured in a fall (17.0% vs. 5.8%, $\chi^2=85.89$, $p<0.001$). The rates of complicated MTBIs, stratified by age group, are presented in Figure 3. Rate of complicated MTBIs increased with age.

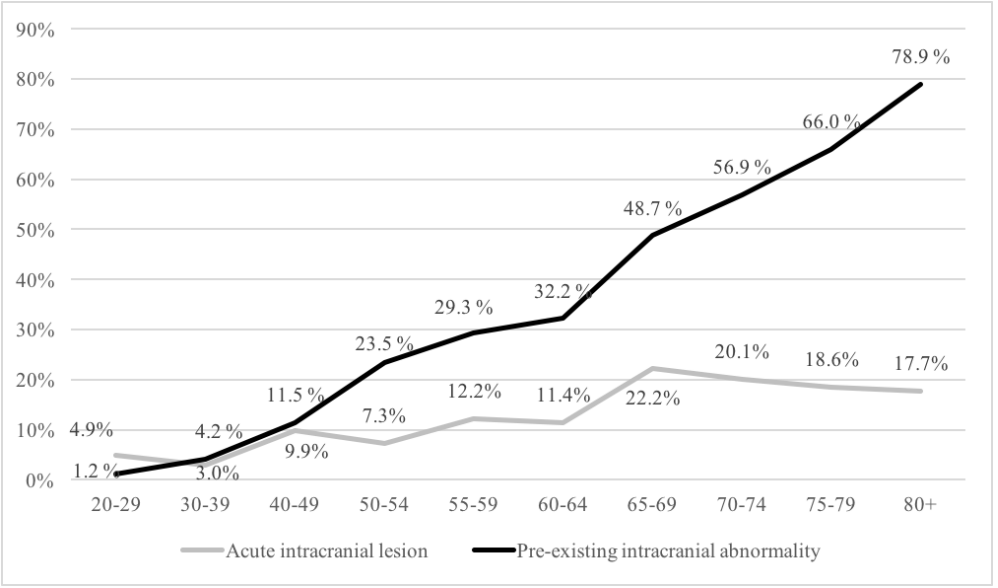


**Figure 3.** Percentage of acute and pre-existing intracranial lesions stratified by age groups

The rates of pre-existing abnormalities on CT, stratified by age groups, are illustrated in Figure 3. Rate of pre-existing lesions increased dramatically with age. In the total MTBI sample, 34.0% had a pre-existing abnormality and 18.7% had more than one pre-existing abnormality. Small vessel ischemic disease occurred in 21.0%, ischemic lesions in 7.2%, generalized atrophy in 17.9%, and post-traumatic lesions were found in 2.8%. Among older adults (age 55 and older), those with CT evidence of brain atrophy were less likely to have a complicated MTBI than those without obvious atrophy (12.6% vs. 19.0%, $\chi^2=8.52$, $p=0.004$). The rate of

complicated MTBIs in older adults (age 55 and older) who had a pre-existing neurodegenerative disease was similar to those who did not have a neurodegenerative disease (14.1% vs. 17.6%, $\chi^2$=1.64, p=0.200).

In a logistic regression with the total MTBI sample (n=2,766), a number of variables were associated with a higher rate of acute intracranial lesions. The results of the logistic regression analysis are summarized in Table 16. In the single covariate models (producing unadjusted ORs), male gender, older age, cause of injury, lower GCS, chronic alcohol abuse, and pre-existing traumatic lesions on CT were significant predictors. In the multivariable model, significant independent predictors were male gender (OR=1.68, 95% CI 1.27-2.21), age (OR=1.04, 95% CI 1.03-1.05), a pre-existing traumatic lesion (OR=1.99, 95% CI 1.12-3.56), chronic alcohol use (OR=1.84, 95% CI 1.29-2.63), certain mechanisms of injury [being a pedestrian or bicyclist in a traffic accident (OR=7.54, 3.05-18.65), or falling from a height (OR=4.32, 1.82-10.23), ground-level falls (OR=3.9, 1.75-8.68) vs. a motor vehicle accident], and a GCS of 14 (OR=4.35, 95% CI 2.69-7.05) or 13 (OR=7.70, 95% CI 3.26-18.18) vs. 15.

Interestingly, cerebral atrophy was associated with significantly lower risk for an acute traumatic intracranial abnormality (OR=0.48, 95% CI 0.34-0.68). Small vessel ischemic disease also was associated with lower risk for having a complicated MTBI (OR=0.58, 95% CI 0.41-0.81). Of note, the multivariable modeling indicates that age and sustaining an MTBI due to ground-level fall were independently associated with having a positive head CT, suggesting that the high rate of CT abnormalities associated with ground-level falls was not entirely confounded by older adults having more falls than younger adults.

**Table 16.** Logistic regression analysis of acute intracranial lesions.

| | Suspected and Confirmed MTBI Sample (n=2,766) | | | | | |
|---|---|---|---|---|---|---|
| | Unadjusted | | | Adjusted | | |
| **Predictor, n (%)** | **p-value** | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** |
| Gender | | | | | | |
| Female, n=1,242 (44.9%) | ref | | | ref | | |
| Male, n=1,524 (55.1%) | 0.026 | 1.31 | 1.03-1.66 | <0.001 | 1.68 | 1.27-2.21 |
| Age, years | <0.001 | 1.03 | 1.02-1.03 | <0.001 | 1.04 | 1.03-1.05 |
| Cause of injury | | | | | | |
| Motor vehicle accident, n=275 (9.9%) | ref | | | ref | | |
| Traffic accident as pedestrian or bicyclist, n=145 (5.2%) | <0.001 | 7.59 | 3.19-18.11 | <0.001 | 7.54 | 3.05-18.65 |
| Fall from a height, n=304 (11.0%) | <0.001 | 4.66 | 2.03.10.72 | 0.001 | 4.32 | 1.82-10.23 |
| Ground-level fall, n=1,454 (52.6%) | <0.001 | 6.54 | 3.04-14.04 | 0.001 | 3.90 | 1.75-8.68 |
| Other, n=535 (19.3%) | 0.019 | 2.68 | 1.18-6.12 | 0.008 | 3.15 | 1.34-7.39 |
| Unknown, n=53 (1.9%) | <0.001 | 7.83 | 2.77-22.11 | 0.032 | 3.36 | 1.11-10.21 |
| Alcohol use preceding injury | | | | | | |
| No, n=1,151 (41.6%) | ref | | | ref | | |
| Yes, n=660 (23.9%) | 0.297 | 1.17 | 0.87-1.57 | 0.559 | 1.12 | 0.76-1.64 |
| Unknown, n=955 (34.5%) | 0.625 | 1.07 | 0.82-1.40 | 0.579 | 1.09 | 0.81-1.46 |
| Chronic alcohol abuse, n=488 (17.6%) | <0.001 | 1.63 | 1.24-2.15 | <0.001 | 1.84 | 1.29-2.63 |
| GCS | | | | | | |
| 15, n=1,558 (56.3%) | ref | | | ref | | |
| 14, n=97 (3.5%) | <0.001 | 5.00 | 3.20-7.81 | <0.001 | 4.35 | 2.69-7.05 |
| 13, n=27 (1.0%) | <0.001 | 8.23 | 3.80-17.82 | <0.001 | 7.70 | 3.26-18.18 |
| 3-12, n=92 (3.3%)* | --- | --- | --- | --- | --- | --- |
| Unknown, n=992 (35.9%) | 0.282 | 1.15 | 0.89-1.49 | 0.860 | 1.02 | 0.78-1.34 |
| Small vessel ischemic disease, n=581 (21.0%) | 0.154 | 1.22 | 0.93-1.61 | 0.001 | 0.58 | 0.41-0.81 |
| Neurodegenerative disease, n=229 (8.3%) | 0.236 | 1.27 | 0.86-1.88 | 0.750 | 0.93 | 0.60-1.45 |
| Pre-existing traumatic lesion on CT, n=77 (2.8%) | <0.001 | 3.00 | 1.79-5.02 | 0.02 | 1.99 | 1.12-3.56 |
| Cerebral atrophy, n=495 (17.9%) | 0.967 | 0.99 | 0.73-1.35 | <0.001 | 0.48 | 0.34-0.68 |

Note: Unadjusted parameter estimates were derived from single predictor models. Adjusted parameters were derived from a model containing all predictors, and therefore refer to the independent effect of a given predictor, controlling for other predictors.

* In this subgroup, there were no intracranial lesions.

## 7.4 Monitoring after a Negative Head CT

Figure 4 illustrates the study process to identify patients with delayed complications within 72 hours following a CT negative HI. The majority (n=1,811, 74.1%) of the patients with a negative head CT were discharged home or to the local health center ward from the ED. Within the first 72 hours after the CT, 27 (1.1%) patients returned to the ED. The reasons for returning were: (i) prolongation or (ii) worsening of the HI-related symptoms (n=10 and n=10), (iii) decline in general condition (n=5), and (iv) being called for readmission (n=2). A repeated head CT was performed on 12 (44.4%) of the returned patients and none of the scans revealed an acute lesion. Ten of the discharged patients died (0.6%). The cause of death was unrelated to the primary HI in all of the cases. The main causes of death were chronic pulmonary and cardiovascular diseases.

Of the 632 (25.9%) CT-negative patients admitted to the hospital ward from the ED, a head CT was repeated on 46 (7.3%) patients within the first 72 hours. The reasons for repeated imaging were (i) routine control (n=21), (ii) prolongation of the HI-related symptoms (n=13), (iii) worsening of the HI-related symptoms (n=6), (iv) decline in general condition (n=1), and (v) new HI during the hospital stay (n=1). Ten of the CT-negative patients who were admitted to the hospital died of causes unrelated to HI (0.4%).

Only one (0.2%) patient showed an acute traumatic intracranial lesion related to the HI in the repeated imaging. The patient with a traumatic lesion on the second CT was a 16-year-old male who was riding a moped and collided with a bus. He was wearing a helmet. No LOC occurred. On admission, he was conscious but somewhat confused. The first head CT showed no intracranial lesions. The body CT showed small bilateral lung contusions, a small right-sided pneumothorax, and fractures of the left femur and pelvis. In the hospital ward, the patient had no neurological symptoms. Due to the high-energy trauma, a repeated head CT was performed the following day. The follow-up CT revealed a small posterior contusion in the parietal lobe. The contusion did not require any neurosurgery. The patient was discharged from the hospital after the surgical treatment of the femur and pelvis fractures.

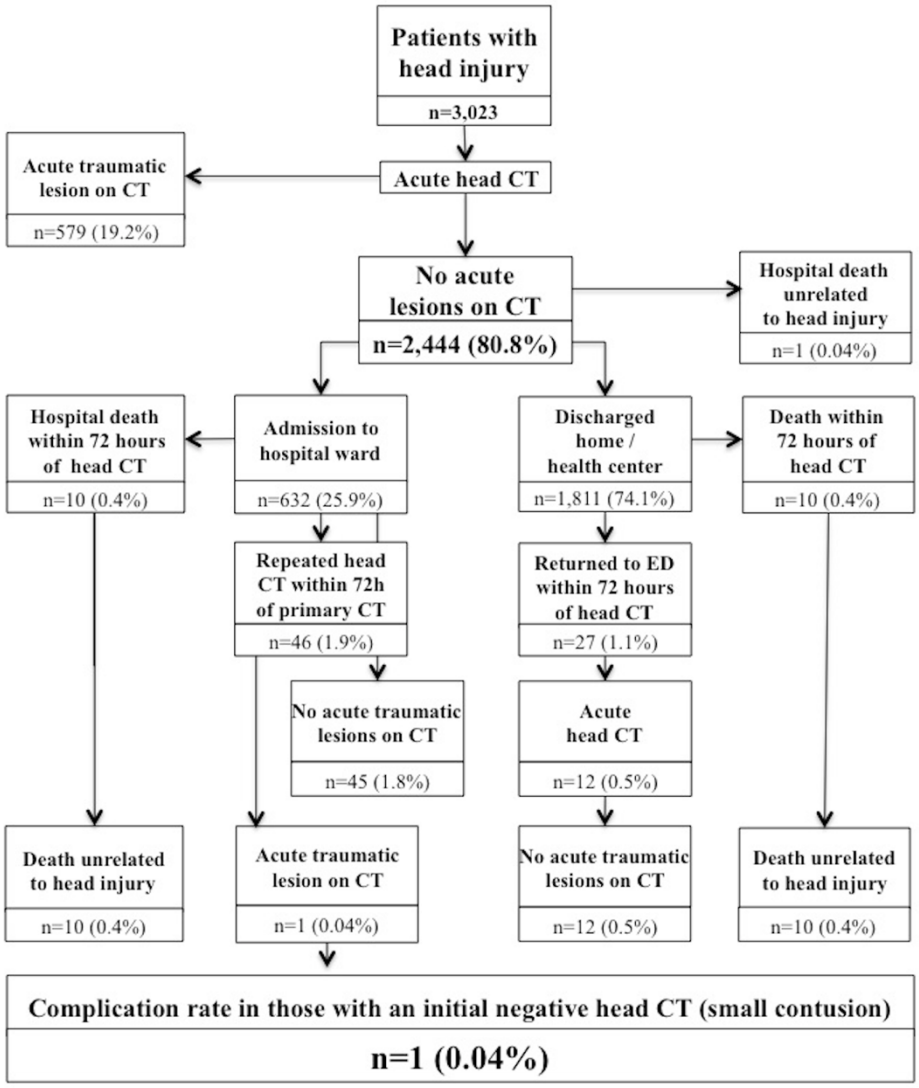


**Figure 4.** Study process to identify patients with intracranial complications within 72 h following a primarily negative head CT (reprinted with permission from Elsevier)

# 8 DISCUSSION

## 8.1 Study Population

Researchers and clinicians often regard TBI as a heterogeneous injury or condition. Many different mechanisms of injury can cause TBI and a number of different pathological changes are possible. Naturally, a large part of the heterogeneity is also due to individual heterogeneity. When the entire population of adults who sustain HI is considered, there is enormous variability in pre-existing health problems. These pre-existing problems could have an influence on acute, subacute, and long-term outcome.

The TBI studies carried out in Tampere University Hospital have sought to enroll a previously healthy group of adults who sustained an MTBI and study their outcome (Losoi et al., 2014; Luoto et al., 2014; 2013; Silverberg et al., 2015). The strict study criteria excluded nearly all patients who sustain HI. Furthermore, many of the excluded patients are at increased risk for poor outcome. If one tries to focus purely on the consequences of MTBI in patients without pre-existing conditions, it leads to studying a small, non-representative subgroup of patients who do not have known risk factors for poor outcome. Such limited approach may have value if we want to study the consequences of MTBI in *sensu stricto*. Selection bias causes limitations that have to be considered when interpreting study findings and eventually drawing clinical conclusions.

We have learned substantially about outcome from MTBI over the past few decades, and much of that knowledge would have been impossible to gather without study designs that enrolled people with specific characteristics and excluded people with certain pre-existing conditions. The growing recognition of the complexity of outcome from MTBI and of the limitations of previous research have led to the development of CDE, multicenter studies, and large-scale national and international data sharing collaborations (Maas et al., 2015; Tosetti et al., 2013; Yue et al., 2013).

The results of this thesis are significant for researchers and clinicians who work with patients who have sustained MTBIs. It is well established that adults who sustain TBIs of all severities are at increased risk for depression (Bombardier et al.,

2010; Seel et al., 2003) but some of that risk might be explained by genetic, pre-existing health and mental health factors, or post-injury health factors. It can be difficult for researchers to carefully and systematically document the broad range of factors that might be related to specific outcomes.

In regards to cognitive outcomes, researchers have reported that many factors are associated with worse performance on cognitive testing, such as attention deficit hyperactivity disorder (ADHD) (Alderson et al., 2013; Frazier et al., 2004), learning disabilities (Swanson et al., 2009), depression (Snyder, 2013), hypertension (Gifford et al., 2013), diabetes (Cheng et al., 2012), obesity (E. Smith et al., 2011), sleep problems such as insomnia (Fortier-Brochu et al., 2012) and sleep apnea (Olaithe and Bucks, 2013), alcohol abuse (Stavro et al., 2013), drug abuse (Baldacchino et al., 2012; Laws and Kokkalis, 2007), burden of white matter hyperintensities (Kloppenborg et al., 2014), and pre-clinical Alzheimer's disease (Bäckman et al., 2005).

Likewise, a rapidly growing field of research is studying the microstructural architecture of white matter after MTBI using DTI (A. Gardner et al., 2012; Sharp and Ham, 2011; Shenton et al., 2012). It is important to note, however, that white matter changes have been documented in association with numerous conditions, such as developmental conditions, e.g. ADHD (van Ewijk et al., 2012) and learning disabilities (Vandermosten et al., 2012), depression (Maller et al., 2010), hypertension (Gons et al., 2010), isolated nonspecific white matter hyperintensities (Lange et al., 2014), diabetes (Hoogenboom et al., 2014), obesity (Stanek et al., 2011), aging (Madden et al., 2012), smoking (Umene-Nakano et al., 2014), alcohol abuse (Monnig et al., 2013) and drug abuse (Baker et al., 2013; Baldacchino et al., 2012; Barker et al., 2004; Bell et al., 2011).

Pre-injury health problems affect the outcome of MTBI. If those complicating factors, such as depression, are not taken into account and treated effectively, the recovery from the injury itself may be hindered and prolonged. In MTBI, when it comes to assessing the outcome, it seems that "it's not just the injury, it's the kind of head".

## 8.2 Comorbidities and TBI

Table 13 illustrates that a variety of pre-injury diseases and disorders as well as regular medication are common in most of the patients sustaining a HI. The most common comorbid health problems were circulatory, neurological, psychiatric, and endocrine disorders. The most common medication was cardiovascular medication, followed by medication affecting the central nervous system, and blood clotting and anemia. Almost half of the screened patients were older than 60. Considering multiple health problems in combination that could have an influence on cognitive, psychological, or neuroimaging outcomes (i.e., mental and behavioral disorders; diseases of the nervous system; diseases of the circulatory system; and endocrine, nutritional, or metabolic diseases), two out of three patients had one or more of these conditions prior to their injury.

