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THE IMPACT OF TRAUMATIC BRAIN INJURY IN OLDER ADULTS

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Abstract

Traumatic Brain Injury (TBI) is defined as an injury to the brain caused by an external force applied to the head or body and is nowadays a major cause of mortality and disability worldwide.
In the last decades, the incidence of TBI has been increasing very fast among adults in the oldest age groups, due to an increasing incidence of fall accidents in this population. It is known that older patients with a TBI diagnosis suffer from more severe consequences than their younger counterparts. However, to date, the lifelong impact of TBI on older patients' wellbeing remains a relatively neglected area in the field of TBI-related research and there are no specific clinical or neurosurgical guidelines for these patients. Therefore, there is a real need for more fundamental research to better understand the impact that TBI has on older patients' lives and to create specific prognostic tools and clinical guidelines for this population.
The main goal of this PhD project is twofold. First of all, it aims at mapping injury patterns, injury severity and risk profiles for TBI in older adults, and at objectively assessing the nature of brain damage, its sequelae in terms of level of dependency, cognitive and motor disturbances, and their impact on quality of life after TBI. Secondly, it aims at creating a new prognostic tool for mortality and functional outcomes after TBI in older patients, in order to help decision making and counseling of families.
This dissertation, characterizes, first, risk factors for and incidence of post-TBI functional decline and dependency, nursing home admission, depression, poor Quality of Life (QoL) and mortality in older patients, based on the results of two systematic reviews and meta-analysis. These systematic reviews and meta-analyses showed that TBI in patients aged ≥ 65 years has a major impact on patients' lives, often leading to functional decline, dependency, nursing home admission and poor QoL, even in mild TBI cases. After neurosurgery, outcomes on older patients are also less favorable than in younger patients, leading to high mortality rates. However, these results indicated that neurosurgery should not be denied in all older patients, since it could improve the functional outcomes and reduce mortality in selected patients.
Second, it presents an overview on patients' demographic characteristics and previous clinical history, injury patterns and severity, clinical management, and outcomes in patients with TBI aged ≥65 years, admitted to UZ Leuven between 1999 and 2019, based on a retrospective clinical database study of >1,000 patients. These results showed that TBI is a very heterogeneous and complex condition, which leads to serious consequences, even in mild TBI cases. We also reported the risks of vitamin K antagonist (VKA) intake prior to TBI for the development of acute subdural hematomas (ASDH) and worse outcomes. Furthermore, we described how neurosurgical treatment in the studied cohort led to the highest 30-day mortality rates, while patients treated conservatively had worse outcomes than patients who underwent delayed surgery.
Over the 20 year study period, we also reported an increase of age and comorbidities, and a marked reduction in neurosurgical interventions and ICU admissions. Together with these changes, there was a trend to less severe injuries, but higher proportion of treatment withdrawals, while at the same time mortality rates decreased. This may indicate a recent change towards better patient-tailored decision making in clinical practice.
Third, it discusses the results obtained from two different clinical trials to assess functional outcome and Quality of Life in patients with TBI aged ≥65 years admitted to UZ Leuven. These studies showed

that mild TBI in older patients often lead to poorer sleep quality, worse cognitive performance, poorer motor function, higher fall risk and reduced QoL 6 months and 1 to 13 years post-TBI.
Fourth, it shows the study of the prognostic factors and development of a prognostic tool for 30-day mortality and 12-month functional outcome based on the international prospective CENTER TBI core study data repository, using advance statistical methods and machine learning techniques. Up to date, no specific prognostic tool for older patients' mortality and functional outcome was available in clinical practice. Therefore, we developed these prognostic models using ML algorithms. The results reported good performance of the models, as mortality within 30 days post-TBI was predicted with an AUC of 0.88-0.89, unfavorable outcomes at 6 months with and AUC of 0.85-0.88 and unfavorable functional outcomes at 12 months with an AUC of 0.85-0.86.
Finally, it reports data on the qualitative analysis of quality of life and real life impact of TBI on older patients using the focus group methodology. With this study we showed that mild TBI in older patients can lead to changes in self-perception, daily life activities and social life 1 to 5 years after the injury, which could contribute to a loss of independence and QoL deterioration, being the acceptance of the situation, optimism, and a good support network protective factors for these patients' well-being after TBI.
The results provided by this dissertation are expected to contribute to the improvement of the clinical care of older patients with TBI, with the overall goal of maintaining independence for activities of daily living and a good QoL in these patients.

Beknopte samenvatting

Traumatisch hersenletsel wordt gedefinieerd als een letsel aan de hersenen veroorzaakt door een externe kracht op het hoofd of het lichaam, en het is tegenwoordig wereldwijd een belangrijke oorzaak van sterfte en invaliditeit.
In de laatste decennia is de incidentie van traumatisch hersenletsel zeer snel toegenomen bij volwassenen in de oudste leeftijdsgroepen, als gevolg van een toenemende incidentie van valongevallen in deze populatie. Het is bekend dat oudere patiënten met deze diagnose ernstigere gevolgen ondervinden dan hun jongere tegenhangers. Tot op heden blijft de levenslange impact van hersen trauma op het welzijn van oudere patiënten echter een relatief verwaarloosd op het gebied van hersentrauma-gerelateerd onderzoek en er zijn geen specifieke klinische of neurochirurgische richtlijnen voor deze patiënten. Daarom is er een reële behoefte aan meer fundamenteel onderzoek om de impact van hersentrauma op het leven van oudere patiënten beter te begrijpen en om specifieke prognostische instrumenten en klinische richtlijnen voor deze populatie te creëren.
Het hoofddoel van dit doctoraatsproject is tweeledig. Ten eerste beoogt het letselpatronen, letselernst en risicoprofielen voor hersentrauma bij ouderen in kaart te brengen, en de aard van het hersenletsel, de gevolgen ervan in termen van mate van afhankelijkheid, cognitieve en motorische stoornissen, en hun impact op de levenskwaliteit na hersentrauma objectief te beoordelen. Ten tweede beoogt het een nieuw prognostisch instrument te creëren voor mortaliteit en functionele uitkomsten na hersentrauma in de oudere bevolking, om de besluitvorming en begeleiding van families te ondersteunen.
Dit proefschrift karakteriseert, ten eerste, risicofactoren voor en incidentie van post-hersentrauma functionele achteruitgang en afhankelijkheid, verpleeghuisopname, depressie, slechte kwaliteit van leven en mortaliteit in de oudere bevolking, gebaseerd op de resultaten van twee systematische reviews en meta-analyses. Deze systematische reviews en meta-analyses toonden aan dat hersentrauma bij ouderen een grote impact heeft op het leven van patiënten, vaak leidend tot functionele achteruitgang, afhankelijkheid, verpleeghuisopname en slechte kwaliteit van leven, zelfs in milde hersentrauma gevallen. Na neurochirurgie zijn de uitkomsten bij oudere patiënten ook minder gunstig dan bij jongere patiënten, wat leidt tot hoge sterftecijfers. Deze resultaten wijzen er echter op dat neurochirurgie niet bij alle oudere patiënten moet worden geweigerd, aangezien het de functionele resultaten kan verbeteren en de mortaliteit bij geselecteerde patiënten kan verminderen.
Ten tweede wordt een overzicht gegeven van de demografische kenmerken en eerdere klinische voorgeschiedenis van patiënten, letselpatronen en ernst, klinische behandeling en uitkomsten bij hersentrauma patiënten ≥65 jaar die tussen 1999 en 2019 in het UZ Leuven werden opgenomen, op basis van een retrospectieve klinische databankstudie van >1.000 patiënten. Deze resultaten toonden aan dat hersentrauma een zeer heterogene en complexe aandoening is, die tot ernstige gevolgen leidt, zelfs in milde hersentrauma gevallen. Wij rapporteerden ook de risico's van inname van vitamine K-antagonisten voorafgaand aan hersentrauma voor de ontwikkeling van acute subdurale hematomen en slechtere uitkomsten. Voorts beschreven wij hoe neurochirurgische behandeling in het bestudeerde cohort leidde tot de hoogste 30-dagen mortaliteit, terwijl patiënten die conservatief werden behandeld, slechtere resultaten hadden dan patiënten die een uitgestelde operatie ondergingen.
Gedurende de studieperiode van 20 jaar meldden wij ook een toename van leeftijd en comorbiditeiten, en een duidelijke vermindering van neurochirurgische ingrepen en intensieve zorg

opnames. Samen met deze veranderingen was er een trend naar minder ernstige letsels, maar een hoger percentage intrekkingen van behandelingen, terwijl tegelijkertijd het sterftecijfer daalde. Dit kan wijzen op een recente verandering in de richting van beter op de patiënt afgestemde besluitvorming in de klinische praktijk.

Ten derde worden de resultaten besproken van twee verschillende klinische studies ter beoordeling van de functionele uitkomst en de kwaliteit van leven bij hersentrauma-patiënten ≥65 jaar die in het UZ Leuven zijn opgenomen. Deze studies toonden aan dat milde hersentrauma bij oudere patiënten vaak leidt tot slechtere slaapkwaliteit, slechtere cognitieve prestaties, slechtere motoriek, hoger valrisico en verminderde kwaliteit van leven 6 maanden en 1 tot 13 jaar na hersentrauma.

Ten vierde wordt de studie van de prognostische factoren en de ontwikkeling van een prognostisch instrument voor 30-daagse mortaliteit en 12-maands functionele uitkomst op basis van de internationale prospectieve CENTER TBI core study data repository, met behulp van geavanceerde statistische methoden en machine learning technieken. Tot op heden was er geen specifiek prognostisch instrument voor mortaliteit en functionele uitkomst van oudere patiënten beschikbaar in de klinische praktijk. Daarom ontwikkelden wij deze prognostische modellen met behulp van ML-algoritmen. De resultaten meldden goede prestaties van de modellen, aangezien sterfte binnen 30 dagen na hersentrauma werd voorspeld met een AUC van 0,88-0,89, ongunstige functionele uitkomsten na 6 maanden met een AUC van 0,85-0,88 en ongunstige functionele uitkomsten na 12 maanden met een AUC van 0,85-0,86.

Ten slotte worden gegevens gerapporteerd over de kwalitatieve analyse van de kwaliteit van leven en de reële impact van hersentrauma bij oudere patiënten met behulp van de focusgroepmethode. Met deze studie toonden wij aan dat milde hersentrauma bij oudere patiënten kan leiden tot veranderingen in zelfperceptie, dagelijkse levensactiviteiten en sociaal leven 1 tot 5 jaar na het letsel, wat kan bijdragen tot een verlies van onafhankelijkheid en verslechtering van de kwaliteit van leven, terwijl de aanvaarding van de situatie, optimisme en een goed ondersteunend netwerk beschermende factoren zijn voor het welzijn van deze patiënten na hersentrauma.

De resultaten van dit proefschrift zullen naar verwachting bijdragen aan de verbetering van de klinische zorg voor oudere patiënten met hersentrauma, met als algemeen doel het behoud van onafhankelijkheid voor activiteiten van het dagelijks leven en een goede kwaliteit van leven bij deze patiënten.

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List of Abbreviations

AD Alzheimer's disease
ADL Activities of Daily Living
ADP adenosine diphosphate
AHT Arterial Hypertension
AI Artificial Intelligence
AIS Abbreviated Injury Score
ANOVA One way Analysis of Variance
Ant. Intake. Antithrombotic Intake
AOC Alteration Of Consciousness
aPTT Activated Partial Thromboplastin Clotting Time
aSDH Acute Subdural Hematoma
AUC area under the curve
B&B Blocks and Box
B&B RH1 test with the right hand in patients
BBS Berg Balance Scale
BTF Brain Trauma Foundation
C.H. Cardiovascular History
CANTAB Cambridge Neuropsychological Test Automated Battery
CCI Charlson Comorbidity Index
CINAHL Cumulative Index to Nursing and Allied Health Literature
CIQ Community Integration Questionnaire
CNS Central Nervous System
CPR Cardiopulmonary Resuscitation
CRASH Corticosteroid Randomization after Significant Head Injury
cSDH Chronic Subdural Hematoma
CSF Cerebrospinal Fluid
csv comma-separated values
CT Computed Tomography
CVA Cerebrovascular Accident
DAI Diffuse Axonal Injury
DC Decompressive Craniectomy
DKI Diffusion Kurtosis Imaging
DNR code 1 Do not reanimate
DNR code 2 Do not extend therapy
DNR code 3 Progressively reduce therapy
DNR ''Do not resuscitate'' order
DOACs Direct Oral Anticoagulants
DRS Disability Rating Scale
DTI Diffusion Tensor Imaging
DWI Diffusion Weighted Imaging
E Elderly

ED Emergency Department
EDH Epidural Hematoma
FA fractional anisotropy
FAM Functional Assessment Measure
FIM Functional Independence Measure
FL Frontal Lobe
FLAIR fluid attenuated inversion recovery
fMRI functional MRI
FSE Functional Status Examination
FU follow-up
GABA Gamma-Aminobutyric Acid
GCS Glasgow Coma Scale
GOSE Glasgow Outcome Scale Extended
Hem. Vol. Hematoma Volume
ICD International Statistical Classification of Diseases and Related Health Problems
ICH Intracerebral Hemorrhage
ICP Intracranial Pressure
ICU Intensive Care Unit
ID Identifier
IMPACT International Mission for Prognosis and Analysis of Clinical Trials in TBI
INR International Normalized Ratio
IQR Inter-quartile range
ISS Injury Severity Score
IVH Intraventricular Hemorrhage
IVW inverse variance weighted average
KNN K-Nnearest Neighbors
LH1 first attempt with left hand
LH2 second attempt with left hand
LOC Loss of Consciousness
LOS length of hospital stay
MCI Mild Cognitive Impairment
MCS Mental Component Summary
MESH Medical Subject Headings
ML Machine Learning
MMSE Mini Mental Score Extended
MOT Motor Screening
MOTML mean latency from the display of a stimulus to correct response
MRI Magnetic Resonance Imaging
mRS Modified Rankin Scale
MTT Multitasking
MTTLMD median latency of response (from stimulus appearance to button press)
NR Not Reported
OARS Older Americans' Resources and Services scale
OAT Oral Antithrombotic Therapy
OL Occipital Lobe

OTS One Touch Stockings of Cambridge
OTSMDLFC median latency, measured from the appearance of the stocking balls until the first box choice was made by the subject
OTSPSFC total number of assessed trials where the subject chose the correct answer on their first attempt
PAL Paired Associated Learning
PALFAMS28 number of times a subject chose the correct box on their first attempt when recalling the pattern locations
PALTEA28 number of times the subject chose the incorrect box for a stimulus on assessment problems, plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach
PCS Physical Component Summary
PD Parkinson's disease
PL Parietal Lobe
Pol polypharmacy
PRISMA Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO International Prospective Register of Systematic Reviews
PSQI Pittsburgh Sleep Quality Index
PTA post-traumatic amnesia
QoL Quality of Life
QOLIBRI Quality of Life after Brain Injury
QOLIBRI-OS Quality of Life after Brain Injury Overall Scale
Rehab rehabilitation
rER Rough Endoplasmic Reticulum
RGA retrograde amnesia
RH1 first attempt with right hand
RH2 second attempt with right hand
ROC receiver operating characteristic
ROI region of interest
RTI Reaction Time
RTIFMDMT median time taken for a subject to release the response button and select the target stimulus
RTIFMDRT median duration it took for a subject to release the response button after the presentation of a target stimulus
RVP Rapid Visual Information Processing
RVPMDL median response latency on trials where the subject responded correctly
RVPPFA number of sequence presentations that were false alarms divided by the number of sequence presentations that were false alarms plus the number of sequence presentations that were correct rejections
SAH Subarachnoid Hemorrhage
SciELO Scientific Electronic Library Online
SD standard deviation
SDH subdural hematoma
SF-6D Six-dimensional health state short form
SF-12 12-Item Short Form Survey

SF-36 36-Item Short Form Survey
SHAP SHapley Additive exPlanations
Skull Fr skull fracture
Surg Brain Surgery
SWI Susceptibility Weighted Imaging
SWM Spatial Working Memory
SWMBE468 number of times the subject incorrectly revisits a box in which a token has previously been found
SWMBE number of times the subject incorrectly revisits a box in which a token has previously been found
SWMS number of times a subject begins a new search pattern from the same box they started with previously
TAI Traumatic Axonal Injury
TBI Traumatic Brain Injury
TDP-43 TAR DNA-binding protein 43
TICS Telephonic Interview for the Cognitive Status
TL Temporal Lobe
TUG Timed Up and Go
TYM Test Your Memory
UK United Kingdom
US United States of America
VIF Variance Inflation Factor
VKA vitamin K antagonist
WHODAS WHO Disability Assessment Schedule
WOS Web Of Science
Y Young

Chapter 1

Introduction

Traumatic Brain Injury (TBI) is defined as an injury to the brain caused by an external force applied to the head or body (1) and is nowadays a major cause of mortality and disability worldwide (2).
In the last decades, the incidence of TBI has been increasing very fast among adults in the oldest age groups, due to an increasing incidence of fall accidents in this population (3). It is known that older patients with a TBI diagnosis suffer from more severe consequences than their younger counterparts (4–8). However, to date, the lifelong impact of TBI on these patients' wellbeing remains a relatively neglected area in the field of TBI-related research (9) and there are no specific clinical or neurosurgical guidelines for these patients (10,11). Therefore, there is a real need for more fundamental research to better understand the impact that TBI has on older patients' lives and to create specific prognostic tools and clinical guidelines for this population.

This dissertation presents data on injury mechanisms, clinical presentation, clinical management and outcomes in patients ≥65 years old with TBI, in order to contribute to the future creation of specific guidelines for the clinical management of older TBI patients and to create prognostic tools for functional outcomes and mortality in this population.

In this chapter, an introduction on the topic will be provided by the presentation of an overview of the anatomy of the human head (section 1.1) and the description of the TBI condition (section 1.2). Section 1.3 will explain the most common changes observed in the ageing brain and its consequences. In section 1.4 the particularities of TBI in the older population will be discussed. Finally, the research gaps that originated this dissertation will be presented in section 1.5.

1.1 Anatomy of the human head

The human head is a complex anatomical unit, composed of multiple soft and hard-tissue structures (12).
The osseous structure that composes the head is the skull. It is formed by 28 bones and can be divided into three main sections: the cranium, which surrounds and protects the brain; the facial skeleton; and the mandible (Figure 1.1) (12).

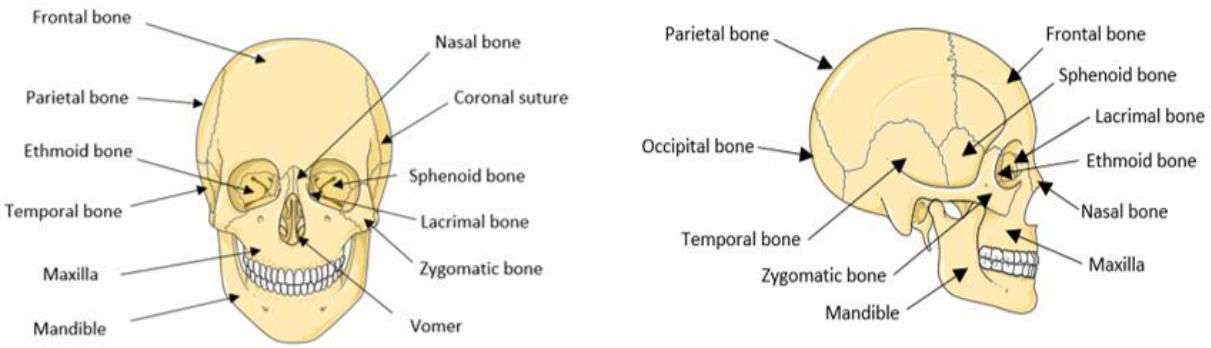


Figure 1.1 Frontal and side view of the skull. Adapted from (14).

Covering the skull, we can find the scalp. It is a five-layerd tissue, composed, from an upper to lower view, of: scalp skin, subcutaneous layer, gala aponeurotica, subgaleal layer and pericranium (12).

Inside the cranium, the cranial cavity contains the brain, which is one of the most complex organs of our body (12). Together with the spinal cord, the brain forms the central nervous system (CNS) and its main function is to interpret and process the information from our environment and elaborate a response to it (13).

The brain can be differentiated in three main structures, each one with different functions. From a lower to upper view, these structures are (13):

- Brain stem: it is composed of the medulla oblongata, pons and mesencephalon. It contains most of the cranial nerves' nuclei and all the tracts that connect the forebrain with the spinal cord. It is responsible for autonomic processes, such as the heart rate or breathing.

- Cerebellum: it is a large structure, which comprises 10.5% of the total brain weight, and it is responsible of the balance and coordination of movement.

- Supratentorial brain: it is composed of the diencephalon and mesencephalon.

    - Diencephalon: it is located between the telencephalon and the brainstem and contains the dorsal thalamus, hypothalamus, ventral thalamus, and epithalamus. It processes the information that travels from most of the ascending sensory pathways to the cerebral cortex.

    - Telencephalon: it is the largest structure of the human brain, constituting 85% of the total brain weight. It is responsible for the sensory perception, information processing, and executive functions. This region is divided in two cerebral hemispheres and has an outer surface, called cerebral cortex.

The cerebral cortex consists of layers of neuron cell bodies, which have a particular configuration containing peaks (called gyri), that are separated by valleys (sulcus). This structure is divided into six

brain lobes: frontal, parietal, temporal, occipital, limbic and insular (Figure 1.2). It is the responsible structure for functions such as memory, language processing, judgment, etc (13).

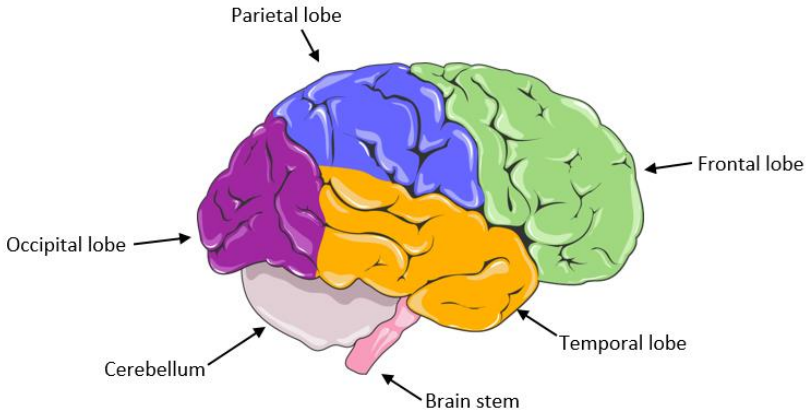


Figure 1.2. Anatomy of the human brain. Adapted from (14).

The individual structural and functional unit of the nervous system is the neuron or nerve cell. These cells are spread across the central nervous system, together with the glial cells, which provide nutrition, remove waste products, and maintain the electrochemical surroundings of neurons (13).

The main components of the neurons are (13):

- Dendrites: these structures usually branch from the cell body, having the appearance of a tree. They receive signals from other neurons through the contact with their axons, by forming the synapse, and contain numerous types of mitochondria, endoplasmic reticulum, vesicles, neurofilaments, microtubules, Nissl bodies, polyribosomes and free ribosomes.

- Cell body: also called soma, is the metabolic center of the neuron. Abundant mitochondria, ribosomes and an extensive rough endoplasmic reticulum (rER) and Golgi complex are present in this structure.

- Axons: they arise from the cell body and can extend for long distances. They contain a proximal part, called initial segment, and an axoplasm, which contains dense bundles of microtubules and neurofilaments that function as structural elements. The axons usually end in fine branches known as terminal arbors, where the functional point of contact between neurons, called synapse, is located.

  These structures are represented in Figure 1.3.

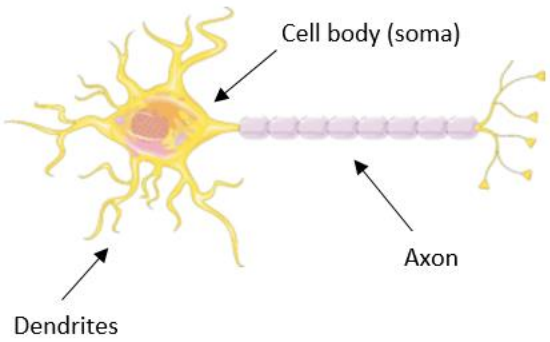


Figure 1.3. Anatomy of the neuron. Adapted from (14).

The electrochemical synapse is the most common type of synapse in the brain. It consists of a presynaptic element, which is part of an axon, a gap called the synaptic cleft, and the postsynaptic region of the innervated neuron or effector structure. In the synapse, an electrical impulse, called action potential, originates the release of a neuroactive substance, which is usually a neurotransmitter, neuromodulator or neuromediator, into the synaptic cleft. Then, the neuroactive substance is stored in synaptic vesicles in the presynaptic element and will be released into the synaptic space by the fusion of these vesicles with the presynaptic membrane. In this way, neurons receive information from either the environment or other nerve cells, they process information, and send information to other neurons or effector tissues (13).

In the brain, macroscopically, we can differentiate two types of matter: gray matter and white matter. The neuronal cell bodies, usually grouped in function-specific clusters, intermixed with myelinated and unmyelinated fibers, constitute the gray matter. The white matter is, however, formed by bundles of axons wrapped in a lipoprotein, called myelin. All the information entering or leaving the cerebral cortex travels through the subcortical white matter (13).

The human nervous system is extremely delicate. For this reason, the brain is covered by some membranous layers, called meninges, that are located under the skull (Figure 1.4). Their main function is to protect the brain. Moreover, they are also the support framework for important arteries, veins, and sinuses in the brain, and they enclose a fluid-filled cavity, the subarachnoid space, that is vital to the survival and normal function of the brain (13).

The human meninges are composed of the dura mater, arachnoid mater, and pia mater. The dura mater is the outermost portion, adherent to the inner surface of the skull. The inner two layers of the meninges, are the leptomeninges: arachnoid mater and the pia mater (13).
The arachnoid is a thin cellular avascular layer, which does not contain nerve fibers and is attached to the overlying dura. With the exception of the arachnoid trabeculae, this layer is separated from the pia mater by the subarachnoid space. The subarachnoid space contains cerebrospinal fluid (CSF) (Figure 1.5), which provides some nutrients for the brain and protects the brain from mechanical shock. The pia mater is located on the surface of the brain and closely follows its gyri and sulci (13).

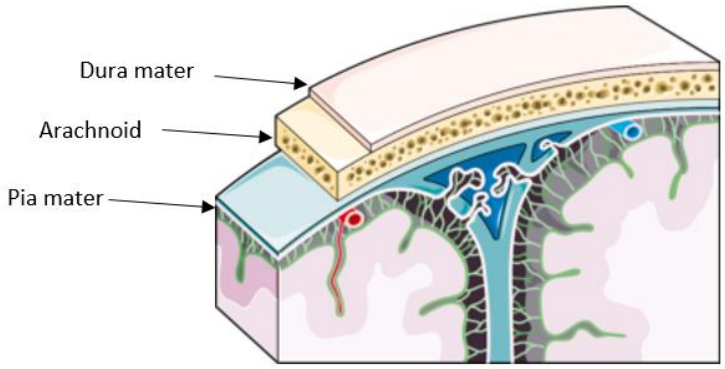


Figure 1.4 . Overview of the meningeal layers. Adapted from (14).

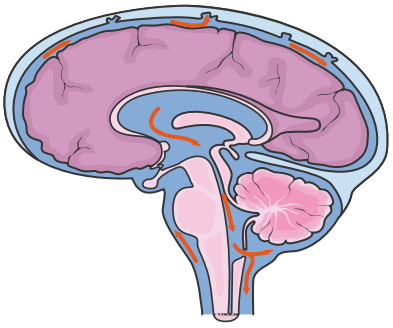


Figure 1.5 . Circulation of the cerebrospinal fluid (CSF) in the brain (represented with the red arrows). Obtained from (14).

1.2 Traumatic Brain Injury

1.2.1 Definition

Traumatic Brain Injury (TBI) is defined as an injury to the brain caused by an external force applied to the head or body (1) and it is nowadays a huge public health problem, affecting people of all ages worldwide and being a major cause of death and disability (2).

TBI is a heterogeneous disorder, which can be caused by different types of mechanical forces and can be categorized as open or closed head injury (15). Open head injuries occur when an object penetrates the brain and are infrequent (15). In this dissertation, we will focus on closed-head injuries, where two types of forces can take place (15):

- Contact forces: they are caused by the impact to the head. They can have effects locally or close to the impact side (15), and are the main cause of skull fractures (16).

- Inertial forces: they are caused by the acceleration of the head, which can lead to the differential movement of the brain inside the skull and can cause brain damage (15). These inertial forces can be translational or rotational, depending on their direction of the accelerations causing them (15–17):

- Translational or linear: occurs when the brain moves in an antero-posterior direction, in a straight line, without rotation.

- Rotational: occurs when the brain rotates around its center of gravity.

These forces could occur in isolation. However, they commonly act in combination, leading to brain damage (15). The most frequent brain injury types in TBI cases are:

- Acute subdural hematoma (ASDH): it is a blood collection located between the dura and the arachnoid mater, in the subdural space. It can be originated from the rupture of a bridging vein, the laceration of a superficial cortical blood vessel, or they can appear secondary to an underlying contusion (18).

- Epidural hematoma: it is a blood collection located between the skull and the dura mater. It is usually caused by the laceration of a meningeal artery by a skull fracture (18).

- Intraparenchymal hematoma: it is a collection of blood within the brain tissue, which usually originates from a brain contusion and occurs when a hemorrhagic lesion, located in the brain parenchyma, becomes a blood clot of a greater volume (18).

- Cerebral contusion: it can be defined as a focal hemorrhage found in the cerebral cortex, associated to necrosis and surrounding edema. Contusions can also expand into the white matter, causing a mass effect in the brain (19). The frontal and temporal lobes are their most frequent location (18).

- Diffuse axonal injury (DAI): it is the axonal damage that occurs due to the sudden acceleration-deceleration or rotation forces applied to the head (20). These forces can cause the stretching and torsion of the axons, leading to multiple ruptures. Once the axonal damage is produced, a series of biochemical events initiate, leading to a disruption of the neural connections in the damaged area (21).

- Concussion: it can be defined as a mild form of brain injury, which affects the brain functioning temporarily (22). In these patients, no structural changes can be observed in the brain (23). The most common symptoms of a concussion are: headache, photo/phonophobia, dizziness, nausea, concentration or memory difficulties, mood disturbances and sleep alteration. These symptoms usually resolve spontaneously. However, some patients experience a delayed recovery, presenting a post-concussion syndrome (24).

1.2.2 Pathophysiology of TBI

The pathophysiology of TBI typically comprises a primary injury, which leads to a structural damage caused by the physical destruction of tissues at the moment of the impact, and the secondary injury, which appears as a cascade of biochemical, electrical and inflammatory physiologic events, as a consequence of the primary tissue damage (25).

Following a TBI, many pathobiological changes can occur, such as :

- Presence of excitatory neurotoxicity: after TBI, there is frequently a neuroexcitatory response, which causes widespread neuroexcitation and ionic flux, among other changes (26), leading to an excessive excitatory aminoacid signaling, mainly altering the glutaminergic and GABAergic function (27). This produces an imbalance in the normal excitation and inhibition necessary to control brain functions (28).