Alcohol intoxication increases the risk for sustaining a TBI (Bombardier et al., 2002; Savola et al., 2005). Intoxication makes the initial assessment of the injury more difficult and can lead to an over- or underestimation of injury severity in the acute phase. Alcohol abuse predicts unfavorable psychiatric outcomes, such as depression (Bombardier et al., 2010; Dikmen et al., 2004; Seel et al., 2003). Alcohol misuse may lead to a "vicious cycle" in which high-risk use may predispose to depression, and depression may lead to alcohol relapse (Horner et al., 2005).

A variety of mental disorders are common after TBI but causal relations between TBI and mental problems remains poorly understood. There are relatively few studies about the prevalence of mental disorders both before and after the TBI (Koponen et al., 2002; Whelan-Goodinson et al., 2009). In context of these small studies, TBI may increase the risk of psychiatric illness, especially affective disorders. Sareen and colleagues highlighted a history of mental disorder as a risk factor for mental health problems post-injury (Sareen et al., 2013). Post-TBI anxiety and depression is associated with worse outcome across the domains of occupation, interpersonal relationships, and living skills (Whelan-Goodinson et al., 2008). There is a high risk of having a psychiatric disorder after TBI when the same disorder was present before the injury (Whelan-Goodinson et al., 2010). Bombardier and colleagues also highlighted that prior depression is a risk factor for post-injury depression (Bombardier et al., 2010). However, the majority of cases of depression and anxiety were novel, suggesting that also other factors than pre-TBI psychiatric status contributes to psychiatric outcome after TBI. Female gender, lower education, and pain were also associated with post-injury depression and

unemployment and older age were associated with anxiety (Whelan-Goodinson et al., 2010).

Older adults are an important subgroup of TBI patients, and their proportion is growing as the population ages and as a result of fall-related injuries. Geriatric patients sustaining a MTBI (GCS of 13–15) tend to have more intracranial lesions and more often require neurosurgical interventions than younger people (Mack et al., 2003). The hospitalization rate for adults ages 65 and older is more than double when compared to younger adults (Coronado et al., 2005). Predicting outcomes and providing care in the older population with TBI is challenging (Kristman et al., 2014; Thompson et al., 2006).

Gardner and colleagues (R. C. Gardner et al., 2014) have suggested that older adults who sustain a TBI, even mild, are at an increased risk of developing dementia—even after controlling for known comorbidities. In our study, the rate of comorbidities was much higher than in the study by Gardner and colleagues, possibly because they relied on a database in which diagnoses were recorded, whereas in the present study a chart review was conducted for each patient. This study shows that a large percentage of patients who sustain a HI have pre-existing neurological, cardiovascular, and other diseases associated with increased risk for dementia. This possible confounding factor should be remembered if patients with TBI are compared with healthy controls (Y.-K. Lee et al., 2013). A history of more severe TBI (moderate to severe) may be associated with an increased risk for future dementia (Raj et al., 2017).

## 8.3 Pre-existing Structural Imaging Findings in TBI patients

Pre-existing non-traumatic lesions were common in patients with TBI but they did not increase the risk of sustaining a CT positive MTBI. The vulnerability of the brain itself may not increase the risk of intracranial abnormalities in the elderly. Instead, the underlying increased risk for intracranial abnormalities associated with aging may be general frailty caused by several factors (e.g., aging process, other comorbidities, and antithrombotic medication) as poorer health and functioning predicts the occurrence of TBI in elderly (Dams-O'Connor et al., 2016).

A common belief is that cerebral atrophy is a risk factor for acute and chronic SDH. To our knowledge, only one study suggests that cerebral atrophy may predispose to traumatic intracranial hemorrhage (Dunham et al., 2014). In our study, the association was the opposite. It may be that patients suffering from

ischemic small vessel disease tend to have lower GCS or altered mental state on admission than healthier individuals and the symptoms are at least partly due to the degenerative disease itself and not because of the brain injury *per se*. One may speculate that the brain burdened with chronic ischemia may be more vulnerable to the neuronal dysfunction after HI but not to structural damage.

Advanced age is a well-known risk factor for intracranial abnormalities in HI (Coronado et al., 2005; Haydel et al., 2000; Moore et al., 2012; Mower et al., 2005; National Institute for Health and Clinical Excellence, 2007; Rathlev et al., 2006; Stiell et al., 2001b; Styrke et al., 2007; Undén et al., 2013). The present study highlights that older age increases the risk of any CDE intracranial abnormality fairly linearly across adulthood, though may plateau around the age of 60-70 years. Falls are the leading cause of TBI among elderly people (Chan et al., 2013; Coronado et al., 2005; Koskinen and Alaranta, 2008; Styrke et al., 2007; Thompson et al., 2006). The risk of falling could be associated with intrinsic risks that occur with aging (e.g., chronic medical conditions, impaired balance, slower reaction times, decreased muscle strength, impaired cognition, and use of medications that predispose to postural hypotension and dizziness).

In concordance with previous studies, chronic alcohol abuse increased the risk of having an acute traumatic lesion on head CT. Acute intoxication, however, did not increase the risk of intracranial abnormalities. Alcohol abuse is common before TBI, with a prevalence of 37 to 51% (Parry-Jones et al., 2011). In our study, 18.4% had a history of alcohol abuse. Both acute and chronic alcohol abuse may impair decision-making, motor control, and inhibitory control. Binge drinking is the most common pattern of drinking among trauma patients, and the injuries of such patients typically result from assaults, traffic accidents, and falls (Savola et al., 2005).

## 8.4 Diagnosis of MTBI in the ED

MTBI can be diagnosed in the ED if the patient meets the diagnostic criteria. What makes the diagnosis challenging is that the CT scan is the only objective diagnostic tool. The rate of intracranial lesions is much higher in moderate and severe TBI but even a severe TBI is possible without intracranial trauma seen on CT. CT may not reveal all intracranial non-hemorrhagic lesions, especially not DAI (Saboori et al., 2007). MRI has better sensitivity in finding traumatic lesions, even though it loses some of its potential within weeks after injury (Brandstack et al., 2006;

Orrison et al., 1994; Provenzale, 2007). MRI is helpful when the diagnosis is unsure based on the traditional TBI signs (LOC, PTA, GCS, mental alterations and focal neurological deficits).

Even though the GCS is a one of the most important concepts in the TBI field, it does not fully describe the characteristics of injury. Primarily, GCS was developed "to assess depth and duration of loss of consciousness" and was aimed as a mechanistic diagnostic measure (Teasdale and Jennett, 1974). GCS is an easy way to rapidly assess gross alterations in consciousness after TBI, but it is not the whole truth. The decades-old approach of classifying TBI severity solely based on the GCS can be improved by considering neuroimaging findings. GCS should be supplemented by the clinical assessment of PTA and LOC but both are prone to confounds. An injury severity classification system that incorporates neuroimaging findings could improve outcome prediction, resource allocation, and patient stratification in clinical trials (Maas et al., 2011).

The medical records on PTA, LOC, and GCS are part of the foundation of TBI diagnosis. Too often these crucial factors are not recorded which can make the initial diagnosis of TBI questionable. The importance of a thorough medical history, focusing on the injury mechanism and confounding factors along with a careful neurological examination including GCS, mental state, and PTA measurements cannot be highlighted enough.

## 8.5 Acute Intracranial Abnormalities in TBI

TBI is not a single disease but a spectrum of pathologies which vary in terms of etiology, mechanisms, severity, and treatment, with widely different outcomes (Lingsma et al., 2010; Maas et al., 2015). The clinical severity of TBI ranges from minor (minimal complaints, no visible structural damage) to fatal injuries.

Many guidelines recommend advanced age as an indication for CT (Coronado et al., 2005; Haydel et al., 2000; Moore et al., 2012; Mower et al., 2005; National Institute for Health and Clinical Excellence, 2007; Rathlev et al., 2006; Stiell et al., 2001b; Styrke et al., 2007; Undén et al., 2013). In line with these, aging was associated with an increased risk of sustaining a CT-positive brain injury in our study. Liberal use of CT in the elderly population may also be one reason for having high numbers of CT-positive TBI in this patient group. There are several reasons for high numbers of head CT scans in the elderly. Geriatric patients have often neurodegenerative disease making the medical history taking difficult or even

impossible. Preinjury anticoagulation and/or antiplatelet medication become more abundant as the population ages. Falls are common in the elderly population, and at the same time, the leading cause of TBI is falls.

Cerebral atrophy, and fragile, less-elastic bridging veins that are prone to disruption are thought to predispose the aged to acute intracranial lesions, even in the setting of low-energy trauma. A common belief is that cerebral atrophy is a risk factor of acute SDH. The evidence, however, to support this notion is scarce. In essence, the relationship between cerebral atrophy and intracranial bleeding has been derived from expert opinion. To our knowledge, only one study suggests that cerebral atrophy may predispose to traumatic intracranial hemorrhage (Dunham et al., 2014). In our study the association was the opposite. Interestingly, cerebral microangiopathy was also inversely associated with the risk of acute traumatic intracranial abnormalities. Cerebral microangiopathy is associated with intracerebral bleeding (deep brain hemorrhages, cerebral microbleeds) (C. Moran et al., 2012). It seems, however, that this blood vessel pathology does not comprehensively predispose to CT-positive intracranial traumatic lesions.

The vulnerability of the brain itself may not increase the risk of acute intracranial trauma abnormalities in the elderly. Instead, the underlying cause may be general frailty caused by several factors (e.g. aging process, other comorbidities and antithrombotic medication), as poorer health and functioning predicts TBI in elderly (Dams-O'Connor et al., 2016). Falls are the leading cause of TBI among elderly people (Chan et al., 2013; Coronado et al., 2005; Koskinen and Alaranta, 2008; Styrke et al., 2007; Thompson et al., 2006). The risk of falling could be associated with intrinsic risks that occur with aging (e.g. chronic medical conditions, impaired balance, slower reaction times, decreased muscle strength, impaired cognition, and use of medications that predispose to postural hypotension and dizziness). The high incidence of TBI may rather be because of the frequent falls and not because of poorer macroscopic brain integrity or more severe degeneration (microangiopathy, previous injuries, atrophy, and degenerative diseases).

Blood alcohol levels and the risk of HI tend to increase simultaneously and especially binge drinking is associated with TBI (Savola et al., 2005). In concordance to previous studies, chronic alcohol abuse increased the risk of having an acute traumatic lesion on head CT. Acute intoxication, however, did not increase the risk of intracranial abnormalities. Alcohol abuse is common before TBI, prevalence being 37% to 51% (Parry-Jones et al., 2011). Pre-injury alcohol use and problems predict the continuation of heavy use and alcohol problems after

TBI (Bombardier et al., 2003). Acute alcohol intoxication may affect the GCS scores (Jacobs et al., 2010; Scheenen et al., 2016) but there are studies implicating that alcohol intoxication does not significantly alter the GCS score in trauma patients with TBI, except for patients with the severest injuries. (Lange et al., 2010a; Sperry et al., 2006). Both acute and chronic alcohol abuse may impair decision making, motor control, and inhibitory control (Gilman et al., 2008).

One can have a structurally more severe brain injury with a high GCS score and vice versa. The GCS does not tell, what kind of an injury has occurred. The rate of traumatic lesions is much higher in moderate to severe TBI but it is possible to suffer a severe TBI without intracranial trauma seen on CT. CT underestimates many intracranial nonhemorrhagic lesions, especially DAI (Paterakis et al., 2000). The pathoanatomical lesion, however, does not entirely determine the course of recovery in MTBI. Widely variable patterns of injury and pathology may be seen on structural imaging in patients with similar grades of clinical severity as assessed by GCS score (Saatman et al., 2008).

Most MTBIs are not associated with visible abnormalities on structural neuroimaging. A complicated MTBI, in the original definition, was differentiated from an uncomplicated mild TBI by the presence of: (i) a depressed skull fracture, and/or (ii) a trauma-related intracranial abnormality (e.g., hemorrhage, contusion, or edema) (Williams et al., 1990).

In our study, one in six MTBI patients has a traumatic CT finding. The frequency of CT abnormalities in MTBI patients with hospital admission in different studies has been between 4.7% and 38.9% (Borczuk, 1995; Jeret et al., 1993; Livingston et al., 1991; Ono et al., 2007; Saboori et al., 2007; Stein and Ross, 1992; Stiell et al., 2005; Thiruppathy and Muthukumar, 2004). CT findings seem to predict poorly the long-term symptoms and sequelae in MTBI patients (Carroll et al., 2014; Stulemeijer et al., 2008) and MRI findings explain only some of the variability in outcome (Yuh et al., 2013). The outcome prediction in MTBI has proven to be difficult. To a large extent, the recovery from MTBI depends on a diverse range of biopsychosocial factors (pre-injury mental health, gender, acute psychological distress) (Cassidy et al., 2014; Silverberg et al., 2015).

Current approaches to the characterization of disease severity have not changed in decades. The classification of TBI based on the GCS does not include factors related to pathophysiology (Saatman et al., 2008). The spectrum of injury severity is wide, and a categorization into a limited number of categories (e.g. mild, moderate and severe TBI) may lead to loss of valuable information.

## 8.6 Observing after TBI and Delayed Complications

In the present study, the overall rate of complications within the first 72 h was 0.04% after initial negative head CT. There were no life-threatening complications or complications needing neurosurgery. As there was only one patient with complications, the prediction of the need for hospitalization was impossible.

Advanced age and the use of anticoagulation or antiplatelet medication have been found to be associated with an increased the risk for intracranial bleeding, need for neurosurgery, and mortality (Moore et al., 2012; Nishijima et al., 2012; Peck et al., 2011). However, some recent studies have suggested that even patients with anticoagulation or antiplatelet medicine do not need routine repeated head CT (Peck et al., 2011), or could even be discharged, if the primary CT is negative (Nishijima et al., 2012).

Some authors have suggested that even most patients on VKA with minor HI can be discharged home with negative initial imaging result (Rendell, 2014). This strategy may be acceptable in select populations, but some investigators have reservations about this liberal strategy e.g. in more elderly populations (Miller et al., 2015). The most recent systematic review and meta-analysis does not support a routine hospital observation for 24 h or repeat cranial CT scans in all patients suffering from MTBI with a normal initial scan who were anticoagulated with VKA before injury (Chauny et al., 2016). CT scanning for all anticoagulated patients with HI is not cost-effective compared with selective use of CT scanning based on guidelines recommendations (Kuczawski et al., 2016).

Observation and/or repeated head CT scans may still be warranted in specific patients presenting increased risk of delayed bleeding. These include patients with supratherapeutic INR levels (defined as INR > 3.0), with more serious mechanisms of injury (e.g., traffic accident), or with concomitant antiplatelet therapy (Menditto et al., 2012b; Pieracci et al., 2007). Also, patients living without family members unable to monitor signs of neurologic deterioration, patients unable to return to the ED, or patients unable to understand the discharge advice could potentially be kept under observation for a period of time. Ground level falls are a significant risk factor for TBI and in turn falls and syncope are common in the elderly population. Falls are frequently a symptom of other cardiovascular or neurologic disease that may require a period of observation independent of the risk of delayed intracranial bleeding.

The present study results are in line with those findings. Even though the exact number of patients using anticoagulation in the present cohort is unknown, most

certainly this large, quite aged, sample included a considerable number of patients using this medication. We did not discover any warfarin-medicated patients with a complication.

The single patient with a complication (i.e., a posterior contusion) after an initial negative CT was a young male with a high-energy trauma. The small contusion that was visible in the second CT was also seen on a brain MRI taken a month after the injury. The negative finding on the primary head CT scan can mostly be explained by the short time delay between the injury and the scanning (1.0 h). It is recognized that not all parenchymal lesions are visible on CT when the imaging is conducted shortly after the injury (Lobato et al., 1997).

Trained radiologists on call may not detect all brain contusions, but the severest findings are well noticed (Laalo et al., 2009). Emergency physicians with radiological training can decently interpret cranial CT scans with very good inter-rater agreement with neuroradiologists. Emergency physicians seldom miss clinically relevant findings on head CT (Al-Reesi et al., 2010; Mucci et al., 2005). In our study, the two neuroradiologists did all the readings of the scans. A structured form was used in imaging data collection. As a part of the normal acute management, the primary head CT was mainly interpreted by a radiology resident and additionally by the on-call emergency physician. The treatment decisions of the patients within this study were based on these on-call interpretations.

We do not have the data about the on-call interpretations. We were unable to assess the inter-rater agreement of our study neuroradiologists, on-call radiology residents and radiology consultants. As part of common practice, all head CT scans obtained during the on-call hours are read by a neuroradiologist the following day. Any differences found between these two readings are recorded and the patient is contacted if necessary. Based on this, the results of this study most likely would not have been different if the CT data was based on the interpretations made by the hospital staff as part of routine work.

Our sample had 110 CT-negative patients with a GCS score of 3 to 12 on admission. There are several possible explanations for low GCS scores. Stroke, alcohol and substance abuse, comorbid acute and chronic diseases as well as medication or sedation may impair consciousness even though the brain injury is minimal or non-existent.

## 8.7 Limitations and Strengths of the Study

This study represents a large population-based HI sample that is commonly seen in the ED internationally. The sample includes a wide severity spectrum of HIs that were treated at the ED at varying time delays post-injury (median = 4.3 h, interquartile range 1.3-35.7 h). The initial study population is diverse in many ways, as it has subjects of different age, gender and trauma mechanisms. The study findings are generalizable and can be easily applied into clinical practice.

All patients had high-quality CT scans that were interpreted by board certified neuroradiologists. The data derived from CT scans covers all core elements of CDE in TBI. These factors make the CT data detailed and comprehensive.