- Metabolic changes: the extracellular release of excitatory aminoacids, mainly glutamate, can trigger a metabolic dysfunction after injury (29), leading to a brief period of hyper glycosis in the acute phase (30).

- Neuroinflammation: after the trauma, the primary tissue damage causes inflammation, by releasing extravasated blood products, intracellular and intra-axonal content, and increasing oxidative stress (31). Therefore, the microglia activates and peripheral immune cells also infiltrate in the brain. (32). As a consequence, cerebral edema forms, causing brain swelling and increased intracranial pressure, which are risk factors for unfavorable outcomes after TBI (26).

- Vascular changes: abnormal vascular responses can also occur in acute and chronic phases post-TBI (26). Furthermore, severe forms of head injury are also associated with a loss of cerebrovascular autoregulation, as a direct functional response to the traumatic episode, where cerebral blood flow becomes directly pressure passive dependent on the systemic blood pressure to elicit either hyperperfusion or hypoperfusion (33).

- Neuronal damage: the vascular changes, immune response and the direct damage to the brain's fragile structure can lead to the disruption of the neuronal circuitry and even the necrotic cell loss or induction of apoptosis (34). This causes a series of complex neuronal functional changes that impact posttraumatic neurologic function and subsequent recovery (35).

- Protein misfolding: TBI has also been associated to protein misfolding, being a risk factor for delayed neurodegeneration and dementia, including Alzheimer's disease and chronic traumatic encephalopathy (36).

After the injury, some neurorestorative events also take place in the brain, such as neurogenesis, gliogenesis, angiogenesis, synaptic plasticity, and axonal sprouting. These processes contribute to the recovery after TBI (37).

1.2.3 Epidemiology of TBI

The incidence of TBI is increasing very fast worldwide (38), to the point that it has been estimated that 69 million people suffer TBI every year (39), which has an estimated economic cost of 60.43 billion US dollars annually (35).

In Europe, the reported TBI incidence ranged between 47.3 and 694 per 100,000 population per year (40,41). The most common causes of TBIs are fall accidents and road traffic accidents, which together account for approximately 50% of the cases (3). However, it is important to take into account that the proportion of TBIs caused by traffic accidents has decreased in the last years, and correspondingly, there has been an increase in the proportion of cases attributed to fall accidents (25), which are more common in the oldest age groups (42). Therefore, the rate of TBIs has now a peak incidence among adults older than 75 years old (3), as one every three persons >60 years old and one every two persons >80 years old have a fall accident every year (43).

Regarding the TBI injury severity, it has been calculated that 80% of the TBI cases are classified as mild, 10% as moderate TBI and 10% as severe TBI, following the Glasgow Coma Scale (GCS) classification (44).

Most patients with TBI are admitted to an emergency department (ED). In the US, 80% of the patients with TBI are treated in an ED. Moreover, in Europe, the overall incidence of hospital admissions for TBI was calculated to be 235 per 100,000 persons annually (33), while in the US was 93.8 per 100,000 persons (45), and in Canada of 74 per 100,000 persons (46).

The head has been the body region most commonly associated with mortality in trauma (47). In the US, 30.5% of all injury-related deaths involve a TBI (45) and the mortality risk after a TBI has been estimated to be 7 times bigger than the mortality risk for the general population (48). However, even higher mortality rates are seen in low-income and middle-income countries (49).

TBI also results frequently in long-term disability (50). In the last years a decline in TBI mortality has been found, mainly due to the changes in traffic policy and the improvements in clinical care (51). Nevertheless, public health prevention strategies specific for older patients are necessary to potentially reduce TBI's incidence in this age group (52). The huge negative impact that TBI has for the patients and society is clear and efficient solutions are necessary to reduce the current TBI-associated problems.

1.2.4 Diagnosis, clinical management and outcomes

TBI is a very heterogeneous condition. Differences in the cause of TBI, the biomechanical characteristics of the forces applied to the head, and the patients' demographic characteristics and previous clinical history lead to different clinical presentations, ranging from mild alterations of consciousness to mortality (53). Importantly, TBI is not an acute event, but a trigger of progressive injury which could last for months or years, leading to long-term disability (48).

In the assessment of TBI, the injury severity is usually classified by the acute level of consciousness of the patient, using the GCS score. Based on this scoring system, TBI severity can be categorized into mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS 3-8) (44). This categorization provides with very useful information of diagnostic and prognostic value. However, it is important to repeat this assessment frequently, as deteriorations in short periods of time are possible (54). Furthermore, additional neurologic signs should also be assessed in the patients, such as any lateralization signs within the motor examination or the pupil status, among others (55).

CT scans of the brain and skull are the most commonly used neuroimaging techniques for patients with TBI, in order to identify intracranial lesions, which may require immediate surgical intervention to relief mass effect on the brain (55).

The main objectives in the medical management of TBI are: the reduction of the cerebral edema and intracranial pressure (ICP), the prevention of the hypoxia or ischemia of the tissues, the reduction of the inflammation and metabolic demand with neuroprotection purposes, the correction of coagulopathies and the prevention of complications. An accurate diagnosis and clinical management of these patients is of huge importance to reduce mortality and long-term disability (55).
In the last decades, evidence-based medical approaches and the development of guidelines for the management of patients with TBI have substantially improved the clinical care of these patients. Nowadays, it is possible to perform more accurate disease phenotyping, due to the recent advances in neuroimaging and biomarker development (56).
In the neuroimaging field, advanced MR sequences, including susceptibility weighted imaging (SWI) and diffusions weighted imaging (DWI) have a higher sensitivity for detecting small lesions, such as microhemorrhages and traumatic axonal injury (42). Furthermore, techniques such as diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) have a big potential for the visualization of complex microstructural changes in these patients (57).
Biochemical biomarkers are also rapidly evolving and have a big potential in the TBI field to diagnose and characterize TBI, to track disease processes and to establish prognosis in these patients. Up to date, they can differentiate between neuronal and glial damage and provide insight into inflammatory neurodegenerative and regenerative processes (58).
TBI is associated with mortality, and physical, cognitive, and psychological disturbances, which can have a big impact on the patients' lives (59).
Assessing functional outcomes and QoL after TBI is usually a complex task, as it is sometimes difficult to identify specific consequences associated to specific types of brain damage (60).
Tools such as the Glasgow Outcome Scale (GOS) (61), GOS extended (62) and Quality of Life after Brain Injury (QOLIBRI) (63) are among the most used functional assessment techniques in clinical practice.
TBI can cause motor and sensory deficits, leading to a significant handicap that limits the return to the patients' previous lives (59). Moreover, cognitive impairments are also very frequently found in these patients, who can present deficits of attention, memory, information processing speed, and executive functioning (64). Furthermore, TBI has been identified as a risk factor for dementia (59).

Psychiatric disorders, such as depression, anxiety, and psychosis, as well as other maladaptive behaviors and personality changes, can also appear in these patients (59).

The combination of physical, cognitive, and emotional impairments creates a major obstacle for re-entry into the community. Decreased social contact, depression, and loneliness, combined with physical disabilities may severely deteriorate the patients QoL (59). In Europe, TBI accounts for the greatest number of total years lived with disability (65).

The most significant improvements in these patients, especially in the physical status, seem to happen during the first 6 months (66). However, outcomes may change after greater periods of time post-injury, both in the direction of recovery or progressive deterioration. Nevertheless, TBI is a chronic condition that can lead to deterioration even several years after the injury (36).

Up to date, there is still a lot of uncertainty surrounding outcome prediction in TBI (67). Predicting survival, functional deterioration and the recovery timeline in a TBI patient is, in many occasions, a very difficult task (67). Therefore, there is a need for improved prognostic tools for these patients.

1.3 The ageing brain

In the last decades, life expectancy has considerably increase worldwide, to the point that, by 2050, the population >60 years old is expected to reach around 2.1 billion people (68). However, despite this great improvement, as the older population increases, the financial burden of age-related health disorders will increase and preventive and therapeutic solutions are necessary in our society (68).
Ageing is a natural and irreversible process, associated not only with changes in the physical appearance and function of the organism, but also molecular changes. Genomic instability, telomere shortening, epigenetic alterations, loss of proteostasis, stem-cell ageing and dysfunction of intercellular communication are frequent hallmarks found during the ageing process (69,70).
The ageing process is also very relevant in the brain, leading to multiple physiological and structural changes. With age, the brain suffers a decline in autophagy (71), an altered metabolism (72), vascular changes (5,73,74), changes in the morphology of the neurons (75), alterations in neural plasticity (75) and a decrease in the brain volume and weight (76).
Furthermore, previous studies have shown that all aged brains show characteristic changes that are linked to neurodegeneration (77). The presence of amyloid plaques, neurofibrillary tangles, Lewy bodies, inclusions of TAR DNA-binding protein 43 (TDP-43), synaptic dystrophy, the loss of neurons and the loss of brain volume has also been identified in autopsy studies of brains of aged people who had not been diagnosed with a neurological disease (77,78).
These features vary greatly between individuals and it is unknown whether these changes are the precursors to neurodegeneration and disease or simply the products of brain ageing (79). However, ageing is a risk factor for neurodegeneration, and neurodegenerative disorders are one of the most relevant conditions for this population (80). Moreover, the ageing process usually leads to physiological and functional changes, such as deterioration in the balance system, muscle weakness, joint problems, cognitive decline and/or polypharmacy, among others, which increase their predisposition for fall accidents (4,73,81,82) and have a negative impact on the recovery process (83,84). Therefore, the older population has an increased risk of sustaining TBI (4,5), and often struggle with significant challenges after injury and an unclear recovery trajectory (84).

1.4 Traumatic Brain Injury in the older population

The incidence of TBI amongst older patients has been increasing in the last decades (4,85), mainly due to their more active lifestyles (81), leading to a higher risk of fall accidents (81).
The population ≥65 years old represents, currently, 10% of the patients with TBI worldwide (86). This incidence is expected to increase even more in Europe and double to 30% by 2060 (82). Moreover, 50% of the TBI-related deaths occur in this population currently (86).

Most TBI cases in older patients are classified as mild TBI (87). However, the term “mild TBI” could be a misnomer, as it refers to the initial functional status of the patient after TBI and not to the further course following admission, and these patients are particularly at risk for injuries with delayed mass effect and secondary deterioration (88–90).

The impact of TBI differs among different age groups. Outcomes in older patients with TBI are known to be worse than in their younger counterparts (4,5). Even mild TBI in these patients can lead to an exacerbation of the age-related functional decline, causing long-lasting physical, cognitive, behavioral and psychosocial impairments (90), which lead to a low Quality of Life (QoL) and additional mortality (4,5). Therefore, early diagnosis and identification of patients at risk, and tailored management of the older patients following a TBI, may help to improve outcomes and improve quality of life (81).

The primary goal of medical management in TBI is to safeguard the patient's Quality of Life (QoL) (91) by attempting to safeguard function, which can be affected by TBI long after the initial medical treatment phase (92,93). However, to date, the severity of brain trauma in the older patients is usually underestimated (94) and the lifelong impact of TBI on these patients' independence and wellbeing remains a relatively neglected area in the field of TBI-related research (9). Furthermore, despite the advances in clinical care in the last decades, the currently existing clinical guidelines for the management of patients with TBI do not specifically address the challenges which are usually found in older patients (81).

Older patients with TBI are usually treated less aggressively than younger patients. This might be the result of the higher GCS scores found at admission in this population, as well as recent ethical issues in regard to neurosurgical interventions (95). However, previous studies have shown that an increased level of trauma activation and neurosurgical interventions could improve these patients outcomes (96,97).

Furthermore, rehabilitation is also a key element in the recovery from TBI and it can determine the patients' outcomes. Nevertheless, despite its high importance, the rate of older patients who receive rehabilitation 3 months post-TBI is lower than in younger patients (98). Potentially resulting from this, older patients with TBI have higher disability rates after TBI (99).
The majority of the clinical decisions for these patients are based on the possible benefits or burdens of the treatment and the expected changes in their outcome and QoL (100). In those cases where outcomes are not expected to result in an improved function, life-sustaining interventions are most likely not performed (100). However, outcome prognosis in this population is still unclear (101), as up-to-date, there are not specific prognostic tools for mortality and functional outcomes in this population. Therefore, clinical decisions in these cases are challenging and difficult, and are taken in the context of high uncertainties. There is the need for the creation of specific prognostic tools which may assist clinical decision making and make the degree of uncertainty less problematic.

1.5 Research gap

TBI cases in the older population have been rising dramatically over the past two decades. However, the impact of TBI in older adults is still not well understood. Historically, TBI has been considered as a disease of the young population. In the last two decades, the calculated mean age of the studied TBI population in literature was of 32.73 years (9). In this period, the TBI research field has thoroughly focused on understanding the TBI phenomenon in sports players, war veterans and victims of traffic accidents. However, now that the age of patients with TBI is increasing, there is no corresponding

increase in the age of the included patients in TBI research studies and the attempts of translating the scarce evidence to clinical practice are failing (9).

The existing prognostic tools for the condition, such as the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) and Corticosteroid Randomization after Significant Head Injury (CRASH), have not been validated for the older population, lose reliability with age, and do not consider the loss of function after TBI. Moreover, the existing evidence-based clinical guidelines for TBI do not state specific recommendations for older patients and no guidelines are available for operative neurosurgical treatment of these patients. Therefore, the clinical management of older TBI patients is still a challenge associated with difficult ethical decisions.

There is a real need for more fundamental research to better understand the impact that TBI has on older patients' lives and to create specific prognostic tools and clinical guidelines for this population.

In order to achieve this, first, injury patterns, injury severity, clinical presentation, clinical management, functional outcomes and mortality in older TBI patients should be thoroughly investigated in order to better characterize the particularities associated with TBI in older patients. Then, advanced statistical methods and machine learning (ML) models should be used in order to achieve functional outcome and mortality predictions in these patients. Improved knowledge and the creation of age-specific prognostic tools will contribute to the creation of clinical guidelines and the improvement and tailoring of these patients' clinical care in the future.

Chapter 2

General Aim

In this chapter, we describe the way by which the previously explained research gaps are approached in this dissertation. We do this first by stating the general objectives of this research and then by describing the individual objectives and thesis outline.

2.1 General research objective

We have previously seen in Chapter 1 that there is a need for more fundamental research to better understand the impact that TBI has on older patients' lives and to create specific prognostic tools and clinical guidelines for this population.
In order to study these gaps, we hypothesized that :

- TBI in adults aged ≥ 65 years differs from TBI in younger people in terms of injury mechanisms, injury types, co-morbidities and outcomes.
- TBI, including mild TBI, is a potential life changing event in older patients, including an underestimated risk of loss of independence and reduction of quality of life. Furthermore, it carries an increased risk for cognitive decline and dementias, and a substantial risk of functional loss and mortality.
- Although different than in the general adult population, predictive factors for functional outcome and mortality after TBI in older patients exist and can contribute to a specific prognostic tool to aid decision making and family counseling.

Therefore, the goal of this PhD project is twofold. First of all, it aims at mapping injury patterns, injury severity and risk profiles for TBI in older patients, and at objectively assessing the nature of brain damage, its sequelae in terms of level of dependency, cognitive and motor disturbances, and their impact on quality of life after TBI. Secondly, it aims at creating a new prognostic tool for mortality and functional outcomes after TBI in the older population, in order to help decision making and counseling of families.

2.2 Specific objectives

In order to achieve the general aims, the following specific objectives have been proposed for this dissertation:

Objective 1: Characterization of the mechanisms, injuries, clinical presentation, co-morbidities, clinical management and outcomes of TBI in older adults

A thorough description of the patients' demographics, injury patterns, injury severity, clinical presentation, clinical management and outcomes, mainly in terms of mortality, will be provided through the retrospective analysis of the clinical records of more than a thousand patients aged ≥ 65 years admitted to University Hospitals Leuven (UZ Leuven) for TBI between 1999 and 2019. The study of such an extensive dataset, collected over 2 decades, will help us to better understand the TBI phenomenon in older patients and to better understand the temporal changes on injury mechanism, clinical management and outcome in these patients. This will contribute to improve patients' and family counseling, and to set the future direction of a better clinical care for the patients with TBI aged ≥65 years.

Objective 2: Characterization of functional outcomes and impact on Quality of Life of TBI in older patients

First, the results of two systematic reviews and meta-analyses will be reported with the objective of documenting risk factors for and incidence of post-TBI functional decline and dependency, nursing home admission, depression, poor Quality of Life (QoL) and mortality in the older population.
Second, data on the results of telephonic and written cognitive, QoL and sleep quality evaluations performed 1 to 13 years post-TBI in those patients will be presented.
Finally, data on prospective cognitive and motor functions, sleep quality and QoL assessments, performed in patients ≥ 65 years old admitted to UZ Leuven between 2019 and 2022 6 months post-TBI, will be used to explain the short-term outcomes after TBI. All the studied outcomes will be correlated to the patients' clinical history details and injury characteristics, brain MRI results 6 months post-TBI and biomarker analyses for a more comprehensive understanding.

Objective 3: Investigation of prognostic factors for mortality within 30 days and outcomes 6 and 12 months post-TBI in a large international multicenter prospective data repository

Prognostic factors for 30-day mortality and unfavorable functional outcomes 6 and 12 months post-TBI will be studied in an international prospective dataset, the CENTER-TBI database, which was collected in centers from 20 countries across Europe and Israel (102) and contains data of approximately 1,000 patients with TBI aged ≥65 years, registered at different timepoints, from hospital admission to 12 months follow-up.
Specific prognostic tools for these outcome measures will be created using advanced statistical methods and machine learning techniques in Python.

Due to the prospective nature and big sample size of the dataset, we believe that this is the best available data source to achieve this goal.

Objective 4: In-depth assessment of quality of life and real life impact of TBI in older adults by means of a focus group study

A qualitative assessment of the main difficulties that older TBI patients suffer after the accident and how those affect their quality of life will be performed through the focus group study qualitative methodology, in a group of 6 patients with TBI ≥65 years old, admitted to the University Hospitals Leuven between 2016 and 2022.
The qualitative nature of this study will allow us to pinpoint the most relevant aspects in the patients' life after TBI and how those affect QoL. This information cannot be collected through standardized quantitative QoL questionnaires that will be use to achieve Objective 2. Therefore, in this way, we expect to thoroughly understand QoL changes in older patients with TBI with the combination of qualitative and quantitative methods. This will have a big potential impact for clinical decision making in the future.

2.3 Thesis Outline

The previously explained objectives will be achieved through the following chapters. Chapter 3 will characterize risk factors for and incidence of post-TBI functional decline and dependency, nursing home admission, depression, poor Quality of Life (QoL) and mortality in the older population, based on the results of two systematic reviews and meta-analyses. Chapter 4 will present an overview on patients' demographic characteristics and previous clinical history, injury patterns and severity, clinical management, and outcomes in patients with TBI aged ≥65 years, admitted to UZ Leuven between 1999 and 2019, based on a retrospective clinical database study of >1,000 patients.
Chapter 5 will discuss the results obtained from two different clinical trials. First, a study in which telephonic and written cognitive, QoL and sleep quality evaluations were performed 1 to 13 years post-injury in patients with TBI ≥65 years old admitted to UZ Leuven and a control group of healthy volunteers with similar demographic characteristics. Second, a controlled prospective study where injuries, serum-based injury biomarkers, and cognitive and motor functions, MRI of the brain and quality of life 6 months post-injury were studied in patients ≥65 years old admitted to UZ Leuven with a mild TBI and where MRI results and cognitive and motor results were compared to those obtained from healthy volunteers ≥65 years old.
Chapter 6 will show the study of prognostic factors and development of a prognostic tool for 30-day mortality and 12-month functional outcome based on the international prospective CENTER TBI data repository, using advance statistical methods and machine learning techniques.
Chapter 7 will report data on the qualitative analysis of quality of life and real life impact of TBI in older patients using the focus group methodology.
Finally, in chapter 8, all the obtained findings will be summarized and a general discussion will be proposed in which the findings are confronted with and weighted against existing evidence. Suggestions on how to continue the work presented in this dissertation will be also given.

Chapter 3

The impact of Traumatic Brain Injury on older patients' functional outcome and well-being

In this chapter, Section 3.1 will present the results obtained from a systematic review and meta-analysis on risk factors for and incidence of post-TBI functional decline and dependency, nursing home admission, depression and poor Quality of Life (QoL) in the older population (103). Then, Section 3.2 will show the results obtained from a systematic review and meta-analysis on outcomes after neurosurgical treatment in this population.

3.1 Functional outcome, dependency and well-being after traumatic brain injury in older patients

This section is based on:

Gavrila Laic, R.A., Bogaert, L., Vander Sloten, J., Depreitere, B. with Gavrila Laic, R.A. (corresp. author) (2021). Functional outcome, dependency and well-being after traumatic brain injury in the elderly population: A systematic review and meta-analysis. Brain and Spine, 1, Art.No. 100849

3.1.1 Abstract

Introduction: Traumatic brain injury (TBI) rates in older patients are increasing worldwide, mainly due to fall accidents. However, TBI's impact on these patients' lives has not been thoroughly investigated.
Research question: This systematic review and meta-analysis aims at describing post-TBI incidence of functional decline, dependency, nursing home admission, reduced quality of life and depression in older patients.
Materials and methods: A systematic literature search was performed in PubMed, EMBASE, Web Of Science, BIOSIS, Current Contents Connect, Data Citation Index, MEDLINE, SciELO, Cochrane library and CINAHL. Study selection was conducted by two independent reviewers. Meta-analysis was performed using a random-effects model.
Results: Twenty-seven studies were included in the qualitative synthesis and twenty-five in a random-effects meta-analysis. The prevalence of unfavorable functional outcomes after TBI was 65.2% (95% CI: 51.1- 78.0). Admission to a nursing home had a pooled prevalence of 28.5% (95% CI: 17.1-41.6) and dependency rates ranged between 16.9% and 74.0%. A reduced quality of life was documented throughout follow-up with SF12/36 scores between 35.3-52.3/100. 2.6-4.8% of the patients with mild

TBI reported depressive symptoms. A large heterogeneity was found among studies for functional outcomes and discharge destination.
Discussion and conclusion: In conclusion, older patients have a significant risk for functional decline, dependency, nursing home admission and low quality of life following TBI. Moreover, more severe injuries lead to worse outcomes. These findings are important to provide accurate patient and family counseling, set realistic treatment targets and aim at relevant outcome variables in prognostic models for TBI in older patients.

3.1.2 Introduction

Traumatic brain injury (TBI) is defined as a physical and/or functional injury to the brain caused by an external force (1) and its incidence amongst older patients has been increasing in the last decades (3,4,85). Most cases of TBI in patients aged ≥65 years are classified as mild TBI (87), following the Glasgow Coma Scale (GCS) (44). However, the term "mild TBI" could be a misnomer, as these patients are particularly at risk for injuries with delayed mass effect and secondary deterioration (88–90).
Older patients, conventionally defined as patients with a chronological age ≥65 years old in most TBI studies (92,98,112,113,104–111), are at risk for a worse recovery after TBI (85,106,114–117). Poor premorbid condition, neurological sequelae and overall deconditioning lead to an increased risk for psychosocial changes (6), disability (7) and secondary medical complications (8).
The primary goal of medical management in TBI is to safeguard the patient's Quality of Life (QoL)(91), which can be affected by TBI long after the initial medical treatment phase (92,93). However, the lifelong impact of TBI on older patients' wellbeing remains a relatively neglected area in the field of TBI-related research to date (9).
Better insight into this matter may help (1) clinicians to set realistic treatment targets, (2) patients and families to gain understanding by improved counseling, and (3) researchers to underpin most relevant outcome determinants in the development of prognostic models for this population. We hypothesize that TBI in older patients is associated with a high likelihood of significant functional decline, which easily leads to dependency, and in turn is associated with reduced QoL and depression in this age group (6,7,114,118).
Therefore, the main objective of the current study is to document risk factors for and incidence of post-TBI functional decline and dependency, nursing home admission, depression and poor QoL in the older population.

3.1.3 Methods

Study registration
The protocol for this systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number [CRD42020212288]) and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) 2020 statement (119) [Fig 3.1] and the Cochrane Handbook for Systematic Reviews of Interventions (120).

Search strategy and study selection

The systematic search was performed in October 2020 in PubMed, EMBASE, Web Of Science (WOS) Core Collection, BIOSIS Citation Index, Current Contents Connect, Data Citation Index, MEDLINE, SciELO Citation Index, the Cochrane Central Register of Controlled Trials and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Language was restricted to English. There was no restriction on publication date. The used MESH (Medical Subject Headings) terms were ”Aged”, “Geriatrics’’, ‘’gerontology’’, "Nursing Homes", "Health Services for the Aged", "Homes for the Aged", "Housing for the Elderly", "Brain Injuries, Traumatic", "qualitative research" and "Case-Control Studies".

Studies’ inclusion was limited to clinical, multi-center, case-control or qualitative studies; performed in hospitals, rehabilitation centers and health care facilities for older patients; including ≥15 patients who sustained a TBI at ≥65 years (as a subset of a broader cohort or as an independent cohort of older patients); using one of the assessment instruments included in Appendix 3A or reporting nursing home admission rates.

Studies were excluded if they included patients with a different pre-existing neurological condition or previous alcohol/drugs abuse or did not specifically associate outcomes to the TBI severity (given by the GCS).

Data extraction and analysis

First, references obtained from the systematic search were entered and deduplicated into EndNote X9 (Clarivate Analytics, Philadelphia). Second, titles and abstracts were screened for concordance with the in- and exclusion criteria using Rayyan QCRI software. Full texts of selected studies were then reviewed for final inclusion. The selection process was performed independently by two researchers blinded from each other. Disagreement in results was resolved through mutual discussion. When necessary, a third reviewer was consulted for arbitrage. Data extraction was performed using a standardized data collection form, including the first author’s name, publication year, study design, sample size and number of dropouts, TBI injury severity, brain damage location, age of participants, sex of participants, number of months between TBI and assessment, metrics used and outcomes. In case of incomplete or ambiguous data, the corresponding author was contacted via e-mail. All included studies were subjected to descriptive analyses. For studies including a ≥16 years old cohort, only the results of the subset of patients ≥65 years were taken into account.

Quality assessment

The methodological quality of the studies was assessed using the Downs and Black Scale (121) [Appendix 3B] and classified as excellent (26–27), good (20–25), fair (15–19) and poor (≤14).

Statistical analysis

Two random-effects meta-analyses were conducted using tidyverse, meta and metafor packages in R 4.1.0, using the inverse variance weighted average method (IVW) (122), in order to calculate combined prevalences. The DerSimonian and Laird method was used to obtain Tau^2 (123) and the Freeman-Turkey double arcsine transformation method to calculate combined prevalences (124). Clopper-Pearson confidence intervals for individual studies were reported (125). Heterogeneity was quantified using I^2 and interpreted as low (0%–30%), moderate (30%–50%), substantial (50%–80%) and considerable (80%–100%) (126). Publication bias was assessed using funnel plots of the combined prevalences.

3.1.4 Results

The database search retrieved a total of 14,407 citations. 11,229 articles were screened by title and abstract and 1,974 full-text articles were assessed for eligibility, of which 27 articles were included in the qualitative synthesis [Fig 3.1 and tables 3.1 to 3.5] and 25 were meta-analyzed. 40.7% of the included studies had a poor quality and 59.3% a fair quality [Appendix 3B].

Demographic and study characteristics

The included studies were retrospective or prospective observational studies performed in single or multi-center settings, or based on regional or national databases. The number of included patients ranged between 29 to 36,288. Follow-up duration across studies ranged from hospital discharge to 4 years post-TBI [Tables 3.1 to 3.5].

Functional outcome

Functional outcome was assessed using the Glasgow Outcome Score (GOS) and the Extended Glasgow Outcome Score (GOS-E) in 15 studies [Table 3.1], of which 14 could be meta-analyzed [Figures 3.2 and 3.3].

GOS is scored following a scale where 1 corresponds to death, 2 to vegetative state, 3 to severe disability, 4 to moderate disability and 5 to good recovery (61). GOS-E is scored as: 1 (death), 2 (vegetative state), 3 (lower severe disability), 4 (upper severe disability), 5 (lower moderate disability), 6 (upper moderate disability), 7 (lower good recovery) to 8 (upper good recovery) (62). GOS 1-3 and GOS-E 1-4 are considered as unfavorable outcomes. Results are visualized in Figure 3.4.

The pooled prevalence of unfavorable outcomes was 65.2% (95% CI: 51.1- 78.0) at 12 months post TBI in patients with mild, moderate and severe TBI. A significant heterogeneity between studies was found (I^2=97%, p<0.01) [Fig 3.2 and 3.3] and the asymmetric funnel plot indicates publication bias [Fig 3.3].

In patients with mild TBI, 45.8% had unfavorable outcomes at hospital discharge, including 16.5% who died (107). Rates of good recovery at discharge after mild TBI varied between 2.4 and 71.0% (104,106,107). At 6 months post mild TBI, rates of unfavorable outcomes between 6.2 and 20% were reported (105,127), while these were of 2.5% at 1 year (108).

For moderate TBI, at 6 months FU, 53.3-85.7% of the patients had unfavorable outcomes (105,127), and for moderate and severe TBI combined the 6 months unfavorable outcome rate reportedly was 80.0% (110).

For patients who sustained severe TBI, outcomes were unfavorable in 79.3% at hospital discharge (128), 41.8-89.9% 3-6 months post TBI (105,111,129) and 72.2-89.0% 1 year post-TBI (112,113).

Differences regarding recovery in patients with mild TBI were observed across studies performed in different regions. While Mohindra et al (127) and Julien et al (107) reported very low or unexisting ''good recovery'' rates in India and Canada, respectively, higher recovery rates were reported by Hawley et al (104), Choi et al (105) and Mosenthal et al (106) in the United Kingdom (UK), Korea and United States (US).

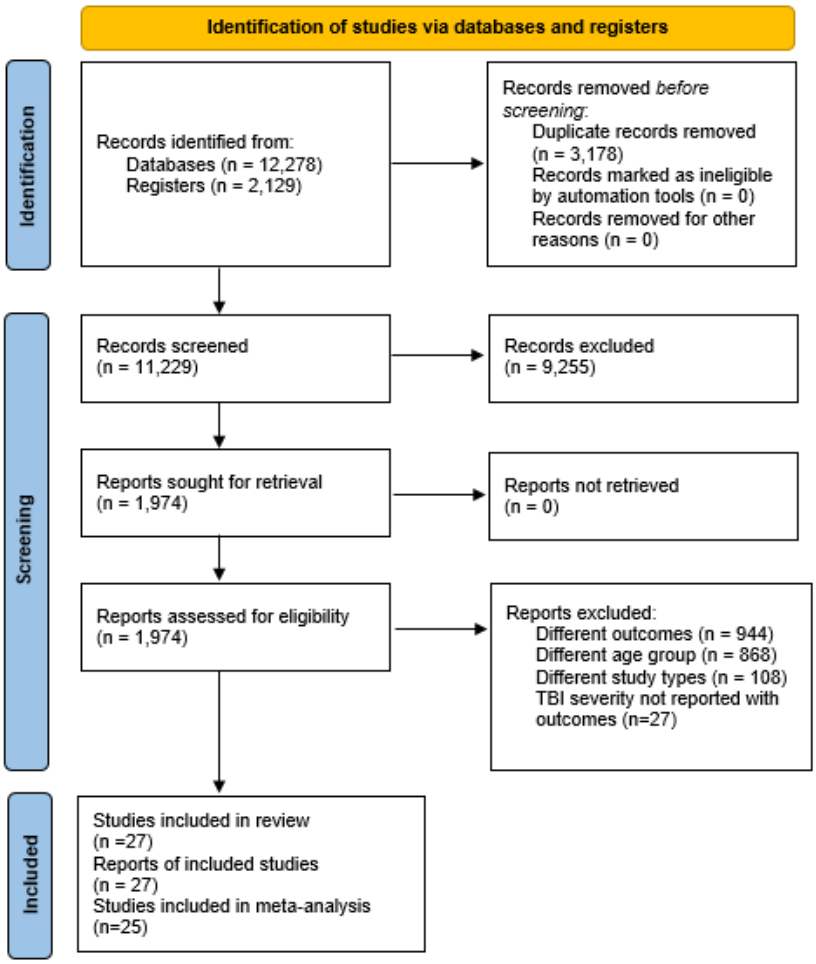


Figure 3.1. PRISMA Flow Diagram

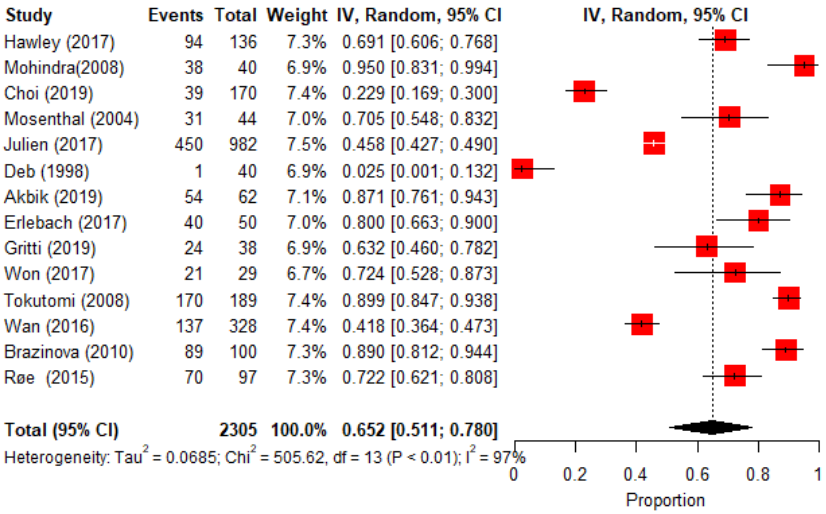


Figure 3.2. Meta-analysis results for unfavorable functional outcomes

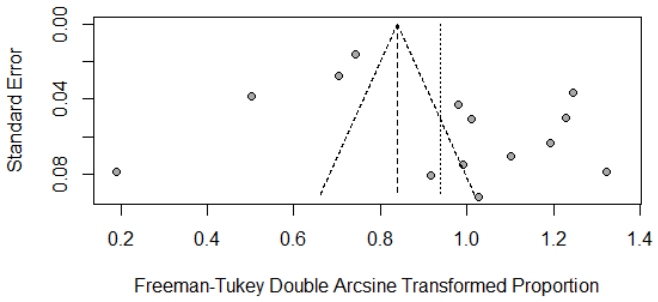


Figure 3.3. Funnel plot for the studies used in the unfavorable functional outcomes meta-analysis, indicating the TBI effect estimate on unfavorable outcomes in the included studies. The horizontal axis indicates the variance of each study's proportion and the vertical axis standard errors. The diagonal lines represent the 95% confidence limits and the vertical line the summary effect of TBI on the studied outcome.

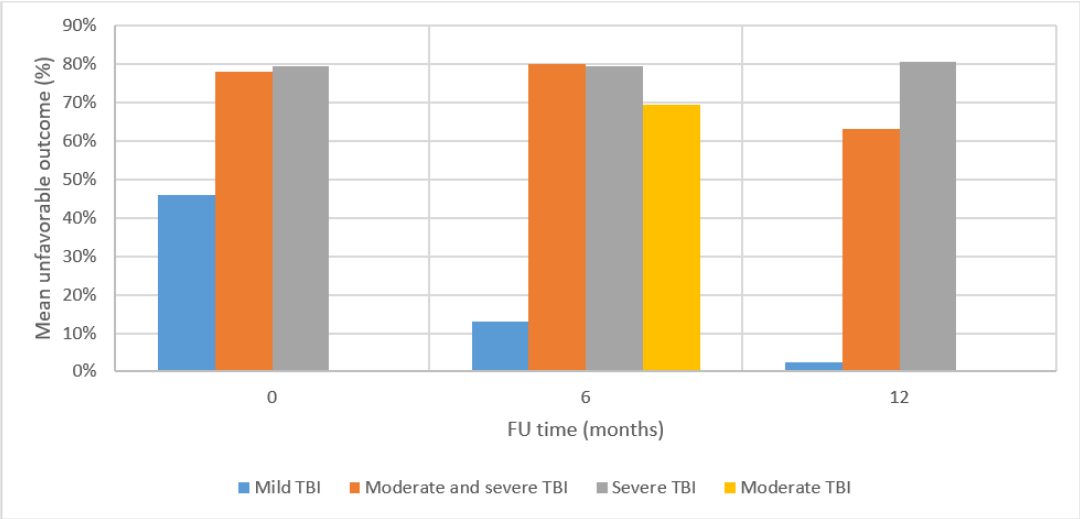


Figure 3.4. Mean rates of unfavorable functional outcomes for the different TBI severities at different follow-up time points

Activities of daily living (ADL) dependency and social integration

ADL dependency was assessed in 8 studies using the Functional Independence Measure (FIM), Older Americans' Resources and Services scale (OARS) (130), the Community Integration Questionnaire (CIQ) (131) and non-standardized evaluations [Tables 3.2 and 3.3].

FIM is an 18-item functional assessment scale containing a motor and cognitive domain. Motor scores range between 13 (lowest) and 91 (highest level of independence), cognitive scores between 5 (lowest) and 35 (highest level of independence) and total score between 18 (lowest) and 126 (highest level of independence) (132).

OARS is a 28-point questionnaire which assesses different ADL activities, scored on a 0-2 scale. Scores range between 0 (complete dependency) and 28 (complete independency) (130).

The CIQ is a 15-item questionnaire which assesses home integration, social integration and productive activity. Total scores range from 0 (low integration) to 29 points (high integration), with a maximum score of 10 points for home integration, 12 points for social interaction and 7 points for productive activity (131).

In patients with mild TBI, at hospital discharge, a dependency rate of 38.6% was registered (106). At 6 months follow-up, Brousseau *et al* (133) found a functional decline in 7.0% of the patients, defined as

a reduction of 3 points on the OARS scale from their emergency department visit to FU, while on the other hand Mosenthal *et al* (106) showed an improvement in FIM scores in 20.5% of the patients at 6 months post mild TBI. At 1 year follow-up, 65-74 year-old patients had an average of 1.3 ADL difficulties and 75-84 year-old patients an average of 2.2 ADL difficulties (115).

Considering patients with mild and moderate TBI, Miller *et al* (134) found that at hospital discharge 24.0% of the patients 70-79 years old, 33.0% of the patients 80-89 years old and 39.0% of the patients ≥ 90 years old were dependent.

For patients with moderate and severe TBI, at hospital discharge Susman *et al* reported dependency rates of 35.8%, 16.9% and 33.6%, for motor function, expression and feeding, respectively (92).

For severe TBI cases, Lilley *et al* found that 67.8% of the patients were dependent for one or more ADL activities at hospital discharge (135). At 2-4 years FU, 74.0% of the patients were dependent for mobility, of which 49.3% needed help for transfers and 41.9% needed help for climbing stairs, and 73.0% were dependent for self-care (136).

Discharge destination

Discharge destination from hospital discharge to 4 years post TBI was reported in 12 articles [Table 3.4].

In patients with mild TBI, 5.8% to 34.2% were discharged to a nursing home (115,137–139) and 35.0% continued residence beyond one year (115).

Considering patients with mild and moderate TBI, Miller *et al* (134) found that 24.0% of the 70-79 years-old, 33.0% of the 80-89 years-old and 39.0% of the ≥90 years-old patients were discharged to an institution (134).

Rates of nursing homes discharge ranged between 28.3-54.0% in studies considering both moderate and severe TBI (92,140). In patients with severe TBI, this rate was 67.8% at hospital discharge (135), 10.3% at 3 months, 14.4% at 6 months (98), 5.1-16.5% at 12 months (98,113) and 22.1% at 24-48 months (136).

Similar rates of nursing home admissions for patients with mild TBI were reported by Khan et al (139), Velez et al (138) and Thompson et al (115) in the US, which were higher than the rate reported by Schmidt et al (137) in Switzerland. No similarities were found in studies conducted in the US for patients with moderate and severe TBI (115,140,141).

A high heterogeneity between studies was found in the 12 meta-analyzed studies (I^2=100%, p<0.01) [Fig 3.5 and 3.6]. The asymmetric funnel plot indicates publication bias [Fig 3.6]. The pooled prevalence of nursing home admission was of 28.5% (95% CI: 17.1-41.6).

Table 3.1. Summary of studies which assessed functional outcomes using GOS and GOS-E

Study (year)	TBI severity (given by GCS)	ISS	Type of study	Study settings	Country	N ≥ 65 years old	LOS (days)	Comorbidities	Pre-injury anticoagulation (N)	Time post-TBI (months)	Outcome				
											Death (%)	Persistent vegetative state (%)	Severe disability (%)	Moderate disability (%)	Good recovery (%)
Hawley (2017) (104)	All	NR	Retrospective	National database	UK	575 (439 mild TBI and 136 moderate or severe TBI)	65-74 years old: median (IQR)=11(15) 75-84 years old: median (IQR)=14(25) ≥ 85 years old: median (IQR)=16(23)	NR	NR	Hospital discharge	143 (24.9%) patients: 35 patients 65-74 years old, 46 75-84 years old and 62≥85 years old. 80 of them had a moderate or severe TBI.	-	29 (5.0%) patients: 11 patients 65-74 years old, 13 75-84 years old and 5 ≥85 years old. 14 of them had a moderate or severe TBI	79 (13.7) patients: 27 patients 65-74 years old, 33 75-84 years old and 19 ≥85 years old. 10 of them had a moderate or severe TBI.	358 (62.3%) patients: 127 patients 65-74 years old, 130 75-84 years old and 101 ≥85 years old. 32 of them had a moderate or severe TBI and 306 had a mild TBI.
Mohindra (2008) (127)	All	NR	Retrospective	Hospital	India	45 ≥70 years old (5 mild TBI, 7 moderate TBI and 33 severe TBI)	NR	NR	NR	6	5 (71.4%) patients with moderate TBI and 24 (72.7%) of the patient	1 (14.3%) patients with moderate TBI and 8 (24.2%) of the patients with	1 (20.0%) patients with mild TBI	4(80.0%) patients with mild TBI, 1 (14.3%) of the patients with moderate TBI and 1	-

											s with severe TBI	severe TBI		(3.0%) patient with severe TBI	
Choi (2019) (105)	All	21 patients minor (1-8); 53 moderate (9-15); 56 serious (16-24); 40 severe (≥25)	Retrospective	Hospital	Republic of Korea	170 (129 mild TBI, 15 moderate TBI and 26 severe TBI)	NR	NR	NR	6	8 (6.2%) patients with mild TBI, 8 (53.3%) with moderate TBI and 23 (88.5%) with severe TBI			118 (91.5%) patients with mild TBI, 10 (66.7%) with moderate TBI and 3 (11.5%) with severe TBI	
Mosenthal (2004) (106)	Mild	NR	Retrospective	Multi-center	US	44	NR	NR	NR	Hospital discharge	Unknown	Unknown	Unknown	Unknown	13 (29.5%)
Julien (2017) (107)	Mild	Median=25 (results only reported for 952 patients)	Retrospective	Hospital	Canada	982	Median (IQR)=11 (17)	NR	439 (44.7%)	Hospital discharge	162 (16.5%)	31 (3.2 %)	256 (26.1%)	508 (51.7%)	24 (2.4%)
Deb (1998) (108)	Mild	NR	Retrospective	Hospital	UK	40	NR	NR	NR	12	0 (0.0%)	0 (0.0%)	1 (2.5%)	12 (30.0%)	-
Akbik (2019) (109)	Moderate and severe	NR	Retrospective	Level I trauma center	US	62 (31 GCS >9	Median=9	37 patients hypertension, 10 atrial	37	Hospital discharge	24 (38.7%) patients with a	4 (6.5%) patients	26 (41.9%) patients with a mean	6 (9.7%) patients with a mean	2 (3.2%) patients with a mean

						and 31 GCS≤9)		fibrillation, 12 diabetes, 14 coronary artery disease, 8 CVA, 8 neoplastic process, 7 dementia			mean GCS = 7.81 ±4.09	with a mean GCS = 7.81 ±4.09	GCS=11.16 ± 3.6	GCS=9.86± 4.34	GCS=9.86± 4.34
Erlebach (2017) (110)	Moderate and severe	Median (IQR)=20 (11)	Retrospective	Hospital	Switzerland	50	9.2±8.5 (in ICU)	1 patient stroke, 5 TBI, 1 epilepsy, 10 diabetes, 35 cardiovascular diseases, 4 psychiatric disorder and 8 alcohol/drug abuse	27	6	40 (80.0%)			10 (20.0%)	
Gritti (2019) (142)	Moderate and severe	NR	Retrospective	Hospital	Italy	38 ≥70 years old	NR	15 patients diabetes and 27 hypertension	35	12	15 (39.5%)	1(2.6 %)	8 (21.0%)	7(18.4%)	7(18.4%)
Won (2017) (128)	Severe	NR	Retrospective	Single center	Germany	29 ≥80 years old	9.1±6.2	59 patients hypertension, 30 atrial fibrillation, 26 type 2 diabetes, 44 cardiovasc	51	Hospital discharge	23 (79.3%)			6 (20.7%)	

								ular diseases, 20 respiratory insufficiency, 14 renal failure, 8 hematological disease, 51 metabolic disease, 8 previous stroke, 34 pneumonia, 3 sepsis							
Tokutomi (2008) (129)	Severe	Mean (SD)= 26 (9)	Retrospective	National database	Japan	189> 70 years old	NR	52.4% of the cases	NR	3-6	131 (69.3%)	17 (9.0%)	22 (11.6%)	9 (4.8%)	
Haller (2017) (98)	Severe	Median (IQR)=25 (12)	Prospective observational	Multi-center	Switzerland	97	NR	10 patients psychiatric disorders and 16 alcohol abuse	26	3, 6 and 12	Mean GOS-E 6 (range 3-8) at 3 and 6 months, and mean GOS-E 7 (range 5-8) at 12 months				Unknown
Wan (2016) (111)	Severe	NR	Retrospective	Hospital	China	328	NR	51 patients	NR	6	60 (18.3%)	77 (23.5%)		35 (10.7%)	
Brazinova (2010) (112)	Severe	Median= 20	Prospective observational	Multi-center	Austria, Bosnia and Herzegovi	100	NR	NR	NR	12	89 (89.0%)			11 (11.0%)	

					na, Croatia, Macedonia, and Slovakia							
Røe (2015) (113)	Severe	NR	Prospective observational	Multi-center	Norway	97 (of which 51 ≥71 years old)	NR	35 patients 65-74 years old and 45 ≥75 years old	21 patients 65-74 years old and 37 patients ≥75 years old	12	20 (44.0%) the patients 65-74 years old and 44 (86.0%) patients ≥75 years old	26 (56.0%) patients 65-74 years old and 7 (14 .0%) patients ≥75 years old

N=number; GCS=Glasgow Coma Scale; All=Mild, moderate and severe TBI; ISS=Injury Severity Score; NR=not reported; LOS=length of hospital stay due to TBI; CVA=cerebrovascular accident; Severe disability=GOS of 3 or GOS-E of 3 or 4; Moderate disability= GOS of 4 or GOS-E of 5 or 6; Good recovery= GOS of 5 or GOS-E of 7 or 8; UK=United Kingdom ; US=United States of America

Table 3.2. Summary of studies which assessed ADL dependency after TBI using FIM

Study (year)	**TBI severity (given by GCS)**	**ISS**	**Type of study**	**Study settings**	**Country**	**N ≥ 65 years old**	**LOS (days)**	**Comorbidities**	**Pre-injury anticoagulation**	**Time post-TBI (months)**	**Outcomes**		
											FIM motor (mean)	**FIM cognition (mean)**	**FIM total (mean)**
Mosenthal (2004) (106)	Mild	NR	Retrospective	Multi-center	US	44	NR	NR	NR	Hospital discharge and 6	27 (61.4%) total independence at hospital discharge and at 6 months, 3 patients (6.8%) worse FIM than at discharge, 20 patients (45.5%) unchanged FIM and 9 patients (20.5%) improved FIM		
Susman (2002) (92)	Moderate and severe (mean GCS 8.7)	Mean±SD= 17.4± 8.7	Retrospective observational study	Database	US	3244	NR	NR	NR	Hospital discharge	Abnormal FIM locomotion: 1161 patients (35.8%) Abnormal FIM expression: 548 patients (16.9%) Abnormal FIM feeding: 1090 patients (33.6%)		

Lecours (2012) (136)	Severe	NR	Retrospective observational study	Level I and level II trauma center	Canada	95 (44 65-74 years old, 42 75-84 years old and 9 ≥85 years old)	NR	NR	NR	24-48	42.6 (SD 9.5): 40.5 (SD 11.6) in the 65-74 years old, 41.5 (SD 10.5) in the 65-74 years old and 41.0 (SD 17.0) in the ≥85 years old	17.8 (SD 5.4)	Unknown

N=number; GCS=Glasgow Coma Scale; ISS=Injury Severity Score; NR=not reported; LOS=length of hospital stay due to TBI;US=United States of America

Table 3.3. Summary of studies which assessed ADL dependency and integration using CIQ, OARS and non-standardized assessments

Study (year)	**TBI severity (given by GCS)**	**ISS**	**Type of study**	**Study settings**	**Country**	**N ≥ 65 years old**	**LOS (days)**	**Comorbidities**	**Pre-injury anticoagulation**	**Time post-TBI**	**Type of assessment**	**Outcomes**
Kinsella (2014) (143)	Mild	NR	Retrospective	Hospital	Australia	50	Median (IQR)=4 (5)	NR	NR	3 months	CIQ	CIQ home mean 5.8 (SD 2.9); CIQ social 8.3 (SD 2.6)
Brousseau (2017) (133)	Mild	NR	Prospective observational	Multi-center	Canada	344	NR	0-1 comorbidities in 51 patients, 2-4 in 148 and 5-13 in 143	NR	6 months	OARS	24 patients (7.0%) had functional decline
Thompson (2012) (115)	Mild	65-74 years old : mean (SD)=17.9 (11.7 75-84 years old: mean (SD)= 7.5 (10.9)	Retrospective	National database	US	309	NR	In the 65-74 years group: 42.9% of the patients CCI=0, 28.4% CCI=1, 14.5% CCI=2 and 14.2% CCI≥3 In the 75-84 years group: 28.8% CCI=0, 29.6% CCI=1,	NR	12 months	Interview/non-standardized assessment	In the 65-74 years group patients had by mean 1.3 (SD 2.7) ADL difficulties and in the 75-84 years group a mean of 2.2 (SD 3.2). The number of ADL difficulties pre-injury was 0 in 87% of the 65-74 years-old and 71.5% of the 75-84 years-old

								17.0% CCI=2, 24.6% ≥3				
Miller (2017) (134)	Mild and moderate	NR	Retrospective	National database	US	36288	NR	NR	NR	Hospital discharge	Interview/non-standardized assessment	76.0% of the 70-79 years old group, 67.0% of the 80-89 years old group and 61.0% of the ≥ 90 years old group were independent at discharge
Lilley (2016) (135)	Severe	Median (IQR)= 5 (10)	Retrospective	National database	US	90	Median (IQR)=8 (14)	41.9% CCI=0, 30.2% CCI=1, 16.3% CCI=2, 11.6 CCI ≥3	78.3% of the patients	Hospital discharge	Interview/non-standardized assessment	61 patients (67.8%) were dependent for one or more ADL
Lecours (2012)(136)	Severe	NR	Retrospective	Level I and level II trauma center	Canada	95	NR	NR	NR	24-48 months	Interview/non-standardized assessment	69 of 136 participants (>55 years old) needed no help to transfer to chair, wheelchair, or bed and 79 of 136 participants (>55 years old) needed minimal help with stairs

N=number; GCS=Glasgow Coma Scale; ISS=Injury Severity Score; NR=not reported; LOS= length of hospital stay due to TBI; CCI=Charlson Comorbidity Index; US=United States of America

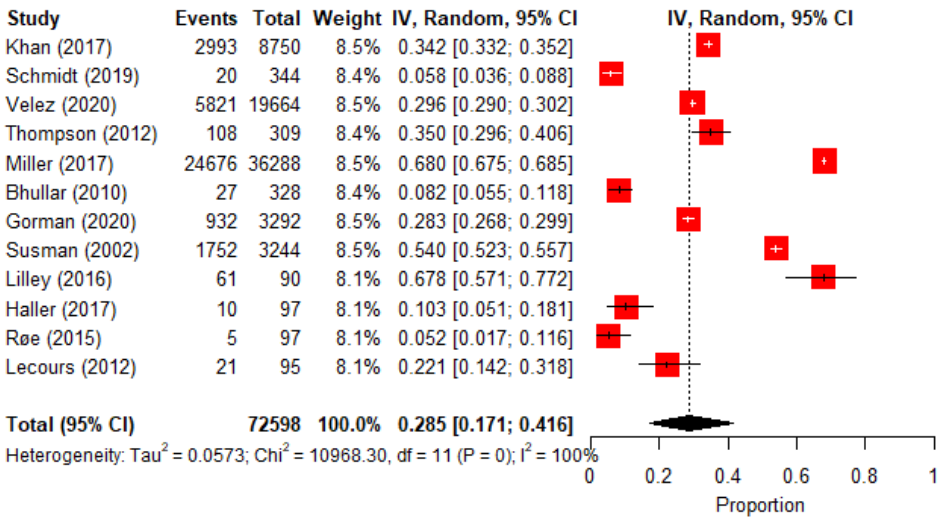


Figure 3.5. Meta-analysis results for nursing home admissions

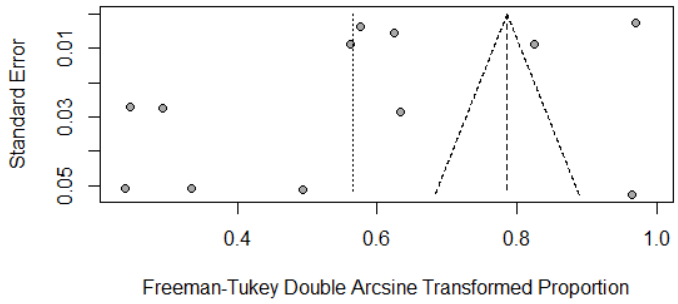


Figure 3.6. Funnel plot for the studies used in the nursing home admissions meta-analysis, indicating the TBI effect estimate on nursing home admissions in the included studies. The horizontal axis indicates the variance of each study's proportion and the vertical axis standard errors. The diagonal lines represent the 95% confidence limits and the vertical line the summary estimate of the effect of TBI on the studied outcome.

QoL

QoL was assessed using the 12-Item Short Form Survey (SF-12) (144), 36-Item Short Form Survey (SF-36) (145) and Six-dimensional health state short form (SF-6D) (146) in 3 studies [Table 3.5 and Figure 3.7].

SF-12 (144) and SF-36 (145) assess the impact of health on patients' everyday life on a scale ranging between 0 (low QoL) and 100 (high QoL). Both questionnaires contain a Physical Component Summary (PCS) and a Mental Component Summary (MCS) (144,145). The average reported population score is 50 (147,148). SF-6D evaluates role participation, social functioning, bodily pain, mental health and vitality (146). Scores range between 0.0 (worst health state) to 1.0 (best health state) (146).

Table 3.4. Summary of studies which addressed nursing home admission after TBI

Study (year)	TBI severity (given by GCS)	ISS	Type of study	Study settings	Country	N ≥ 65 years old	LOS (days)	Comorbidities	Pre-injury anticoagulation (N)	Time post-TBI (months)	Outcomes
											N patients discharged to a nursing home (%)
Khan (2017) (139)	Mild	Median (IQR)=17 (11)	Retrospective	National database	US	8750	NR	NR	NR	HD	2993 (34.2%)
Schmidt (2019) (137)	Mild	NR	Retrospective	Level I trauma center	Switzerland	344 (141 patients 65-74 years old, 125 75-84 years old and 78 ≥85 years old)	Mean (SD)=2(2)	9.3% of the patients had diabetes, 22.7% psychiatric diseases and 5.2% musculoskeletal diseases	NR	HD	20 (5.8%): 1 patient 65-74 years old, 6 75-84 years old and 13 ≥85 years old
Velez (2020) (138)	Mild	Median=11	Retrospective	National database	US	19664	NR	Median CCI=4	NR	HD	5821(29.6%)
Thompson (2012) (115)	Mild	65-74 years old : mean (SD)=17.9 (11.7) 75-84 years old: mean (SD)= 7.5 (10.9)	Retrospective	National database	US	309	NR	In the 65-74 years group: 42.9% of the patients CCI=0, 28.4% CCI=1, 14.5% CCI=2 and 14.2% CCI≥3 In the 75-84 years group: 28.8% CCI=0, 29.6% CCI=1, 17.0% CCI=2, 24.6% ≥3	NR	12	108 (35.0%), of which 10.4% were 65-74 years old and 24.6 75-84 years old
Miller (2017) (134)	Mild and moderate	NR	Retrospective	National database	US	36288	NR	NR	NR	HD	*76.0% of the 70-79 years old group, 67.0% of the 80-89 years old group and 61.0% of the ≥ 90 years old group were

											discharged to home or prison
Bhullar (2010) (141)	Moderate	65-80 years old: mean=12 >80 years old: mean=11	Retrospective	Level II trauma center	US	328	NR	NR	NR	HD	27 (8.2%)
Gorman (2020) (140)	Moderate and severe	Median (IQR)= 17 (9)	Retrospective	National database	US	3292	NR	Median CCI=4	NR	HD	931 (28.3%)
Susman (2002) (92)	Moderate and severe (mean GCS=8.7)	Mean±SD= 17.4± 8.7	Retrospective	Database	US	3244	NR	NR	NR	HD	1752 (54.0%)
Lilley (2016) (135)	Severe	Median (IQR)= 5 (16-26)	Retrospective	National database	US	90	Median (IQR)=8 (14)	41.9% CCI=0, 30.2% CCI=1, 16.3% CCI=2, 11.6 CCI ≥3	78.3%	HD	61 (67.8%)
Haller (2017) (98)	Severe	Median (IQR)=25 (12)	Prospective observational	Multi-center	Switzerland	97	NR	10 patients psychiatric disorders and 16 alcohol abuse	26	3	10 (10.3%) at 3 months, 14 (14.4%) at 6 months and 16 (16.5%) at 12 months
Røe (2015)(113)	Severe	NR	Prospective observational	Multi-center	Norway	97 (46 65-74 years old and 51 ≥75 years old)	NR	35 patients 65-74 years old and 45 patients ≥75 years old	21 65-74 years old and 37 p ≥75 years old	12	5 (5.2%): 4 patients 65-74 years old and 1 patient ≥75 years old
Lecours (2012) (136)	Severe	NR	Retrospective	Level I and II trauma center	Canada	95	NR	NR	NR	24-48	21 (22.1%)

N=number; GCS=Glasgow Coma Scale; ISS=Injury Severity Score; NR=not reported; LOS= length of hospital stay due to TBI; CCI=Charlson Comorbidity Index; US=United States of America; HD=hospital discharge

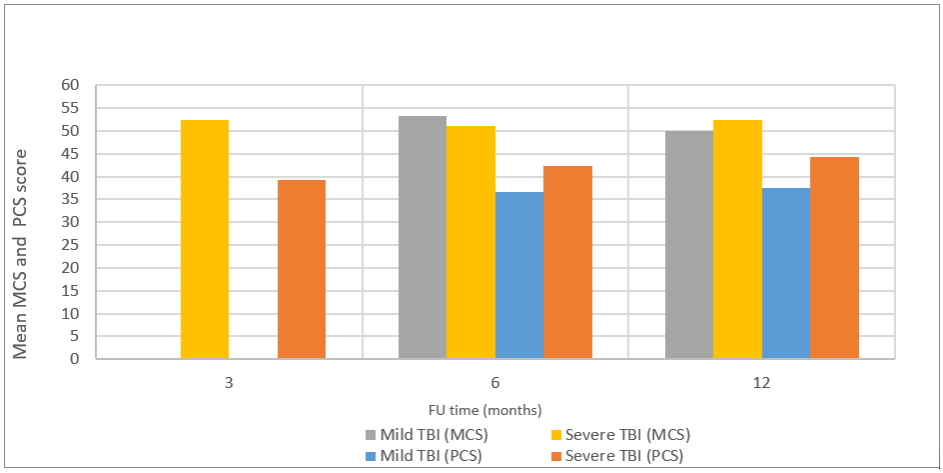


Figure 3.7. Mean MCS and PCS scores for the different TBI severities at different follow-up time point

In patients with mild TBI, Kinsella *et al* reported an average PCS score of 36.7 (143), and average MCS of 52.1 at 6 months follow-up (143). At 12 months, Thompson *et al* reported PCS SF-12 scores of 39.5 for the 65-74 year old patients and 35.3 for the 75-84 year olds (115), while average MCS scores were 51.7 for the 65-74 year old patients and 48.2 for the 75-84 year olds (115).

In severe TBI cases, Haller *et al* found a mean SF-12 PCS score of 39.2 and a mean MCS score of 52.3 at 3 months, a mean PCS score of 42.3 and mean MCS score of 51.2 at 6 months, and a mean PCS score of 44.2 and mean MCS score of 52.3 at 12 months (98).

Depression

One study retrospectively studied depression 1 year post mild TBI in 309 patients ≥65 years old from a national database in US (115). Assessment was performed through the self-report question: ‘‘Before your injury, did a doctor ever tell you that you had depression?’’ and through the Center for Epidemiologic Studies Depression Scale-Revised at follow-up, which is a 20-item questionnaire whose scores range from 0 to 60 (149). Higher scores indicate the presence of more depressive symptomatology (149).

One year after mild TBI, depressive symptoms were found in 4.8% of the 65-74 years old patients and 2.6% of the 75-84 years old patients (115).

3.1.5 Discussion

This study assesses QoL, functional outcome, dependency, nursing home admission rate and incidence of depression in patients of ≥65 years old who sustained TBI.

The results show a prevalence for unfavorable functional outcomes of 65.2% (95% CI: 51.1-78.0) and a prevalence of nursing home admission of 28.5% (95% CI: 17.1-41.6). Dependency rates range between 16.9% and 74.0%, with outcomes worsening with increasing severity and age and with unclear recovery over time. QoL was found to be particularly decreased as indicated by reported PCS scores ranging between 35.3-44.2/100 at 3-12 months post TBI. This is far below the population average scores (50/100 (147,148)). In contrast, the MCS scores were similar to the population average

scores, ranging between 48.2-52.3/100 at 6-12 months follow-up. 2.6-4.8% of patients with mild TBI reported depressive symptoms.