The data collection was done retrospectively and therefore the amount of missing or unknown information (e.g., alcohol intoxication) was quite large. In addition, there is a large amount of missing data in the medical records on PTA, LOC, and GCS, which are part of the foundation of TBI diagnosis. These findings highlight the importance of a thorough medical history, focusing on the injury mechanism and confounding factors along with a careful neurological examination including GCS, mental state, and PTA measurements. The presence of PTA was noted much more often in MTBI patients than in more severe TBI patients. Often those with moderate and severe TBIs have additional injuries that dominate clinical attention or they are unconscious at arrival and only progress to post-traumatic amnesia after being transferred from the ED. There also might be a tendency for some physicians to document more specific injury criteria following MTBI, especially in those with isolated HI, and document fewer criteria in ED situations when the person has an obvious moderate or severe TBI that is predominantly treated by a neurosurgeon.

CT criteria in the ED were based on the Scandinavian guidelines. Considering the extent of missing data, the guideline compliance of the ED physicians seems questionable. Apparently, some patients in the sample did not fulfill the Scandinavian CT criteria and therefore were CT imaged without solid indications. In contrast, it is possible that some HI patients did not undergo CT imaging although they met the criteria. In our sample, one in four (n=776, 25.7%) did not have clearly documented clinical signs or symptoms of TBI in their medical records, which might reflect the absence of those signs, incomplete documentation, or both.

The CT data used in this study was not based on the on-call interpretation, but on a retrospective interpretation by our study neuroradiologists. The differences between these interpretations were not studied.

Our sample contained a small number of patients who were classified as sustaining an MTBI, even though they had a GCS less than 13. In this group, low GCS had likely resulted from intoxication, medications, or other medical conditions. There is a possibility that the injury of some of these cases was incorrectly classified. Finally, the study examined only patients with MTBI who attended an ED. Rates of CT abnormalities in patients who do not seek acute care at an ED are not known.

## 8.8 Future Perspectives

Most of the MTBI studies have biased samples that do not represent the majority of the population who sustain an MTBI. There is a need for research on various subgroups (e.g. patients who have pre-injury mental disorders or substance abuse). Targeting specific subgroups to address specific research questions is feasible. Instead of excluding patients with pre-existing health problems, we can increase knowledge and develop better care following MTBI by studying different groups. Successful TBI research and clinical care needs wider collaboration than what we have seen in the past. Recent work in the field of TBI research sounds promising. International multicenter studies, such as TRACK–TBI study, aim to translate the research into successful treatment.

The comorbidity of TBI patients is common, but the effect of different preinjury health problems and diseases is very poorly known. More comprehensive studies about the relationship of other diseases and TBI are needed in order to improve the knowledge of the interplay of preinjury health problems and brain injury.

TBI is increasingly common in the elderly, but geriatric TBI has received little attention. There is a significant gap in the literature as current care of older adults with TBI is guided mainly by guidelines derived from previous work primarily done in younger adults. Even though previous studies of adults with TBI have contributed to the care of this population, the failure to discern that the older TBI patient presents with different physiological and psychological needs frequently limits them.

TBI is an expensive disease, and great amount of TBIs are caused by preventable injury mechanisms (most importantly falls). Studies focusing on prevention strategies could provide useful information how to lower the incidence of TBI. Alcohol is a major, yet preventable risk factor for TBI.

Further studies are still needed to identify and better describe the patients who are at higher risk of delayed bleeding. Even with the current evidence strongly suggesting that routine observation is not useful, clinical judgment should be used when making decisions about discharging.

Delayed intracranial bleeding has been studied thoroughly in patients with VKA (e.g. warfarin). In the future, the role of VKAs is diminishing as newer anticoagulative compounds are gaining ground. The risk for delayed bleeding with these non-vitamin K anticoagulants (NOAC) is not well known.

Intracranial abnormalities are common in the MTBI, but the clinical relevance and impact of these lesions on long-term outcome is poorly known. More research is needed about those patients who recover slowly, how to increase the likelihood of good prognosis and how to intervene early on to prevent incomplete recovery.

# 9 CONCLUSIONS

We provided a detailed description of CT findings in patients with HI of all severities. This study represents a large population-based sample of HI patients who are commonly treated in the EDs. The study findings are generalizable and can be easily applied into clinical practice. The most common traumatic lesions are SDH, SAH and contusions, throughout the whole severity spectrum of TBI. A substantial number of patients suffering a MTBI have traumatic intracranial lesions on head CT. Pre-existing lesions are common in patients suffering TBI, but they did not increase the risk of suffering a CT positive TBI. Older age, however, is a significant and independent risk factor for acute intracranial lesions. Alcohol abuse is a common risk factor and was found to increase the risk of traumatic intracranial abnormalities. The age over 65 years strongly associates with intracranial injuries and the risk increases directly with advancing age.

Approximately 1 in 6 patients who present to the ED with suspected or confirmed mild TBI will have a trauma-related intracranial abnormality on day-of-injury CT. The frequency of CT findings is much lower than in moderate to severe TBI, but the type and location of lesions is very similar. Clinicians and researchers should also be aware that within the spectrum of MTBI, patient demographics (older age and male gender), pre-injury exposures (alcohol abuse, but not brain pre-existing lesions), mechanism of injury (falls and being struck by a motor vehicle), and impaired consciousness following injury (GCS<15) are all associated with an increased incidence of acute traumatic intracranial abnormality.

In the present study, which includes head injuries of all severity, the probability of delayed life-threatening complications was negligible when the primary CT scan revealed no acute traumatic lesions. Therefore, routine repeated CT scanning or observation is not warranted when the primary CT scan is negative. Our findings suggest that all HI patients with a negative CT scans and normal level of consciousness can be discharged without observation.

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# 12 ORIGINAL PUBLICATIONS

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# Who Gets Head Trauma or Recruited in Mild Traumatic Brain Injury Research?

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## Abstract

Mild traumatic brain injury (mTBI) is a public health problem. Outcome from mTBI is heterogeneous in part due to pre-injury individual differences that typically are not well described or understood. Pre-injury health characteristics of all consecutive patients ($n = 3023$) who underwent head computed tomography due to acute head trauma in the emergency department of Tampere University Hospital, Finland, between August 2010 and July 2012 were examined. Patients were screened to obtain a sample of working age adults with no pre-injury medical or mental health problems who had sustained a ''pure'' mTBI. Of all patients screened, 1990 (65.8%) fulfilled the mTBI criteria, 257 (8.5%) had a more severe TBI, and 776 (25.7%) had a head trauma without obvious signs of brain injury. Injury-related data and participant-related data (e.g., age, sex, diagnosed diseases, and medications) were collected from hospital records. The most common pre-injury diseases were circulatory (39.4%-43.2%), neurological (23.7%-25.2%), and psychiatric (25.8%-27.5%) disorders. Alcohol abuse was present in 18.4%-26.8%. The most common medications were for cardiovascular (33.1%-36.6%), central nervous system (21.4%-30.8%), and blood clotting and anemia indications (21.5%-22.6%). Of the screened patients, only 2.5% met all the enrollment criteria. Age, neurological conditions, and psychiatric problems were the most common reasons for exclusion. Most of the patients sustaining an mTBI have some pre-injury diseases or conditions that could affect clinical outcome. By excluding patients with pre-existing conditions, the patients with known risk factors for poor outcome remain poorly studied.


**Key words:** brain injury; comorbidity; concussion; head injury; patient recruitment

## Introduction

Mild traumatic brain injury (mTBI) has been considered a public health problem.[1,2] Heterogeneity in outcome from this injury is influenced by a range of pre-injury individual characteristics, such as older age,[3] gender,[4,5] substance abuse,[6,7] mental health,[3,4] and neurological problems.[8] Mild TBI prevalence is distributed bimodally, with peaks among those in the 15 to 24 age group and those older than 65.[9] The risk of ground level falls resulting in traumatic brain injury (TBI) increases in older adults.[10,11] Adults ages 75 and older have the highest rates of TBI-related hospitalization and death.[12] A greater number of mTBIs occur in males than in females.[9,13] Pre-morbid neurological conditions and disorders (e.g., degenerative, cerebrovascular, or demyelinating disease; cerebral atrophy or white matter hyperintensities; or epilepsy) are fairly common in patients who sustain an mTBI.[14] Pre-injury psychiatric conditions (e.g., anxiety, depression, sleep disorders, post-traumatic stress, bipolar disorder, schizophrenia) also are common, although there are relatively few large-scale studies on the rate of pre-injury mental health problems.[3,14–16] Alcohol abuse (both regular and occasional) is a well-known and common risk factor for TBI.[17–19]

Many TBI studies recruit fundamentally biased samples that are not generalizable to the population of persons who sustain an mTBI.[20] For example, older adults with pre-existing psychiatric and neurological problems are frequently seen in the emergency departments (EDs) because of an mTBI but they are often excluded in mTBI studies. Studying strictly selected samples may be necessary for some studies but such studies are limited in terms of translating research findings into everyday clinical practice. Luoto and colleagues showed that by applying strict and elaborate study criteria, only a small minority of all consecutively screened patients

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could be enrolled.[14] The incidence of pre-injury health problems in the population of people who sustain an mTBI is not well documented.

We hypothesized that people who sustain mTBIs are likely to have other health problems that could affect outcome from their injury. This study describes the characteristics of a large inception cohort ($n = 3023$) of head trauma patients who underwent computed tomography (CT) in an ED. The objectives of this study were to provide a comprehensive description of the pre-injury health characteristics of a cohort of patients who sustain head trauma and undergo evaluation in an ED, and to determine the number of people with specific pre-injury health problems (such as neurodegenerative diseases, prior brain injury, psychiatric problems, or hypertension), singly and in combination. As a secondary aim, we describe how 98% of them ultimately got excluded when trying to do an mTBI outcome study with previously healthy adults.

## Methods

### Study framework and ethics

This study is part of the Tampere Traumatic Head and Brain Injury Study. Participants were enrolled from the ED of the Tampere University Hospital (Tampere, Finland) between August 2010 and July 2012. The ED provides health services for a joint municipal authority of 22 municipalities (both urban and rural) with a total of approximately 470,000 residents. The patient pool for this study consisted of all consecutive patients who underwent head CT due to acute head trauma ($n = 3023$). All consecutive patients undergoing head CT due to acute head injury were screened to obtain a sample of working age adults with no pre-injury medical or mental health problems who had sustained a ''pure'' mTBI.

The enrollment protocol included three inclusion criteria and nine exclusion criteria. Subjects were included in the study if they: 1) met mTBI criteria of the World Health Organization (WHO) Collaborating Center for Neurotrauma Task Force[21]; 2) were between ages 18 and 60 years; and 3) were residents of the hospital district. Subjects were excluded on the basis of the following criteria: 1) premorbid neurological problems (brain tumor, neurodegenerative disease, cerebrovascular or demyelinating disease, cerebral palsy, white matter lesions, epilepsy); 2) prior psychiatric developmental disorders (chronic alcohol or substance abuse; mood, somatoform, personality, or anxiety disorders; schizophrenia spectrum and other psychotic disorders; or developmental disorders such as attention-deficit hyperactivity disorder [ADHD]); 3) past TBI (a head injury meeting at least mTBI criteria); 4) regular psychoactive medication use; 5) neurosurgery (any intracranial surgery or endovascular procedure for the index injury or a prior injury); 6) problems with vision or hearing (better ear hearing level 0.5-4.0 kHz ≥40 dB or vision 0.3 [decimal] or less with glasses); 7) first language other than Finnish; 8) a time interval between injury and ED admission of more than 72 h; and/or 9) declined to participate in the study. The major causes of exclusion were age criteria not met ($n = 1552$; 51.3%), mTBI criteria not met ($n = 1033$; 34.2%), psychiatric problems ($n = 915$; 30.3%) and/or neurological problems ($n = 770$; 25.5%). Notably, there was major overlap in the causes of exclusion, because some patients fulfilled multiple criteria. Ethics approval was obtained from the Ethical Committee of Pirkanmaa Hospital District (code: R10027), Finland.

Mild TBI was defined according to the criteria proposed by the WHO Collaborating Center for Neurotrauma Task Force on Mild Traumatic Brain Injury,[21] where mTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria include one or more of the following: 1) confusion or disorientation, loss of consciousness for 30 min or less, post-traumatic amnesia for less than 24 h, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; and 2) Glasgow Coma Scale score of 13–15 after 30 min post-injury or later on presentation for health care. These manifestations of mTBI must not be because of drugs, alcohol, medications, other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries, or intubation), other problems (e.g., psychological trauma, language barrier, or coexisting medical conditions), or penetrating craniocerebral injury.

### Data collection

Data collection was performed semi-retrospectively from hospital records. The reviewed hospital records included information from prior visits to Tampere University Hospital and regional (Pirkanmaa) public health care centers. As part of the aforementioned prospective mTBI study project (Tampere Traumatic Head and Brain Injury Study), a research nurse and a research physician (T.M.L.) screened the ED patient admission list for potential ''pure'' mTBI patients during office hours. Patients who met all 12 study criteria according to the primary patient record screening were examined in the ED by the research physician. Participant-related data included age, sex, and the reasons for exclusion. Injury-related variables included time of injury, time of arrival to the ED, mechanism of injury, and alcohol and/or narcotics intoxication (breathalyzer and/or blood test) at the time of injury. The mechanism of injury was categorized.

TBI-related clinical variables included eye-witnessed loss of consciousness, seizures, disorientation, retrograde and/or anterograde amnesia, and focal neurological deficits. The on-call ED physician identified amnesia using an interview regarding pre- and post-injury events. Only the presence or absence of amnesia was noted; the duration of amnesia was not assessed. No structured forms or standardized measures for amnesia were used. Destination after ED was categorized into four groups: home, hospital ward, local health center, or death. Health problems and diseases were assessed according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*.[22] Information on current medication at the time of injury was classified into 17 subgroups according to the Finnish Commercial Drug Catalog (Pharmaca Fennica), which is based on WHO's Anatomical Therapeutic Chemical Classification System codes. In the ED, a non-contrast head CT was performed with a 64-row CT scanner (Lightspeed VCT; GE Healthcare, Waukesha, WI). Referral criteria for acute head CT were based on the former Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries.[23] Head CT was performed in the ED within 72 h. All head CT scans were analyzed and systematically coded by two neuroradiologists (A.B., A.K.).

### Statistical analyses

Mann-Whitney U tests were computed for continuous variables and Pearson chi-square tests for categorical variables. The statistical significance level was set at 5% for all analyses. IBM SPSS Statistics 22 (IBM Corp., Armonk, NY) was used to perform the analyses.

## Results

Health problems and diseases in the cohort and subgroups are summarized in Table 1. The number of older adults, stratified by age, who were excluded were as follows: 60–69 years, $n = 393$ (13.0%); 70–79 years, $n = 373$ (12.3%); 80–89 years, $n = 487$ (16.1%); and 90 years and older, $n = 125$ (4.1%). Diseases of the circulatory system were common (39.4%-43.2%), especially in those older than 60 (71.9%). Diseases of the nervous system, broadly defined, were present in approximately one in four people (23.7%-25.2%), with a higher rate found in those older than 60

Table 1. Health Problems and Diseases in the Cohort

| | *Total Sample* | | *MTBI* | | *Moderate-Severe TBI* | |
|---|---|---|---|---|---|---|
| | n = *3,023* | | n = *1,990* | | n = *257* | |
| | n | % | n | % | n | % |
| Diseases of the circulatory system | 1,192 | 39.4 | 808 | 40.6 | 111 | 43.2 |
| Diseases of the respiratory system | 277 | 9.2 | 183 | 9.2 | 21 | 8.2 |
| Mental and behavioral disorders | 780 | 25.8 | 548 | 27.5 | 70 | 27.2 |
| Chronic detrimental alcohol use (during the last two years) | 557 | 18.4 | 405 | 20.4 | 69 | 26.8 |
| Regular substance abuse (during the last two years) | 108 | 3.6 | 76 | 3.8 | 6 | 2.3 |
| Schizophrenia, schizotypal, or delusional disorder | 52 | 1.7 | 35 | 1.8 | 4 | 1.6 |
| Affective disorder (during the last year) | 312 | 10.3 | 220 | 11.1 | 24 | 9.3 |
| Neurotic, stress-related, and somatoform disorder | 39 | 1.3 | 31 | 1.6 | 0 | 0 |
| Adulthood personality disorder or disturbance of conduct | 47 | 1.6 | 31 | 1.6 | 1 | 0.4 |
| Mental retardation | 19 | 0.6 | 13 | 0.7 | 0 | 0 |
| Mental developmental disorder | 15 | 0.5 | 10 | 0.5 | 1 | 0.4 |
| Diseases of the nervous system | 717 | 23.7 | 502 | 25.2 | 61 | 23.7 |
| Brain tumor* | 26 | 0.9 | 21 | 1.1 | 1 | 0.4 |
| Degenerative disease | 250 | 8.3 | 177 | 8.9 | 21 | 8.2 |
| Demyelinating disease | 7 | 0.2 | 5 | 0.3 | 0 | 0 |
| Stroke or a transient cerebral ischemic attack | 301 | 10 | 227 | 11.4 | 16 | 6.2 |
| Cerebral palsy | 8 | 0.3 | 5 | 0.3 | 1 | 0.4 |
| Cerebral atrophy and/or white matter lesions more than related to age | 205 | 6.8 | 151 | 7.6 | 10 | 3.9 |
| Epilepsy | 137 | 4.5 | 97 | 4.9 | 11 | 4.3 |
| Prior brain injury | 311 | 10.3 | 231 | 11.6 | 30 | 11.7 |
| Endocrine, nutritional, and metabolic diseases | 566 | 18.7 | 381 | 19.1 | 46 | 17.9 |
| Diseases of the digestive system | 212 | 7 | 142 | 7.1 | 18 | 7.0 |
| Diseases of the genitourinary system | 184 | 6.1 | 118 | 5.9 | 15 | 5.8 |
| Diseases of the musculoskeletal system and connective tissue | 365 | 12.1 | 247 | 12.4 | 21 | 8.2 |
| Certain infectious and parasitic diseases | 82 | 2.7 | 56 | 2.8 | 7 | 2.7 |
| Neoplasms | 169 | 5.6 | 113 | 5.7 | 15 | 5.8 |
| Diseases of the blood | 67 | 2.2 | 44 | 2.2 | 6 | 2.3 |
| Diseases of the eye and adnexa | 120 | 4 | 85 | 4.3 | 9 | 3.5 |
| Diseases of the ear and mastoid process | 43 | 1.4 | 25 | 1.3 | 4 | 1.6 |
| Diseases of the skin and subcutaneous tissue | 69 | 2.3 | 48 | 2.4 | 7 | 2.7 |
| Pregnancy, childbirth, and the puerperium | 0 | 0 | 0 | 0 | 0 | 0 |
| Certain conditions originating in the perinatal period | 0 | 0 | 0 | 0 | 0 | 0 |
| Congenital malformations. deformations and chromosomal abnormalities | 12 | 0.4 | 10 | 0.5 | 1 | 0.4 |
| **Combinations of Health Problems** | | | | | | |
| Mental and behavioral disorders OR diseases of the nervous system | 1,324 | 43.8 | 934 | 46.9 | 112 | 43.6 |
| Diseases of the circulatory system OR endocrine, nutritional, or metabolic diseases | 1,349 | 44.6 | 916 | 46.0 | 116 | 45.1 |
| Mental and behavioral disorders OR diseases of the nervous system OR diseases of the circulatory system OR endocrine, nutritional, or metabolic diseases | 2,014 | 66.6 | 1,381 | 69.4 | 171 | 66.5 |
| Mental and behavioral disorders OR diseases of the nervous system OR diseases of the circulatory system OR endocrine, nutritional, or metabolic diseases OR diseases of the musculoskeletal system and connective tissue | 2,078 | 68.7 | 1,420 | 71.4 | 172 | 66.9 |