Higher injury severity was associated with poorer functional outcomes. However, this is not the case for QoL, where only subtle differences were observed between patients with mild and severe TBI and, in some cases, the reported QoL scores were lower for patients with mild TBI.
To date, there is a relative scarcity of evidence and lack of detail in studies reporting on TBI outcomes in older patients (3,4). Particularly, only three studies investigated QoL in older patients. While dependency in ADL is a strong predictor of declining QoL (150,151), the relation between mood changes and function is not straightforward. As the safeguarding of acceptable QoL is the primordial goal of any medical treatment, documented QoL outcomes following TBI in older persons are of major importance for treatment guidance and counseling. Nevertheless, to date, we could find no guidelines on the management of TBI in the older patients.

We hypothesized that TBI in older patients often results in significant functional decline and poor QoL, and the obtained results seem to confirm this. Moderate and severe TBI have a significant impact on dependency and QoL in older patients, while mild TBI has a potentially strong impact. Interestingly, Haller *et al*, Kinsella *et al* and Thompson *et al* found that health-related QoL was impaired to the same extent in mild as in severe TBI (98,115,143). This might be explained by the definition of ''mild TBI'', following the GCS, not being sufficiently reliable in older patients. These patients are at a particular risk of deterioration after hospital admission (88–90) and, therefore, the impact of mild TBI should not be underestimated. Furthermore, we believe that QoL depends on a large amount of factors about the patients' lives and not only the patients' status after TBI. This could lead, in some cases, to subjective results. Therefore, it could be that in some cases patients with mild TBI potentially perceive their limitations as a serious burden, while patients surviving moderate and severe TBI may be rather positive, outweighing the disabilities by their happiness to be still alive.
A limitation of the current study is the scarcity of published literature documenting outcomes of TBI in older patients, particularly in terms of QoL and depression. Moreover, the review was limited to studies written in English. However, the main limitation is the inter-study variability in outcome scales used, study settings and timings of assessment applied.
Furthermore, the included studies generally contained insufficient detail to correct for patients' heterogeneity, comorbidities, injury characteristics and clinical management in this population. An attempt to compare studies with similar characteristics has been performed. However, this has not been possible in all the cases due to the variability in outcome scoring, in combination with the impossibility for actual stratification. The establishment and application of an international reporting standard would be very useful.
Finally, if all the included studies would have contained more detail on patient and injury characteristics and management, this could have enabled a meta-analysis for all the included outcomes, which was not possible.
The results from this review illustrate the major burden of TBI in the older patients, primarily for the patients and their families. Second, to society, which is reflected in needs for outpatient supplies and residential care facilities and associated costs. In contrast, research in this field is, to date, rather limited and no clinical guidelines for the management of TBI in older adults exist. Better insight into outcomes and risk factors for poor outcome, ideally resulting in the development of prognostic models specific for older TBI patients, can improve counseling of patients and their families, and help

caregivers to set realistic treatment targets, particularly in situations of severe TBI where often surgical decisions need to be made fast and treatment withdrawal might be a humane alternative. Further clinical research in this field is therefore urgently needed in order to facilitate clinical guideline development.

3.1.6 Conclusion

TBI in older adults has a major impact on patients' lives, often leading to functional decline, dependency, nursing home admission and poor QoL. This is particularly true in moderate and severe TBI, but potentially also true in mild TBI. Older age and injury severity are risk factors for poor functional outcome, while poor QoL is seen in all severities of TBI.

Table 3.5. Summary of studies which addressed QoL after TBI

Study (year)	TBI severity (given by GCS)	ISS	Type of study	Study settings	Country	N ≥ 65 years old	LOS (days)	Comorbidities	Pre-injury anticoagulation	Time post-TBI (months)	Type of assessment	Outcomes
Kinsella (2014) (143)	Mild	NR	Retrospective	Hospital	Australia	50	Median (IQR)=4 (5)	NR	NR	6	SF-12	Mean SF-12 PCS score 36.71 (SD 10.7); mean SF-12 MCS score 53.2 (SD 8.8)
Thompson (2012) (115)	Mild	65-74 years old : mean (SD)=17.9 (11.7 75-84 years old: mean (SD)= 7.5 (10.9)	Retrospective	National database	US	309	NR	NR	NR	12	SF-36 and SF-6D	Mean SF-36 PCS score: 39.5(SD 17.2) in the 65-74 years old group and 35.3 (SD 17.4) in the 75-84 years old group Mean SF-36 MCS score: 51.7 (SD 16.5) in the 65-74 years old group and 48.2(SD 18.4) in the 75-84 years old group Mean SF-6D: 0.73 (SD 0.25) in the 65-74 years old group and 0.67 (SD 0.26) in the 75-84 years old group
Haller (2017) (98)	Severe	Median (IQR)=25 (12)	Prospective observational	Multi-center study	Switzerland	97	NR	10 patients psychiatric disorders, 16 alcohol abuse	26 patients	3, 6 and 12	SF-12	Mean SF-12 PCS score 39.2 (range 30.7-50.0); mean SF-12 MCS score 52.3 (range 44.7-55.7) at 3 months, mean SF-12 PCS score 42.3 (34.9-52.8); mean SF-12 MCS score 51.2 (45.3-57.1) at 6 months and mean SF-12 PCS score 44.2 (34.3-52.8); mean SF-12 MCS score 52.3 (45.8-57.2) at 12 months

N=number; GCS=Glasgow Coma Scale; ISS=Injury Severity Score; NR=not reported; LOS=length of hospital stay due to TBI; US=United States of America

3.2 Neurosurgical treatment and outcomes after traumatic brain injury in older patients

This section is based on:

Voorspoels L., Gavrila Laic R. A., Vander Sloten, J., Depreitere, B. Neurosurgical treatment and outcomes after traumatic brain injury in the elderly: A systematic review and meta-analysis. [Manuscript submitted for publication to World Neurosurgery].

3.2.1 Abstract

The incidence of traumatic Brain Injury (TBI) in the older population is rapidly increasing nowadays. The older population is a fast-growing age group in society and this population often suffers from multiple deteriorations and comorbidities, which lead to an increased fall risk. Age is a well-known negative predictor of outcome after TBI. However, to date, there are no specific guidelines for the clinical management and neurosurgical treatment of older TBI patients. In order to educate future guidelines, the main objective of this systematic review and meta-analysis is to investigate functional outcomes in older TBI patients who underwent neurosurgical treatment for TBI.

A systematic search was performed in PubMed, Embase, Cochrane library and Web of Science Core collection. Articles including patients with TBI aged ≥65 years who underwent a neurosurgical intervention in the context of TBI management, with at least three months of functional follow up post-TBI, were considered in this study.

Twenty-five studies were included in the systematic review and fifteen were further meta-analyzed. At 6 month follow-up, favorable outcome rates ranged between 11.4% and 75.0%. The pooled prevalences obtained by the meta-analysis for favorable outcome and mortality were 31.8% and 44.6%, respectively.

In conclusion, the overall outcome for older patients who underwent a neurosurgical intervention for TBI is rather poor. Future research should invest in predictive models and dedicated selection criteria for surgery in order to tailor TBI management to individual needs and recovery potential.

3.2.2 Introduction

The population over 65 years is rapidly increasing in our contemporary society (81). Nowadays, the older population has a more active lifestyle than they used to have in the past (81,82,105). However, the ageing process is associated with physiological and functional changes, such as deterioration in the balance system, muscle weakness, joint problems, cognitive decline and/or polypharmacy, among others, which increase their predisposition for fall accidents (4,73,81,82). As a consequence, older adults also have an increased risk of sustaining a traumatic brain injury (TBI) (4,5).

TBI is an acquired injury to the brain caused by an external force applied to the head (1,54) and its severity is usually categorized using the Glasgow Coma Scale (GCS), which classifies TBI severity as mild (GCS 13-15), moderate (GCS 9-12) or severe (GCS 3-8)(44). In older patients, 80% of the TBI cases are classified as ''mild'' TBI (81,152). Nevertheless, the term 'mild' refers to the initial functional status of the patient upon admission after TBI and not to the further course. In younger patients (<65 years

old), a mild TBI most frequently stays mild further on, but older patients more frequently suffer from gradual neurological decline in the hours following admission (74).
The nature of TBI differs among different age groups with older patients being more prone to injuries with evolving mass effect such as cerebral contusion and acute subdural hematoma The ageing process leads to multiple physiological and structural changes in the brain, such as brain atrophy and vascular changes, among others (5,73,74). Age has been repeatedly shown to be an independent negative predictor of outcome (153,154). Older patients with a TBI diagnosis suffer more often from prolonged hospitalizations, long-term morbidity, permanent disability at several domains, low quality of life (QoL) and increased mortality (4,5) than younger patients.
Despite the higher risk for poor functional and quality of life outcomes, there are no specific clinical guidelines for the management of older TBI patients. It has been demonstrated that practice variability is high for TBI-related mass lesions in older patients (155). It has not been proven to be wrong to adopt similar surgical strategies as in younger patients, hence, neurosurgical interventions are not unfrequently applied (10,11). This includes decompressive craniectomy (DC) and mass lesion evacuation through craniotomy as the most frequent surgery types (156,157).
Previous studies have shown that DC leads to lower mortality rates. However, the effective benefit in terms of improved functional outcome is still not clear (158–160). Moreover, both DC and craniotomy are high risk interventions, as they need general anesthetics, have an invasive character and lead to a high risk of complications (161). An emerging neurosurgical procedure is the endoscopic evacuation of a hematoma through a small craniotomy or a burr hole. In such case, the advantage is the less invasive character, which could be preferred in older patients with their severe comorbidities (162). It may be expected that the type of neurosurgery is a considerable predictive factor for the functional outcome in older TBI patients (163).
It is still unknown whether age is strictly associated with unfavorable functional outcome following a neurosurgical procedure in the context of TBI (81).
The present systematic review aims at describing long-term outcomes following a neurosurgical intervention for TBI in older patients, in order to educate neurosurgical guidelines specific to these patients in the future.

3.2.3 Methods

This is a systematic review performed in June 2021, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (119). The protocol of this systematic review was registered on PROSPERO (CRD42021260369).

Search strategy and selection criteria
A systematic search was performed in PubMed, Embase, Cochrane library and Web of Science Core collection the 12th June 2021. The article selection was restricted to articles in English, but not to publication date.
The articles were included based on the following inclusion criteria: articles involving patients with a medical history of TBI at a minimum age of 65 years old, using a neurosurgical treatment strategy and including functional follow-up for at least three months by one of the following functional outcome measuring scales: Extended Glasgow Outcome Scale (GOSE), Functional Independence Measure (FIM), Disability Rating Scale (DRS), Functional Assessment Measure (FAM), Functional Status Examination

(FSE), Barthel Index, Rivermead Post concussion Symptoms Questionnaire, WHO Disability Assessment Schedule (WHODAS), Community Integration Questionnaire (CIQ) or Modified Rankin Scale (mRS).

Articles were excluded if they included patients who were younger than 65 years old, patients who had known neurological diseases before TBI or an intracranial hematoma with a different etiology than trauma, who only underwent conservative treatment or ICP monitoring, who suffered a penetrating TBI or a chronic subdural hematoma or if there was no follow-up for at least three months using one of the scales mentioned above in this study.

All the retrieved articles were collected and deduplicated in Endnote 20. The study selection was conducted in 2 stages by two independent reviewers (LV and RG) using Rayyan QCRI software. First, articles were screened by title and abstract. Second, the full-text of the remaining studies was examined for final inclusion. Any disagreement between the two researchers was resolved through discussion. If necessary, a third reviewer was consulted for arbitrage (BD). The study selection process is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) 2020 flow diagram (Figure 3.8) (119).

The following categories were used to classify the studies' methodological quality: excellent (26-27), good (20-25), fair (15-19) and poor (≤14) (121).

The data extraction was performed using the methodology explained in section 3.1.3 (103).

Statistics

A descriptive statistical analysis of all the included studies was performed, obtaining measurements of the means or variations between age groups and treatment groups by Pearson correlation or Mann-Whitney U test using the software R 4.1.1. P-values <0.05 were considered as statistically significant. Moreover, studies which provided the sufficient information were included in a meta-analysis the Metaprop package in R 4.1.1.

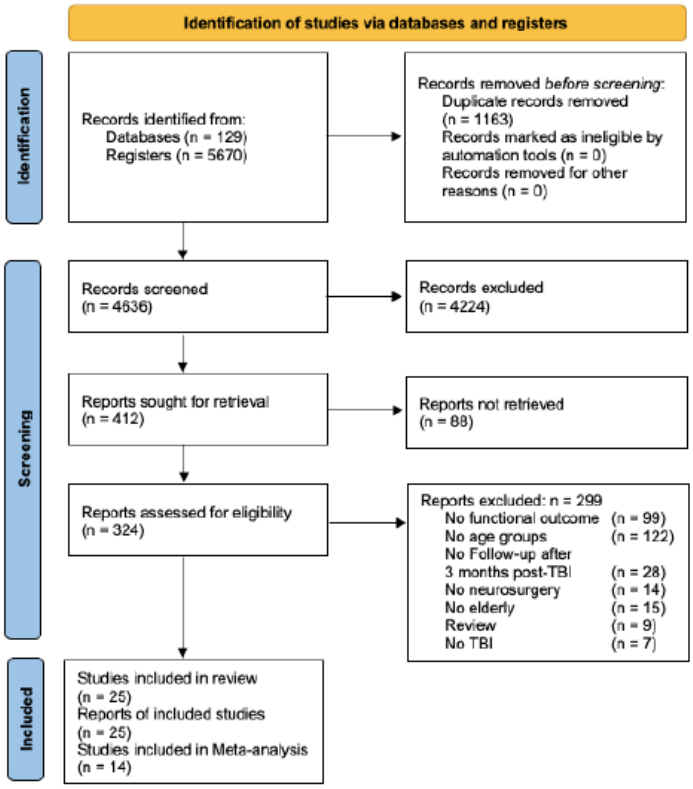


Figure 3.8. PRISMA Flow Diagram

3.2.4 Results

Search results

A total of 5,799 results were obtained from the systematic search in PubMed, Embase, Cochrane Library and Web of Science Core Collection. After deduplication, 4,636 articles were left. 4,224 articles were excluded by title and abstract. Of the remaining 412, 88 articles were not retrieved. After full-text screening, a total of 25 studies were included in the systematic review and 15 were further meta-analyzed.

The risk of bias assessment, based on the Downs and Blacks scale (121), indicated that 88% of the studies had "fair" quality and 12% had "poor" quality [Appendix 3B].

Demographic characteristics

The demographic characteristics of all the included studies are summarized in table 3.6.

A total of 1,676 patients, with a mean age of 72.9 years old (range 65-101 years old), were studied in the 25 included studies.

These studies were published between 2005 and 2021 and used either a prospective or a retrospective method. The time of follow up post-TBI ranged from 3 months until 12 months. Ten studies compared the outcomes of older patients with TBI with the outcomes of younger patients (<65 years old) (73,105,157,164–170). Comparisons between neurosurgery and conservative treatment were performed in eight studies (73,105,111,112,128,170–172).

Functional outcome

The GOS was used in nineteen studies as functional outcome measure (10,11,165,166,168–174,82,97,109,111,112,128,157,164) and the GOSE (73,105,167) and the mRS (161,162,175) were both used in three studies [Table 3.7]. The following scales were not found in any of the included studies: Functional Independence Measure, Disability Rating Scale, Functional Assessment Measure, Functional Status Examination, Barthel Index, Rivermead Post concussion Symptoms Questionnaire, WHO Disability Assessment Schedule and Community Integration Questionnaire.

Three types of neurosurgical intervention were considered in the included studies. Eighteen studies used DC with GOS or GOSE as outcome measure (10,11,167–174,105,109,111,128,157,164–166). Fourteen studies used craniotomy with GOS, GOSE or mRS as outcome measure (10,73,168,170,172,174,82,97,105,109,111,128,161,165). Three studies used a small craniotomy with endoscopic neurosurgery with mRS as outcome measure (112,161,162,175). One study did not report the used neurosurgical intervention (112).

Glasgow Outcome Scale (GOS)

GOS is scored following a scale where 1 corresponds to death, 2 to vegetative state, 3 to severe disability, 4 to moderate disability and 5 to good recovery. GOS 1-3 are considered as unfavorable outcomes (61) . Favorable outcome rates ranged between 22.9-34.4% at 3 months post-TBI (11,109,128,168), between 13.4-75.0 % at 6 months (11,82,172,174,97,109,111,157,165,169–171) and between 11.3-56.5% at 1 year post-TBI (10,128,157,164,173,176).

When considering the different types of neurosurgical interventions, favorable outcome after craniotomy ranged between 13.4-40.5% (82,97), after DC between 11.4-56.5% (11,157,164,169,173), and after craniotomy or DC between 11.3-75.0% % (10,105,171,174,109,111,112,128,165,167,168,170) at 3-12 months FU.

Hamed et al. found a statistically significant higher probability of favorable outcome in the population <70 years old (39.0%) compared with the population >70 years old (20.0%) (p=0.008) (165). *Kim et al.* confirmed age as an independent predictor for functional outcome (168). *Hanko et al.* and *Skoglund et al.* however, found no significant correlation between age and functional outcome, respectively at 3 and 6 months (166,170).

Brazinova et al. investigated the prognostic factors affecting the functional outcome after neurosurgery in older patients with an admission GCS of 3 or 4. After 12 months 20.0% of the patients were still alive, of which 11.0% presented favorable outcome and 9.0% unfavorable outcome (112).

Bus et al. investigated the functional outcome and mortality rate at 12 months post-TBI after neurosurgery based on admission GCS score. Patients with GCS ≥9 had a favorable outcome in 68.0% and patients with GCS ≤8 had a favorable outcome in 32.0% (10).

Hamed et al. found that after craniotomy or DC patients with mild TBI had a favorable outcome in 50.0% and patients with moderate to severe TBI had a favorable outcome in 21.3% at 6 months post-TBI (165).

Bus et al. compared craniotomy and DC, resulting in a favorable outcome of 26.0% and 20.0%, respectively, at 12 month FU. The patients included were >65 years old with an acute subdural hematoma (ASDH) or subacute subdural hematoma from 2000 until 2015, resulting in 74 patients undergoing craniotomy and 10 patients undergoing DC (10). *Hamed et al.* included 153 patients >70 years old with ASDH who underwent craniotomy and 43 who underwent DC. The favorable outcome rate was of 29.4% for craniotomy and 14.0% for DC at 6 month FU (165).

Extended Glasgow Outcome Scale (GOSE)

GOSE is scored as: 1 (death), 2 (vegetative state), 3 (lower severe disability), 4 (upper severe disability), 5 (lower moderate disability), 6 (upper moderate disability), 7 (lower good recovery) to 8 (upper good recovery) (62). GOSE 1-4 are considered as unfavorable outcomes (62).

This scale was used by three studies (73,105,167) [Table 3.7]. The favorable outcome at 6 months post-TBI ranged between 18.2%-59.0% (73,105,167).

Merzo et al. detected a significant difference in the favorable outcome at 6 months after craniotomy between patients ≥65 years old (22.2%) and <65 years old (61.4%) (p<0.05) (73).

Hinzman et al. observed a negative correlation between age and GOSE at 6 months (Pearson coefficient 0.5082; p = 0.011)(167).

Choi et al. investigated predictive factors for favorable outcome in older TBI patients after neurosurgery, but the researchers were not able to find significant predictors (OR = 0.876, p = 0.88) (105).

Modified Rankin Scale (mRS)

The mRS is commonly applied in neurology to establish the degree of disability after stroke (173). It is a numerical scale whose scoring system ranges from 0 to 6: 0 = no symptoms, 1 = no significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, 6 = death (177). A score ≤2 indicates favorable outcome and a score >2 unfavorable outcome.

The three articles using mRS as outcome scale are summarized in table 3.8 (161,162,175). The favorable outcome at 3 months post-TBI ranged between 26.7-36.4% (162,175) and at 6 months post-TBI was 20.0% (161).
Kuge et al. found a linear correlation between age and mRS (Pearson correlation 0.62; p = 0.0144) (175) in older patients. Nevertheless, no correlation among age and mRS was found by *Goto et al*. in patients with a mean GCS score of 13 (Pearson correlation of -0.28; p = 0.4047) (162). *Katsuki et al.* compared endoscopic neurosurgery with small craniotomy and craniotomy as a therapeutic option for intracranial hematoma, but no significant difference between the outcomes based on mRS and mortality was found (161).

Mortality
Twenty-four of the twenty-five included articles evaluated mortality. Two of them studied craniotomy and found mortality rates ranging between 35.1-67.2% 6 months post-TBI (82,97). Six of them studied DC (157,164,166,169,173) [Table 3.9]. At 3 months the mortality rate was 61.4% (11), at 6 months it ranged between 17.4- 87.1 (11,157,169) and at 12 months between 17.4%-81.8% (157,164,173).

Twelve of the studies investigated both craniotomy and DC (10,105,109,165,167,168,170,174), reporting mortality rates ranging between 43.5%-65.6% (109,128,168), 20.0%-62.3% (105,109,111,165,167,170–172,174) and 65.2-76.3 (10,112) at 3, 6 and 12 months post-TBI, respectively. Two of them studied small craniotomy with endoscopic neurosurgery and found a mortality rate of 13.3-18.2% at 3 months (162,175). One of them reported a mortality rate for this surgery of 33.3% at 6 months (161).

The conservative treatment groups had a mortality rate ranging from 20%-80% at 6 months compared to the mortality rate of the surgery groups which was 33%-65% (73,111,171,172). The mortality in the surgery group was non-significantly lower in patients <65 years old than in the older patients, where mortality rates ranged between 20%-39% at 3 months (166,168) and 5-13% at 6 months (73,157,167,170). *Merzo et al.* reported a significant difference in mortality rate between patients <65 years old (12.3%) and older patients (37.0%) (p<0.005) (73).

Table 3.6. Summary of the demographic characteristics of the included studies

Study (year)	Study Design	Study setting	N ≥ 65y (patients)	Mean age (years) (range)	Conservative vs. Neurosurgery	TBI Severity	Type of assessment	Follow Up (months)	Type of Neurosurgery
Akbik (2019) (109)	Retrospective	Single Center	62	78.0 (65.0-93.0)	No	All	GOS	3 and 6	Craniotomy DC
Benedetto (2017) (82)	Retrospective	Single Center	67	80.5 (71.0-94.0)	No	All	GOS	6	Craniotomy
Brazinova (2010) (112)	Prospective	Multi Center	80	74.2	Yes	Severe	GOS	12	Craniotomy DC
Bus (2019) (10)	Retrospective	Single Center	69	75.0 (65.0-88.0)	No	All	GOS	12	Craniotomy DC
Choi (2019) (105)	Retrospective	Single Center	39	54.3 (16.0-96.0)	Yes	All	GOSE	6	Craniotomy DC
De Bonis (2011) (173)	Prospective	Single Center	44	76.6 (66.0-94.0)	No	All	GOS	12	DC
Fotapokoulus (2016) (157)	Retrospective	Single Center	23	42.8 (6.0-83.0)	No	Moderate and Severe	GOS	6 and 12	DC
Goto (2011) (162)	Prospective	Single Center	11	87.0 (66.0-95.0)	No	All	mRS	3	Small craniotomy with Endoscopic neurosurgery
Hamed (2016) (165)	Prospective	Single Center	196	73.0	No	All	GOS	6	Craniotomy DC
Hanko (2017) (166)	Prospective	Single Center	5	58.8	No	N/A	GOS	3	DC
Hinzman (2014) (167)	Prospective	Multi Center	5	48.0 (23.0-79.0)	No	All	GOSE	6	Craniotomy DC
Katsuki (2020) (161)	Retrospective	Single Center	15	Endoscopic: 86.0 (70.0-101.0)	No	All	mRS	6	Craniotomy Small craniotomy with Endoscopic neurosurgery
Kim (2009) (168)	Retrospective	Database	64	51.8 (2.0-83.0)	No	All	GOS	3	Craniotomy DC
Kuge (2021) (175)	Prospective	Single Center	15	85.0 (73.0-96.0)	No	All	mRS	3	Small craniotomy with Endoscopic neurosurgery

Merzo (2015) (73)	Retrospective	Single Center	33	Y: 39.0; O: 73.0	Yes	N/A	GOSE	6	Craniotomy
Nasi (2018) (169)	Retrospective	Database	70	50.0 (14.0-86.0)	No	All	GOS	6	DC
Paldor (2020) (11)	Retrospective	Single Center	57	73.0 (65.0-89.0)	No	All	GOS	3 and 6	DC
Pompucci (2007) (164)	Retrospective	Single Center / Database	20	53.0 (6.0-94.0)	No	All	GOS	12	DC
Senft (2013) (174)	Retrospective	Single Center	8	72.4 (63.0-85.0)	No	Moderate and Severe	GOS	6	Craniotomy DC
Shimoda (2014) (172)	Retrospective	Database	478	76.0	Yes	All	GOS	6	Craniotomy DC
Skoglund (2005) (170)	Retrospective	Single Center	5	44.0 (6.0-81.0)	Yes	All	GOS	6	Craniotomy DC
Taussky (2012) (97)	Retrospective	Single Center	37	73.0	No	All	GOS	6	Craniotomy
Trevisi (2020) (171)	Retrospective	Multi Center	147	80.0 (70.0-99.0)	Yes	All	GOS	6	DC
Wan (2016) (111)	Retrospective	Single Center	70	73.5	Yes	Severe	GOS	6	Craniotomy DC
Won (2017) (128)	Retrospective	Single Center	56	85.0 (80.0-96.0)	Yes	N/A	GOS	3	Craniotomy DC

N = number of patients; All= mild, moderate and severe TBI; N/A=not specified; Y=young; O=older patients; GOS= Glasgow Outcome Scale; GOSE= Glasgow Outcome Scale Extended; mRS= Modified Rankin Scale; DC=Decompressive Craniectomy

Table 3.7. Summary of studies which assessed functional outcomes after TBI using GOS (first 19) and GOS-E (last 3)

Study (year)	**Study Design**	**Study setting**	**N ≥ 65yo (patients)**	**TBI Severity**	**Follow Up (months)**	**Functional Outcome**				
						Death (%)	**Persistent Vegetative (%)**	**Severe Disability (%)**	**Moderate Disability (%)**	**Good Recovery (%)**
Akbik (2019) (109)	Retrospective	Single Center	62	All	3 and 6	27 (43.5%)	4 (6.5%)	14 (22.6%)	3m: 17 (27.4%) 6m: 19 (30.6%)	
Benedetto (2017) (82)	Retrospective	Single Center	67	All	6	45 (67.2%)	13 (19.4%)		9 (13.4%)	
Brazinova (2010) (112)	Prospective	Multi Center	80	Severe	12	61 (76.3%)			9 (11.3%)	

Bus (2019) (10)	Retrospective	Single Center	69	All	12	45 (65.2%)	0 (0.0 %)	8 (11.6%)	7 (10.1%)	9 (13.0%)
De Bonis (2011) (173)	Prospective	Single Center	44	All	12	36 (81.8%)			8 (18.2%)	
Fotapokoulus (2016) (157)	Retrospective	Single Center	23	Moderate and Severe	6 and 12	6m: 4 (17.4%) 12m: 4 (17.4%)	6m: 3 (13.0%) 12m: 3 (13.0 %)	6m: 3 (13%) 12m: 3 (13%)	6m: 5 (21.7%) 12m: 5 (21.7%)	6m: 8 (34.8%) 12m: 8 (34.8%)
Hamed (2016) (165)	Prospective	Single Center	196	All	6	64 (32.7%)	81 (41.3%)		51 (26.0%)	
Hanko (2017) (166)	Prospective	Single Center	5	N/A	3	Mean = GOS 2 (Persistent Vegetative state)				
Kim (2009) (168)	Retrospective	Database	64	All	3	42 (65.6%)			22 (34.4%)	
Nasi (2018) (169)	Retrospective	Database	70	All	6	61 (87.1%)			8 (11.4%)	
Paldor (2020) (11)	Retrospective	Single Center	57	All	3 and 6	3m: 35 (61.4%) 6m: 37 (64.9%)	3m: 7 (12.3%) 6m: 5 (8.8%)		3m: 12 (21.1%) 6m: 12 (21.1%)	3m: 1 (1.8%) 6m: 1 (1.8%)
Pompucci (2007) (164)	Retrospective	Single Center / Database	20	All	12	16 (80.0%)			4 (20.0%)	
Senft (2013) (174)	Retrospective	Single Center	8	Moderate and Severe	6	2 (25.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	4 (50.0%)
Skoglund (2005) (170)	Retrospective	Single Center	5	All	6	1 (20.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	3 (60.0%)
Shimoda (2014) (172)	Retrospective	Database	478	All	6	298 (62.3%)	94 (19.7%)		86 (18.0%)	
Taussky (2012) (97)	Retrospective	Single Center	37	All	6	13 (35.1%)	1 (2.7%)	8 (21.6%)	15 (40.5%)	
Trevisi (2020) (171)	Retrospective	Multi Center	147	All	6	64 (43.5%)	51 (34.7%)		32 (21.8%)	
Wan (2016) (111)	Retrospective	Single Center	70	Severe	6	23 (32.9%)	14 (20.0%)		33 (47.1%)	
Won (2017) (128)	Retrospective	Single Center	56	N/A	3	27 (48.2%)	1 (1.8%)	8 (14.3%)	9 (16.1%)	11 (19.6%)
Choi (2019) (105)	Retrospective	Single Center	39	All	6	16 (41.0%)			23 (59.0%)	
Hinzman (2014) (167)	Prospective	Multi Center	5	All	6	1 (20.0%)	0 (0.0%)	3 (60.0%)	0 (0.0%)	1 (20.0%)
Merzo (2015) (73)	Retrospective	Single Center	33	N/A	6	10 (30.3%)	11 (33.3%)		6 (18.2%)	

N = number of patients; All = mild, moderate and severe TBI; GOS = Glasgow outcome scale; y= years old; m=months; N/A=not specified

Table 3.8. Summary of studies which assessed functional outcomes after TBI using mRS

Study (year)	Study Design	Study setting	N ≥ 65yo (patients)	TBI Severity	Follow Up (months)	Functional Outcome						
						Death (%)	Severe Disability (%)	Moderately Severe Disability (%)	Moderate Disability (%)	Slight Disability (%)	No disability, only symptoms (%)	No symptoms (%)
Goto (2011) (162)	Prospective	Single Center	11	All	3	2 (18.2%)	1 (9.1%)	3 (27.3%)	1 (9.1%)	3 (27.3%)	0 (0.0%)	1 (9.1%)
Katsuki (2020) (161)	Retrospective	Single Center	15	All	6	5 (33.3%)	3 (20.0%)	3 (20.0%)	1 (6.7%)	2 (13.3%)	0 (0.0%)	1 (6.7%)
Kuge (2021) (175)	Prospective	Single Center	15	All	3	2 (13.3%)	2 (13.3%)	5 (33.3%)	2 (13.3%)	1 (6.7%)	1 (6.7%)	2 (13.3%)

N = Number of patients, yo= years old; All= mild, moderate and severe TBI; mRS= Modified Rankin Scale

Meta-analysis of favorable functional outcome

Fourteen studies using GOS or GOSE as functional outcome measure at 6 months follow up were included in the meta-analysis (11,73,170–172,174,82,97,105,111,157,165,167,169).

The pooled prevalence for unfavorable functional outcomes was 68.2% (95% CI). The wide range found among the results of the meta-analyzed studies indicates high heterogeneity among studies [Figure 3.9]. This is further demonstrated by the significant Chi-square test for heterogeneity of 88.19 and the I2 value of 85%. The Funnel Plot presents an asymmetric shape, which points at potential publication bias [Figure 3.10].

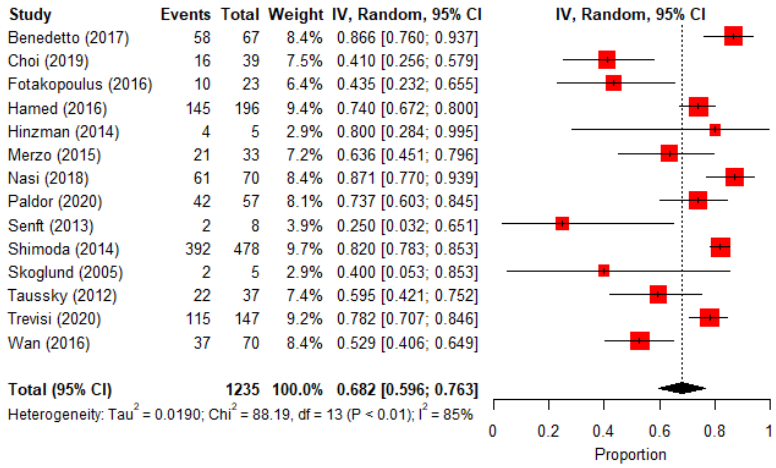


Figure 3.9. Forest Plot for unfavorable outcome

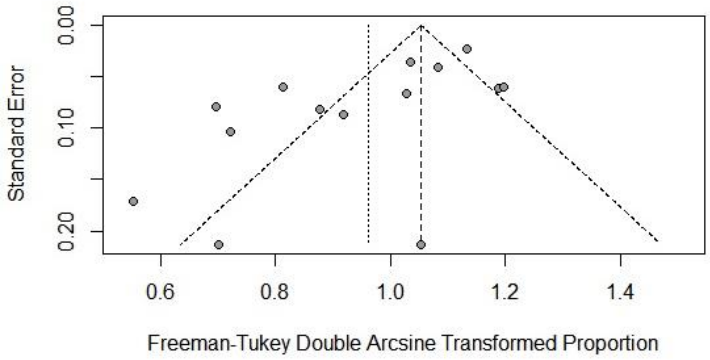


Figure 3.10. Funnel Plot for unfavorable outcome, indicating the TBI effect estimate on unfavorable outcomes in the included studies. The horizontal axis indicates the variance of each study's proportion and the vertical axis standard errors. The diagonal lines represent the 95% confidence limits and the vertical line represents the summary estimate of the effect of TBI on the studied outcome.

Table 3.9. Summary of studies with reported mortality rates

Study (year)	Study Design	Study setting	N ≥ 65yo (patients)	TBI Severity	Type of assessment	Follow Up (months)	Type of Neurosurgery	Mortality (N (%))
Akbik (2019) (109)	Retrospective	Single Center	62	All	GOS	3 and 6	Craniotomy DC	3 and 6m: 27 (43.5%)
Benedetto (2017) (82)	Retrospective	Single Center	67	All	GOS	6	Craniotomy	45 (67.2%)
Brazinova (2010) (112)	Prospective	Multi Center	80	Severe	GOS	12	Craniotomy DC	61 (76.3%)
Bus (2019) (10)	Retrospective	Single Center	69	All	GOS	12	Craniotomy DC	45 (65.2%)
Choi (2019) (105)	Retrospective	Single Center	39	All	GOSE	6	Craniotomy DC	16 (41.0%)
De Bonis (2011) (173)	Prospective	Single Center	44	All	GOS	12	DC	36 (81.8%)
Fotapokoulus (2016) (157)	Retrospective	Single Center	23	Moderate and Severe	GOS	6 and 12	DC	6 and 12m: 4 (17.4%)
Goto (2011) (162)	Prospective	Single Center	11	All	mRS	3	Small craniotomy with Endoscopic neurosurgery	2 (18.2%)
Hamed (2016) (165)	Prospective	Single Center	196	All	GOS	6	Craniotomy DC	64 (32.7%)
Hanko (2017) (166)	Prospective	Single Center	5	N/A	GOS	3	DC	N/A
Hinzman (2014) (167)	Prospective	Multi Center	5	All	GOSE	6	Craniotomy DC	1 (20.0%)
Katsuki (2020) (161)	Retrospective	Single Center	15	All	mRS	6	Craniotomy Small craniotomy with Endoscopic neurosurgery	5 (33.3%)
Kim (2009) (168)	Retrospective	Database	64	All	GOS	3	Craniotomy DC	42 (65.6%)
Kuge (2021) (175)	Prospective	Single Center	15	All	mRS	3	Small craniotomy with Endoscopic neurosurgery	2 (13.3%)
Merzo (2015) (73)	Retrospective	Single Center	33	N/A	GOSE	6	Craniotomy	10 (30.3%)
Nasi (2018) (169)	Retrospective	Database	70	All	GOS	6	DC	61 (87.1%)

Paldor (2020) (11)	Retrospective	Single Center	57	All	GOS	3 and 6	DC	3m: 35 (61.4%) 6m: 37 (64.9%)
Pompucci (2007) (164)	Retrospective	Single Center / Database	20	All	GOS	12	DC	16 (80.0%)
Senft (2013) (174)	Retrospective	Single Center	8	Moderate and Severe	GOS	6	Craniotomy DC	2 (32.0%)
Shimoda (2014) (172)	Retrospective	Database	478	All	GOS	6	Craniotomy DC	298 (62.3%)
Skoglund (2005) (170)	Retrospective	Single Center	5	All	GOS	6	Craniotomy DC	1 (20.0%)
Taussky (2012) (97)	Retrospective	Single Center	37	All	GOS	6	Craniotomy	13 (35.1%)
Trevisi (2020) (171)	Retrospective	Multi Center	147	All	GOS	6	Craniotomy DC	64 (43.5%)
Wan (2016) (111)	Retrospective	Single Center	70	Severe	GOS	6	Craniotomy DC	23 (32.9%)
Won (2017) (128)	Retrospective	Single Center	56	N/A	GOS	3	Craniotomy DC	27 (48.2%)

N = number of patients, All= mild, moderate and severe TBI

Meta-analysis of mortality

Fifteen studies considering craniotomy or DC as neurosurgical intervention and reporting a mortality rate at 6 months post-TBI were included in the meta-analysis (11,73,169–172,174,82,97,105,109,111,157,165,167).

The pooled prevalence of mortality 6 months post-TBI was 44.6% (95% CI). This meta-analysis also has a high heterogeneity [Figure 3.11], which is shown by the significant Chi-square test of 150.78 and the I2 value of 91%. The Funnel Plot presents an asymmetric shape, concluding potential publication bias [Figure 3.12].

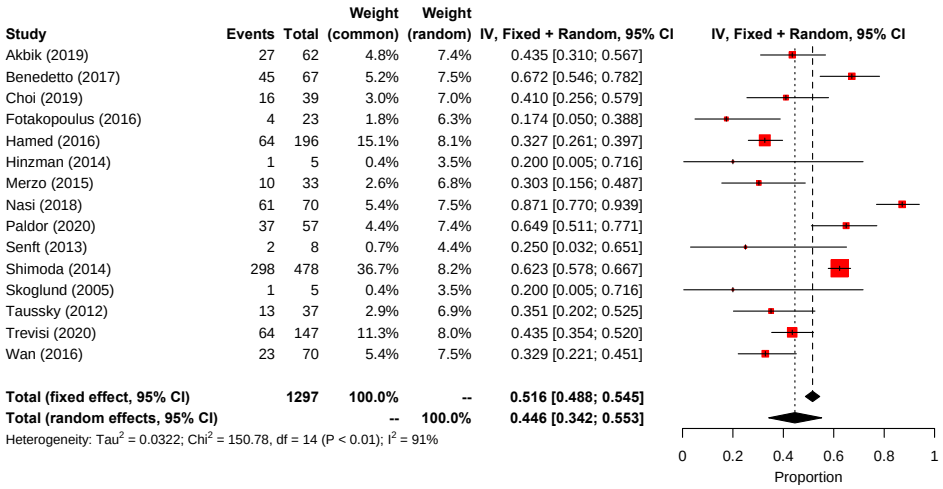


Figure 3.11. Forest Plot for mortality

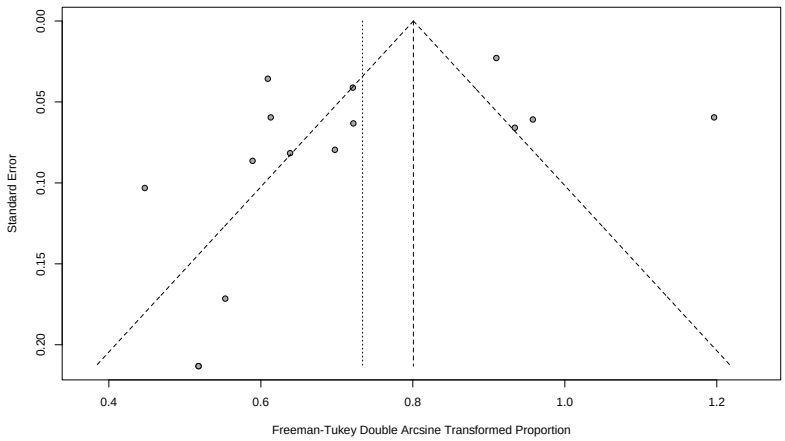


Figure 3.12. Funnel Plot for mortality, indicating the TBI effect estimate on mortality in the included studies. The horizontal axis indicates the variance of each study's proportion and the vertical axis standard errors. The diagonal lines represent the 95% confidence limits and the vertical line represents the summary estimate of the effect of TBI on the studied outcome.

3.2.5 Discussion

This systematic review and meta-analysis studied functional outcomes and mortality rates in patients with TBI ≥65 years old who underwent a neurosurgical intervention to reduce intracranial hypertension. Functional outcomes were evaluated at 3, 6 and 12 months post-TBI using GOS, GOSE and mRS. Favorable outcome rates ranged between 22.9-34.4% at 3 months (11,109,128,168), between 13.4-75.0 % at 6 months (11,82,172,174,97,109,111,157,165,169–171) and between 11.3-56.5% at 1 year (10,128,157,164,173,176). The pooled prevalence for unfavorable functional outcomes was 68.2% (95% CI) and for mortality 44.6% (95% CI) at 6 months FU, which is high.

The most mentioned predictive factor for unfavorable outcome (73,105,175,112,157,161,165,167,168,171,172) and mortality (154,172,178,179) after TBI was age. *Hamed et al.* found a statistically significant higher probability of favorable outcome in the population <70 years old (39.0%) compared with the population >70 years old (20.0%) (p=0.008) (165) and *Merzo et al.* detected a significant difference in the favorable outcome and mortality at 6 months after craniotomy between patients ≥65 years old and <65 years old (p<0.05) (73).
This has also been reported by previous studies (85,106,114–117,153) and might be due to the fact that, in the older population, comorbidities and the general deconditioning caused by the ageing process can lead to an increased risk of medical complications (8), psychosocial changes (6) and disability (7).
However, not all studies report significant age effects (73,105,167,179,180). The latter may be secondary to small sample sizes of the groups ≥65 years old, the lack of consensus on the cut off age considered as older patient or the consideration of different age ranges in the included studies (181).

Apart from age, GCS severity (4,82,178), midline shift and bilateral absence of pupil reactivity have been related to poor outcome in general literature (11,82,97,128,165,166,168,169,171,172). In older adults, *Bus et al.* found that the functional outcome was not significantly different for different TBI severity categories, but patients with a mild or moderate TBI had a lower mortality rate than patients with a severe TBI (10). Furthermore, previous studies have reported that even mild TBI in older adults is potentially associated with poor outcome (182). *Hamed et al.* found that after craniotomy or DC patients with mild TBI had unfavorable outcomes in 50.0% of the cases (165). Hence, in older adults, the severity of mild TBI should not be underestimated.

Slightly higher rates of favorable outcome were reported after DC versus craniotomy in some studies on older adults. Favorable outcome after craniotomy ranged between 13.4%-40.5 (82,97), and after DC between 11.4-56.5% (11,157,164,169,173), at 3-12 months FU. However, findings are not uniform. While *Bus et al.* did not find any significant difference in mortality rate or favorable outcome between craniotomy and DC (10), *Hamed et al.* reported significantly higher rates of favorable outcome after craniotomy than DC (p<0.005)(165). *Katsuki et al.* compared craniotomy and small craniotomy with endoscopic neurosurgery without any significant difference in outcome (161). Only a limited number of studies investigated the effect of neurosurgical procedure and they had varying in- and exclusion criteria and sample sizes, precluding strong conclusions.

When surgery and conservative treatment are compared in older adults, Shimoda et al. and Wan et al. favored neurosurgical treatment, since in their studies it improved functional outcomes and

reduced mortality (111,172). Conversely, Trevisi et al. encouraged conservative treatment, as according to their findings, older patients with a good admission GCS score have a more favorable functional outcome following conservative treatment (171). Although the Brain Trauma Foundation (BTF) guidelines provide rather strict radiological criteria for surgical management of traumatic intracranial hematomas (183), there seems to be substantial practice variation between centers when managing older patients with TBI (184).
A recent studied published by Van Essen et al. found that in adults >65 years old with aSDH, there was no difference in outcome between patients treated in centers with a more aggressive approach and centers adopting an initial conservative treatment (155). This intriguing finding warrants further investigation on the subject.

The importance of the time between TBI and neurosurgery was not investigated by most included studies. *Trevisi et al.* concluded that there was no significant difference in functional outcome based on time until surgery, (171). Also *Bus et al.* found no relation between the time until surgery and the functional outcome (10). *Shimoda et al.* presented a higher probability of favorable outcome if neurosurgery took place in the first four hours (172).

In this review we found a high heterogeneity among the observations reported in the included studies. This is most likely caused by the low number of included studies and the differences in sample sizes among them, which in many cases were rather small. As a result, it remains difficult to impossible to come to unequivocal conclusions, although rather poor outcomes following surgery for TBI in older patients was a consistent observation. Similar poor outcomes were reported by a previous meta-analysis on overall outcomes after TBI in older patients in 2021, which also referred to the same limitations (103).
The scarcity of literature on the management of TBI in the older patients represents a significant knowledge gap. Most studies on TBI use age above 65 years as exclusion criterion (4,7,9,154,172,178). Considering the homogeneity of the population in terms of a lower prevalence of comorbidities, the study of younger patients is preferred for obvious reasons, as it leads to less ambiguous outcomes (9). Furthermore, neurosurgery in older patients with TBI is still subject to practice variation and uncertainty, given the poorer outcomes in older adults (111,172), resulting in more withdrawal of invasive treatments (9,111,172,178,185,186). As a result of this vicious reasoning, scientific studies are few and no investments are made in better selection criteria for surgery or invasive treatments.

The results obtained from this systematic review and meta-analysis indicate that the overall outcome of TBI in older adults is rather poor despite neurosurgical interventions. Obviously there is a bias in that patients undergoing a neurosurgical intervention are the ones with the most severe injuries. However, a neurosurgical intervention may still contribute to a favorable outcome in selected patients, and therefore should not be denied completely to those patients who may potentially benefit. To date, there is a shortage of literature describing management and outcomes in older patients with TBI, resulting in difficulties to offer appropriate clinical guidance for these patients' therapeutic management. A need is felt to develop separate prognostic models for TBI in older adults and to establish separate guidelines, and this should be based on evidence. Hence, prospective studies are needed to fill the knowledge gaps.

3.2.6 Conclusion

Older patients have less favorable outcomes and higher mortality rates after a neurosurgical intervention for TBI than younger patients. However, neurosurgery should not be completely denied in all older patients, since good outcomes are reported in selected patients. Current evidence does not allow to guide proper patient selection and propose specific surgical treatments. The systematic review unraveled a huge heterogeneity in reported findings, but particularly pointed at the scarcity of relevant literature. Hence, in order to proceed to age-specific guidelines, prospective studies are highly needed.

Appendix 3

Appendix 3A. Assessment techniques included in our study selection inclusion criteria

Assessment technique	Outcome
WHO Disability Assessment Schedule (WHODAS)	Functional outcome
Functional Independence Measure (FIM)	Functional outcome
Glasgow Outcome Scale (GOS)	Functional outcome
GOS-Extended (GOS-E)	Functional outcome
Disability Rating Scale (DRS)	Functional outcome
Functional Assessment Measure (FAM)	Functional outcome
Functional Status Examination (FSE)	Functional outcome
Community Integration Questionnaire (CIQ)	Functional outcome
Barthel Index	Functional outcome
Patient Reported Outcomes Measurement Information System (PROMIS)	Functional outcome
Rivermead Postconcussion Symptoms Questionnaire	Functional outcome/depression
Trauma outcome profile (TOP)	Functional outcome/depression
European Brain Injury Questionnaire (EBIQ)	Functional outcome/QoL
General Health Questionnaire-30 (GHQ-30)	Functional outcome/depression
Hamilton Depression Rating Scale (HAM-D)	Depression
Mini International Neuropsychiatric Interview	Depression
Wimbledon Self-Report Scale	Depression
Beck's Depression Inventory (BDI)	Depression
Patient Health Questionnaire 9-item depression scale (PHQ-9)	Depression
Center for Epidemiologic Studies-Depression Scale [CES-D]	Depression
Anxiety and depression scales from the Symptom Checklist-90	Depression and anxiety
Hospital anxiety and depression scale (HADS)	Depression and anxiety
Beck's anxiety inventory (BAI)	Anxiety
36-Item Short Form Survey (SF-36)	QoL
12-Item Short Form Survey (SF-12)	QoL
Short-Form Six-Dimension (SF- 6D)	QoL
Quality of Life after Brain Injury (QOLIBRI)	QoL
Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS)	QoL
Quality of Life Interview (QoLI)	QoL
QOLIBRI Proxy version (Q-Pro)	QoL
Traumatic Brain Injury Quality of Life (TBI-QOL)	QoL
World Health Organization Quality of Life-BREF (WHOQOL-BREF)	QoL
World Health Organization Quality of Life 100 (WHOQOL-100)	QoL
EuroQol-5D (EQ-5D)	QoL
NeuroQol	QoL
Sickness Impact Profile (SIP)	QoL
Flanagan Quality of Life Scale (FQolS)	QoL
Perceived Quality of Life Scale (PQoL)	QoL
Satisfaction With Life Scale (SWLS)	QoL
Life Satisfaction Questionnaire (LiSat-11)	QoL
Life Satisfaction Index I-A (LSI-A)	QoL
Freiburg Questionnaire of Coping with Illness (FQCI)	QoL/depression
Profile of mood states (POMS)	QoL/depression

Appendix 3B. Studies' quality assessment based on the Downs and Blacks scale

Author (year)	Reporting									External validity				Internal validity-bias						Internal validity - confounding (selection bias)						Power	T	Quality
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27		
Akbik (2019) (109)	1	1	1	1	0	1	0	0	1	0	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	16	Fair
Bhullar (2010) (141)	0	0	0	1	0	1	0	0	0	1	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	11	Poor
Brazinova (2010) (112)	1	1	1	1	0	1	0	0	0	0	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	14	Poor
Brousseau (2017)(133)	1	1	1	1	0	1	1	0	1	0	1	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0	14	Poor
Choi (2019) (105)	1	1	1	1	0	1	1	0	0	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	16	Fair
Deb (1998) (108)	1	1	1	1	0	1	1	0	1	0	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	17	Fair
Erlebach (2017) (110)	1	1	1	1	0	1	1	0	1	1	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	17	Fair
Gorman (2020) (140)	1	1	1	1	0	1	0	0	0	1	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	14	Poor
Gritti (2019) (142)	1	1	1	1	0	1	1	0	1	1	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	17	Fair
Haller (2017) (98)	1	1	1	1	0	1	1	0	1	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	16	Fair
Hawley (2017) (104)	1	1	0	1	0	1	1	0	0	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	15	Fair
Julien (2017) (107)	1	1	1	1	0	1	1	0	0	1	1	0	1	0	1	0	1	1	1	1	1	1	0	0	0	0	0	16	Fair
Khan (2017) (139)	1	1	1	1	0	1	1	0	0	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	16	Fair
Kinsella (2014) (143)	1	1	1	1	0	1	0	0	0	0	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	14	Fair
Lecours (2012) (136)	1	1	0	1	0	1	1	0	1	1	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	15	Fair
Lilley (2016) (135)	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	18	Fair
Miller (2017) (134)	1	1	0	1	0	1	0	0	0	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	12	Poor
Mosenthal (2004) (106)	1	1	0	1	0	1	1	0	1	1	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	16	Fair
Mohindra (2008) (127)	0	0	0	1	0	1	0	0	0	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	10	Poor
Røe (2015) (113)	1	1	1	1	1	1	1	0	0	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	15	Fair

Schmidt (2019) (137)	1	1	1	1	1	1	1	0	0	1	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	16	Fair
Susman (2002) (92)	1	1	0	1	0	1	0	0	0	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	14	Poor
Thompson (2012) (115)	1	1	0	1	0	1	0	0	0	1	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	13	Poor
Tokutomi (2008) (129)	1	1	0	1	0	1	1	0	0	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	13	Poor
Velez (2020) (138)	1	1	1	1	0	1	1	0	0	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	16	Fair
Wan (2016)(111)	1	1	1	1	0	1	1	0	0	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	14	Poor
Won (2017) (128)	1	1	1	1	0	1	1	0	0	1	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	13	Poor

1-27 refer to questions 1-27 of the Downs and Blacks scale (121); T=total score

Downs and Blacks scale's questions (121):

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described ?
4. Are the interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of patients lost to follow-up been described?
10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
14. Was an attempt made to blind study subjects to the intervention they have received ?
15. Was an attempt made to blind those measuring the main outcomes of the intervention?
16. If any of the results of the study were based on "data dredging", was this made clear?
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?
18. Were the statistical tests used to assess the main outcomes appropriate?
19. Was compliance with the intervention/s reliable?
20. Were the main outcome measures used accurate (valid and reliable)?
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
23. Were study subjects randomised to intervention groups?
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26. Were losses of patients to follow-up taken into account?
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

All questions were scored on the following scale: yes=1, unable to determine=0 and no=0

Chapter 4

Retrospective assessment of injuries, co-morbidities, clinical management and outcomes over a 20 years range after TBI based on the UZ Leuven patient database

In this chapter, section 4.1 will provide an overview on patients' clinical history, injury severity and clinical presentation, clinical management and outcomes in older patients with TBI admitted to UZ Leuven in the last two decades (182). In section 4.2, we will specifically discuss those variables in older patients with TBI who were under antithrombotic treatment prior to TBI. Finally, in section 4.3, we will report data on the investigation of the effects of early versus late evacuation of an acute subdural hematoma (ASDH) on these patients outcome.

4.1 Traumatic brain injury in the older population: a 20-year experience in a tertiary neurosurgery center in Belgium

This section is based on:

Laic, R.A G., Vander Sloten, J., Depreitere, B. (2022). Traumatic brain injury in the elderly population: a 20-year experience in a tertiary neurosurgery center in Belgium. ACTA NEUROCHIRURGICA, 164 (5), 1407-1419. doi: 10.1007/s00701-022-05159-0

4.1.1 Abstract

Purpose Traumatic Brain Injury (TBI) rates in the older population are rapidly increasing worldwide. However, there are no clinical guidelines for the treatment of TBI in older patients to date. This study aims at describing injury patterns and severity, clinical management and outcomes in older patients with TBI, which may contribute to specific prognostic tools and clinical guidelines in the future.
Methods Clinical records of 2,999 patients with TBI ≥65 years old admitted in the University Hospital Leuven (Belgium) between 1999 and 2019 were manually screened and 1,480 cases could be included. Records were scrutinized for relevant clinical data.
Results The median age in the cohort was 78.0 years (IQR=12). Falls represented the main accident mechanism (79.7%). The median Glasgow Coma Score on admission was 15 (range 3-15). Subdural hematomas were the most common lesion (28.4%). 90.1% of all patients were hospitalized and 27.0%

were admitted to intensive care. 16.4% underwent a neurosurgical intervention. 11.0% of all patients died within 30 days post-TBI. Among the 521 patients with mild TBI, 28.6% were admitted to ICU, 13.1% had a neurosurgical intervention and 30-day mortality was 6.9%.
Conclusion TBI is a life changing event, leading to severe consequences in the older population, especially at higher ages. Even mild TBI is associated with substantial rates of hospitalization, surgery and mortality in older adults. The characteristics of the older population with TBI is subject to changes over time.

4.1.2 Introduction

Traumatic Brain Injury (TBI) is defined as an injury to the brain caused by an external force applied to the head or body (1). It constitutes a significant health and socioeconomic problem worldwide (187). Increasing life expectancy is associated with an increasing incidence of fall accidents in older adults (43). Over the past two decades, this has led to a steep rise of TBI incidence in this population in industrialized countries (4,188,189). Fall accidents in older adults are intertwined with age-related issues, such as muscle weakness, visual decline, equilibrium disturbance, comorbid conditions and polypharmacy (190).
In addition, the potential presence of cognitive decline and the risk of delayed intracranial mass effect from acute subdural hematoma and/or cerebral contusions complicate the initial assessment of TBI severity in older patients. TBI severity classification by the Glasgow Coma Scale (GCS)(191), is therefore known to lose accuracy at higher ages (192). Most TBI cases in older patients are classified as mild TBI (87). However, they have a higher risk of suffering from more severe consequences than their younger counterparts (88–90).
Age has been proposed as one of the most reliable prognostic factors after TBI (153), with older age being a risk factor for higher mortality and worse functional outcome (154). Besides the presence of different injury and patient characteristics in older adults , the ageing process interferes with physical and psychological potential for recovery and adaptation (117). Older patients are more likely to suffer from emotional, psychosocial, cognitive and motor sequelae (6), with an increased risk for lasting disability (7), dependency (8), medical complications (8), and depression (193). Although the phenomenon has been reported in descriptive papers and series, there is a scarcity of prospective studies on acute management and rehabilitation of TBI in older patients (21). Reset-ASDH, a recently launched randomized controlled trial in the Netherlands and Belgium comparing immediate surgery versus initially conservative management for acute subdural hematomas in older patients for which clinical equipoise exists, is the first of its kind. As a result, there are no clinical guidelines specific to this population, although considerable practice variation between centers has been described (194,195), and the existing prognostic tools for TBI lose reliability with age (196).
Insight into the pathology and its heterogeneity, treatment decisions and short-term outcomes are necessary to help to set the scene for improved patient and family counseling and to better delineate research gaps. We describe patient and injury characteristics, management and hospital outcomes in a large retrospective cohort of more than a thousand patients aged ≥ 65 years old, admitted for TBI in a Belgian tertiary neurotrauma center.

4.1.3 Methods

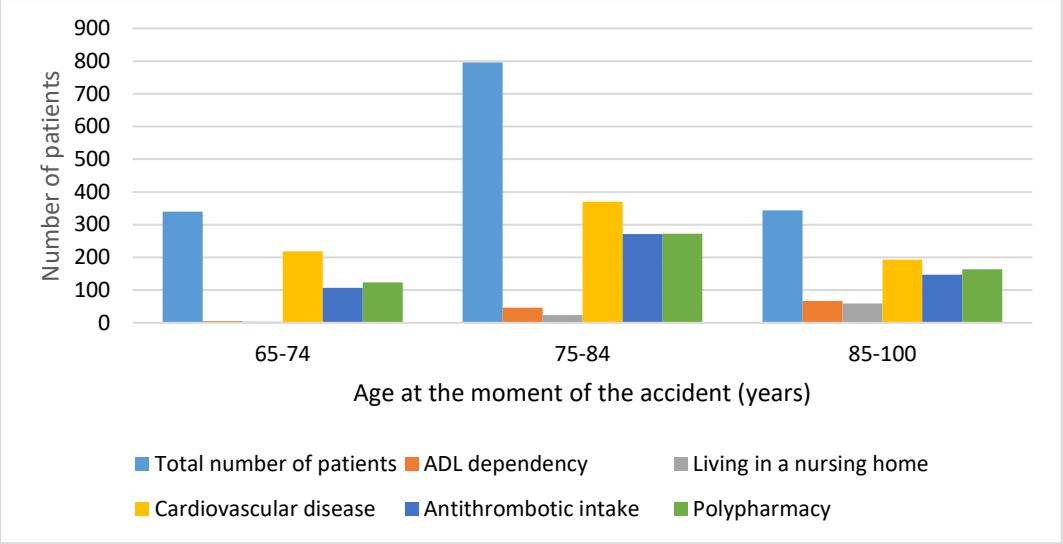
We retrospectively reviewed the clinical records of 2,999 patients ≥65 years old admitted to emergency ward and/or inpatient wards of the University Hospital Leuven (Belgium) between 1999 and 2019 with a diagnosis of TBI, including all degrees of severity.
The University Hospital Leuven is a national reference center for neurotrauma and the hospital settings and referral patterns are unchanged since 1999.
Eligible patients were identified by the reporting service of the hospital and based on the registered diagnostic codes using the International Statistical Classification of Diseases and Related Health Problems (ICD) 9. All records were manually screened.
Patients were excluded if TBI occurred at an age below 65, if they suffered a cerebrovascular accident before TBI and if they had a preexisting neurological condition affecting functional outcomes (except for dementia and Parkinson's disease). Also chronic subdural hematomas were excluded, as in those cases the relation to the traumatic event is indirect and therefore the presentation is totally different than acute TBI.
All patients fulfilling the inclusion and exclusion criteria were included in a digital database (Access 2016, Microsoft). The registered variables on medical history, accident, injuries, management and outcome are listed in Appendix 4A. Injury severity was defined following the GCS and classified as mild TBI (GCS 13-15), moderate TBI (GCS 9-12) and severe TBI (GCS 3-8) (44). Polytrauma was defined as an Injury Severity Score (ISS) ≥16 in multiple organ systems.
The digital database was transferred to a comma-separated values (csv) file for analysis. Descriptive statistical analyses detailing patient and injury characteristics, management and outcomes were performed using Pandas, Numpy and Scikit-learn packages in Python 3.7 (Python Software Foundation) and Excel 2016 (Microsoft).
After descriptive analysis of the entire cohort, subsequent descriptive statistical sub-analyses were performed, including categorization in TBI severity (mild, moderate, severe) according to the registered GCS prior to / upon admission, and categorization into the following 4 subgroups: patients without a previous diagnosis of a neurodegenerative condition or substance abuse, patients with documented alcohol abuse before TBI, patients diagnosed with dementia prior to TBI and patients diagnosed with Parkinson's disease (PD) before TBI. Furthermore, variables were compared between four/five-year time intervals of admission and between different age groups. ANOVA was used to test each variable's differences in different conditions.

4.1.4 Results

Patient characteristics and previous medical history

A total of 2,999 patients were screened, of whom 1,519 patients did not fulfill the in-/exclusion criteria, due to suffering the TBI at an age below 65 years old (despite being ≥65 years old at the time of recruitment), having suffered a cerebrovascular accident before TBI, presenting with a preexisting neurological condition affecting functional outcomes (except for dementia and Parkinson's disease) and/or presenting a chronic subdural hematoma.