*Parenchymal tumor of any size or superficial tumor of over 10 mm

(36.1%). A history of prior brain injury was present in 10.3%-11.7%. Mental and behavioral disorders were present in approximately one in four people (25.8%-27.5%). Chronic detrimental alcohol abuse was present in 18.4%-26.8%, and an affective disorder in the past year was present in 9.5%-11.1%. Endocrine, nutritional, and metabolic diseases were present in approximately one in five people (17.9%-19.1%). Pre-existing diseases and disorders of the musculoskeletal system and connective tissue were present in 8.2%-12.4% people. Combinations of health problems and diseases also were calculated to illustrate the prevalence of having one or more health condition that might influence mTBI outcome. About half of the cohort had either diseases of the circulatory system or mental and behavioral disorders (43.6%-46.9%). Two-thirds had mental and behavioral disorders; diseases of the nervous system; or circulatory system, endocrine, nutritional, or metabolic diseases (66.5%-69.4%).

Table 2 summarizes the medication use of the study patients by subgroups. About half of the cohort had at least one regular

Table 2. Medication Use in the Cohort

| | *Total sample* | | *MTBI* | | *Moderate-Severe TBI* | |
|---|---|---|---|---|---|---|
| | n = *3,023* | | n = *1,990* | | n = *257* | |
| | n | % | n | % | n | % |
| Regular medication | 1,582 | 52.3 | 1,088 | 54.7 | 117 | 45.5 |
| Cardiovascular medication | 1,051 | 34.8 | 729 | 36.6 | 85 | 33.1 |
| Medication affecting blood clotting and anemia | 651 | 21.5 | 436 | 21.9 | 58 | 22.6 |
| Central nervous system medication | 870 | 28.8 | 612 | 30.8 | 55 | 21.4 |
| Antimicrobial medication | 73 | 2.4 | 46 | 2.3 | 7 | 2.7 |
| Analgesic medication | 352 | 11.6 | 243 | 12.2 | 26 | 10.1 |
| Pulmonary medication | 200 | 6.6 | 134 | 6.7 | 14 | 5.4 |
| Gastrointestinal medication | 398 | 13.2 | 275 | 13.8 | 33 | 12.8 |
| Hormones and contraceptives | 297 | 9.8 | 203 | 10.2 | 16 | 6.2 |
| Sexual and urinary organ medication | 157 | 5.2 | 105 | 5.3 | 17 | 6.6 |
| Diabetes medication | 258 | 8.5 | 171 | 8.6 | 22 | 8.6 |
| Cancer medication; immunosystem modulators | 47 | 1.6 | 33 | 1.7 | 3 | 1.2 |
| Bone tissue medication | 47 | 1.6 | 36 | 1.8 | 2 | 0.8 |
| Dermatological medication | 18 | 0.6 | 14 | 0.7 | 1 | 0.4 |
| Ophtalmological medication | 81 | 2.7 | 57 | 2.9 | 2 | 0.8 |
| Otological medication | 0 | 0 | 0 | 0 | 0 | 0 |
| Muscle relaxants | 4 | 0.1 | 3 | 0.2 | 0 | 0 |
| Vitamins and minerals | 378 | 12.5 | 267 | 13.4 | 26 | 10.1 |

medication (45.5%-54.7%). The most common medication was cardiovascular medication, used by more than one in three patients (33.1%-36.9%). Medication affecting blood clotting and anemia was used by more than one-fifth of patients (21.5%-22.6%). At least one in four patients (21.4%-30.8%) were using central nervous system medication.

The effect of applying exclusion criteria on the sample size in the screening process is shown in Table 3. The number of patients with co-occurring exclusion criteria is presented in Table 4 (i.e., the frequency and percentage of participants who met more than one exclusion criteria). Only 2.5% of the screened patients met all the criteria. Of all the patients screened ($n = 3023$), 1990 (65.2%) fulfilled the mTBI criteria, the rest having a moderate or severe TBI ($n = 257$, 8.5%) or a head trauma without clear signs of brain injury ($n = 776$, 25.7%). Patients with mTBI were divided in two groups:

Table 3. Application of Exclusion Criteria to the Study Cohort

| *Exclusion criterion* | n | % |
|---|---|---|
| Not a mild TBI | 1,033 | 34.2 |
| Older than 60 years | 1,378 | 45.6 |
| Younger than 18 years | 185 | 6.1 |
| Psychiatric Problem | 915 | 30.3 |
| Neurological Problem | 770 | 25.5 |
| Psychoactive Medication | 835 | 27.6 |
| >72 Hours from Injury to Arrival in ED | 506 | 16.7 |
| Past TBI | 311 | 10.3 |
| Neurosurgery | 168 | 5.6 |
| Not a Resident of the Hospital District | 166 | 5.5 |
| First Language Not Finnish | 72 | 2.4 |
| Problems with Hearing or Vision | 47 | 1.6 |
| Declined to Participate | 105 | 3.5 |
| **Total Enrolled (Out of 3,023) After Applying the Above Criteria** | **75** | **2.5** |

excluded mTBI sample ($n = 1,915$) and final mTBI sample ($n = 75$). The final mTBI sample consisted of patients who met all the study criteria after applying the inclusion and exclusion criteria listed in Table 3. Age, not a mTBI premorbid neurological problems, and premorbid psychiatric problems were the three most common reasons for exclusion. More than one in four had neurological ($n = 770$; 25.5%) or psychiatric ($n = 915$; 30.3%) disorders, and over half had either of these or both ($n = 1066$; 55.7%) in the excluded mTBI group.

Statistical comparisons were performed between those with mTBIs who were included versus those who were excluded in relation to injury-related and clinical variables. The comparison between these two samples is presented in Table 5.

## Discussion

Researchers and clinicians commonly consider TBI a ''heterogeneous'' injury, condition, or disease. This is because there are many different mechanisms of injury and parts of the brain that can be differentially damaged. Of course, a large part of the heterogeneity also is attributable to the heterogeneity of people being injured. In 1937, Symonds[24] wrote, ''the symptom picture depends not only upon the kind of injury, but upon the kind of brain'' and ''a good deal, of course, will depend, not only on what kind of a person he was before the injury, but upon the situation he has to meet.'' When we consider the entire population of adults who sustain head trauma, as illustrated by the large cohort presented in this study, there is tremendous variability in pre-existing health problems—and these pre-existing problems could have an influence on acute, subacute, and post-acute outcome assessment measures, recovery time, and long-term symptoms and problems.

Table 1 illustrates that most of the patients sustaining a head trauma are experiencing a variety of pre-injury diseases and disorders and are taking regular medication. The most common comorbid health problems were circulatory, neurological, psychiatric, and endocrine disorders. The most common medication was

TABLE 4. COEXISTENCE OF THE INCLUSION AND EXCLUSION CRITERIA *N* (%)

| | *Not a mild TBI* | *Age criteria not met* | *Psychiatric Problem* | *Neurological Problem* | *Psychoactive Medication* | *Past TBI* | *Not a Resident of the Hospital District* | *First Language Not Finnish* | *> 72 Hours from Injury to Arrival in ED* | *Neurosurgery* | *Problems with Hearing or Vision* | *Declined to Participate* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Not a mild TBI | 1,033 (34.2) | 460 (15.2) | 263 (8.7) | 212 (7.0) | 247 (8.2) | 80 (2.6) | 72 (2.4) | 22 (0.7) | 144 (4.8) | 98 (3.2) | 17 (0.6) | 7 (0.2) |
| Age criteria not met | | 1,552 (51.3) | 295 (9.8) | 605 (20.0) | 505 (16.7) | 97 (3.2) | 54 (1.8) | 8 (0.3) | 274 (9.1) | 79 (2.6) | 38 (1.3) | 0 |
| Psychiatric Problem | | | 916 (30.3) | 194 (6.4) | 415 (13.7) | 155 (5.1) | 22 (0.7) | 8 (0.3) | 130 (4.3) | 63 (2.1) | 8 (0.3) | 1 (0.03) |
| Neurological Problem | | | | 771 (25.5) | 403 (13.3) | 89 (2.9) | 17 (0.6) | 3 (0.1) | 134 (4.4) | 66 (2.2) | 14 (0.5) | 0 |
| Psychoactive Medication | | | | | 835 (27.6) | 89 (2.9) | 13 (0.4) | 3 (0.1) | 167 (5.5) | 50 (1.7) | 18 (0.6) | 1 (0.03) |
| Past TBI | | | | | | 311 (10.3) | 5 (0.2) | 6 (0.2) | 27 (0.9) | 50 (1.7) | 1 (0.03) | 2 (0.07) |
| Not a Resident of the Hospital District | | | | | | | 166 (5.5) | 12 (0.4) | 9 (0.3) | 15 (0.5) | 0 | 0 |
| First Language Not Finnish | | | | | | | | 72 (2.4) | 13 (0.4) | 2 (0.1) | 1 (0.03) | 0 |
| > 72 Hours from Injury to Arrival in ED | | | | | | | | | 506 (16.7) | 22 (0.7) | 9 (0.3) | 0 |
| Neurosurgery | | | | | | | | | | 168 (5.6) | 3 (0.1) | 0 |
| Problems with Hearing or Vision | | | | | | | | | | | 47 (1.6) | 0 |
| Declined to Participate | | | | | | | | | | | | 105 (3.5) |

cardiovascular medication, followed by medication affecting the central nervous system and blood clotting and anemia. Almost half of the screened patients were older than 60. Considering multiple health problems in combination that could have an influence on cognitive, psychological, or neuroimaging outcomes (i.e., mental and behavioral disorders; diseases of the nervous system; diseases of the circulatory system; and endocrine, nutritional, or metabolic diseases), two out of three people in the cohort had one or more of these conditions before their injury.

Some of these findings are well established in the literature. Alcohol intoxication is a common risk factor for sustaining a TBI.[17,25] Acute intoxication makes the initial assessment of the injury more difficult and can lead to an over- or underestimation of injury severity in some clinical situations. Alcohol abuse predicts unfavorable psychiatric outcomes, such as depression.[26–28] Alcohol misuse may lead to a ''vicious cycle,'' in which high-risk use may predispose to depression and depression may lead to alcohol relapse.[29]

A variety of mental disorders are common after TBI but their causality remains poorly understood. There are relatively few studies about the prevalence of mental disorders both before and after the TBI.[30,31] Sareen and colleagues highlighted history of mental disorder as a risk factor for mental health problems post-injury.[32] Post-TBI anxiety and depression is associated with worse outcome across the domains of occupation, interpersonal relationships, and living skills.[16] There is a high risk of having a psychiatric disorder after TBI when the same disorder was present prior to injury.[33] Bombardier and colleagues also highlighted that prior depression is a risk factor for post-injury depression.[28]

Older adults represent an increasingly important patient group, mostly as a result of fall-related injuries. Due to the frailty of geriatric patients, those who sustain a mild brain injury (Glasgow Coma Scale score of 13–15) tend to have more intracranial lesions and more often require neurosurgical interventions than younger people.[34] The hospitalization rate for adults ages 65 and older is more than double, compared with younger adults.[35] Predicting outcomes and providing care in the older population with TBI is challenging.[12,20]

A recent study by Gardner and colleagues[36] suggested that older adults who sustain a TBI, including an mTBI, are at significantly increased risk of developing dementia—even after controlling for known comorbidities. In our study, the rate of comorbidities was much higher than in the study by Gardner and colleagues, possibly because they relied on a database in which diagnoses were recorded, whereas in the present study a chart review was conducted for each patient. The present study shows that a large percentage of patients who sustain a head trauma necessitating CT scanning have pre-existing neurological, cardiovascular, and other diseases associated with increased risk for dementia. This is a possible confounding factor if patients with TBI are compared with healthy controls, who may differ in many ways from patients prone to TBI.[37]

Our research team, over several years, has sought to enroll a ''pure'' healthy group of adults who sustained an mTBI and study their acute[14,38,39] and post-acute outcome. The strict study criteria excluded basically all people who form the vast majority of TBI patients seen in clinical practice. Moreover, many of these excluded patients are at increased risk for poor outcome. If we try to focus purely on the consequences of mTBI and exclude patients with pre-existing conditions, we end up studying a small, non-representative subgroup of patients who do not have known risk factors for poor outcome. This approach has value if we want to study the

Table 5. Comparison between the Enrolled and Excluded Samples

| | *Enrolled MTBI* n = *75* | | *Excluded MTBI* n = *1,915* | | |
|---|---|---|---|---|---|
| | *Median (IQR)* | | *Median (IQR)* | | p-*value* |
| **Age, years** | 36.6 (27.5-47.6) | | 60.1 (35.9-78.4) | | <0.001 |
| **Time intervals, hours** | | | | | |
| From injury to ED admission | 1.6 (1.0-3.5) | | 4.8 (1.4-46.5) | | <0.001 |
| From injury to primary head CT | 3.0 (2.0-5.8) | | 6.8 (2.8-48.8) | | <0.001 |
| From ED admission to primary head CT | 1.0 (0.6-1.6) | | 1.1 (0.6-1.9) | | NS |
| From primary head CT to hospital discharge | 7.6 (2.2-37.3) | | 6.6 (2.3-28.2) | | |
| Hospital stay | 9.3 (3.7-38.7) | | 9.0 (3.9-30.6) | | |
| | **n** | **%** | **n** | **%** | |
| **Gender** | | | | | NS |
| Men | 45 | 60 | 1,086 | 56.7 | |
| Women | 30 | 40 | 829 | 43.3 | |
| **CT within 24 hours post-injury** | 68 | 90.7 | 1,287 | 67.2 | <0.001 |
| **CT within 48 hours post-injury** | 72 | 96.0 | 1,431 | 74.7 | <0.001 |
| **Mechanism of injury** | | | | | |
| Ground-level falls | 10 | 13.3 | 1,077 | 56.2 | <0.001 |
| Falls from a height | 12 | 16.0 | 204 | 10.7 | NS |
| Car accidents | 12 | 16.0 | 132 | 6.9 | 0.003 |
| Violence-related injuries | 5 | 6.7 | 158 | 8.3 | NS |
| Other | 7 | 9.3 | 123 | 6.4 | NS |
| Bicycle accidents | 11 | 14.7 | 85 | 4.4 | <0.001 |
| Unknown | 0 | 0 | 45 | 2.3 | NS |
| Sports | 13 | 17.3 | 40 | 2.1 | <0.001 |
| Motorcycle accidents | 5 | 6.7 | 29 | 1.5 | 0.001 |
| Traffic accidents as an pedestrian | 0 | 0 | 22 | 1.1 | NS |
| Moped accidents | 0 | 0 | 22 | 1.1 | |
| **Location of direct head impact** | | | | | <0.001 |
| Maxillar | 12 | 16.0 | 254 | 13.3 | NS |
| Mandibular | 11 | 14.7 | 56 | 2.9 | <0.001 |
| Right frontal | 7 | 9.3 | 165 | 8.6 | NS |
| Left frontal | 8 | 10.7 | 160 | 8.4 | |
| Right temporal | 2 | 2.7 | 150 | 7.8 | |
| Left temporal | 9 | 12.0 | 124 | 6.5 | |
| Right parietal | 5 | 6.7 | 70 | 3.7 | |
| Left parietal | 7 | 9.3 | 70 | 3.7 | 0.012 |
| Right occipital | 15 | 20.0 | 382 | 19.9 | NS |
| Left occipital | 11 | 14.7 | 375 | 19.6 | |
| Unknown | 21 | 28.0 | 721 | 37.7 | NS |
| **Location of follow-up treatment** | | | | | <0.001 |
| Home | 52 | 69.3 | 765 | 39.9 | |
| Health center | 1 | 1.3 | 488 | 25.5 | |
| Other health care facility | 0 | 0 | 68 | 3.6 | |
| Hospital | 22 | 29.3 | 577 | 30.1 | |
| Death | 0 | 0 | 17 | 0.9 | |
| **Alcohol intoxication** | | | | | <0.001 |
| Yes | 10 | 13.3 | 510 | 26.6 | |
| No | 65 | 86.7 | 761 | 39.7 | |
| Unknown | 0 | 0 | 644 | 33.6 | |
| **LOC** | | | | | <0.001 |
| Yes | 28 | 37.3 | 434 | 22.7 | |
| No | 21 | 28.0 | 363 | 19.0 | |
| Not witnessed/Unknown | 26 | 34.7 | 1,118 | 58.4 | |
| **Amnesia** | | | | | <0.001 |
| Yes | 59 | 78.7 | 578 | 30.2 | |
| No | 16 | 21.3 | 422 | 22.0 | |
| Unknown | 0 | 0 | 915 | 47.8 | |

(*continued*)

TABLE 5. (CONTINUED)

| | *Enrolled MTBI* n = *75* | | *Excluded MTBI* n = *1,915* | | |
|---|---|---|---|---|---|
| | *Median (IQR)* | | *Median (IQR)* | | p-*value* |
| **Glasgow Coma Scale** | | | | | < 0.001 |
| 15 points | 63 | 84.0 | 1,049 | 54.8 | |
| 14 points | 3 | 4.0 | 83 | 4.3 | |
| 13 points | 0 | 0 | 25 | 1.3 | |
| N/A | 9 | 12.0 | 745 | 38.9 | |
| **Computed Tomography (CT)** | | | | | |
| CT-Positive, Trauma-Related | 7 | 9.3 | 383 | 20.0 | 0.022 |
| CT-Positive, Trauma-Related, No Pre-Existing Findings | 7 | 9.3 | 238 | 12.4 | NS |
| CT-Positive, Pre-Existing Findings, No Trauma-Related Findings | 0 | 0 | 572 | 29.9 | < 0.001 |
| **Diagnosed Disease / Medical Condition** | | | | | |
| Diseases of the circulatory system | 8 | 10.7 | 800 | 41.8 | < 0.001 |
| Diseases of the respiratory system | 8 | 10.7 | 175 | 9.2 | NS |
| Mental and behavioural disorders | 0 | 0 | 548 | 28.6 | < 0.001 |
| Diseases of the nervous system | 3 | 4.0 | 499 | 26.1 | < 0.001 |
| Endocrine, nutritional and metabolic diseases | 7 | 9.3 | 374 | 19.5 | 0.01 |
| Diseases of the digestive system | 2 | 2.7 | 140 | 7.1 | 0.045 |
| Diseases of the genitourinary system | 1 | 1.3 | 117 | 6.1 | 0.034 |
| Diseases of the musculoskeletal system and connective tissue | 7 | 9.3 | 240 | 12.5 | |
| Certain infectious and parasitic diseases | 0 | 0 | 56 | 2.9 | |
| Neoplasms | 1 | 1.3 | 112 | 5.8 | 0.038 |
| Diseases of the blood | 0 | 0 | 44 | 2.3 | |
| Diseases of the eye and adnexa | 0 | 0 | 85 | 4.5 | 0.027 |
| Diseases of the ear and mastoid process | 1 | 1.3 | 24 | 1.3 | |
| Diseases of the skin and subcutaneous tissue | 0 | 0 | 48 | 2.5 | |
| Pregnancy, childbirth and the puerperium | 0 | 0 | 0 | 0 | N/A |
| Certain conditions originating in the perinatal period | 0 | 0 | 0 | 0 | |
| Congenital malformations, deformations, and chromosomal abnormalities | 1 | 1.3 | 9 | 0.5 | NS |
| **Medications** | | | | | |
| Cardiovascular medication | 8 | 10.7 | 721 | 37.7 | < 0.001 |
| Medication affecting blood clotting and anemia | 0 | 0 | 436 | 22.8 | < 0.001 |
| Central nervous system medication | 0 | 0 | 612 | 32.0 | < 0.001 |
| Microbe medication | 0 | 0 | 46 | 2.4 | < 0.001 |
| Analgesic medication | 1 | 1.3 | 242 | 12.6 | < 0.001 |
| Pulmonary medication | 4 | 4.0 | 131 | 6.8 | < 0.001 |
| Gastrointestinal medication | 0 | 0 | 275 | 14.4 | < 0.001 |
| Hormones and contraceptives | 7 | 9.3 | 196 | 10.2 | < 0.001 |
| Sexual and urinary organ medication | 0 | 0 | 105 | 5.5 | < 0.001 |
| Diabetes medication | 1 | 1.3 | 170 | 8.9 | < 0.001 |
| Cancer medication, immunosystem modulators | 1 | 1.3 | 32 | 1.7 | < 0.001 |
| Bone tissue medication | 0 | 0 | 36 | 1.9 | < 0.001 |
| Dermatological medication | 0 | 0 | 14 | 0.7 | < 0.001 |
| Ophtalmological medication | 0 | 0 | 57 | 3.0 | < 0.001 |
| Otological medication | 0 | 0 | 0 | 0 | N/A |
| Muscle relaxants | 0 | 0 | 3 | 0.2 | < 0.001 |
| Vitamins and minerals | 2 | 2.7 | 265 | 13.8 | < 0.001 |

NS = Not significant; N/A = Not available

consequences of mTBI sensu stricto, but the limitations caused by selection bias have to be considered when drawing clinical conclusions. We have learned a tremendous amount about outcome from mTBI over the past few decades, and much of that knowledge was possible given study designs that enrolled people with specific characteristics and excluded people with certain pre-existing conditions. However, the increasing recognition of the complexity of outcome from mTBI and of the limitations of previous research have led to the development of common data elements, multicenter studies, and large-scale national and international data-sharing collaborations.[40–42]

Indeed, the results of this study have important implications for researchers and clinicians who work with those who have sustained mTBIs. It is well established that adults who sustain TBIs of all severities are at increased risk for depression[27,28] but some of that risk might be conferred from genetic, pre-existing health and mental health factors, or post-injury health factors—and it can be difficult for researchers to carefully and systematically document the broad range of factors that might be related to specific outcomes. In regards to cognitive outcomes, researchers have reported that many factors are associated with worse performance on cognitive testing, such as (ADHD,[43,44] learning disabilities,[45]

depression,[46] hypertension,[47] diabetes,[48] obesity,[49] insomnia,[50] sleep apnea,[51] alcohol abuse,[52] drug abuse,[53,54] burden of white matter hyperintensities,[55] and pre-clinical Alzheimer's disease.[56] Similarly, there is tremendous interest in studying the microstructural architecture of white matter following mTBI using diffusion tensor imaging.[57–59] In this context, it is important to appreciate that white matter changes have been documented in association with developmental conditions, such as ADHD[60] and learning disabilities,[61] depression,[62] hypertension,[63] isolated nonspecific white matter hyperintensities,[64] diabetes,[65] obesity,[66] aging,[67] smoking,[68] alcohol abuse,[69] drug abuse,[53,70–72] and even in children and adolescents who were exposed to drugs prenatally.[73–75] The heterogeneity of the pre-injury characteristics of people who sustain mTBIs reinforces the importance of the biopsychosocial model[76] for conceptualizing outcome following mTBI.

There are some limitations in this study. Clinical variables of the excluded patients were mainly collected retrospectively from hospital records and hence some relevant information was missing. This may have influenced both the number of different criteria and the significance of the comparisons of clinical TBI signs. We do not have more detailed information of the diseases and the medications of the excluded patients, which makes it difficult to compare the characteristics of our study samples in greater detail. It was not possible to control the heterogeneity of decision-making on CT scanning in the ED by the on-call ED physician. The Scandinavian guidelines were used in the ED but most likely these were not followed consistently. Due to this variation in the imaging, the sample includes patients that would not have needed a CT scan according to the guideline, and we might have missed some patients who should have undergone a CT scan but were discharged without imaging (although the results suggest that a fairly liberal use of CT scanning was present over the study period). Finally, the study examined only patients with mTBI treated in a hospital, and we have no estimates available for patients treated outside the hospital. This study was conducted in a publicly-funded health care system where in practice, all mTBI patients who are considered to need an acute head CT were evaluated at the study hospital.

Most of the mTBI studies have patient samples that do not represent the majority of the population who sustain an mTBI. This study shows that mTBI patients are a heterogeneous group and there is a need for research on various subgroups (e.g., older adults and patients who have pre-injury neurological or mental disorders). Targeting specific subgroups to address specific research questions is feasible. For example, it would be interesting to enroll subgroups prospectively who have pre-existing mental health, substance abuse, or neurological problems to determine if early intervention has positive effects on symptom and functional outcome within the first three months following injury, examine the extent to which evidence-informed symptomatic treatment facilitates positive outcomes, or to document recovery trajectories and treatment needs in these at-risk patients. Instead of excluding patients with pre-existing health problems, we can advance knowledge and improve care following mTBI by explicitly studying these groups.

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The authors alone are responsible for the content and writing of the paper. GLI has been reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or presenting research relating to mild TBI and sport-related concussion at meetings, scientific conferences, and symposiums. He has a clinical and consulting practice in forensic neuropsychology involving individuals who have sustained mild TBIs. He is a co-investigator, collaborator, or consultant on grants relating to mild TBI. For the remaining authors, no competing financial interests exist.

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# Characterizing the Type and Location of Intracranial Abnormalities in Mild Traumatic Brain Injury

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## Abstract

*Objective:* The incidence of intracranial abnormalities after mild traumatic brain injury (TBI) varies widely across studies. This study describes the characteristics of intracranial abnormalities (acute/pre-existing) of a large representive head injury sample CT-imaged in an emergency department (ED).

*Methods:* CT scans were systematically analyzed/coded in the TBI Common Data Elements framework. Logistic regression modeling was used to quantify risk factors for traumatic intracranial abnormalities in mild TBIs. This cohort included all patients who were treated at the ED of the Tampere University Hospital (2010-2012) and underwent head CT after a suspected TBI (N=3,023), including 2,766 with mild TBI and a reference group with moderate-severe TBI.

*Results:* The most common traumatic lesions on CT in mild TBIs and moderate-severe TBIs were subdural hematoma, subarachnoid hemorrhage, and contusions. Every sixth (16.1%) mild TBI patient had an intracranial lesion compared to 5/6 (85.6%) in the moderate-severe TBI group. The distribution of different types of acute traumatic lesions was similar among mild and moderate-severe TBIs. Pre-existing CT findings were more common among those with mild TBIs compared to those with moderate-severe TBIs. Having a past traumatic lesion was associated with increased risk for an acute traumatic lesion, but neurodegenerative and ischemic lesions were not. Lower Glasgow Coma Scale, male sex, older age, falls, and chronic alcohol abuse were associated with higher risk of acute intracranial lesion in mild TBI.

*Conclusions:* These findings underscore the heterogeneity of neuropathology associated within the "mild" TBI classifcation. Pre-existing brain lesions are common in the MTBI patients and the rate of pre-existing lesions increases with age. Acute traumatic lesions are fairly common in MTBI; every sixth patient had a positive CT scan. Older adults, especially males, who fall represent a susceptible group for acute CT-positive TBI.

## Introduction

Mild traumatic brain injuries (MTBI) are common in sports,[9] daily life,[15] and military service.[18] The "mild" classification is delineated from more severe forms of TBI by a loss of consciousness (LOC) duration of 30 minutes or less, Glasgow Coma Scale (GCS) of at least 13, and a duration of post-traumatic amnesia (PTA) not exceeding 24 hours. MTBIs occur on a broad spectrum—from extremely mild injuries in sports in which an athlete appears to recover within hours or days, to a high velocity injury in a motor vehicle accident that abuts the moderate TBI severity range. The MTBI classification includes patients with a trauma-related macroscopic intracranial abnormality on a day-of-injury computed tomography (CT), such as an epidural hematoma, subdural hematoma, or contusion, as long as the operational criteria for "mild" injury are met based on LOC, GCS, and PTA. This subgroup with acute traumatic intracranial abnormalities has been termed a complicated MTBI.[63] Patients with complicated MTBIs, as a group, are more likely to have early cognitive deficits[2,24,29,63] and worse medium[62,63] and long-term[58] functional outcome. However, there are studies that have not found worse outcomes.[25,31,37,43]

The incidence of acute CT-positive intracranial lesions in MTBI varies widely between 4.7% and 38.9% across individual studies.[23,54] The wide range in incidence is partially explained by varying enrollment of patients with lower GCS scores, because GCS scores below 15 are associated with an increased risk for intracranial injury.[42] For those with GCS scores in the mild range (i.e., 13-15), each one point drop in GCS score is associated with a substantially increased rate of intracranial abnormalities.[61] Epidural hematomas, focal contusions, subarachnoid hemorrhages, and subdural hematomas are the most common CT-positive lesions seen in in moderate to severe TBI patients.[36,45] The frequency is lower but the distribution appears similar for MTBI.[17,55] In those who have sustained MTBIs, only about 1% of lesions require acute neurosurgery.[21,52,55] Certain patient and injury factors have been associated with increased risk of a trauma-related intracranial

abnormalities after MTBI, including older age,[47] pre-existing medical conditions such coagulopathy,[26,40] alcohol intoxication at the time of injury,[12,17] lower GCS (i.e., 13 or 14 vs. 15),[61] and dangerous causes of injury such as motor vehicle accidents and falls from a height.[55] The effects of other characteristics such as neurodegenerative diseases, brain atrophy, or chronic alcohol abuse on risk for traumatic intracranial lesions, are not well known. As well, the relative strength of association of characteristics such as age and cause of injury with CT findings is not well understood.

To systematically document and control for heterogeneity in TBI clinical trials neuroimaging Common Data Elements (CDE) were developed for TBI.[10,16] The motivation for creating a CDE database is to enable the eventual characterization of the natural history and predictive factors in TBI. The structure of a CDE set for neuroimaging has implications for how patients entering clinical trials will be classified, stratified, and treated. To our knowledge, no study has described in detail the intracranial abnormalities after MTBI according to the CDEs.

The primary aim of this study was to describe the type and location of intracranial abnormalities (both acute and pre-existing lesions) in a large generalizable inception cohort (N=3,023) of patients who sustained head trauma and underwent CT in an emergency department, providing incidences rates for the TBI neuroimaging CDEs. Secondary aims were to (i) compare and contrast the CT abnormalities in MTBI versus moderate to severe TBI, (ii) investigate the association between pre-existing and acute CT lesions, and (iii) investigate the impact of common pre-injury factors (such as age and alcohol abuse) on the incidence of acute intracranial lesions.

## Methods

The patient pool for this study included all consecutive patients who were treated at the ED of the Tampere University Hospital between August 2010 and July 2012 and who underwent head CT after a suspected TBI (N=3,023; age range=0.3-103.8 years). The ED provides health services for a joint municipal authority of 22 municipalities (both urban and rural), the catchment area being approximately 470,000 residents. The Tampere University Hospital is the second largest trauma center in Finland and the only neurosurgical referral center in the area. The ED of Tampere University Hospital treats approximately 3,000 head injury patients annually. This number includes everything from a bump to the head to severe surgically-treated TBI. The approximate number of head injury patients treated during the data collection period was 6,000. Ethics approval for the study was obtained from the Ethics Committee of Pirkanmaa Hospital District, Tampere, Finland (code: R10027).

The data collection was extracted retrospectively from hospital records by the study authors. Participant-related data included age, sex, substance abuse, and diagnosed diseases. The pre-existing and comorbid conditions were extracted from the hospital records related to the index injury and all available prior medical history from the records; no additional diagnostic testing was performed. Chronic alcohol abuse was defined according to the International Classification of Diseases, Tenth Revision, codes F10.1 and F10.2. Injury-related variables included time of injury, time of arrival to the ED, cause of injury, and alcohol (breathalyzer and/or blood alcohol level) and/or narcotics intoxication at the time of injury. The cause of injury was categorized. Clinical variables relating to TBI included eye-witnessed LOC, seizures, disorientation, PTA, and focal neurological deficits. The on-call ED physician identified amnesia using an open interview regarding pre- and post-injury events.

Only the presence or absence of amnesia was coded; the duration of amnesia was usually not noted in the records. No structured forms or standardized measures for amnesia were used.

We used the WHO definition of MTBI.[3] Based on the chart review, we grouped the patients in three categories by their injury severity: (i) patients with head injury who were triaged to CT-head but had missing data in their medical records relating to TBI severity indicators (these cases are called "suspected MTBI" in the following text), (ii) patients that met WHO criteria for MTBI based on the details documented in their medical records ("confirmed MTBI"), and (iii) moderate to severe TBI (more severe TBI than defined by the WHO criteria, i.e., GCS <13, LOC > 30 min, or PTA > 24 hours). When the chart review revealed evidence that GCS was likely lowered by non-brain injury factors (n=92), TBI severity classification was made on the basis of LOC and PTA. This is consistent with WHO criteria which states: "these manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries".[19] GCS obtained 30 minutes post-injury or upon presentation to the ED (whichever came later) was used in the present analyses.

In the ED, a non-contrast head CT was performed with a 64-row CT scanner (GE, Lightspeed VCT, WI, USA) for all consecutive patients with a head injury. Referral criteria for acute head CT were based on the 2000 Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries.[22] Head CT was performed in the ED within 72 hours of injury. All CT scans were analyzed and systematically coded by the two neuroradiologists (A.B. and A.K.) using a structured and detailed case report form designed for this study. CT findings were defined as acute or pre-existing. Acute lesions included subdural hemorrhage and effusion, epidural hemorrhage and effusion, diffuse axonal injury (DAI) lesions, edema, compression of the cerebrospinal fluid spaces, midline shift,

contusions, hydrocephalus, pneumocephalus, skull and facial bone fractures, subarachnoid hemorrhage, nontraumatic intracranial hemorrhage, and acute ischemia. Pre-existing findings included ischemic lesions, post-traumatic lesions, microangiopathy/small vessel ischemic disease, general atrophy, and intracranial tumors. Pre-existing small vessel disease was considered if either periventricular or subcortical patchy low density areas in cerebral white matter were found and compared with normal brain parenchyma with no mass effect. The study data was collected before the CDEs for TBI imaging were established. However, all CDEs possible with non-contrast structural CT scan were included.[16]

MTBI and moderate to severe TBI groups, as well as subgroups with versus without acute intracranial abnormalities were compared with $\chi^2$ for proportions and t tests for group mean differences. Unconditional logistic regression modeling was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of acute intracranial abnormalities while controlling for multiple confounders (demographic, clinical variables, and pre-existing imaging features).