A total of 1,480 patients were included in the final analysis. 259 were admitted between 1999 and 2003, 410 between 2004 and 2009, 338 between 2010 and 2014 and 473 between 2015 and 2019.
Age distribution and comorbidities are summarized in Figure 4.1. Detailed cardiovascular comorbidity registered for this study is summarized in Appendix 4B.



ADL=activities of daily living

Figure 4.1. Distribution of comorbidities in different age groups

The demographic characteristics and relevant medical history are shown in Table 4.1.

Median age was 78.0 years. 52.4% were female. 68.5% of patients were ≥75 years old. A higher prevalence of comorbidities was found at older ages (Pearson's correlation r=1.0, p <0.01).

The highest number of patients was admitted between 2015 and 2019. A progressive increase in the patients' age was observed over the study period, with the highest median age at injury found between 2015 and 2019 (80.0 years old, p<0.01). Moreover, a higher rate of cardiovascular conditions, anticoagulant intake and polypharmacy prior to TBI was found in patients after 2009 (p<0.01).

Table 4.1. Patients characteristics and previous medical history

	Total (N=1480)	**1999-2003 (N=259)**	**2004-2009 (N=410)**	**2010-2014 (N=338)**	**2015-2019 (N=473)**	
Age at injury (years) (median; IQR)	78.0; 12.0	76.0;10.5	78.0;10.8	77.0;13.0	80.0;13.0	
Gender (female (N (%))/ male (N (%)))	775 (52.4)/705 (47.6)	127 (49.0)/ 132 (51.0)	211 (51.5)/ 199 (48.5)	174 (51.5)/ 164 (48.5)	263 (55.6)/210 (44.4)	0.34
Dependent for ADL before TBI (N (%))	118 (8.0)	12 (4.6)	33 (8.0)	27 (8.0)	46 (9.7)	0.12
Living in a nursing home before TBI (N (%))	86 (5.8)	2 (0.8)	23 (5.6)	14 (4.1)	47 (9.9)	<0.01
Cardiovascular history (N (%))	781 (52.8)	107 (41.3)	198 (48.3)	206 (60.9)	270 (57.1)	<0.01
Anticoagulants intake (N (%))	525 (35.5)	45 (17.4)	125 (30.5)	159 (47.0)	196 (41.4)	<0.01
Polypharmacy (N (%))	560 (37.8)	72 (27.8)	133 (32.4)	133 (39.3)	222 (46.9)	<0.01
Musculoskeletal problems prior to TBI (N (%))	307 (20.7)	15 (5.8)	37 (9.0)	107 (31.7)	148 (31.3)	<0.01

Walking aid before TBI (N (%))	46 (3.1)	2 (0.8)	3 (0.7)	10 (3.0)	31 (6.6)	<0.01

ADL=activities of daily living; IQR=Inter-quartile range

Accident and injury characteristics

Accident and injury characteristics are summarized in Table 4.2. An analysis of coexistence of different types of brain injuries is included in Appendix 4C. An overview of the demographic, accident and injury characteristics per injury severity category is summarized in Appendix 4D.

Falls were the main cause of TBI (79.7%) and most falls occurred at home (28.4 %).

We found a higher proportion of mild TBI than moderate and severe TBI at admission, and the median GCS was 15 (IQR=13-15). Subdural hematomas were the most common brain injury type (28.4%), followed by skull fractures (24.5%), subarachnoid hemorrhage (22.9%) and brain contusions (18.2%). The frontal lobe (FL) and temporal lobe (TL) were the most common locations for brain contusions.

Upon admission, 10.3% of the patients were disoriented, 15.9% had a decrease of consciousness, 24.1% amnesia, 9.1% speech problems, 8.6% weakness in 1 or more limbs and 7.4% suffered a seizure.

Table 4.2. Patients' injury characteristics and clinical status upon admission.

	Total group (N=1480)	**Fall accident (N=1179)**	**Bicycle accident (N=161)**	**Traffic accident (N=90)**	**ANOVA p value**
Total GCS (median; IQR) *	15; 2	15; 2	15; 5	15; 4	0.08
Polytrauma (N (%))	201 (13.6)	108 (9.2)	40 (24.8)	40 (44.4)	<0.01
Brain contusion (N (%))	269 (18.2)	208 (17.6)	40 (24.8)	14 (15.6)	0.15
FL	104 (7.0)	78 (6.6)	17 (10.6)	6 (6.7)	0.30
PL	31 (2.1)	24 (2.0)	6 (3.7)	1 (1.1)	0.99
TL	114 (7.7)	92 (7.8)	17 (10.6)	3 (3.3)	0.23
OL	32 (2.2)	29 (2.5)	2 (1.2)	1 (1.1)	1.0
Subdural hematoma (N (%))	421 (28.4)	349 (29.6)	43 (26.7)	18 (20.0)	0.14
Subarachnoid hemorrhage (N (%))	339 (22.9)	272 (23.1)	40 (24.8)	20 (22.2)	0.48
Epidural hematoma (N (%))	64 (4.3)	45 (3.8)	13 (8.1)	4 (4.4)	0.89
Intracerebral hematoma (N (%))	26 (1.8)	20 (1.7)	2 (1.2)	1 (1.1)	0.09
Skull fracture (N (%))	362 (24.5)	264 (22.4)	64 (39.8)	11 (12.2)	<0.01
Died within 24h post-TBI (N (%))	63 (4.3)	51 (4.3)	4 (2.5)	6 (6.7)	0.60

*in patients with known GCS, IQR=inter-quartile range; FL= frontal lobe, PL=parietal lobe, TL= temporal lobe, OL=occipital lobe

Table 4.3 shows the evolution over time for injury pattern and accident characteristics observed in our cohort between 1999 and 2019.

The highest incidence of fall accidents was observed between 2010 and 2014 (82.2% of the cases). However, the differences in fall accidents rate over time were not statistically significant (p=0.40). Bicycle accidents were more frequent between 2015 and 2019 (14.6%, p=0.01) and traffic accidents between 1999 and 2003 (8.5%, p=0.05). The median total GCS was 13 between 1999 and 2003, and 15 from 2004 to 2019 (p<0.01). A decrease in mortality within 24h post-TBI was found after 2010 (p=0.01).

Table 4.3. Changes in injury patterns and accident characteristics between 1999 and 2019

	1999-2003 (N=259)	**2004-2009 (N=410)**	**2010-2014 (N=338)**	**2015-2019 (N=473)**	**ANOVA p value**
Fall accident as cause of TBI (N (%))	200 (77.2)	330 (80.5)	278 (82.2)	371 (78.4)	0.40
Bicycle accident as cause of TBI (N (%))	26 (10.0)	33 (8.0)	33 (9.8)	69 (14.6)	0.01
Traffic accident as a cause of TBI (N (%))	22 (8.5)	31 (7.6)	17 (5.0)	20 (4.2)	0.05
Polytrauma (N (%))	31 (12.0)	56 (13.7)	38 (11.2)	76 (16.1)	0.20
Total GCS (median; IQR)	13; 6	15; 2	15;2	15;1	<0.01
Mild TBI (N (%))	57 (22.0)	149 (36.3)	154 (45.6)	164 (34.7)	
Moderate TBI (N (%))	22 (8.5)	14 (3.4)	19 (5.6)	18 (3.8)	
Severe TBI (N (%))	24 (9.3)	29 (7.1)	28 (8.3)	22 (4.7)	
Brain contusion (N (%))	62 (23.9)	71 (17.3)	67 (19.8)	69 (14.6)	0.01
Subdural hematoma (N (%))	93 (35.9)	113 (27.6)	98 (29.0)	117 (24.7)	0.01
Died within 24h post-TBI (N (%))	14 (5.4)	26 (6.3)	13 (3.8)	10 (2.1)	0.01

IQR=Inter-quartile range

Clinical management

The clinical management of the included patients is summarized in Table 4.4. The clinical management and outcomes for each injury severity are summarized in Appendix 4E.

90.1% of the patients were hospitalized for a median length of 7 days (IQR=18). 27.0% were admitted to the Intensive Care Unit (ICU) and 16.4% underwent a neurosurgical intervention. Subdural hematoma evacuation was the most frequent surgical intervention (11.7% of patients). Of the 233 patients that underwent a neurosurgical intervention, a redo surgery was performed in 27 (11.6%), with recurrent SDH evacuation the most frequent intervention (17 patients; 7.3%). Only 5.7% of the patients with dementia and 5.1 % of the patients with PD had a neurosurgical intervention. Compared to patients who did not undergo a neurosurgical intervention, surgical patients had higher mortality rates (63.5%), longer ICU stay length (median 12 days) and longer hospitalization (median 23 days).

Hospitalization rates decreased since 2014, although the difference in hospitalization rates over time was not statistically significant (p=0.09). The median hospitalization length progressively decreased since 1999 (p<0.01). Moreover, the highest ICU admission, tracheotomy and neurosurgical intervention rates were registered between 1999 and 2003, followed by a decrease thereafter (p=0.04, p<0.01 and p<0.01, respectively).

Table 4.4. Patients' clinical management

	Total group (N=1417*)	1999-2003 (N=245*)	2004-2009 (N=384*)	2010-2014 (N=325*)	2015-2019 (N=463*)	ANOVA p value
Hospitalization (N (%))*	1277 (90.1)	219 (89.4)	358 (93.2)	303 (93.2)	397 (85.7)	0.09
Hospitalization length (days) (median; IQR)*	7; 18	13;26	8;19	5;14	4;15	<0.01
ICU admission (N (%))*	382 (27.0)	80 (32.7)	92 (24.0)	92 (28.3)	112 (24.2)	0.04
Intubation (N (%)) *	167 (13.1)	31 (12.7)	47 (12.2)	37 (11.5)	44 (9.5)	0.50
Sedation (N (%)) *	123 (8.7)	29 (12.0)	28 (7.3)	27 (8.3)	33 (7.2)	0.12
Tracheotomy (N (%)) *	21 (1.5)	13 (5.3)	3 (0.8)	2 (0.6)	3 (0.6)	<0.01
Neurosurgical intervention (N (%))*	233 (16.4)	71 (29.0)	61 (15.9)	55 (16.9)	40 (8.6)	<0.01
ICP monitoring	105 (7.4)	25 (10.0)	15 (3.9)	17 (5.3)	17 (3.6)	<0.01
Subdural hematoma evacuation	166 (11.7)	51 (20.8)	47 (12.2)	34 (10.4)	23 (4.9)	<0.01
Intracerebral hematoma evacuation	7 (0.5)	3 (1.2)	1 (0.2)	3 (0.9)	1 (0.2)	0.24
Contusion evacuation	6 (0.4)	2 (0.8)	19 (0.5)	20 (0.6)	0 (0.0)	0.37
Decompressive craniectomy	4 (0.3)	0 (0.0)	8 (0.2)	10 (0.3)	28 (0.6)	0.53
Skull base plasty	3 (0.2)	2 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	0.13
Epidural hematoma evacuation	4 (0.3)	2 (0.8)	2 (0.5)	0 (0.0)	0 (0.0)	0.15

N=number of patients; IQR=inter-quartile range; ICU= Intensive Care Unit; ICP=intracranial pressure; *the number of patients included in this category excludes the number of patients who died within 24 h post-TBI

Outcomes

Thirty day mortality of the patients who survived ≥24 h post-TBI was 7.9% (6.9% of the patients with mild TBI, 20.0% with moderate TBI and 83.6% with severe TBI). A ''Do not resuscitate'' order (DNR) code was registered in 26.7% of the cases. In 25.1% of cases, the DNR code was set during hospitalization for TBI because of an estimated poor prognosis.

Within the period 1999-2019, 24.4% of the surviving patients became dependent for their activities of daily living (ADL) and 17.5% were admitted to a nursing home (17.1% of the patients with mild TBI, 15.7% with moderate TBI and 9.0% with severe TBI). Dependency was not mentioned in 72.4% of the cases and nursing home admission was not mentioned in 71.1%. Re-admission for any medical reason after first TBI was recorded in 59.4% of the patients and 25.0% had ≥1 recurrent falls in that follow-up period. In the further post-TBI course, 12.1% of the patients were diagnosed with dementia, 3.3% with Mild Cognitive Impairment (MCI) and 1.7% with Parkinson's disease (PD).

Patients aged ≥85 years and patients with the diagnosis of dementia had the highest DNR order and mortality within 30-day post TBI rates (p<0.01) [Table 4.6].
''Do not attempt resuscitation'' (DNR) orders were registered in 28.0% of the patients with mild TBI, 35.7% with moderate TBI and 35.3% with severe TBI. DNR orders were prescribed more frequently for patients admitted after 2004 (p=0.07 for DNR code 1 and p<0.01 for DNR codes 2 and 3) and the lowest 30 day mortality rate was registered between 2015 and 2019 (5.4%, p=0.01).

Table 4.5. DNR orders and mortality

	Total (N=1417*)	**1999-2003 (N=245*)**	**2004-2009 (N=384*)**	**2010-2014 (N=325*)**	**2015-2019 (N=463*)**	**ANOVA p value**
DNR code 1 (N (%))*	77 (5.4)	7 (2.9)	18 (4.7)	19 (5.8)	33 (7.1)	0.07
DNR code 2 (N (%))*	214 (15.1)	22 (8.5)	70 (18.2)	59 (18.2)	63 (13.6)	<0.01
DNR code 3 (N (%))*	88 (6.2)	2 (0.8)	23 (6.0)	32 (9.8)	31 (6.7)	<0.01
DNR orders set post-TBI (N (%)*	356 (25.1)	29 (12.0)	103 (26.8)	104 (32.0)	118 (25.4)	<0.01
Mortality within 30 days post-TBI (N (%))*	112 (7.9)	25 (10.2)	31 (8.1)	31 (9.5)	25 (5.4)	0.01

DNR=''Do not attempt resuscitation'' order ; DNR code 1=''Do not reanimate'', DNR code 2=''Do not extend therapy''; DNR code 3=''Progressively reduce therapy'';*the number of patients included in this category excludes the number of patients who died within 24 h post-TBI.

Table 4.6. DNR orders and mortality by age group

	Patients 65-74 years old (N=512)	**Patients 75-84 years old (N=578)**	**Patients ≥85 years old (N=327)**	**ANOVA p value**
DNR code 1 (N (%))*	13 (2.5)	37 (6.4)	27 (8.3)	<0.01
DNR code 2 (N (%))*	49 (9.6)	93 (16.1)	73 (22.3)	<0.01
DNR code 3 (N (%))*	20 (3.9)	44 (7.6)	36 (11.0)	<0.01
DNR orders set post-TBI (N (%)*	78 (15.2)	165 (28.5)	126 (38.5)	<0.01
Mortality within 30 days post-TBI (N (%))*	37 (7.2)	68 (11.8)	58 (17.7)	<0.01

DNR=''Do not attempt resuscitation'' order ; DNR code 1=''Do not reanimate'', DNR code 2=''Do not extend therapy''; DNR code 3=''Progressively reduce therapy'';*the number of patients included in this category excludes the number of patients who died within 24 h post-TBI.

4.1.5 Discussion

This study assessed co-morbidities, accident mechanisms, injury patterns, clinical management and outcomes in a retrospective cohort of 1480 patients with TBI ≥65 years old in a single tertiary hospital. The results represent a detailed snapshot of TBI in older adults. Over 50% of this population has cardiovascular morbidity, over one third takes an antithrombotic drug and over one third is subject to polypharmacy. A fall is the accident mechanism in over three quarters of patients, and the first documented GCS is in the 13-15 range. However, for a high number of the included patients, the GCS at admission was unknown.

Mass lesions, subdural hematomas and cerebral contusions in particular, appeared in 28.4% resp. 18.2%. These are lesions that develop their maximum volume only after admission, explaining deterioration and subsequent neurosurgical intervention in 16.4% of the patients, in spite of initial high GCS. Similar results were observed in the study of Shibahashi et al in 2021, where the median GCS score for patients ≥65 years old ranged between 13-14 and higher aSDH and in-hospital mortality rates were observed in this group, when compared to younger patients (197).

When dependency and nursing home admission are not explicitly mentioned in the records, it is not certain that this did not took place. Still, it was explicitly mentioned that 24.4% of these patients became dependent for daily activities and 17.5% were admitted to a nursing home post-TBI. As expected, older age was associated with higher 30-day mortality and prognosis was also more grim in patients known with dementia or Parkinson's disease. An astonishing 11.1% of patients had documented alcohol abuse, most often being directly related to the cause of the accident, and these patients were younger and did not seem to suffer a worse prognosis. Considering the spectrum of age, co-morbidities, anti-thrombotic use and polypharmacy, one has to conclude that heterogeneity – inherent to TBI – is even more pronounced in TBI in older patients. The latter factors are frequently encountered in the older populations (190,198–203), have a substantial effect on the acute and post-acute course, and play an important role in the evolution and functional recovery after TBI. Cardiovascular diseases are frequently associated with anticoagulant intake (204), which increases the risk for intracranial hematoma development and secondary expansion of hematomas after TBI (199,200). Moreover, polypharmacy has been associated with lower GCS, increased risk for complications after TBI, worse functional outcomes, longer hospital stays (190) and higher mortality (201).
In addition to this heterogeneity, we could observe changing patterns for some characteristics over the 20 years study period. There was a gradual increase in the number of patients and patients' age over time, which could be explained by the increasing life expectancy during this period (62) as well as altering activity patterns (205). Along with age, patients admitted after 2004 had higher rates of co-morbidities, and polypharmacy, but also of pre-injury dependency. Accident mechanisms were subject to slight changes over the study period, as the rate of traffic accidents decreased and the incidence of falls increased, and most recently more bicycle accidents were seen. The first may be explained by the effect of traffic safety measures and campaigns, while the ongoing increase in the proportion of falls reflects that older people remain active and mobile as long as possible. For this reason, e-bikes are particularly popular among older adults, which explains the increase of bicycle accidents. We found no differences in types of injuries associated with different accident mechanisms. Although rates of polytrauma increased, TBI severity seemed to decrease over time: initial GCS improved, the incidence of subdural hematomas decreased and less deaths within 24 hours were observed.

Meanwhile, also a gradual change towards less aggressive management seems to have taken place. After 2004, a decrease in the rate of ICU admission, intubation and tracheostomy was observed, along with lower neurosurgical intervention rates. In the 1999-2005 period 58.0% of subdural hematomas were surgically evacuated, which dropped to 19.8% in the 2015-2019 period. In 1999-2003 all 24 patients with severe TBI received ICP monitoring, and in 2015-2019 this decreased to 17 out of 22. To a certain extent, the less aggressive management may be explained by the observed evolution to less severe TBI, but it is unsure whether this tells the entire story. For instance, from 1999 till 2019 a gradual increase in the use of decompressive craniectomy is seen. The substantial decrease in 30-day

mortality from 10.2% to 5.4% between 1999-2003 and 2015-2019 may illustrate that better and more patient-tailored decisions were being made. On the same note, we saw an increase of the use of DNR codes, particularly after 2004.

ICU admission, neurosurgical intervention, DNR code allocation, ADL-dependency and nursing home admission were more frequent in moderate and severe TBI, but were still substantial in mild TBI. 90.0% of patients with mild TBI were hospitalized for a median length of 7 days, 28.6% were admitted to the ICU and 13.1% underwent a neurosurgical intervention. 30-day mortality in this group was as high as 6.9%. Moreover, almost one quarter of older patients that sustained mild TBI became dependent and almost one fifth was admitted to a nursing home. Previous studies have pointed at the challenge of assessing TBI severity in older patients because of age-related issues such as co-morbidities or cognitive decline (206) and GCS losing reliability with age (207). Therefore, the term ''mild TBI'' in this population could be considered a misnomer (8,106). Furthermore, neurological comorbidities may interact with TBI outcome. To date, these interactions have not been thoroughly explored. Alcohol abuse has been associated with a more pronounced brain damage (208), and a higher likelihood of mood disorders (209) and suicide attempts (210) post TBI. Our results in older adults show that patients with alcohol abuse were more disoriented and had higher amnesia rates upon admission, but did not have worse outcomes. In this particular cohort, this may be explained by the patients with documented abuse being younger.

Dementia and Parkinson's disease are risk factors for fall accidents (211,212). Several reports in literature have focused on the neurodegenerative processes initiated by TBI, potentially increasing the risk for dementia following TBI (213–215). We saw that 12.0% of patients developed dementia during the course of their post-TBI lives. Prevalence of dementia in the overall older population is estimated to range from 5.5% (216) to 11,3% (217,218), which is slightly lower than the rates observed in our cohort. It is unknown, though, whether TBI accelerates the course of the neurodegenerative disease in patients with known dementia or Parkinson's Disease. Our study does not allow to draw conclusions on this matter. We did find that these patients had higher rates of co-morbidities, dependency and polypharmacy, which is a sufficient explanation for worse outcomes. Particularly in dementia, there is a markedly higher proportion of treatment withdrawal decisions.

To the best of our knowledge, no clinical series have been published with a sample size similar to the present one. Nevertheless, the current study has limitations. The study is retrospective in nature, and although many clinical details could be retrieved in the effort of going through all records, the lack of prospectively collected standardized outcome measurements represents a serious shortcoming. Functional outcome was fragmented and quality of life data were not available. Information about dependency and nursing home admission was also limited. Still, we believe that the detailed reporting of pre-injury, injury, management and complications, together with their evolution over time, allows for valuable insights, not in the least on how to organize future research. The authors have initiated a prospective case-control study on mild TBI in older adults that includes biomarkers, MR imaging, functional assessment and quality of life. A next limitation is in the small sample size of certain subgroups.

The current study illustrates the heterogeneity, complexity and potentially serious impact of TBI on the lives of older patients. Decision making is difficult, with several areas of clinical equipoise and a risk for treatment decisions based on center's culture rather than tailored to the patient (184). Neurosurgical and ICU interventions can increase the chance of recovery and minimize the risk of neurologic decline, while, on the other hand, they may prolong suffering without benefit (219,220). To date, research in the field of TBI in older adults is rather limited, and there is an obvious lack of

clinical guidelines and accurate prognostic tools, in spite of increasing incidence. Our findings on the characteristics of this population can be valuable information to raise awareness and that can help patient and family counseling. The changing patterns over time may represent a trend within the trend of shifting demographics in TBI. Among many challenges, the top priority in this particular population – maybe even more than in younger patients - is the aim to carefully weigh the expected effect of any action on quality of life. Therefore, and within this heterogenic context, the call for prognostic models specific to this population is real. Hence, the real need is for prospective data repositories with carefully collected outcome and quality of life data. The results of the CENTER-TBI and TRACK-TBI analyses on older patients subcohorts, are eagerly awaited.

4.1.6 Conclusion

TBI is a heterogeneous and complex condition, even more so in older than in younger patients, with serious consequences, even in patients with mild TBI. Over the 20 year study period in the present series, an increase of TBI cases, age and comorbidities, and a marked reduction in neurosurgical interventions and ICU admissions was observed, along with a trend to less severe injuries but a higher proportion of treatment withdrawals, while at the same time mortality rates decreased. This may indicate better patient-tailored decision making and needs further investigation. Particularly in this frail population that continues to change and to increase, there is a strong need for prospective data collection and prognostication modelling to support the best possible individual decision making.

4.2 Long-term outcomes after Traumatic Brain Injury in older patients on antithrombotic therapy

This section is based on:
Gavrila Laic, R.A, Verhamme, P., Vander Sloten, J., Depreitere, B. Long-term outcomes after Traumatic Brain Injury in elderly patients on antithrombotic therapy. [Manuscript submitted for publication to Acta Neurochirurgica].

4.2.1 Abstract

Older patients receiving antithrombotic treatment have a significantly higher risk of developing an intracranial hemorrhage when suffering traumatic brain injury (TBI), potentially contributing to higher mortality rates and worse functional outcomes. It is unclear whether different antithrombotic drugs carry a similar risk. Therefore, this study aims to investigate injury patterns and long-term outcomes after TBI in older patients treated with antithrombotic drugs.
The clinical records of 2,999 patients ≥65 years old admitted to the University Hospitals Leuven (Belgium) between 1999 and 2019 with a diagnosis of TBI, spanning all injury severities, were manually screened. A total of 1,443 patients who had not experienced a cerebrovascular accident prior to TBI nor presented with a chronic subdural hematoma at admission were included in the analysis. Relevant clinical information, including medication use and coagulation lab tests, was manually registered and statistically analyzed using Python and R.

In the overall cohort, 418 (29.0%) of the patients were treated with acetylsalicylic acid before TBI, 58 (4.0%) with vitamin K antagonists (VKA), 14 (1.0%) with a different antithrombotic drug and 953 (66.0%) did not receive any antithrombotic treatment. The median age was 81 years (IQR=11). The most common cause of TBI was a fall accident (79.4% of the cases) and 35.7% of the cases were classified as mild TBI.
Patients treated with vitamin K antagonists had the highest rate of subdural hematomas (44.8%, $p=0.02$), hospitalization (98.3%, $p=0.03$), intensive care unit admissions (41.4%, $p<0.01$) and mortality within 30 days post-TBI (22.4%, $p<0.01$). The number of patients treated with adenosine diphosphate (ADP) receptor antagonists and Direct Oral Anticoagulants (DOACs) was too low to draw conclusions about the risks associated with these antithrombotic drugs.

In conclusion, in a large cohort of older patients, treatment with VKA prior to TBI was associated with a higher rate of acute subdural hematoma and a worse outcome, compared with other patients. However, intake of low dose aspirin prior to TBI did not have such effects. Therefore, the choice of antithrombotic treatment in older patients is of utmost importance with respect to risks associated with TBI, and patients should be counselled accordingly. Future studies will determine whether the shift towards DOACs is mitigating the poor outcomes associated with VKA after TBI.

4.2.2 Introduction

Traumatic Brain Injury (TBI) is a leading cause of morbidity and mortality worldwide (49,221,222). For older adults, TBI is currently the fifth cause of death (223). As a result of increasing life expectancy, the proportion of older adults (≥ 65 years old) in the population is rapidly growing (223). The reported high frequency of TBI in the older population mainly associated with falls (154) and the unique physiological alterations specific to this frail population make them more susceptible to succumb to TBI than their younger counterparts. Moreover, it is known that older patients with TBI most often arrive in the hospital in a good neurological status and deteriorate subsequently (74). This is especially true in patients who receive antithrombotic treatment (224).

Intracranial hematoma is a common and serious consequence of TBI. It is usually classified based on the anatomical location of the blood into epidural hematoma, acute subdural hematoma, intracerebral hemorrhage, and intraventricular hemorrhage. All types of ICH were shown to be associated with worse prognosis, including increased in-hospital mortality and disability at 6 months after injury, compared with patients without ICH (225,226).

Older patients have a significantly higher risk of sustaining an ICH following impact to the head (5,227). Neuroanatomical changes associated with ageing, such as cerebral atrophy and increased adherence of the dura to the skull, facilitate the tearing of bridging veins in response to external forces to the head, predisposing the older to acute subdural hematomas (SDH) (227). Moreover, the risk of ICH with relatively minor head injury increases substantially in patients under antithrombotic treatment.

Oral antithrombotic therapy encompasses antiplatelet therapy and anticoagulant therapy. It is increasingly employed in clinical practice for the prevention and treatment of cardiovascular conditions (228). It has been previously estimated that 1.2 to 2.8% of the population aged 60-69 years old and 7.3 to 13.7% of the population ≥80 years old have a history of atrial fibrillation (AF) (229,230). Furthermore, 8 out of 1000 persons ≥ 85 years old, per year, suffer a venous thromboembolism (VTE) (231) and 6% of the adults ≥75 years old suffer annually from a valvular heart disease (232).

Antiplatelet therapy is usually prescribed for the primary or secondary prevention of atherothrombosis, low dose aspirin being the most frequently used drug (233). Previous studies have suggested that there is a low risk for worse outcomes post-TBI in patients with mild TBI and pre-injury antiplatelet therapy (234).
Anticoagulant therapy is mostly used for the prevention and treatment of thromboembolic complications of atrial fibrillation, venous thromboembolism and valvular heart disease. In recent decade, DOACs have become the preferred drugs because they cause less intracranial bleeds compared with VKAs (228). However, studies on the impact of the intake of antithrombotic therapy in case of a TBI have yielded inconsistent results. While many studies indicate that patients under antithrombotic treatment have a higher prevalence of ICH (199,235–237), mortality (224,238–241) and worse functional outcome (228) after TBI than patients who do not receive this treatment (199,235–237), other studies have been unable to confirm a significant relationship between the use of antithrombotic drugs and elevated rates of ICH and/or mortality (107,242–244).
Different risks for worse outcomes after TBI have been associated with different types of antithrombotic drugs (198,245). In particular, DOACs have been demonstrated to result in an increased risk of mortality in older patients after TBI (198), while antiplatelets did not show this risk

(198). However, the risk of ICH was reportedly lower in patients under DOACs than in patients under vitamin K antagonists (VKA) (245,246).
The present study aims at investigating how different types of antithrombotic drugs affect injury patterns and long-term outcomes in older patients with TBI in a large single tertiary institution database.

4.2.3 Methods

A manual screening of the clinical records of 2,999 patients ≥65 years old diagnosed with TBI and admitted to the emergency ward and/or hospital wards of the University Hospital Leuven (Belgium) between 1999 and 2019, was conducted.
The list of patients provided to the authors by the hospital's reporting service was based on registered diagnostic codes, following the International Statistical Classification of Diseases and Related Health Problems (ICD) 9. This study was approved by the Research Ethics Committee UZ/KU Leuven.
Patients were excluded if they were under 65 years of age or suffered a cerebrovascular accident before TBI. Patients with a chronic subdural hematoma were also excluded.

In order to compare the different antithrombotic drugs, patients were divided in four different groups for statistical analysis based on the treatment with 1) antiplatelet drugs, 2) Vitamin K antagonists (VKA), 3) other antithrombotic treatment (e.g. low molecular weight heparin and DOACs, and 4) no antithrombotic treatment.

All relevant clinical data, including information about the previous clinical history, medication use, accident, treatment, clinical characteristics, outcome and coagulation blood tests upon admission were manually registered in an Access 2016 database for all the patients who met the inclusion and exclusion criteria. The database was then converted to a comma-separated values (csv) file for the statistical analysis, which was performed using Pandas, Numpy and Scikit-learn packages in Python, and R software.
Injury severity was defined using the Glasgow Coma Scale (GCS) (44) and polytrauma was defined as an Injury Severity Score (ISS) ≥16 in multiple organ systems.

One way Analysis of Variance (ANOVA) was performed to test for differences. Additionally, logistic regression and contrast analyses were also conducted to compare the effects of the different treatments on specific variables of interest, correcting for the following confounders: age, gender, alcohol abuse and polypharmacy.

4.2.4 Results

Demographics, antithrombotic drug use and injury characteristics
A total of 1,480 patients initially met our in-/exclusion criteria. However, 37 of these patients, who were under VKAs and presented normal INR values at admission were excluded from the analysis, as the normal INR indicates a medication under-dose. Hence, a total of 1,443 patients were included in the study [Figure 4.2].