## Results

Demographic and clinical characteristics of the injury severity groups are presented in Table 1. The rates of trauma-related intracranial abnormalities were 11.6%, 16.1%, and 85.6% in the suspected and confirmed MTBI group, confirmed MTBI subgroup, and moderate-severe TBI group, respectively. All of the acute lesions in the "suspected and confirmed MTBI" group are from patients in the "confirmed MTBI" group. Within the suspected and confirmed MTBI group, the rates of those with complicated MTBIs stratified by GCS scores were as follows: 15=10.1%, 14=36.1%, 13=48.1% and in those whose GCS was not available=11.5%. Within the confirmed MTBI subgroup, the rates of those with complicated MTBIs stratified by GCS scores were as follows: 15=14.2%, 14=40.7%, and 13=52.0% and in those whose GCS was not available=15.2%. In the total sample, the rates of traumatic intracranial abnormalities, stratifed by time between injury and CT scanning, were as follows: 0-2 hours (n=158)=29.3%, 3-6 hours (n=129)=23.9%, 7-11 hours (n=58)=10.7%, 12-23 hours (n=49)=9.1%, 24-47 hours (n=37)=6.9%, and 48+ hours (n=109)=20.2%.

Table 1. Characteristics of the study cohort.

| | **Suspected or Confirmed MTBI** | | **Confirmed MTBI** | | **Moderate-Severe TBI** | |
|---|---|---|---|---|---|---|
| | **(n=2,766)** | | **(n=1,990)** | | **(n=257)** | |
| **Variable** | **Median (IQR)** | | **Median (IQR)** | | **Median (IQR)** | |
| Age, years | 56.4 (34.2-77.1) | | 58.4 (34.7-77.8) | | 57.5 (40.0-74.9) | |
| Time intervals, hours | | | | | | |
| Injury to ED admission | 4.5 (1.4-45.0) | | 4.5 (1.4-40.4) | | 2.5 (1.0-8.9) | |
| Injury to head CT | 6.5 (2.6-47.7) | | 6.5 (2.6-44.8) | | 4.3 (1.8-11.2) | |
| ED admission to head CT | 1.0 (0.6-1.8) | | 1.0 (0.6-1.9) | | 0.7 (0.4-1.2) | |
| Head CT to discharge | 6.0 (2.2-27.6) | | 6.6 (2.3-28.4) | | 88.1 (19.9-196.1) | |
| Hospital stay | 8.2 (3.8-29.1) | | 9.0 (3.9-31.2) | | 89.5 (22.1-197.6) | |
| Gender | n | % | n | % | n | % |
| Male | 1,542 | 55.1 | 1,131 | 56.8 | 181 | 70.4 |
| Female | 1,242 | 44.9 | 859 | 43.2 | 76 | 29.6 |
| CT within 24 hours | 1,865 | 67.4 | 1,355 | 68.1 | 218 | 84.8 |
| CT within 48 hours | 2,076 | 75.1 | 1,503 | 75.5 | 235 | 91.4 |
| Cause of injury | | | | | | |
| Motor vehicle accident | 275 | 9.9 | 200 | 10.1 | 23 | 8.9 |
| Traffic accident as pedestrian or bicyclist | 145 | 5.2 | 118 | 5.9 | 22 | 8.6 |

| | Suspected or Confirmed MTBI | | Confirmed MTBI | | Moderate-Severe TBI | |
|---|---|---|---|---|---|---|
| Falls from a height | 304 | 11.0 | 216 | 10.9 | 33 | 12.8 |
| Ground-level falls | 1,454 | 52.6 | 1,087 | 54.6 | 130 | 50.6 |
| Other | 535 | 19.3 | 324 | 16.3 | 29 | 11.3 |
| Follow-up treatment | | | | | | |
| Home | 1,215 | 43.9 | 813 | 41.3 | 28 | 7.6 |
| Health center | 628 | 22.7 | 489 | 24.6 | 28 | 10.9 |
| Other health care facility | 87 | 3.1 | 68 | 3.4 | 4 | 1.6 |
| Hospital | 809 | 29.2 | 599 | 30.1 | 172 | 66.9 |
| Death | 27 | 1.0 | 17 | 0.9 | 41 | 16.0 |
| Alcohol intoxication | | | | | | |
| Yes | 660 | 23.9 | 520 | 26.1 | 81 | 31.5 |
| No | 1,151 | 41.6 | 826 | 41.5 | 92 | 35.8 |
| Unknown | 955 | 34.5 | 644 | 32.4 | 84 | 32.7 |
| Loss of consciousness | | | | | | |
| Yes | 481 | 17.4 | 462 | 23.2 | 103 | 40.1 |
| No | 764 | 27.6 | 384 | 19.3 | 25 | 9.7 |
| Not witnessed / Unknown | 1,521 | 55.0 | 1,144 | 57.5 | 129 | 50.2 |
| Amnesia | | | | | | |
| Yes | 646 | 23.4 | 637 | 32.0 | 38 | 14.8 |
| No | 916 | 33.1 | 438 | 22.0 | 16 | 6.2 |
| Unknown | 1,204 | 43.5 | 915 | 46.0 | 203 | 79.0 |
| Glasgow Coma Scale | | | | | | |
| 13-15 points | 1,682 | 60.8 | 1,223 | 61.5 | 34 | 13.2 |
| 9-12 points | 67 | 2.4 | 13 | 0.7 | 75 | 29.2 |
| 3-8 points | 25 | 0.9 | 2 | 0.1 | 83 | 32.3 |
| N/A | 992 | 35.9 | 752 | 37.8 | 65 | 25.3 |
| Computed tomography (CT) | | | | | | |
| Traumatic Intracranial Abnormality | 320 | 11.6 | 320 | 16.1 | 220 | 85.6 |
| Pre-Existing Abnormality | 941 | 34.0 | 717 | 36.0 | 44 | 17.1 |

Specific CT findings stratified by the injury severity groups are presented in Table 2. In the total MTBI group, the rates of specific abnormalities were as follows: subdural hematoma=8.4%, subarachnoid hemorrhage=5.0%, and contusion=3.9% (see Table 2). Of the 142 contusions (in 109 patients), 52.8% were frontal and 39.4% were temporal in location. Of the 495 subdural hematomas (in 232 patients), 38.8% were frontal, 21.8% were temporal, 22.0% were parietal, and only 7.5% were occipital. For comparison, in the moderate-severe TBI group, the rates of specific abnormalities were as follows: subdural hematoma=63.0%, subarachnoid hemorrhage=55.6%, and contusion=43.6% (see Table 2). Of the 150 contusions (in 112 patients), 50.0% were frontal and 40.0% were temporal in location. Of the 439 subdural hematomas (in 162 patients), 32.1% were frontal, 24.8% were temporal, 21.0% were parietal, and only 9.8% were occipital.

Table 2. Intracranial abnormalities following TBI.

| | Suspected and Confirmed Mild TBI n=2,766 | | Confirmed Mild TBI n=1,990 | | Moderate to Severe TBI n=257 | |
|---|---|---|---|---|---|---|
| **Abnormality/Location** | **f** | **%** | **f** | **%** | **f** | **%** |
| Epidural Hematoma* | 6 | 0.2 | 6 | 0.3 | 15 | 5.8 |
| Subdural Hematoma* | 232 | 8.4 | 232 | 11.7 | 162 | 63.0 |
| Frontal | 192 | 6.9 | 192 | 9.6 | 141 | 54.9 |
| Temporal | 108 | 3.9 | 108 | 5.4 | 109 | 42.4 |
| Parietal | 109 | 3.9 | 109 | 5.5 | 92 | 35.8 |
| Occipital | 37 | 1.3 | 37 | 1.9 | 43 | 16.7 |
| Cerebellar | 3 | 0.1 | 3 | 0.2 | 3 | 1.2 |
| Tentorial | 46 | 1.7 | 46 | 2.3 | 51 | 19.8 |
| Subarachnoid Hemorrhage* | 139 | 5.0 | 139 | 7.0 | 143 | 55.6 |
| Intraventricular* | 33 | 1.2 | 33 | 1.7 | 53 | 20.6 |
| Basal Cisterns | 24 | 0.9 | 24 | 1.2 | 36 | 14.0 |
| Convexity Sulci | 113 | 4.1 | 113 | 5.7 | 124 | 48.2 |
| Contusion* | 109 | 3.9 | 109 | 5.5 | 112 | 43.6 |
| Frontal | 75 | 2.7 | 75 | 3.8 | 75 | 29.2 |
| Temporal | 56 | 2.0 | 56 | 2.8 | 60 | 23.3 |
| Parietal | 6 | 0.2 | 6 | 0.3 | 3 | 1.2 |
| Occipital | 1 | 0.04 | 1 | 0.1 | 2 | 0.8 |
| Cerebellar | 2 | 0.1 | 2 | 0.1 | 8 | 3.1 |
| Brainstem | 2 | 0.1 | 2 | 0.1 | 2 | 0.8 |
| Diffuse Axonal Injury* | 5 | 0.2 | 5 | 0.3 | 9 | 3.5 |
| Cerebrospinal Fluid Space Compression* | 35 | 1.3 | 35 | 1.8 | 75 | 29.2 |
| Ventricles* | 22 | 0.8 | 22 | 1.1 | 58 | 22.6 |
| Basal Cisterns* | 5 | 0.2 | 5 | 0.3 | 41 | 16.0 |
| Convexity Sulci | 22 | 0.8 | 22 | 1.1 | 61 | 23.7 |
| Fractures | 168 | 6.1 | 142 | 7.1 | 112 | 43.6 |
| Skull Fractures* | 76 | 2.7 | 75 | 3.8 | 95 | 37.0 |
| Facial Fractures | 103 | 3.7 | 78 | 3.9 | 44 | 17.1 |
| Pneumocephalus | 10 | 0.4 | 10 | 0.5 | 20 | 7.8 |
| Hydrocephalus | 8 | 0.3 | 6 | 0.3 | 6 | 2.3 |
| Non-Traumatic Hemorrhage | 16 | 0.6 | 13 | 0.7 | 16 | 6.2 |
| Acute Ischemia* | 24 | 0.9 | 17 | 0.9 | 4 | 1.6 |
| Midline Shift* | 45 | 1.6 | 44 | 2.2 | 89 | 34.6 |
| Diffuse edema* | 2 | 0.1 | 1 | 0.1 | 15 | 5.8 |
| **Pre-Existing Abnormalities** | | | | | | |
| Pre-Existing, Post-Traumatic Lesions | 77 | 2.8 | 62 | 3.1 | 5 | 1.9 |
| Pre-Existing, Ischemic Lesions | 198 | 7.2 | 159 | 8.0 | 6 | 2.3 |
| Microangiopathy/Small Vessel Ischemic Disease | 581 | 21.0 | 441 | 22.2 | 26 | 10.1 |
| Generalized Atrophy* | 495 | 17.9 | 377 | 18.9 | 25 | 9.7 |
| Tumors | 21 | 0.8 | 17 | 0.9 | 1 | 0.4 |
| **Summary** | | | | | | |
| Any Traumatic Intracranial Abnormality | 320 | 11.6 | 320 | 16.1 | 220 | 85.6 |
| More than One Traumatic Intracranial Abnormality | 128 | 4.6 | 128 | 6.4 | 144 | 56.0 |
| Any Pre-Existing Abnormality | 941 | 34.0 | 717 | 36.0 | 44 | 17.1 |
| More than One Pre-Existing Abnormality | 518 | 18.7 | 400 | 20.1 | 27 | 10.5 |
| Any Traumatic Intracranial AND Pre-Existing Abnormality | 146 | 5.3 | 133 | 6.7 | 37 | 14.4 |
| Any Traumatic Intracranial OR Pre-Existing Abnormality | 1,212 | 43.8 | 904 | 45.2 | 227 | 88.3 |

Note: *Pathoanatomic lesions listed within the Common Data Elements.[29]

The total MTBI group includes those with a suspected or confirmed MTBI (n=2,766).

The subgroup with complicated MTBIs was older (M=66.7 years, SD=19.9) than those with

uncomplicated MTBIs (M=55.3 years, SD=24.2, $p<0.001$), and men were significantly more likely to have complicated MTBIs than women (12.8% vs. 10.1%, $\chi^2=4.99$, $p=0.026$). Within the complicated MTBI group, the mechanisms of injury were as follows: motor vehicle accident=2.2%, traffic accident as pedestrian or bicyclist=7.5%, fall from a height=10.3%, and ground-level fall=66.3%. Older adults (age 55 and older) who were injured in a ground-level fall had a greater incidence of trauma-related abnormalities than younger adults injured in a fall (17.0% vs. 5.8%, $\chi^2=85.89$, $p<0.001$). The rates of complicated MTBIs, stratified by age group, are presented in Figure 1. Rates of complicated MTBIs increased with age.

The study population included 275 patients who were less than 20 years old. Stratified by age, 27 were 0-5 years old, 24 were 6-10 years old, 82 were 11-15 years old, and 142 were 16-19 years old. Of the 275 patients under the age of 20, 19 had a traumatic lesion (6.9%), six in the 0-5 years age group (22.2%), none in the 6-10 years age group, seven in the 11-15 years age group (8.5%), and six in the 16-19 years age group (4.2%). The most common lesions were subarachnoid hemorrhages and subdural hematomas. Subarachnoid hemorrhage was found in eight patients (three in the youngest group, none in the 6-10 years old age group, one in the 10-15 years old age group, and four in the oldest age group). There were eight subdural hematomas, four in the 11-15 years old age group and four in the 16-19 years old age group. Each of the age groups had more males than females: 18 males in the 0-5 years old group, 16 males in the 6-10 years old group, 52 in the 11-15 years group, and 88 in the 16-19 years old group.

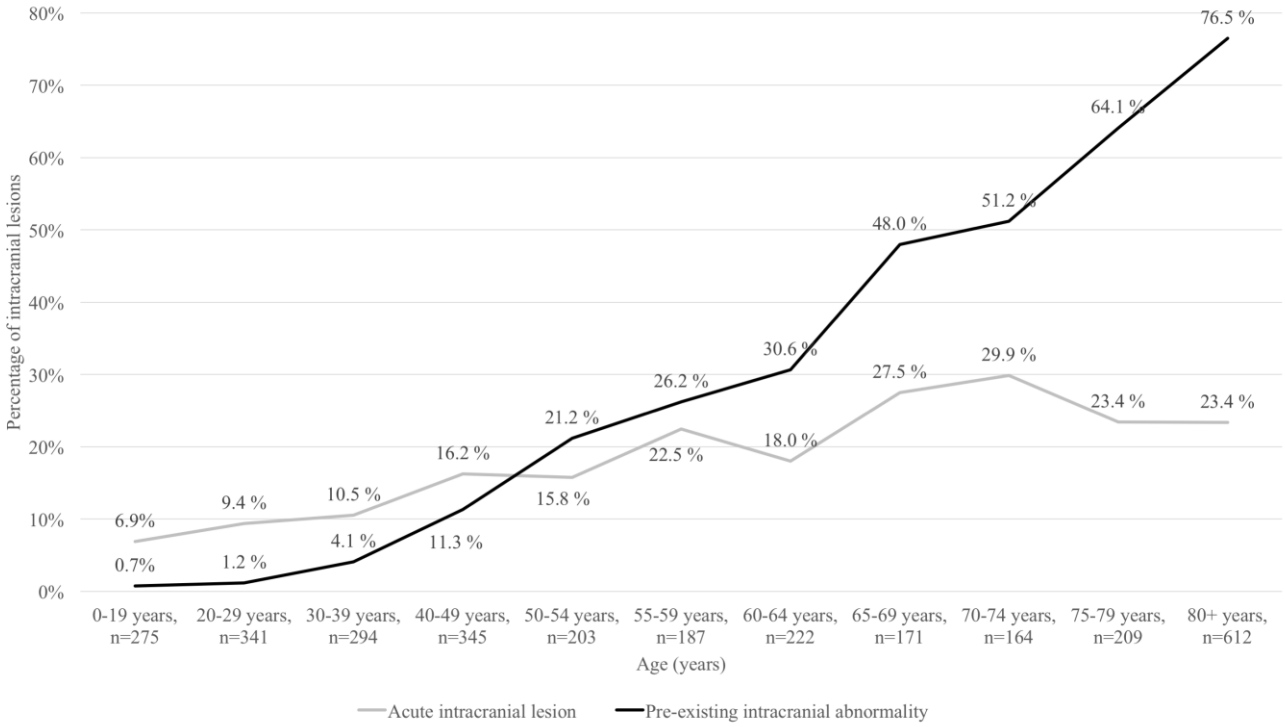


**Figure 1**. The rates of pre-existing abnormalities on CT, stratified by age group

The rates of pre-existing abnormalities on CT, stratified by age group, also are presented in Figure 1. Rates of pre-existing lesions increased dramatically with age. In the total MTBI sample, 34.0% had a pre-existing abnormality and 18.7% had more than one pre-existing abnormality. Small vessel ischemic disease was present in 21.0%, ischemic lesions in 7.2%, generalized atrophy in 17.9%, and post-traumatic lesions were found in 2.8%. Among older adults (age 55 and older), those with CT evidence of pre-existing atrophy were *less likely* to have a complicated MTBI than those without obvious atrophy (12.6% vs. 19.0%, $\chi^2$=8.52, p=0.004). The rate of complicated MTBIs in older adults (age 55 and older) who had a pre-existing neurodegenerative disease was similar to those who did not have a neurodegenerative disease (14.1% vs. 17.6%, $\chi^2$=1.64, p=0.200).

In a logistic regression with the total MTBI sample (n=2,766), a number of variables were associated with a higher rate of acute intracranial lesions. The results of the logistic regression

analysis are presented in Table 3. In the single covariate models (producing unadjusted ORs), male gender, greater age, cause of injury, lower GCS, chronic alcohol abuse, and pre-existing traumatic lesions on CT were significant predictors. In the multivariable model, significant independent predictors were male gender (OR=1.68, 95% CI 1.27-2.21), age (OR=1.04, 95% CI 1.03-1.05), having a pre-existing traumatic lesion (OR=1.99, 95% CI 1.12-3.56), chronic alcohol use (OR=1.84, 95% CI 1.29-2.63), certain mechanisms of injury [being a pedestrian or bicyclist in a traffic accident (OR=7.54, 3.05-18.65), or falling from a height (OR=4.32, 1.82-10.23), ground-level falls (OR=3.9, 1.75-8.68) vs. a motor vehicle accident], and a GCS of 14 (OR=4.35, 95% CI 2.69-7.05) or 13 (OR=7.70, 95% CI 3.26-18.18) vs. 15. Interestingly, cerebral atrophy was associated with significantly *lower* risk for an acute traumatic intracranial abnormality (OR=0.48, 95% CI 0.34-0.68). Small vessel ischemic disease also was associated with lower risk for having a complicated MTBI (OR=0.58, 95% CI 0.41-0.81). Of note, the multivariable modeling indicates that age and sustaining an MTBI due to ground-level fall were *independently* associated with having a positive head CT, suggesting that the high rate of CT abnormalities associated with ground-level falls was not entirely confounded by older adults having more falls than younger adults.

Table 3. Logistic regression analysis of acute intracranial lesions.

| | **Suspected and Confirmed MTBI Sample (n=2,766)** | | | | | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | | | **Adjusted** | | |
| **Predictor, n (%)** | ***p*** | **OR** | **95% CI** | ***P*** | **OR** | **95% CI** |
| Gender | | | | | | |
| Female, n=1,242 (44.9%) | ref | | | ref | | |
| Male, n=1,524 (55.1%) | 0.026 | 1.31 | 1.03-1.66 | <0.001 | 1.68 | 1.27-2.21 |
| Age, years | <0.001 | 1.03 | 1.02-1.03 | <0.001 | 1.04 | 1.03-1.05 |
| Cause of injury | | | | | | |
| Motor vehicle accident, n=275 (9.9%) | ref | | | ref | | |
| Traffic accident as pedestrian or bicyclist, n=145 (5.2%) | <0.001 | 7.59 | 3.19-18.11 | <0.001 | 7.54 | 3.05-18.65 |
| Fall from a height, n=304 (11.0%) | <0.001 | 4.66 | 2.03.10.72 | 0.001 | 4.32 | 1.82-10.23 |
| Ground-level fall, n=1,454 (52.6%) | <0.001 | 6.54 | 3.04-14.04 | 0.001 | 3.90 | 1.75-8.68 |
| Other, n=535 (19.3%) | 0.019 | 2.68 | 1.18-6.12 | 0.008 | 3.15 | 1.34-7.39 |
| Unknown, n=53 (1.9%) | <0.001 | 7.83 | 2.77-22.11 | 0.032 | 3.36 | 1.11-10.21 |
| Alcohol use preceding injury | | | | | | |
| No, n=1,151 (41.6%) | ref | | | ref | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Yes, n=660 (23.9%) | 0.297 | 1.17 | 0.87-1.57 | 0.559 | 1.12 | 0.76-1.64 |
| Unknown, n=955 (34.5%) | 0.625 | 1.07 | 0.82-1.40 | 0.579 | 1.09 | 0.81-1.46 |
| Chronic alcohol abuse, n=488 (17.6%) | <0.001 | 1.63 | 1.24-2.15 | <0.001 | 1.84 | 1.29-2.63 |
| GCS | | | | | | |
| 15, n=1,558 (56.3%) | ref | | | ref | | |
| 14, n=97 (3.5%) | <0.001 | 5.00 | 3.20-7.81 | <0.001 | 4.35 | 2.69-7.05 |
| 13, n=27 (1.0%) | <0.001 | 8.23 | 3.80-17.82 | <0.001 | 7.70 | 3.26-18.18 |
| 3-12, n=92 (3.3%)* | --- | --- | --- | --- | --- | --- |
| Unknown, n=992 (35.9%) | 0.282 | 1.15 | 0.89-1.49 | 0.860 | 1.02 | 0.78-1.34 |
| Small vessel ischemic disease, n=581 (21.0%) | 0.154 | 1.22 | 0.93-1.61 | 0.001 | 0.58 | 0.41-0.81 |
| Neurodegenerative disease, n=229 (8.3%) | 0.236 | 1.27 | 0.86-1.88 | 0.750 | 0.93 | 0.60-1.45 |
| Pre-existing traumatic lesion on CT, n=77 (2.8%) | <0.001 | 3.00 | 1.79-5.02 | 0.02 | 1.99 | 1.12-3.56 |
| Cerebral atrophy, n=495 (17.9%) | 0.967 | 0.99 | 0.73-1.35 | <0.001 | 0.48 | 0.34-0.68 |

Note: Unadjusted parameter estimates were derived from single predictor models. Adjusted parameters were derived from a model containing all predictors, and therefore refer to the independent effect of a given predictor, controlling for other predictors.

* In this subgroup there were no intracranial lesions.

## Discussion

Mild TBIs vary in terms of mechanisms, pathophysiology, and clinical outcomes.[32,35] We provided a detailed description of CT findings in patients with MTBI (with a reference group of patients with moderate-severe TBI) and documented factors associated with CT abnormalities in patients with MTBI. This study has several strengths. It involved a large unselected sample of head injury patients who were consecutively treated in an ED. Other than requiring a clinically indicated CT scan of the head, we did not apply eligibility criteria, making the study findings generalizable and enabling us to examine the association between a large number of factors and the incidence of intracranial abnormalities. Another strength was that traumatic lesions were systematically coded using pre-specified Common Data Elements recently developed for TBI research.[10,16] We also included a comparison group of patients with moderate to severe TBI. A key finding was that a substantial number of patients sustaining a MTBI have traumatic intracranial lesions on head CT, even those without clear documentation of acute clinical signs of MTBI in their ED medical record. No individual historical or physical examination features can completely rule out intracranial injury following minor head trauma.[13] In our study 11.6-16.1% of MTBI patients had an acute intracranial

lesion, which falls within the range of prior studies.[1,27,33,41,49,53,54,59] We further observed that the type and location of traumatic lesions are similar across the whole severity spectrum of TBI. SDH, SAH, and contusions occurring in the frontal and temporal regions are most common in mild TBI and more severe TBIs.

It is unclear the extent to which macrostructural lesions help explain the heterogeneity of clinical outcomes from mild TBI. Widely variable patterns of pathology may be seen on structural imaging in patients with similar injury severity as assessed by GCS scores.[48] A few prior studies having included CT positive vs. negative as a prognostic factor. Some studies suggest that CT abnormalities are associated with worse outcome[24,63] but some studies have presented opposite results.[56] Few studies have examined the relationship between specific CT findings and outcome.[65] Further research is needed on neuroimaging as a prognostic factor. Consideration of other biopsychosocial factors (e.g., pre-injury mental health, gender, personality factors, resilience, and acute post-injury psychological distress) in a multivariate model will be important in prognostic research.[4,51]

Pre-existing *non-traumatic* lesions were common in patients with TBI, but they were not associated with increased risk of sustaining a CT positive MTBI. Specifically, pre-existing, degenerative and ischemic lesions in the brain did *not* increase the risk for acute traumatic lesions. Instead, the underlying increased risk for intracranial abnormalities associated with aging may be caused by other comorbidities and antithrombotic medication. Poorer health and functioning predict the occurrence of TBI in elderly.[8]A common belief is that cerebral atrophy is a risk factor for acute and chronic SDH. To our knowledge, only one study suggests that cerebral atrophy may predispose to traumatic intracranial hemorrhage.[11] In our study, atrophy was *not* associated with risk for hemorrhage; in fact, the association was the opposite. Advanced age is a well-known risk factor for an intracranial abnormality in head injury. [7,17,38-40,46,55,57,61] The present study highlights that older

age increases the risk of *any CDE* intracranial abnormality fairly linearly across adulthood, though may plateau around age 60-70. Falls are the leading cause of TBI among elderly people.[5,7,28,57,60] The risk of falling could be associated with intrinsic risks that occur with aging (e.g., chronic medical conditions, impaired balance, slower reaction times, decreased muscle strength, impaired cognition, and use of medications that predispose to postural hypotension and dizziness).

Similar to previous studies, chronic alcohol abuse increased the risk of having an acute traumatic lesion on head CT. Acute intoxication, however, did not increase the risk of intracranial abnormalities. Alcohol abuse is common before TBI, with a prevalence of 37% to 51%.[44] In our study, 18.4% had a history of alcohol abuse. Both acute and chronic alcohol abuse may impair decision making, motor control, and inhibitory control.[68] Binge drinking is the most common pattern of drinking among trauma patients, and the injuries of such patients typically result from assaults, traffic accidents, and falls.[50] Those who have severe alcoholism may not present at the ED as often as occasional binge drinkers after a head injury. Chronic alcohol abusers are often brought to the ED by emergency medical services indicating a more severe trauma. This may partially explain why chronic alcohol abuse was associated with increased risk for traumatic lesions but alcohol intoxication was not.

The rate of acute traumatic lesions is much higher in moderate to severe TBI but it is possible to suffer a severe TBI without intracranial trauma visible on CT. CT underestimates many intracranial nonhemorrhagic lesions, especially DAI.[41] The decades-old approach of classifying TBI severity based on the GCS could be improved by considering neuroimaging findings. GCS is often supplemented by the clinical assessment of PTA and LOC, but both are prone to confounds. An injury severity classification system that incorporates neuroimaging findings could improve outcome prediction, resource allocation, and patient stratification in clinical trials.[34]

The present study has important limitations. First, the clinical variables were collected retrospectively from hospital records and hence some relevant information was missing. This may have introduced bias into our estimation of the relationship between patient and injury characteristics and CT findings. Second, the decision to order a head CT was left to the on-call ED physician's clinical judgment. This "usual care" methodology likely resulted in some patients getting scanned that would not have needed to according to the Scandinavian guideline[22] and we might have missed some patients who should have undergone a CT scan but were discharged without imaging (although the results suggest that a fairly liberal use of CT scanning was present over the study period). Third, the Scandinavian guidelines were used in the ED but most likely these were not followed consistently. We do not have data about the patients who did not undergo head CT scan. The percentages of MTBI patients with specific pathologies is an approximation because it does not include the subgroup who were not triaged for CT. Some people with the mildest form of a mild TBI likely were not scanned, so the rate of abnormalities in the MTBI group is likely greater than the total population of those presenting to the ED (and, of course, that rate does not apply to those who do not present to the ED). It is probable that the amount of CT positive injuries would be smaller in the mild head trauma patients who did not have a head CT scan performed. Fourth, in our sample, one in four (n=776, 25.7%) did not have clearly documented clinical signs or symptoms of TBI in their medical records, which might reflect the absence of those signs, incomplete documentation, or both. Fifth, our sample contained a small number of patients who were classified as sustaining an MTBI, even though they had a GCS less than 13. In this group, low GCS had likely resulted from intoxication, medications, or other medical conditions. There is a possibility that the injury of some of these cases was incorrectly classified. Finally, all CT scans were analyzed and systematically coded by two neuroradiologist study authors using a structured and detailed case report form designed for this study, but we did not conduct a study relating to intra-rater or inter-

rater reliability of this case report form. The reliability of CT findings may be limited by the subjective nature of the visual interpretations and by the qualitative nature of reporting[20] as well as the experience and training of the reader (eg., ED physician, radiologist, or neuroradiologist).[14,30] In our study, the scans were coded by two experienced neuroradiologists. In prior studies, interobserver reproducibility is good even between multiple readers with varying backgrounds when interpreting CT imaging features of TBI.[6,14] Some studies have reported poorer interobserver agreement, but it seems that major findings are seldom missed.[30] Overall, the discrepancy rate is low (0.8%; 95% CI: 0.4%, 1.6%) in head CT scans.[64] Future research could examine both intra-rater and inter-rater reliability of this coding system.

Approximately two out of three patients were CT scanned within the first 24 hours after injury. On the other hand, one out of four patients were scanned more than 48 hours following injury. The temporal trends on how well certain traumatic lesions are visible on brain CT should be noted. Acute (first hours after injury) imaging can result in false negative scans; for example, some contusions do not demarcate as early as others. Furthermore, with delayed (days after injury) scanning some minor subarachnoid bleeds can be missed because these lesions have already reasorbed. These CT-related limitations should be kept in mind when interpreting our findings.

The anatomic characteristics of the child's brain might make it more susceptible than the adult brain to certain types of injuries following head trauma. The head is larger in proportion to the body surface area, and stability is dependent on the ligamentous rather than bony structure. Subdural and subarachnoid hemorrhages were the most common intracranial lesions in the current study. The assessment of pediatric head trauma patients is different from the adults. Even in the pediatric population, the mainstay of imaging is CT, but the significant radiation exposure must be considered. It is possible, that some of the pediatric TBI patients at our hospital had MRI as their first imaging study.

In this study, there was a large amount of missing data in the medical records on PTA, LOC, and GCS which are part of the foundation of TBI diagnosis. These findings highlight the importance of a thorough medical history, focusing on the injury mechanism and confounding factors along with a careful neurological examination including GCS, mental state, and PTA measurements. The presence of PTA was noted much more often in MTBI patients than in more severe TBI patients. Often those with moderate and severe TBIs have additional injuries that dominate clinical attention or they are unconscious at arrival and only progress to post-traumatic amnesia after being transferred from the ED. There also might be a tendency for some physicians to document more specific injury criteria following MTBI, especially in those with isolated head trauma, and document fewer criteria in ED situations when the person has an obvious moderate or severe TBI. Finally, the study examined only patients with MTBI who attended an ED. Rates of CT abnormalities in patients who do not seek acute care at an ED are not known.

## Conclusions

Approximately 1 in 6 patients who present to the ED with suspected or confirmed mild TBI will have a CDE trauma-related intracranial abnormality on day-of-injury CT. The frequency CT findings is much lower than in moderate to severe TBI, but the type and location of lesions is very similar. Clinicians and researchers should also be aware that within the spectrum of MTBI, patient demographics (older age and male gender), pre-injury exposures (alcohol abuse, but not brain pre-existing lesions), mechanism of injury (falls and being struck by a motor vehicle), and reduced consciousness following injury (GCS<15) are all associated with an increased incidence of intracranial abnormality. Further research is needed to translate this knowledge into refined MTBI clinical stratifications and prognostics.

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Figure legend:

Grey line: acute intracranial lesions

Black line: pre-existing intracranial abnormality

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# Necessity of monitoring after negative head CT in acute head injury

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ABSTRACT

*Objective:* The main objective of this study was to evaluate the incidence of delayed complications in acute head injury (HI) patients with an initial normal head computed tomography (CT).
*Materials and methods:* This retrospective study included 3023 consecutive patients who underwent head CT due to an acute HI at the Emergency Department (ED) of Tampere University Hospital (August 2010–July 2012). Regardless of clinical injury severity, the patients with a normal head CT were selected ($n$ = 2444, 80.9%). The medical records of these patients were reviewed to identify the individuals with a serious clinically significant complication related to the primary HI. The time window considered was the following 72 h after the primary head CT. A repeated head CT in the hospital ward, death, or return to the ED were indicative of a possible complication.
*Results:* The majority ($n$ = 1811, 74.1%) of the patients with a negative head CT were discharged home and 1.1% ($n$ = 27) of these patients returned to ED within 72 h post-CT. A repeated head CT was performed on 12 (44.4%) of the returned patients and none of the scans revealed an acute lesion. Of the 632 (25.9%) CT-negative patients admitted to the hospital ward from the ED, a head CT was repeated in 46 (7.3%) patients within 72 h as part of routine practice. In the repeated CT sample, only one (0.2%) patient had a traumatic intracranial lesion. This lesion did not need neurosurgical intervention. The overall complication rate was 0.04%.
*Conclusion:* In the present study, which includes head injuries of all severity, the probability of delayed life-threatening complications was negligible when the primary CT scan revealed no acute traumatic lesions.



## Introduction

### *Background*

Acute head injury (HI) is one of the most common causes for visits to emergency departments (EDs), with an annual incidence being 100–790 per 100,000 persons [1]. In the ED setting, non-contrast computed tomography (CT) has a well-established role in the management of patients with HI [2,3]. It is fast, cost-effective [4], and it identifies intracranial haemorrhages and skull fractures that require neurosurgical intervention. Depending on the applied CT guidelines [5–11], 6–12% of patients with HI have an acute traumatic intracranial lesion on CT [7–9,11,12]. In contrast, the large majority of HI patients evaluated and treated in the ED are CT-negative.

### *Importance*

After a negative CT, delayed intracranial haemorrhage or cerebral oedema are rare but recognized life-threatening complications of HI that may demand neurosurgical procedures or be fatal [13,14]. In a review, only 3 out of 62,000 patients were

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deemed to have experienced an early adverse outcome despite a negative CT, a Glasgow Coma Scale (GCS) score of 15, and a normal neurological examination on initial presentation [2]. The crucial question is which patients are at risk to develop these infrequent complications and can these patients be identified before hospital discharge? Routine hospital monitoring following a CT-negative HI to enable early identification and treatment of possible adverse events is conservative, expensive, and not supported by the literature to date. Increased treatment costs and consumed ED personnel resources caused by unnecessary hospital monitoring could be prevented by early recognition of patients with a risk of a complication.

*Goals of this investigation*

This study focused on a large sample of patients with HIs of varying clinical severity. Two main objectives were addressed. First, we evaluated how many HI patients with an initial negative head CT showed a life-threatening or a clinically significant intracranial complication within 72 h of their initial head CT. Second, we aimed to characterize the patients with complications in order to predict which patients would need hospital observation.