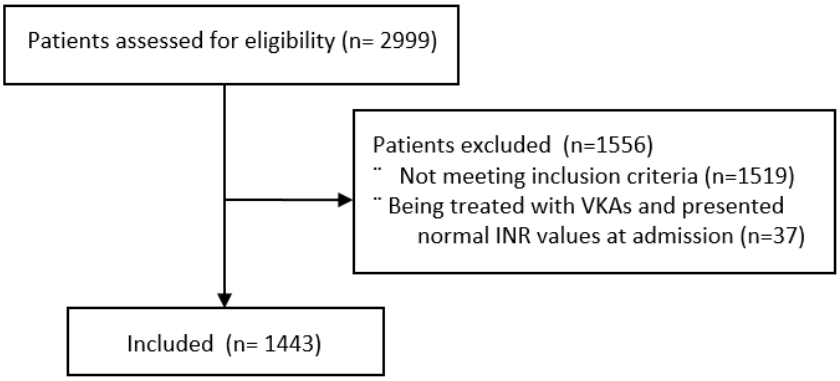


Figure 4.2. Description of patients' inclusion and exclusion to the database

Table 4.7. Demographic characteristics of the included patients

Number of patients (N)		1443
Cardiovascular history (N (%))		752 (52.1)
Polypharmacy (N(%))		544 (37.7)
Antithrombotic drug use (N (%))		490 (34.0)
Antiplatelet drugs	Acetylsalicylic acid (N (%))	416 (28.8)
	Clopidogrel (N(%))	2 (0.1)
Of which treated with dual antiplatelet therapy (N (%))		17 (4.1)
Of which treated with mono therapy (N (%))		411 (98.3)
Anticoagulant drugs	Vitamin K antagonist (N (%))	58 (4.0)
Of which treated with a combination of antiplatelet and anticoagulant agents (N (%))		3 (5.2)
Other antithrombotic drugs (e.g. DOAC, low molecular weight heparine,…)		14 (1.0)

DOAC=Direct Oral Anticoagulant

52.3% of the patients were female and 47.7% were male. The median age was 81 years (IQR=11). A history of cardiovascular diseases was documented in 52.1% of the patients, with arterial hypertension and hypercholesterolemia being the most prevalent conditions in our cohort. 37.7% of the patients were taking at least 6 medications at the time of admission, which was considered as polypharmacy. 34.0 % of the included patients were receiving pre-injury antithrombotic therapy. 29.0 % received antiplatelet treatment with acetylsalicylic acid, 4.0% vitamin K antagonists and 1.0% other antithrombotic drug types (e.g. DOAC, adenosine diphosphate receptor antagonists, etc). The coagulation status in the laboratory tests upon hospital admission for each of the four groups included in the analysis is described in Table 4.8.

Table 4.8. Coagulation problems at hospital admission

	Antithrombotics (N=490)			**No antithrombotic drugs (N=953)**	**ANOVA p value**
	Antiplatelet (N=418)	**VKA (N=58)**	**Other (N=14)**		
Platelet count <100 (N (%))	7 (1.7)	0 (0.0)	0 (0.0)	22 (2.3)	0.54
INR ≥1.5 (N (%))	34 (8.1)	54 (93.1)	2 (14.3)	50 (5.2)	<0.01

INR (mean; SD)	1.2 (0.4)	2.5 (1.3)	1.4 (0.3)	1.2 (0.6)	<0.01
aPTT (mean; SD)	28 ; 4	36; 7	36; 10	29;12	<0.01

VKA=Vitamin K antagonist; aPTT= Activated Partial Thromboplastin Clotting Time; INR=International Normalized Ratio

The injury characteristics of the patients included in the four groups are described in Appendix 4D.
The included patients had a median age ranging between 77 and 84 years old when they sustained the TBI. Patients without antithrombotic treatment were the youngest (p<0.01).
Furthermore, 79.4% of the patients suffered the TBI due to a fall, 11.1% due to a bicycle accident, and 6.2% due to a traffic accident.
The most prevalent injury severity in our cohort was mild TBI (35.7% of the cases) and 13.7% of the patients had the TBI in the context of a polytrauma.

Brain injury characteristics

The brain injuries observed on the admission CT scan are described in Table 4.9.
Patients taking vitamin K antagonist treatment had the highest acute subdural hematoma rate (44.8%, p=0.02). The presence of acute subdural hematomas was not statistically significantly affected by any of the studied confounders [Table 4.10]. Furthermore, the contrast analysis revealed that patients receiving vitamin K antagonists had a significantly higher risk of suffering acute subdural hematomas than patients receiving antiplatelets (p=0.03) [Table 4.11].
No statistically significant differences were found among groups for brain contusions, subarachnoid hemorrhages, epidural hematomas or ICH (p=0.13, p=0.55, p=0.47 and p=0.73, respectively) [Table 4.9].

Table 4.9. Patients' injury characteristics

	Antithrombotics (N=490)			**No antithrombotics (N=953)**	**ANOVA p value**
	Antiplatelet (N=418)	**VKA (N=58)**	**Other (N=14)**		
Brain contusion (N (%))	77 (18.4)	6 (10.3)	0 (0.0)	178 (18.7)	0.13
Subdural hematoma (N (%))	110 (26.3)	26 (44.8)	2 (14.3)	262 (27.5)	0.02
Subarachnoid hemorrhage (N (%))	90 (21.5)	11 (19.0)	2 (14.3)	228 (23.9)	0.55
Epidural hematoma (N (%))	14 (3.3)	2 (3.4)	0 (0.0)	47 (4.9)	0.47
Intracerebral hematoma (N (%))	7 (1.7)	0 (0.0)	0 (0.0)	17 (1.8)	0.73

VKA=Vitamin K antagonist

Table 4.10. Logistic regression analysis for the effect of the different factors on acute subdural hematomas*

Deviance Residuals:

	Min	**1Q**	**Median**	**3Q**	**Max**
	-1.1879	-0.8231	-0.7752	1.4973	1.9558

Coefficients :

	Estimate	**Std. Error**	**z value**	**Pr(>|z|)**
(Intercept)	-1.942972	0.661848	-2.936	0.00333 **

Gender	-0.172675	0.123614	-1.397	0.16245
Alcohol abuse	-0.144511	0.201224	-0.718	0.47266
Polypharmacy	0.001915	0.131545	0.015	0.98839
Age at injury	0.012594	0.008187	1.538	0.12396
No treatment	0.145929	0.142791	1.022	0.30679
Vitamin K Antagonist treatment	0.819636	0.295210	2.776	0.00550 **
Other treatment	-0.772427	0.773740	-0.998	0.31813

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)
Null deviance: 1624.0 on 1364 degrees of freedom
Residual deviance: 1609.5 on 1357 degrees of freedom
(78 observations deleted due to missingness)
AIC: 1625.5
Number of Fisher Scoring iterations: 4

*Corrected for age, gender, alcohol abuse and polypharmacy

Table 4.11. Contrast analysis for the effect of the different factors on acute subdural hematomas*

	contrast estimate	**SE**	**df**	**z.ratio**	**p.value**
Antiplatelet – No antihrombotics	-0.146	0.143	Inf	-1.022	0.7366
Antiplatelet - Other	0.772	0.774	Inf	0.998	0.7504
Antiplatelet - Vitamin K antagonist	-0.820	0.295	Inf	-2.776	0.0281
No antithrombotics - Other	0.918	0.770	Inf	1.193	0.6310
No antithrombotics - Vitamin K antagonist	-0.674	0.286	Inf	-2.354	0.0862
Other - Vitamin K antagonist	-1.592	0.812	Inf	-1.960	0.2033

*Corrected for age, gender, alcohol abuse and polypharmacy

Clinical management

The patients' clinical management is summarized in Appendix 4H and 4 I.
Patients under VKAs had the highest rate of hospitalization, as well as intensive care unit admission admission (98.3% and 41.4%; p=0.03 and p<0.01, respectively). Neurosurgical interventions were performed in 10.5-19.0% of the patients, the highest surgery rate appeared in patients under VKAs (19.0%, p<0.01).

Outcomes

Within 30 days post-TBI, 11.0% of the patients died. The highest mortality rate was registered for patients taking VKA (22.4%, p<0.01) [Table 4.12], which was statistically significantly higher than the mortality rate for patients receiving antiplatelets (p=0.02) [Table 4.14]. However, the confounders gender and age at injury also had a statistically significant influence on mortality rates (p=0.02 and p<0.01) [Table 4.13].

Moreover, 21.2-48.3% of the patients had a ''Do not resuscitate order'' (DNR) set after TBI, with the highest DNR rate also in patients taking VKAs (p<0.01).
Survival rates at 2 years post-TBI ranged between 55.2% and 78.6%, with the lowest rate in patients taking VKA and the highest in patients receiving 'other' antithrombotic treatment (p<0.01) [Table 4.12].

Table 4.12. Mortality

	Antithrombotics (N=490)			**No antithrombotics (N=953)**	**ANOVA p value**
	Antiplatelet (N=418)	**VKA (N=58)**	**Other (N=14)**		
DNR order post TBI (N (%))	124 (29.7)	28 (48.3)	4 (28.6)	202 (21.2)	<0.01
Mortality within 30 days (N ())	34 (8.1)	13 (22.4)	0 (0.0)	110 (11.5)	<0.01
Survival at 2 years post-TBI (N (%))	319 (76.3)	32 (55.2)	11 (78.6)	714 (74.9)	<0.01

VKA=Vitamin K antagonist; DNR order=''Do not resuscitate'' order

Table 4.13. Logistic regression analysis for the effect of the different factors on mortality within 30 days post-TBI *

Deviance Residuals:

	Min	**1Q**	**Median**	**3Q**	**Max**
	-1.0530	-0.5234	-0.4434	-0.3486	2.6646

Coefficients :

	Estimate	**Std. Error**	**z value**	**Pr(>|z|)**
(Intercept)	-5.58790	0.99254	-5.630	1.8e-08 ***
Gender	-0.43238	0.18300	-2.363	0.01814 *
Alcohol abuse	-0.73307	0.38208	-1.919	0.05504
Polypharmacy	-0.13196	0.19673	-0.671	0.50236
Age at injury	0.04259	0.01205	3.534	0.00041 ***
No treatment	0.57102	0.22715	2.514	0.01194 *
Vitamin K Antagonist treatment	1.11429	0.38366	2.904	0.00368 **
Other treatment	-13.20095	415.62072	-0.032	0.97466

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)
Null deviance: 922.79 on 1339 degrees of freedom
Residual deviance: 886.01 on 1332 degrees of freedom
(103 observations deleted due to missingness)
AIC: 902.01
Number of Fisher Scoring iterations: 14

*Corrected for age, gender, alcohol abuse and polypharmacy

Table 4.14. Contrast analysis for the effect of the different factors on mortality within 30 days post-TBI*

	contrast estimate	**SE**	**df**	**z.ratio**	**p.value**
Antiplatelet – No antihrombotics	--0.571	0.227	Inf	-2.514	0.0578
Antiplatelet - Other	13.201	415.621	Inf	0.032	1.0000
Antiplatelet - Vitamin K antagonist	-1.114	0.384	Inf	-2.904	0.0193
No antithrombotics - Other	13.772	415.621	Inf	0.033	1.0000

No antithrombotics - Vitamin K antagonist	-0.543	0.357	Inf	-1.522	0.4239
Other - Vitamin K antagonist	-14.315	415.621	Inf	-0.034	1.0000

*Corrected for age, gender, alcohol abuse and polypharmacy

Injury characteristics, clinical management and outcomes in patients with polypharmacy

In our cohort, a total of 544 patients, with a median age of 80 years old, had polypharmacy prior to TBI. These patients had a higher rate of subarachnoid hemorrhage (25.9 vs 21.1, p=0.04), median hospitalization length (10 days vs 5 days, p=0.03), lower brain surgery rate (12.7 vs 17.1, p=0.02) and higher DNR order rates post-TBI (29.0 vs 22.2, p<0.01), than patients with no polypharmacy at admission [Table 4.15]

Table 4.15. Injury characteristics, clinical management and outcomes in patients with polypharmacy

	Patients with polypharmacy (N=544)	**Patients with no polypharmacy (N=899)**	**ANOVA p value**
GCS (median;IQR)	15;2	15;4	0.29
Brain contusion (N (%))	93 (17.1)	168 (18.7)	0.41
Subdural hematoma (N (%))	152 (27.9)	248 (27.6)	0.88
Subarachnoid hemorrhage (N (%))	141 (25.9)	190 (21.1)	0.04
Epidural hematoma (N (%))	22 (4.0)	41 (4.6)	0.64
Intracerebral hematoma (N (%))	12 (2.2)	12 (1.3)	0.21
Admission ICU (N (%))	147 (27.0)	224 (24.9)	0.38
Hospitalization (N (%))	463 (85.1)	786 (87.4)	0.21
Hospitalization length (days) (median;IQR)	10;22	5;14	0.03
Brain surgery (N (%))	69 (12.7)	154 (17.1)	0.02
DNR order post TBI (N (%))	158 (29.0)	200 (22.2)	<0.01
Mortality within 30 days (N ())	55 (10.1)	102 (11.3)	0.47

GCS=Glasgow Coma Scale; IQR=Inter-quartile range; ICU=Intensive Care Unit; DNR=Do Not Resuscitate order

4.2.5 Discussion

The current study investigated co-morbidities, accident mechanisms, injury patterns, clinical management and outcomes in a retrospective cohort of 1443 patients with TBI ≥65 years old who received different types of antithrombotic treatment, or no antithrombotic treatment, before TBI.

Our results demonstrated that VKA intake before TBI in older patients increases the risk of having more severe injuries, especially acute subdural hematomas, and leads to higher mortality rates than other antithrombotic drugs. This effect was not observed in patients who received antiplatelet drugs.

Similar results were found by Dossett et al. (228), Prexl et al. (247), Feeney et al. (248) and Posti et al. (246), who reported higher mortality rates in patients taking VKAs. Nevertheless, other studies have not found a correlation between pre-injury VKA intake and mortality (240,249). Maung et al. did not observe a significant difference in mortality rates between patients with TBI taking warfarin and those taking DOACs or no anticoagulant therapy (250). Moreover, Pozzessere et al. (251) and Kobayashi et al. (252) found no difference in the incidence of ICH and mortality between patients taking VKAs and other anticoagulants.

Anticoagulant medication has been widely used in clinical practice for the treatment of different conditions such as pulmonary embolism (PE) in patients with AF (253–258) or cardioembolic acute ischemic stroke (AIS) (254–259). Therefore, in clinical practice, thromboembolic risk and the risk of stroke needs to be outweighed with the risk of suffering an ICH after TBI.

One every three persons >60 years old and one every two persons >80 years old have a fall accident every year (43). Moreover, it has been previously estimated that 8 out of 1000 persons ≥ 85 years old suffer a VTE (231) and 1.7 to 69.8 out of 1000 persons ≥55 years old a stroke every year (260). In the case of patients with AF and no antithrombotic treatment, the prevalence for ischemic stroke is of 5% per year (261).

The effect of DOACs in older TBI patients could not yet be specifically investigated in the current study due to the small sample size of patients treated with this drug. These patients were included in the ''other'' antithrombotic treatments and lower rates of subdural hematomas and mortality were observed in this blended group. However, a previous study published by Posti et al. showed that DOACs are associated with lower mortality than VKAs in patients with TBI (246). Moreover, in a mixed group of 81 anticoagulated trauma patients, Wood et al. reported higher survival rates at discharge for patients receiving DOACs compared to those receiving VKAs (262).
DOACs have also shown greater safety in older patients with AF and VTE (254,258,263–265) and have been associated with lower mortality and better functional outcomes in stroke patients than VKAs (259,266).
Unfortunately, the sample size of this group is not sufficient to draw conclusions on the effect of DOACs on older TBI patients. Nonetheless, VKAs are now largely being replaced by DOACs in clinical practice and we await future studies that can shed light on these effects.

It is important to note that older patients usually have increased risks of poorer outcomes, commonly associated with aging, such as the presence of co-morbidities, as reported in literature (4,267). Multiple studies have indicated that the risk of intracranial hematoma generally increases at higher ages (268–272). In addition, a study performed in 2011 using the National Trauma Data Bank identified preinjury warfarin use as a risk factor for mortality among older patients (228). Nevertheless, our analysis showed that age at injury is not a statistically significant confounder for the presence of acute subdural hematoma in our cohort. This was also shown by Sauter et al, who also demonstrated that age is not associated with intracranial hematoma in patients on oral anticoagulants and with mild traumatic brain injury who were admitted as emergencies (273).

The current study has limitations. The nature of the study is retrospective and, in spite of the fact that a considerable amounts of clinical data were retrieved in the patients' clinical records, missing data regarding patients' outcomes represented one of the main problems we faced. Moreover, there are differences in sample sizes between subgroups, which might be linked to changes in clinical guidelines regarding antithrombotic therapy for the older population over time and was out of the authors control.

The results from this analysis demonstrate how different antithrombotic drug types influence post-TBI outcomes in older patients. Especially, VKAs have shown to lead to a significantly higher risk for subdural hematomas and higher mortality rates than other anticoagulant treatments (246). However,

there has been a shift in clinical practice towards using DOACs instead of VKAs (274), which is particularly relevant given the higher activity levels of older patients. Although DOAC safety cannot be concluded from the current analysis, it seems safer than VKA based on a Finnish study (246).
The current study highlights the particular risk associated with VKA, and this is highly relevant in the context of increasingly active older adults in Western countries, which comes with a risk for head impact and TBI. We believe that this study can therefore offer valuable information in order to weight benefits of VKA against their risks upon prescription and counsel active older adults accordingly. DOACs are now the recommended therapy by guidelines, and the preferred therapy for patients and physicians, in part driven by the lower risk of ICH. Future research also needs to evaluate the impact of DOACs on TBI, since our cohort included only a low number of patients receiving this treatment.
Eventually, such advice should be included in guidelines for choosing for antithrombotic drugs in older adults.

4.2.6 Conclusion

Vitamin K antagonist intake prior to TBI in a large cohort of older patients was associated with a clearly higher rate of acute subdural hematoma and worse outcome, while antiplatelet intake seemed to be much safer. Therefore, adequate and informed antithrombotic treatment selection can help to reduce poor TBI outcomes in older patients. Future studies will determine whether the shift towards DOACs is mitigating the poor outcomes associated with VKA after TBI.

4.3 Neurosurgical treatment in older patients with Traumatic Brain Injury: a 20-year follow-up study

This section is based on:

Gavrila Laic, R. A., Vander Sloten, J., Depreitere, B. Neurosurgical treatment in elderly patients with Traumatic Brain Injury: a 20-year follow-up study. [Manuscript submitted for publication to Brain and Spine].

4.3.1 Abstract

Introduction Traumatic brain injury in older adults can have a substantial impact on patients' quality of life. In this regard, successful treatment strategies are hard to define to date.
Research question In order to facilitate further insight, this study assessed outcomes following acute subdural hematoma evacuation in patients aged ≥65 years in a large patient series.
Material and methods A manual screening of the clinical records of 2,999 patients with TBI, aged ≥65 years, admitted to the University Hospital Leuven (Belgium) between 1999 and 2019, was performed.
Results A total of 149 patients were identified with aSDH, of whom 32 underwent early surgery, 33 underwent delayed surgery and 84 were treated conservatively. Patients who underwent early surgery had the lowest median GCS, poorest Marshall CT scores, longest hospital and ICU stay, and highest intensive care unit admission and redo surgery rates. 30-d mortality was 21.9% in patients undergoing early surgery, 3.0% in patients undergoing late surgery and 16.7% in patients who were treated conservatively.
Discussion and Conclusion In conclusion, patients in whom surgery could not be delayed had the worst presentation and poorest outcomes as opposed in patients in whom delay was possible. Surprisingly, patients treated conservatively had worse outcomes than those treated with delayed surgery. These results might indicate that if the GCS at admission is still adequate, an initial strategy of waiting and seeing might be associated with better outcomes. Future prospective studies with sufficient sample size are warranted to draw more definitive conclusions on the value of early vs. late surgery in older patients with aSDH.

4.3.2 Introduction

The incidence of Traumatic Brain Injury (TBI) in older adults (≥65 years old) has steadily increased over the past decades (275), which is likely to increase even more with ongoing demographic shifts (82).
Older patients with TBI frequently suffer from intracranial hematomas. In particular, acute subdural hematoma (aSDH) is the most common injury type in older adults admitted to hospital after TBI, often accompanied by cerebral contusions (276).
It has been demonstrated that older patients with TBI have higher mortality rates and are less likely to function or live independently after TBI, compared to younger patients (85,277,278). Specifically, lower Glasgow Coma Scale (GCS) scores (82,277), pre-existing systemic diseases (10,278), systemic complications (10), closed basal cisterns (11), midline shift (11), and limited intensive care (173), are risk factors that have been found to contribute to poorer outcomes in older patients.

Treatment strategies in this context are difficult to decide, and surgeons may be faced with a clinical dilemma, or clinical equipoise due to the lack of high-level evidence specific to the older population. Although neurosurgical interventions are frequently applied in older patients with aSDH (10,11), many researchers recommend a more conservative approach, because of the worse outcomes and higher mortality in older patients (173,277). High practice variation has been identified in the management of older patients with aSDH (155), reflecting uncertainty and potential controversy (279,280). Therefore, the current study compared the clinical outcomes of patients with TBI aged ≥65 years who underwent immediate, delayed or no neurosurgical intervention for aSDH, with the aim of contributing to the creation of specific clinical guidelines for these patients in the future.

4.3.3 Methods

A manual screening of the clinical records of 2,999 patients aged ≥65 years, diagnosed of TBI, admitted to the University Hospital Leuven (Belgium) between 1999 and 2019, was performed.
The list of patients provided to the authors by the hospital's reporting service was based on registered diagnostic codes, following the International Statistical Classification of Diseases and Related Health Problems (ICD) 9. Only patients with an Acute Subdural Hematoma (aSDH) were included in the present analysis. The aSDH volumes were calculated on the first CT scan taken at hospital admission using the ABC/2 formula (281).
Patients were excluded if they were under 65 years old, presented with a chronic subdural hematoma (cSDH), had a diagnosis of Alzheimer's disease (AD), Parkinson's disease (PD) or suffered a cerebrovascular accident prior to TBI, had alcohol abuse, were under antithrombotic treatment or presented a Do Not Resuscitate (DNR) order.
All patients' relevant clinical data, including information on previous clinical history, accident, treatment, clinical characteristics and outcomes were manually registered in an Access 2016 database for all patients fulfilling the inclusion and exclusion criteria. This database was translated into a comma-separated values (csv) file for statistical analysis, which was performed using the Pandas, Numpy and Scikit-learn packages in Python.
Injury severity was defined using the Glasgow Coma Scale (GCS) (44) and polytrauma was defined as an Injury Severity Score (ISS) ≥16 in multiple organ systems.

4.3.4 Results

Initially, 272 patients fulfilled our inclusion criteria, of whom 123 were excluded due to antithrombotic medication intake prior to the accident [Figure 4.3]. Therefore, 149 patients were included in the study, all having sustained aSDH, and of whom 32 underwent early decompressive surgery (i.e. Craniotomy within 24h post-TBI), 33 underwent delayed surgery (later than 24h post-TBI, due to clinical deterioration or enlarging hematoma size) and 84 were conservatively treated. The patients' median age at injury ranged from 75 to 78 years. 40.6% of the patients who were treated with early surgery, 33.3% of those treated with delayed surgery and 40.5% of those treated conservatively were ≥80 years old. No statistically significant differences were found between age groups in the different studied groups.
None of the patients included in this cohort were taking antithrombotic medication prior to TBI. 26.2-42.4% of the patients had a history of cardiovascular diseases prior to TBI, 21.2-28.1% were under

polypharmacy, 6.3-12.1% had a history of cancer and 6.0-9.4% had chronic obstructive pulmonary disease (COPD).
Patients treated with early surgery had the highest rate of diabetes (18.8%, p<0.01). Moreover, 3.0% of the patients with delayed surgery and 2.4% of the patients who received conservative treatment were dependent for activities of daily living (ADL) prior to TBI.
The demographic characteristics of each of the included groups has been described in Table 4.16.

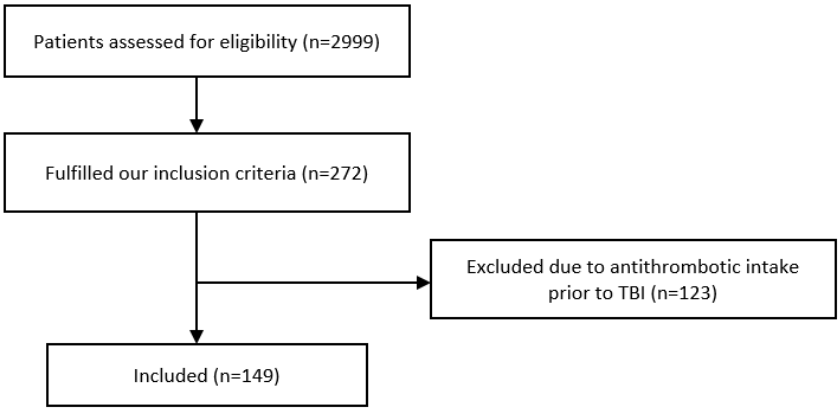


Figure 4.3. Description of patients' inclusion and exclusion

Table 4.16. Demographic characteristics of the patients included in the three studied groups

	Neurosurgery		**Conservative treatment (N=84)**	**ANOVA p value**
	Early surgery (N=32)	**Delayed surgery (N=33)**		
Female/Male (N (%))	21 (65.6)/11 (34.4)	12 (36.4)/21 (63.6)	41 (48.8)/43 (51.2)	0.06
Age at injury (median; IQR)	78;7	75; 10	77; 14	0.72
≥80 years old (N (%))	13 (40.6)	11 (33.3)	34 (40.5)	0.63
Cardiovascular history (N (%))	13 (40.6)	14 (42.4)	22 (26.2)	0.14
Cancer prior to TBI (N (%))	2 (6.3)	4 (12.1)	7 (8.3)	0.95
COPD prior to TBI (N(%))	3 (9.4)	2 (6.1)	5 (6.0)	0.89
Diabetes prior to TBI (N (%))	6 (18.8)	2 (6.1)	2 (2.4)	<0.01
Dependency for ADL (N (%))	0 (0.0)	1 (3.0)	2 (2.4)	0.65
Polypharmacy (N (%))	9 (28.1)	7 (21.2)	20 (23.8)	0.80

NA=not applicable; COPD=chronic obstructive pulmonary disease; ADL=activities for daily living

The main cause of TBI was fall accidents in all studied patients (72.7-82.1%). Patients who underwent early surgery had the lowest median GCS score at admission, while patients who underwent delayed surgery had the highest (GCS of 10 vs. GCS of 15). With regard to CT scan assessment, patients who underwent early surgery had the highest median midline shift, hematoma volume and Marshall CT score [Table 4.17], whereas patients who were treated conservatively more often had associated subarachnoid hemorrhage (38.1%, p=0,03). There were no statistically significant differences among the studied groups for brain contusions, epidural hematomas, intracerebral hemorrhage (ICH) and skull fractures (p=0.13, p=0.36, p=0.46, and p=0.11, respectively). Early surgery was also associated

with longer hospital stays, intensive care unit (ICU) admission rates, longest ICU stay and highest redo surgery rates (p=0.05, p<0.01, p=0.01 and p <0.01, respectively) [Table 4.18].

Table 4.17. Patients' injury characteristics

	Neurosurgery		**Conservative treatment (N=84)**	**ANOVA p value**
	Early surgery (N=32)	**Delayed surgery (N=33)**		
Fall accidents (N (%))	26 (81.3)	24 (72.7)	69 (82.1)	0.51
GCS (median; IQR)	10.0;8	15.0; 1	14; 3	**<0.01**
Brain contusion (N (%))	6 (18.8)	6 (18.2)	28 (33.3)	0.13
Subarachnoid hemorrhage (N (%))	6 (18.8)	6 (18.2)	32 (38.1)	**0.03**
Epidural hematoma (N (%))	2 (6.3)	1 (3.0)	9 (10.7)	0.36
Intraparenchymal hemorrhage (N (%))	0 (0.0)	0 (0.0)	2 (2.4)	0.46
Skull fracture (N (%))	10 (31.3)	4 (12.1)	25 (29.8)	0.11
Midline shift (N(%))	21 (65.6)	20 (60.6)	19 (22.6)	**<0.01**
Midline shift (median; IQR)	5.9;5	4.5;6	0.0;2	**<0.01**
ASDH hematoma volume (mL) (median;IQR)	13.2; 25	11.4; 16	3.1;7	**<0.01**
Marshall CT score (median; IQR)	4;3	3; 1	2;1	**<0.01**

Table 4.18. Patients' clinical management

	Neurosurgery		**Conservative treatment (N=84)**	**ANOVA p value**
	Early surgery (N=32)	**Delayed surgery (N=33)**		
Timing of surgery post-TBI (days) (median; IQR)	0;1	18;22	-	<0.01
Hospitalization after TBI (N (%))	32 (100.0)	26 (78.8)	75 (89.3)	0.02
Hospitalization length (median;IQR)	26; 37	9; 19	9; 17	0.05
ICU admission (N (%))	20 (62.5)	10 (30.3)	26 (31.0)	<0.01
ICU stay length (median;IQR)	8;0	0;4	0; 2	0.01
Redo surgery (N (%))	5 (15.6)	3 (9.1)	0 (0.0)	<0.01

Within 30 days post-TBI, 21.9% of the patients who underwent early surgery, 3.0% of the patients who underwent delayed surgery and 16.7% of the patients who were treated conservatively died. However, the differences in mortality rates among the studied groups were not statistically significant (p=0.08) [Table 4.19].

Table 4.19. Patients' mortality rates

	Neurosurgery		Conservative treatment (N=84)	ANOVA p value
	Early surgery (N=32)	Delayed surgery (N=33)		
Mortality 30 days (N (%))	7 (21.9)	1 (3.0)	14 (16.7)	0.08
Mortality 6 months (N (%))	8 (25.0)	5 (15.2)	25 (29.8)	0.27

4.3.5 Discussion

The results obtained in the current study indicate that conservative treatment is the most often selected treatment strategy for older patients with aSDH. In our cohort, 56.4% of the patients were treated conservatively, 21.5% underwent a neurosurgical intervention within the first 24 h post-TBI, and 22.14% underwent delayed neurosurgery later than 24h post-TBI. Patients who received early surgery were clearly in a poorer state than those in whom the surgeons decided that there was time to delay surgical decompression. The highest mortality rate was observed in the early surgery group (21.9%).

Treatment strategies in patients with TBI are usually chosen based on clinical findings such as GCS, computed tomography (CT) results and intracranial pressure (ICP). However, treatment decision for older patients with TBI are not straightforward. Patient autonomy and Quality of Life need to be considered, and the prognosis of these patients is often rather poor (282). Hence, deciding on a surgical treatment such as craniotomy or craniectomy in older patients easily becomes a challenging decision with little ground for evidence-based support (184,283).

A neurosurgical intervention is often decided because the patient is judged to be able to survive, while a conservative treatment is chosen in occasions in which the outcome is thought to remain unfavorable whatever treatment is chosen (194). The evacuation of a hematoma through a craniotomy can be life-saving, but at the same time may lead to the survival of a patient with a poor quality of life (QoL) or even absence of independent functioning (284,285). Unfortunately, no specific prognostic tools for older patients exist to reliably predict outcomes. Decisions may then also be biased by other factors, such as surgeons' training, different hospital policies, and the intuition and personal opinions of the neurosurgeon (194).