## Methods

*Study design and setting*

This study is a part of the Tampere Traumatic Head and Brain Injury Study. All the data were retrospectively recorded in a separate secure Internet-based head injury registry, which includes all patients with HI who undergo CT at Tampere University Hospital ED specialist unit. Ethics approval for the study was obtained from the ethical committee of Pirkanmaa Hospital District, Finland. In the study, traumatic brain injury (TBI) was defined as the presence of at least 1 of the following: amnesia of any duration, loss of consciousness (LOC) of any duration, posttraumatic disorientation or confusion, or focal neurological abnormality [15].

*Selection of participants*

The original sample, derived from the head injury registry, included all consecutive patients who underwent head computed tomography (CT) due to acute head trauma ($n = 3023$) at the Tampere University Hospital ED's specialist unit between August 2010 and July 2012. The ED provides health services for Pirkanmaa Hospital District, which is a joint municipal authority of 22 municipalities with a total of approximately 470,000 residents. Finland is divided into five major health care regions each having a three-tier health care system: (i) local district hospitals (primary care), (ii) regional central hospitals (secondary care), and (iii) university hospitals (tertiary care). There are several primary and secondary level of care hospitals in the region, but only one tertiary level of care hospital providing neurosurgical care. Accordingly, all TBI care is centralized to the designated tertiary care facility. All acute life-threatening intracranial conditions within the hospital district are treated at the Tampere University Hospital. The study patients constitute a consecutive community-based sample of the Finnish population. The initial study population represents the whole severity spectrum of head trauma from minimal to severe, including TBI and non-TBI patients who were all CT imaged.

*Methods and measurements*

Data collected from the registry included subject- and injury-related data, and clinical information from the ED. Subject-related data included age, gender, and health history including chronic alcohol and/or narcotic abuse, and possible prior brain injuries. The mechanisms of injury and time intervals (injury to ED admission to CT to ED discharge) were recorded. Clinical variables assessed were Glasgow Coma Scale (GCS) in the ED, witnessed LOC, seizures, disorientation, and retrograde and/or anterograde amnesia. ED physicians on-call identified amnesia during an interview regarding pre- and post-injury events. Only the presence or absence of amnesia was noted; the duration of amnesia was not assessed. No structured forms to measure amnesia were used. Destination after ED was categorized into four groups: home, hospital ward, local health centre, or death.

In the ED, an emergency non-contrast head CT scan was performed as per Scandinavian guidelines [16] for all patients with a 64-row CT scanner (Lightspeed VCT; GE, Wisconsin). The guideline recommends that adult patients after head injury with any of the following should have a head CT: (i) GCS $\leq$13, (ii) loss of consciousness, (iii) focal neurological deficits, (iv) therapeutic anticoagulation or haemophilia, (v) clinical signs of depressed skull fracture or skull base fracture, (vi) posttraumatic seizures, (vii) shunt-treated hydrocephalus or (viii) multiple injuries.

In a non-on-call setting, all CT scans were analyzed and systematically coded using a structured data collection form by the two blinded neuroradiologists (A.K. and A.B.). Double-reading of the images was not performed. Acute traumatic intracranial lesions included subdural haematoma and effusion (SDH), epidural haematoma and effusion (EDH), diffuse axonal injury (DAI) lesions, oedema, compression of the cerebrospinal fluid spaces, midline shift, contusions, pneumocephalus, skull fracture, and traumatic subarachnoid haemorrhage.

*Outcomes*

Fig. 1 illustrates the study process to identify patients with intracranial complications within 72 h following an initial negative head CT. To identify patients with delayed intracranial complications, the patient records of all the patients in the registry were reviewed. A repeated head CT in the hospital ward, death, or return to the ED within 72 h was indicative of a possible complication. Decisions on repeated head CT in the hospital ward was based on routine clinical practice. The reasons for repeated imaging were control, prolongation or worsening of the HI-related symptoms, decline in general condition and new head trauma during admission. Detailed data collection was performed on the medical records of the patients with possible complication. The data collection consisted of the reason for the ED return visit, information related to a repeated head CT, and discharge data.

*Analysis*

The normality of the variable distributions was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were analyzed with the Pearson (normal distribution) and Spearman (skewed distribution) correlation coefficients. Group comparisons were tested with the Student's *t*-test (normal distribution) and the Mann–Whitney *U*-test (skewed distribution). The statistical significance level was set at 5% for all analyses. IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA) was used to perform the analyses.

## Results

*Characteristics of the study subjects*

The clinical characteristics of the study patients are summarized in Table 1. For comparison, the characteristics of the CT-negative patients are presented parallel to the whole study group.

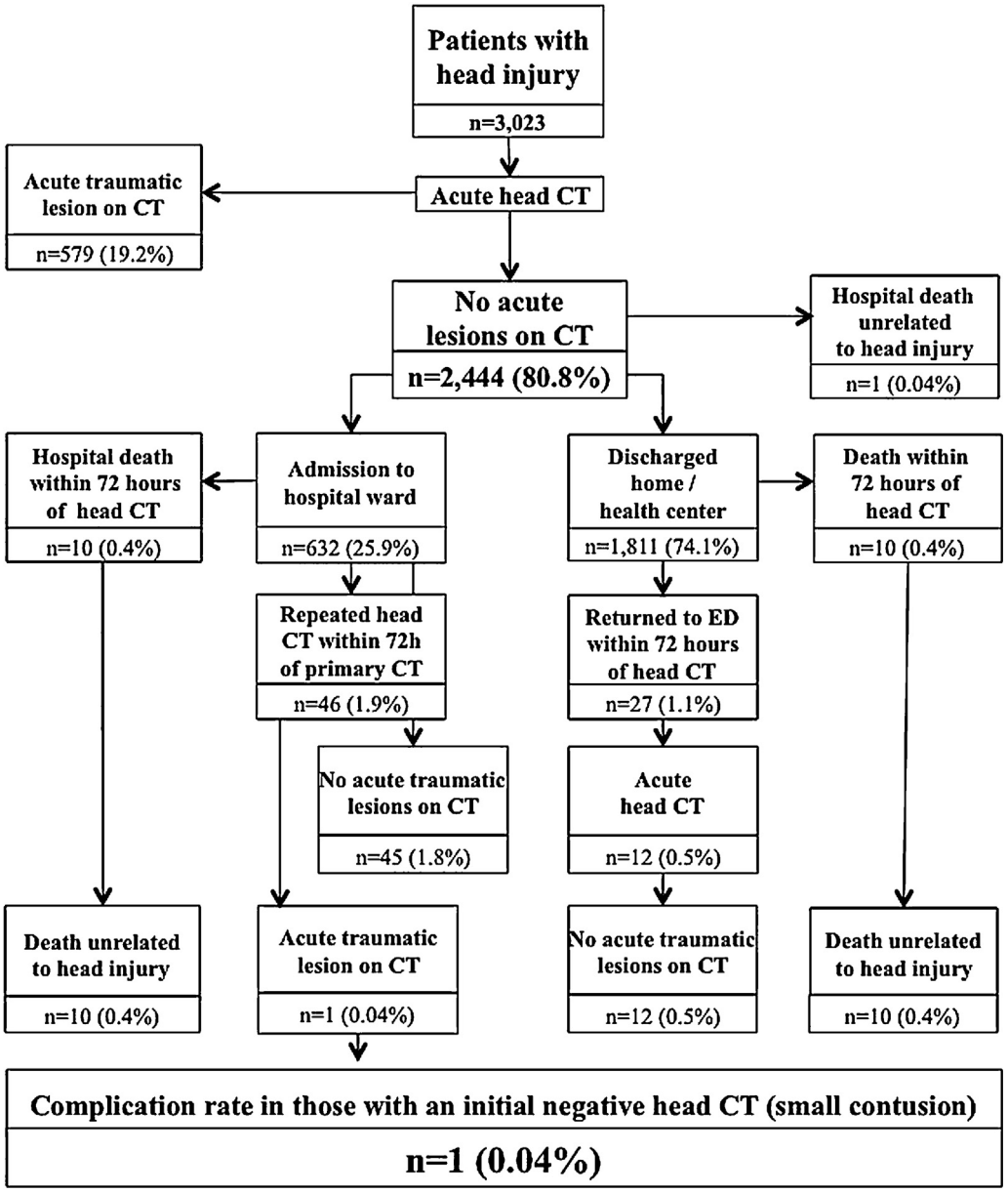


**Fig. 1.** Study process to identify patients with intracranial complications within 72 h following a primarily negative head CT.

The age distribution was skewed ($n$ = 3023, median = 55 years, interquartile range = 34–76), and the majority of the patients (56.4%, $n$ = 1705) were men.

*Main results*

The majority ($n$ = 1811, 74.1%) of the patients with a negative head CT were discharged home or to the local health centre ward from the ED. Of these patients, 1.1% ($n$ = 27) returned to the ED within the first 72 h post-CT. The reasons for returning were: (i) prolongation or (ii) worsening of the HI-related symptoms ($n$ = 10 and $n$ = 10, respectively), (iii) decline in general condition ($n$ = 5), and (iv) being called for readmission ($n$ = 2). A repeated head CT was performed on 12 (44.4%) of the returned patients and none of the scans revealed an acute lesion. Ten ($n$ = 10) of the discharged patients died. In all of these cases, the cause of death was unrelated to the primary head trauma. Chronic pulmonary and cardiovascular diseases were the main causes of death.

Of the 632 (25.9%) CT-negative patients admitted to the hospital ward from the ED, a head CT was repeated on 46 (7.3%) patients within the first 72 h. The reasons for repeated imaging were (i) routine control ($n$ = 21), (ii) prolongation of the HI-related symptoms ($n$ = 13), (iii) worsening of the HI-related symptoms ($n$ = 6), (iv) decline in general condition ($n$ = 1), and (v) new head trauma while inside the hospital ($n$ = 1). Ten of the CT-negative patients who were admitted to the hospital died of causes unrelated to head trauma. Only one (0.2%) patient developed a delayed acute traumatic intracranial lesion related to the HI.

The patient with a traumatic lesion on the secondary head CT was a 16-year-old male who crashed his moped into a bus. He was wearing a helmet. There was no LOC. On admission, he was conscious, although confused. The primary head CT showed no intracranial lesions. Small bilateral lung contusions, a small right-sided pneumothorax, and fractures in the left femur and pelvis were found on the body CT. In the hospital ward, the patient had no neurological symptoms. Due to the high energy trauma a repeated head CT was performed the following day. The follow-up CT revealed a small posterior contusion in the

**Table 1**
Characteristics of the study sample.

| Variable | Whole sample ($n$ = 3023) Median (95% CI range) | CT-negative ($n$ = 2444) Median (95% CI range) |
|---|---|---|
| Age, years | 57.0 (54.1–55.8) | 53.9 (32.1–75.8) |
| Time intervals, h | | |
| From injury to ED admission | 4.3 (52.9–70.3) | 4.3 (1.4–40.1) |
| From injury to primary head CT | 6.2 (54.6–72.0) | 6.3 (2.5–44.6) |
| From ED admission to primary head CT | 1.0 (1.6–1.9) | 1.0 (0.6–1.8) |
| From primary head CT to hospital discharge | 8.2 (52.7–71.2) | 4.8 (2.0–21.8) |
| Hospital stay | 10.1 (54.4–72.9) | 6.8 (3.6–23.3) |

| | Whole sample ($n$ = 3023) | | CT-negative ($n$ = 2444) | |
|---|---|---|---|---|
| | $n$ | % | $n$ | % |
| Gender | | | | |
| Men | 1705 | 56.5 | 1330 | 54.4 |
| Female | 1318 | 43.6 | 1114 | 45.6 |
| CT within 24 h post-injury | 2083 | 68.9 | 1671 | 68.4 |
| CT within 48 h post-injury | 2311 | 76.4 | 1861 | 76.1 |
| Mechanism of injury | | | | |
| Ground-level falls | 1584 | 52.4 | 1240 | 50.7 |
| Falls from a height | 337 | 11.1 | 271 | 11.1 |
| Car accidents | 294 | 9.7 | 272 | 11.1 |
| Violence-related injuries | 224 | 7.4 | 194 | 7.9 |
| Other | 187 | 6.2 | 162 | 6.6 |
| Bicycle accidents | 129 | 4.3 | 96 | 3.9 |
| Unknown | 72 | 2.4 | 44 | 1.8 |
| Sports | 69 | 2.3 | 63 | 2.6 |
| Motorcycle accidents | 55 | 1.8 | 49 | 2.0 |
| Traffic accidents as an pedestrian | 38 | 1.3 | 23 | 0.9 |
| Moped accidents | 34 | 1.1 | 30 | 1.2 |
| Location of follow-up treatment | | | | |
| Home | 1227 | 40.6 | 1186 | 48.5 |
| Health centre | 656 | 21.7 | 544 | 22.3 |
| Other health care facility | 91 | 3.0 | 81 | 3.3 |
| Hospital | 998 | 33.0 | 632 | 25.9 |
| Death | 51 | 1.7 | 1 | 0.04 |
| Alcohol intoxication | | | | |
| Yes | 741 | 24.5 | 578 | 23.6 |
| No | 1243 | 41.1 | 1024 | 41.9 |
| Unknown | 1039 | 34.4 | 842 | 34.5 |
| LOC | | | | |
| Yes | 586 | 19.4 | 417 | 17.1 |
| No | 788 | 26.1 | 709 | 29.0 |
| Not witnessed | 266 | 8.8 | 204 | 8.3 |
| Unknown | 1383 | 45.7 | 1114 | 45.6 |
| Amnesia | | | | |
| Yes | 684 | 22.6 | 540 | 22.1 |
| No | 932 | 30.8 | 864 | 35.4 |
| Unknown | 1406 | 46.5 | 1039 | 42.5 |
| GCS | | | | |
| 13–15 points | 1727 | 57.1 | 1462 | 59.8 |
| 9–12 points | 137 | 4.5 | 80 | 3.1 |
| 3–8 points | 108 | 3.6 | 30 | 1.2 |
| N/A | 1051 | 34.8 | 872 | 35.7 |

parietal lobe. The contusion did not require any additional intervention. The patient was discharged from the hospital after the surgical treatment of the femur and the pelvis fractures.

## Discussion

Among head trauma patients with an initial negative head CT, the overall rate of clinically relevant complications within the first 72 h was 0.04%. There were no life-threatening complications or complications requiring surgery. The very small number of subjects with complications ($n$ = 1) was insufficient to characterize or predict, clinically or statistically, the need for hospitalization.

In past studies, the incidence of intracranial complications following an initial normal head CT has been very low [17]. Advanced age and the use of antithrombotics in the form of warfarin, aspirin, clopidogrel, or a combination, have been found to be associated with an increased the risk for intracranial bleeding, neurosurgical intervention, and mortality [18–20]. However, recent studies suggest that even patients with anticoagulation medicine do not need routine repeated head CT [20], or could even be discharged, if the primary CT is negative [19]. The present study results are in line with those findings. Although the number of patients using anticoagulation in the present cohort is unknown, most certainly this large, quite aged, sample included a considerable number of patients using this medication. We did not discover any warfarin-medicated patients with a complication.

The single patient with a complication (i.e., a posterior contusion) after an initial negative CT was a young male with a high-energy trauma. The small contusion that was visible in the second CT was also seen on a brain MRI taken a month after the injury. The negative finding on the primary head CT can mostly be explained by the short time delay between the injury and the scanning (1.0 h). It is recognized that not all parenchymal lesions are visible on CT when the imaging is conducted shortly after the injury [21].

Radiologists on call might miss brain contusions, but the most severe findings are reported adequately [22]. Trained emergency

physicians can competently interpret head CT with very good agreement with neuroradiologists. Clinically important findings on head CT are not commonly missed by emergency physicians [23,24]. In our study, the CT scans were separately interpreted by two neuroradiologists involved in the study. A structured form was used in the interpretation. As a part of the normal emergency management, the primary head CT was mainly viewed by an on-call radiology resident and additionally by an on-call treating ED physician if needed. The clinical decision-making on the treatment of the patients with HI was based on these on-call interpretations. Unfortunately, we do not have the data regarding the on-call interpretations. In our hospital as part of routine work, all head CT scans are re-interpreted by a neuroradiologist the following day. If discrepancies arise between these two interpretations, appropriate actions are taken. Therefore, the outcome of this study most likely would not have been different if the CT data was based on the on-call interpretations.

One unexpected study finding warrants discussion. There were 110 CT-negative patients with a GCS score of 3–12 points in the ED. These surprisingly low GCS scores can be explained by non-traumatic intracranial lesions (e.g., ischaemic lesions, spontaneous bleeds), alcohol and substance abuse, comorbid acute (e.g., epileptic seizures) and chronic health problems (e.g., neurodegenerative diseases, multicomorbidity), and sedation due to other non-cerebral injuries.

This study represents a large population-based HI sample that is commonly seen in the ED internationally. The sample includes a wide severity spectrum of HIs that were treated at the ED at varying time delays post-injury (range = 0–8, 791.9 h). The study findings are generalizable and can be easily applied into clinical practice. Nevertheless, this study has three limitations. First, the data collection was done retrospectively and therefore the amount of missing or unknown information (e.g., alcohol intoxication) was quite large. Second, CT criteria in the ED were based on the Scandinavian guidelines. Considering the extent of missing data, the guideline compliance of the ED physicians seems questionable. Apparently, some patients in the sample did not fulfil the Scandinavian CT criteria and therefore were CT-imaged without solid indications. In contrast, it is possible that some HI patients did not undergo CT imaging although they met the criteria. Finally, the CT data used in this study was not based on the on-call interpretation but on a retrospective interpretation by our study neuroradiologists. The differences between these interpretations were not studied.

In the present study, which includes head injuries of all severity, the probability of delayed life-threatening complications was negligible when the primary CT scan revealed no acute traumatic lesions. Therefore, routine repeated CT scanning or observation is not warranted when the primary CT scan is negative. Our findings suggest that all head trauma patients with negative CT scans can be discharged without observation.

## Conflict of interest statement

The authors have no conflicts of interest concerning this study.

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