Currently, there is a tendency toward less aggressive treatments in the older patients (282). A recent instrumental variable analysis in aSDH in older adults showed no difference in outcomes between patients treated in an aggressive versus a more conservative center (opting for delayed surgery). In the present analysis, it cannot be discriminated whether these older individuals had a better outcome prognosis with initially conservative treatment versus immediate surgical treatment (111). Thus, the high mortality and morbidity among older patients with TBI can constitute a self-fulfilling prophecy and policy for early surgery (111).

Previous studies have shown controversial results regarding outcomes after neurosurgery in older patients with TBI. Shimoda et al., Wan et al. and *Brazinova et al* reported improved functional

outcomes and reduced mortality in patients who underwent neurosurgical interventions (111,112,172). However, other studies have reported better outcomes after conservative treatment (171).
The favorable results found in some previous studies might indicate that there is still hope for these patients and that indiscriminately rejecting a surgical approach might not always be the best solution. Nevertheless, this needs to be further investigated.

The main limitation of the study was the small sample size of the studied groups, which depended on the number of admitted patients who fulfilled our in-/exclusion criteria. If the patients' in-/exclusion criteria would be broader, including also patients with conditions such as AD and PD, we would not have an homogeneous group to compare treatment strategies and outcomes, which was our main objective. Future randomized clinical trials with larger sample sizes will be necessary to draw more consistent conclusions.
Furthermore, the presented data were retrospectively collected. Therefore, standardized functional outcome measurements were not available for all patients and mortality was the only possible outcome available in all. Future studies should also consider different outcome measures regarding the patients' dependency levels and Quality of Life after neurosurgical intervention and conservative treatment.
Despite these limitations, we believe that this study can positively contribute to reduce the existing research gap in the TBI research field around this matter.

The results obtained from this study seem to indicate that in those cases where the GCS score at admission is still adequate, waiting longer than 24h to perform the neurosurgical intervention can lead to better outcomes. However, these results are based on a low sample size and need to be carefully interpreted. Future prospective larger-size data collection for matched-pair analysis is necessary to draw conclusions. For the moment, individual case analyses should be performed to make clinical decisions. The development of specific prognostic tools and further investigations able to clarify which neurosurgical interventions would be useful for which patients should now be prioritized to improve outcomes and Quality of Life in older patients with TBI.

4.3.6 Conclusion

Patients who underwent early neurosurgical treatment had the highest 30-day mortality rates, but also presented with the most severe injuries at admission. Patients who underwent delayed surgery had a better outcome. Future prospective studies with a sufficient sample size are warranted to draw more definitive conclusions on the value of early vs. late surgery in older patients with aSDH.

Appendix 4

Appendix 4A. Variables registered in our digital database

Variable
Study ID
Gender
Marital status
Date of birth
Date of death (in case of deceased patients)
Age at death (in case of deceased patients)
Current age
Living place before TBI
Was the patient living alone before TBI?
ADL dependency before TBI
Previous history of hematological conditions
Previous history of cardiovascular conditions
Previous anticoagulant intake
Polypharmacy
Previous history of depression
Previous musculoskeletal problems
Previous walking aid
Date of accident
Age at the moment of the accident
Cause of TBI
Type of TBI
Polytrauma
Place of accident
Safety measures used during accident
Accident description
Brain injury type
Brain injury location
GCS (eyes, motor, verbal and total) at the moment of the accident
ICU admission
Date of ICU admission
Date of ICU discharge
Total number of days in ICU
Mortality in ICU
Hospitalization
Number of days between TBI and hospitalization
Date of admission to the hospital
GCS (eyes, motor, verbal and total) at hospital admission
Pupils' size at hospital admission
Pupils' reactivity at hospital admission
Face asymmetry during hospitalization
Tracheotomy
Intubation
Sedation
Paralysis
ICP monitoring
Date of brain surgery
Type of brain surgery
Date of second brain surgery
Type of second brain surgery
Rehabilitation during hospitalization
Type of rehabilitation during hospitalization
Disorientation at hospital admission
Decrease of consciousness at hospital admission
Speech problems at hospital admission

Amnesia after accident
Pain and type of pain at hospital admission
Mini Mental Score Extended (MMSE) during hospitalization
Date of hospital discharge
Total days of hospitalization
Presence of a ''Do not attempt resuscitation'' (DNR) code
DNR code date
Mortality during hospitalization
Mortality within 30 days after TBI
Mortality within 6 months after TBI
Transfer to an institution after hospital discharge
Date of transfer to an institution
Reason of transfer to an institution
Living place after TBI
Does the patient live alone after TBI?
ADL dependency after TBI
Total number of hospitalizations after TBI
Motor disturbances after TBI
Walking aid use after TBI
Pain after TBI
Reason of pain after TBI
Depression/ other psychological problems after TBI
Speech disturbances after TBI
Rehabilitation (and type of rehabilitation) after TBI
Stroke after TBI
Date of stroke after TBI
Number of registered accidents after TBI
Cause of accidents after TBI
Type of accidents after TBI
Place of accidents after TBI
Safety measures after TBI
Post-TBI accidents' description
Brain surgery after hospital discharge
Diagnose of neurodegenerative disorders after TBI
Date of neurodegenerative disorder diagnose
Number of years between TBI and neurodegenerative disease diagnose
MMSE score after hospital discharge
MMSE score date
MMSE score category
Glasgow Outcome Score Extended (GOS-E) 6 months post-TBI
ADL dependency post-TBI
Presence of epilepsy after TBI
Psychiatric problems after TBI

ID=identifier; TBI=Traumatic Brain Injury; GCS=Glasgow Coma Score; ICU=Intensive Care Unit; MMSE= Mini Mental Score Extended; DNR=Do not attempt resuscitation order

Appendix 4B. Registered cardiovascular conditions

Type of cardiovascular condition
Arterial hypertension (AHT)
Hypotension
Tachy-brady syndrome
Arrhythmia
Pacemaker
Atrial fibrillation
Ventricle fibrillation
Venous thrombose
Peripheral vascular disease

Cardiomyopathy
Cardiomegaly
Aortic valve stenosis
Artificial heart valve implantation
Previous myocardial infarct
Angor pectoris
Aneurysm
Hypercholesterolemia
Thoracic pain syndrome
Ischemic heart disease
Ischemic coronary disease
Chronic total occlusion
Carotid stenosis
Cardiac insufficiency
Heart valves' insufficiency
Arterial insufficiency
Coronopathy
Supraventricular tachycardia
Decompensated heart failure (DHF)
Cardiac decompensation Aortic valve stenosis
Ventricle hypertrophy
Alcoholic cardiomyopathy
Venous insufficiency
Inferior cava vein syndrome
Macroangiopathy
Coronary atheromatosis

Appendix 4C. Pearson correlations (r values) for brain injury coexistence

	Concussion	Brain contusion				Subarachnoid hematoma				Subdural hematoma				Epidural hematoma				Intracerebral hematoma	Skull fracture
		FL	PL	TL	OL	FL	PL	TL	OL	FL	PL	TL	OL	FL	PL	TL	OL		
Concussion	-	-0.2	-0.1	-0.2	-0.1	-0.2	-0.1	-0.2	0.0	-0.1	-0.1	-0.1	0.0	-0.1	-0.1	0.0	0.0	-0.1	-0.2
Brain contusion FL	-0.2	-	0.3	0.3	0.1	0.2	0.1	0.1	0.0	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.0	0.0	0.2
Brain contusion PL	-0.1	0.3	-	0.3	0.2	0.0	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.1	0.0	0.0
Brain contusion TL	-0.2	0.3	0.3	-	0.1	0.1	0.1	0.3	0.0	0.1	0.1	0.2	0.2	0.1	0.0	0.1	0.1	0.0	0.1
Brain contusion OL	-0.1	0.1	0.2	0.1	-	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Subarachnoid hematoma FL	-0.2	0.2	0.0	0.1	0.0	-	0.3	0.4	0.1	0.1	0.0	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.2
Subarachnoid hematoma PL	-0.1	0.1	0.1	0.1	0.0	0.3	-	0.4	0.2	0.0	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.00	0.0
Subarachnoid hematoma TL	-0.2	0.1	0.1	0.3	0.0	0.4	0.4	-	0.1	0.1	0.0	0.2	0.0	0.1	0.0	0.0	0.1	0.0	0.2
Subarachnoid hematoma OL	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.1	-	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1
Subdural hematoma FL	-0.1	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.0	-	0.4	0.3	0.0	0.1	0.1	0.0	0.0	0.0	0.1
Subdural hematoma PL	-0.1	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.4	-	0.3	0.2	0.0	0.1	0.0	0.0	0.0	0.0
Subdural hematoma TL	-0.1	0.1	0.1	0.2	0.0	0.1	0.1	0.2	0.0	0.3	0.3	-	0.1	0.0	0.0	0.1	0.1	0.0	0.1
Subdural hematoma OL	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.2	0.1	-	0.0	0.2	0.1	0.1	0.0	0.0

Epidural hematoma FL	-0.1	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.1	0.0	0.0	0.0	-	0.4	0.2	0.0	0.0	0.1
Epidural hematoma PL	-0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.1	0.1	0.0	0.2	0.4	-	0.1	0. 1	0.0	0.1
Epidural hematoma TL	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.1	-	0.0	0.0	0.1
Epidural hematoma OL	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.1	0.0	0.1	0.0	-	0.0	0.0
Intracerebral hematoma	-0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0
Skull fracture	-0.2	0.2	0.0	0.1	0.1	0.2	0.0	0.2	0.1	0.1	0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.0	-

FL= frontal lobe; PL=parietal lobe; TL=temporal lobe; OL=occipital lobe

Appendix 4D. Demographic, accident and injury characteristics per injury severity in our cohort

	Unknown GCS (N=780)	**Mild TBI (N=524)**	**Moderate TBI (N=73)**	**Severe TBI (N=103)**
Demographic characteristics				
Age at injury (years) (median; IQR)	77.0;12.0	79.0;12.0	77.0;12.0	77.0;11.0
Gender (female (N (%)) / male (N (%)))	424 (54.4)/ 356 (45.6)	280 (53.4)/244 (46.6)	25 (34.2)/ 48 (65.8)	46 (44.7)/57 (55.3)
Accident and injury characteristics				
Cause of TBI				
Fall (N (%))	636 (81.5)	420 (80.2)	42 (57.5)	81 (78.6)
Bicycle accident (N (%))	76 (9.7)	56 (10.7)	19 (26.0)	10 (9.7)
Traffic accident (N (%))	40 (5.1)	36 (6.9)	8 (11.0)	6 (5.8)
Other/unknown (N (%))	25 (3.2)	11 (2.1)	4 (5.5)	6 (5.8)
Polytrauma (N (%))	74 (9.5)	78 (14.9)	20 (27.4)	29 (28.2)
Died within 24h post-TBI (N %)	21 (2.7)	3 (0.6)	3 (4.1)	36 (35.0)

N=number of patients; IQR=inter-quartile range

Appendix 4E. Clinical management and mortality per injury severity in our cohort

	Unknown GCS (N=759)	**Mild TBI (N=521)**	**Moderate TBI (N=70)**	**Severe TBI (N=67)**
Clinical management				
Hospitalization (N (%))*	623 (82.1)	469 (90.0)	66 (94.3)	63 (94.0)
Hospitalization length (days) (median; IQR)*	6;13	7;19	32;40	22;30
Admission ICU (N (%))*	125 (16.5)	149 (28.6)	52 (74.3)	50 (74.6)
Tracheotomy (N (%))*	8 (1.1)	2 (0.4)	8 (11.4)	6 (9.0)
Intubation (N (%))*	29 (3.8)	24 (4.6)	42 (60.0)	34 (50.7)
Sedation (N (%))*	19 (2.5)	18 (3.5)	42 (60.0)	25 (37.3)
Neurosurgical intervention (N (%))				
ICP monitoring	30 (4.0)	15 (2.9)	17 (24.3)	15 (22.4)
Subdural hematoma evacuation	82 (10.8)	44 (8.4)	19 (27.1)	20 (29.9)
External ventricular drain	5 (0.7)	5 (1.0)	6 (8.6)	12 (17.9)
Intracerebral hematoma evacuation	4 (0.5)	2 (0.4)	1 (1.4)	1 (1.5)
Decompressive craniectomy	2 (0.3)	1 (0.2)	1 (1.4)	1 (1.5)
Skull base plasty	1 (0.1)	0 (0.0)	1 (1.4)	1 (1.5)
Epidural hematoma evacuation	2 (0.3)	1 (0.2)	0 (0.0)	1 (1.5)
Mortality				
DNR code 1 (N (%))*	4 (5.2)	2 (4.6)	8 (11.9)	1 (1.2)
DNR code 2 (N (%))*	97 (12.8)	90 (17.2)	8 (11.9)	7 (10.6)
DNR code 3 (N (%))*	3 (4.3)	3 (6.2)	8 (11.9)	16 (23.5)
Mortality within 30 days post-TBI (N (%))*	57 (7.5)	36 (6.9)	14 (20.0)	56 (83.6)

N=number of patients; IQR=inter-quartile range; DNR='Do not attempt resuscitation'' order ; DNR code 1=''Do not reanimate'', DNR code 2=''Do not extend therapy''; DNR code 3=''Progressively reduce therapy''; *the number of patients included in this category excludes the number of patients who within 24h post-TBI

Appendix 4F. Coagulation status at hospital admission in patients with alcohol abuse and patients without alcohol abuse

	Patients with alcohol abuse (N=163)	**Patients with no alcohol abuse (N=1280)**	**ANOVA p value**
Platelet count <100 (N (%))	2	27	0.45
INR ≥1.5 (N (%))	12	128	0.28
aPTT (mean; SD)	5.6	29.1; 10.7	0.95

aPTT= Activated Partial Thromboplastin Clotting Time; INR=International Normalized Ratio

Appendix 4G. Injury characteristics for the four studied groups

	Antithrombotics (N=490)			No antithrombotics (N=953)	ANOVA p value
	Antiplatelet (N=418)	VKA (N=58)	Other (N=14)		
Age at the moment of the accident (median; IQR) (median; IQR)	80;10	81;9	84;11	77;12	<0.01
Type of accident (N (%))					
Fall accident	351 (84.0)	53 (91.4)	12 (85.7)	730 (76.6)	0.01
Bicycle accident	36 (8.6)	2 (3.4)	2 (14.3)	120 (12.6)	
Traffic accident	19 (4.5)	2 (3.4)	0 (0.0)	69 (7.2)	
Other	12 (2.9)	1 (1.7)	0 (0.0)	34 (3.6)	
Polytrauma (N(%))	44 (10.5)	6 (10.3)	2 (14.3)	146 (15.3)	0.10
TBI severity					
Mild TBI (N (%))	155 (37.1)	29 (50.0)	6 (42.9)	325 (34.1)	0.09
Moderate TBI (N (%))	15 (3.6)	3 (5.2)	1 (7.1)	53 (5.6)	
Severe TBI (N (%))	15 (3.6)	4 (6.9)	0 (0.0)	78 (8.2)	
Unknown (N (%))	233 (55.7)	22 (37.9)	7 (50.0)	497 (52.2)	

VKA=Vitamin K antagonist; IQR=Inter-quartile range

Appendix 4H. Patients' clinical management characteristics

	Antithrombotics (N=490)			No antithrombotics (N=953)	ANOVA p value
	Antiplatelet (N=418)	VKA (N=58)	Other (N=14)		
Tracheotomy (N (%))	3 (0.8)	0 (0.0)	0 (0.0)	18 (1.9)	0.27
Intubation (N (%))	27 (6.5)	9 (15.5)	3 (21.4)	121 (12.7)	<0.01
Sedation (N (%))	20 (4.8)	5 (8.6)	2 (14.3)	91 (9.5)	0.02
Admission ICU (N (%))	87 (20.8)	24 (41.4)	4 (28.6)	256 (26.9)	<0.01
Hospitalization (N (%))	352 (84.2)	57 (98.3)	12 (85.7)	828 (86.9)	0.03
Hospitalization length (days) (median;IQR)	6;17	8;18	2;11	7;18	0.27

VKA=Vitamin K antagonist; ICU=Intensive Care Unit; IQR=Inter-quartile range

Appendix 4I. Patients' neurosurgical intervention characteristics

	Antithrombotics (N=490)			No antithrombotics (N=953)	ANOVA p value
	Antiplatelet (N=418)	VKA (N=58)	Other (N=14)		
Brain surgery (N (%))	44 (10.5)	11 (19.0)	2 (14.3)	166 (17.4)	0.01
ICP monitoring (N (%))	10 (2.4)	3 (5.2)	1 (7.1)	59 (6.2)	0.03
Subdural hematoma evacuation (N (%))	33 (7.9)	8 (13.8)	1 (7.1)	105 (11.0)	0.25
External ventricular drain (N (%))	4 (1.0)	2 (3.4)	1 (7.1)	23 (2.4)	0.14

Intracerebral hematoma evacuation (N (%))	1 (0.2)	1 (1.7)	0 (0.0)	6 (0.6)	0.50
Contusion evacuation (N (%))	1 (0.2)	0 (0.0)	0 (0.0)	4 (0.4)	0.91
Decompressive craniectomy (N (%))	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.5)	0.46
Lobectomy (N (%))	1 (0.2)	0 (0.0)	0 (0.0)	4 (0.4)	0.91
Skull base plasty (N (%))	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0.67
Epidural hematoma evacuation (N (%))	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)	0.56
Lumbo-external drain (N (%))	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0.79

VKA=Vitamin K antagonist

Chapter 5

Functional outcomes and quality of life after TBI in older patients

In this chapter, Section 5.1 will present the results obtained from a telephone and written cognitive, sleep quality and Quality of Life assessment performed 1 to 13 years in older patients post TBI. Then, Section 5.2 will present the results obtained from a prospective case-control study in a group of patients aged ≥65 years 6 months after mild TBI in which sequelae in terms of radiological outcome, level of dependency, cognitive and motor disturbances, and their impact on quality of life were assessed.

5.1 Long-term cognitive function, sleep quality and Quality of life assessment in older patients after TBI

This section has been adapted from:

Gavrila Laic R.A., Bruyninckx D., Lebegge D., Vander Sloten J., Depreitere B. Long-term cognitive function, sleep quality and Quality of life assessment in elderly patients after TBI. [To be submitted].

5.1.1 Abstract

The incidence of traumatic brain injury (TBI) in the older population has steeply increased over the past decades. To date, there are little to no reports on long-term multidimensional outcomes in this population and very few compare these outcomes with healthy older controls. The present study investigates cognitive function, sleep quality and quality of life (QoL) in patients that sustained a TBI at ages older than 65 years, 1-20 years earlier, and in a group of healthy peers.

Patients that had been admitted to the University Hospitals Leuven with TBI at an age ≥65 between 1999 and 2019 and a group of healthy volunteers with similar demographic characteristics, were recruited for this study. Patients received an invitation for a standardized telephone interview on cognition, sleep quality and quality of life by means of the TICS, PSQI, QOLIBRI and QOLBRI-OS questionnaires. Patients with hearing problems received an invitation for a written standardized questionnaire. For patients not being able to perform any evaluation themselves, caregivers were invited to answer to the AD8 dementia screening questionnaire. Healthy volunteers were subjected to the standardized telephone interview with TICS, PSQI, QOLIBRI and QOLIBRI-OS.

A total of 68 patients and 19 controls were assessed in the study. FU time after TBI ranged from 1 to 13 years. 35 patients performed the telephone interview, 14 patients filled the written questionnaire and 19 caregivers filled the AD8 questionnaire. Median age was 78 for patients (range 69-98) and 75

(range 68-92) for volunteers. Frailty was higher in patients than in volunteers and increased with inability to take part in active assessments.

In patients who participated in the telephone interview, median GCS at TBI admission had been 15 (IQR=1) and the differences in TICS scores between the patients and control group were not statistically significant (p=0.34). Patients who participated in the written evaluation had been admitted for TBI with a median GCS of 14 (IQR=5) and they had a mean TYM score of 44.9 (SD 6.9). Caregivers reported a mean score of 2.7 (SD 2.9) in the AD8 dementia screening interview. Patients had a poorer sleep quality (mean PSQI scores of 6.6 vs 3.5, p<0.01) and lower QoL than the control group (mean total QOLIBRI of 72.4 vs 85.9,p=0.01). Worse sleep quality was associated with worse cognitive performance (r=-0.27, p=0.05), which was associated with worse QoL (r=-0.32, p=0.02).
In conclusion, at long term follow up, mild TBI in patients ≥65 years old was associated with poorer sleep quality and lower overall QoL. Poorer sleep quality was associated with poorer cognitive function and reduced QoL in these patients.

5.1.2 Background

Demographic shift and increased activity in older adults have led to a steep rise in the incidence of traumatic brain injury (TBI) in this population in industrialized countries (4,188,189), predominantly caused by fall accidents and constituting a significant health and socioeconomic problem (187).

It is known that recovery after TBI in older adults is often affected by the presence of co-morbidities and age-related dysfunction, such as visual alterations, cognitive decline, polypharmacy and muscle weakness, among others (4,73,81,82,190). This leads to significantly higher rates of medical complications (8), persistent disability (7), dependency (8), re-admission (115), and depression (193) in this population.

Despite the fact that outcome following TBI is overall poorer in older than in younger patients (13–15), most TBI cases in this population are initially classified as mild (87), based on the Glasgow Coma Scale (GCS) score upon admission (44). However, previous studies have reported that GCS loses reliability at older age (34) and the term ‘’mild TBI’’ in older patients is probably inaccurate (9,35).

In many instances, the functional decline that patients with TBI experience persists over the years following the accident (286). Therefore, TBI is rather a chronic health condition than a single event, sometimes even associated with ongoing progression of functional decline (287). TBI commonly affects cognitive function (288,289) and quality of sleep (290), the effects of which negatively impact overall function and social participation (24), all together resulting in reduced quality of life (QoL) (291).
Despite these known consequences, there is a scarcity of studies focusing on their prevalence in older patients that have sustained a TBI (292). Moreover, given natural functional decline associated with ageing, outcomes in older adults following TBI should be compared with functional status in their healthy peers. Therefore, the present study aims at documenting long term impairments in cognitive function, sleep quality and QoL in both patients that have sustained TBI at ages older than 65 and matched controls.

5.1.3 Methods

Patients ≥65 years old with TBI, admitted to the University Hospital Leuven (Belgium) between 1999 and 2019, were recruited for this study. Eligible patients were identified by the hospital reporting service, based on the International Statistical Classification of Diseases and Related Health Problems (ICD) 9 diagnostic codes. All degrees of TBI severity were included.

Patients were excluded when TBI occurred at an age below 65, when they suffered a cerebrovascular accident before TBI and when they had a preexisting neurological condition. Chronic subdural hematomas were also excluded.

Patients were invited to consent for a telephone cognitive, sleep quality and QoL evaluation. The cognitive evaluation was performed using the Telephonic Interview for the Cognitive Status (TICS) questionnaire. This is an 11-item screening test, with a maximum score is of 41 points. A higher score is an indicator of better cognitive function (293). Sleep quality was assessed through the Pittsburgh Sleep Quality Index (PSQI) questionnaire. This is a 19-question test which evaluates the subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The total score ranges from 0 to 21 and a higher total score is an indicator of worse sleep quality. The cut-off between good sleeper and bad sleeper is usually set at <5 and >5, respectively (294). QoL was assessed using the Quality of Life after Brain Injury (QOLIBRI) and Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS) questionnaires. The scores cover QoL on the domains of Cognition, Self, Autonomy and Daily life, Social Relationships, Emotions and Physical Problems. Total scores range between 0 (worst QoL) and 100 (best QoL) (295).

For those patients who consented to participate but had hearing difficulties preventing a successful telephone evaluation, a written evaluation was performed. In this case, the questionnaires were sent to the patients by post or e-mail, and the patients sent them back to the researchers by post or e-mail after completion. Patients were not supervised by the researchers during the completion of the evaluation and there were no controls. Cognitive function was evaluated with the Test Your Memory (TYM) test, which contains 10 tasks that assess orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming and visuospatial abilities. The maximum score is of 50 and the cut-off for dementia is of ≤42 (296). Sleep quality was assessed by the PSQI questionnaire (294) and QoL was assessed using QOLIBRI and QOLIBRI-OS paper questionnaires (295).

For patients that consented but had difficulties to perform a telephone or written evaluation themselves, the AD8 dementia screening interview written questionnaire was sent to the patients' caregivers by post or e-mail for evaluation. The control group did not perform this evaluation. The AD8 dementia screening interview is an eight-item questionnaire which assesses the participant's cognitive abilities in the areas of memory, temporal orientation, judgment, and function. The total AD8 score ranges from 0 to 8. A score of ≥2 is considered to represent a significant impairment in cognition (297).

A control group of volunteers with similar demographic characteristics as the patient group was recruited. They underwent exactly the same telephone interview to enable comparison.

5.1.4 Results

2,999 patients ≥65 years old with TBI were screened for this study. 947 initially fulfilled our in-/exclusion criteria and were invited to participate in the study. 80 were initially interested in participating in the study, of which 3 died and 9 were lost to follow-up. A total of 68 patients and 19 controls were included in the study. The patient screening and selection is detailed in Figure 5.1. 35 patients were able to have the telephone interview (similar to the controls), 14 filled the written questionnaires and in 19 patients the AD8 questionnaire was filled by their caregivers.

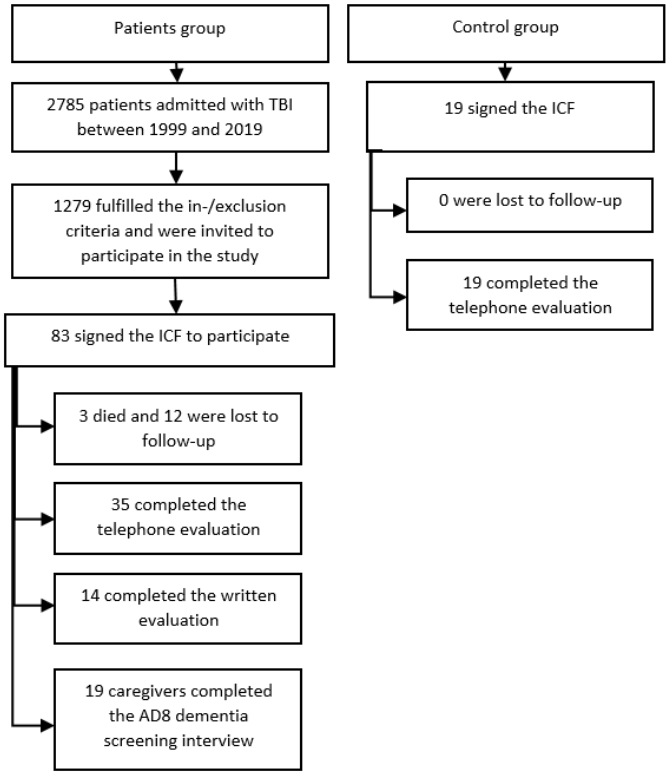


Figure 5.1. Patient and control screening and selection process

Demographics and injury characteristics

The median age was 78 years for the patients (IQR=9) and 75 years for the control group (IQR=11) (p=0.06). 57.4% of the patients and 21.1% of the controls had a previous history of cardiovascular diseases (p<0.01). Furthermore, 38.2% of the patients and 5.3% of the controls were under polypharmacy (p<0.01).

In the patient group, the main cause of TBI were falls (61.8% of the cases) and the median GCS was 15 (IQR=2) upon admission. Skull fractures were the most common injury (29.4% of the patients), followed by acute subdural hematoma (aSDH) (25.0%) and subarachnoid hemorrhage (SAH) (20.6%). 26.5% of the patients were admitted to the ICU, 16.2% underwent brain surgery and 20.6% received rehabilitation post-TBI.

The patients' and controls' demographic and injury characteristics, and clinical management, are shown in Table 5.1.

Table 5.1 Demographic and injury characteristics, and clinical management for the patients and control group

	All included patients (N=68)	**Control group (N=19)**	**t-test p value**
Age (median; IQR)	78; 9	75;11	0.06
Sex (N female (%)/ N male (%))	30 (44.1)/38 (55.9)	8 (42.1)/11 (57.9)	0.95
Previous history of cardiovascular disease (N (%))	39 (57.4)	4 (21.1)	<0.01
Antithrombotic intake (N(%))	22 (32.4)	3 (15.8)	0.13
Polypharmacy (N (%))	26 (38.2)	1 (5.3)	<0.01
Fall accident (N(%)	42 (61.8)	-	-
Bicycle accident (N(%))	22 (32.4)	-	-
Traffic accident (N(%))	4 (5.9)	-	-
GCS (median; IQR)	15;2	-	-
aSDH (N(%))	17 (25.0)	-	-
Contusion (N(%))	10 (14.7)	-	-
SAH (N(%))	14 (20.6)	-	-
EDH(N(%))	3 (4.4)	-	-
IVH (N(%))	1 (1.5)	-	-
Midline shift (median; IQR)	0;0	-	-
Skull fracture (N(%))	20 (29.4)	-	-
Admission ICU (N (%))	18 (26.5)	-	-
Brain surgery (N (%))	11 (16.2)	-	-
Rehabilitation (N (%))	14 (20.6)	-	-

IQR=inter-quartile range; GCS=Glasgow Coma Scale; aSDH=acute subdural hematoma; SAH=subarachnoid hemorrhage; EDH=epidural hemorrhage; IVH=intraventricular hemorrhage; ICU=intensive care unit

While the median age of the patients included in the telephone and written evaluations was 76 and 77 years, respectively, patients included for the caregivers' evaluations had the highest median age (83 years old, p<0.01). No statistically significant differences were found in the previous clinical history, injury characteristics and clinical management among the patients included in the three groups [Table 5.2].

Table 5.2 Demographic and injury characteristics, and clinical management, for the patients included in the telephone, written and caregiver evaluations

	Patients included in the telephone evaluations (N=35)	**Patients included in the written evaluations (N=14)**	**Patients included in the caregivers evaluations (N=19)**	**ANOVA p value**
Age (median; IQR)	76;7	77; 8	83; 7	<0.01
Sex (N female (%)/ N male (%))	14 (40.0)/21 (60.0)	5 (35.7)/ 9 (64.3)	11 (57.9)/ 8 (42.1)	0.36
Previous history of cardiovascular disease (N (%))	16 (45.7)	9 (64.3)	14 (73.7)	0.12
Antithrombotic intake (N(%))	11 (31.4)	3 (21.4)	8 (42.1)	0.46
Polypharmacy (N (%))	9 (25.7)	6 (42.9)	11 (57.9)	0.06
Fall accident (N(%)	20 (57.1)	10 (71.4)	12 (63.2)	0.65
Bicycle accident (N(%))	13 (37.1)	4 (28.6)	5 (26.3)	0.69
Traffic accident (N(%))	2 (5.7)	0 (0.0)	2 (10.5)	0.46
GCS (median; IQR)	15; 1	14; 5	15; 3	0.29

aSDH (N(%))	8 (22.9)	4 (28.6)	5 (26.3)	0.91
Contusion (N(%))	5 (14.3)	2 (14.3)	3 (15.8)	0.99
SAH (N(%))	8 (22.9)	2 (14.3)	4 (21.1)	0.80
EDH(N(%))	2 (5.7)	0 (0.0)	1 (5.3)	0.67
IVH (N(%))	1 (2.9)	0 (0.0)	0 (0.0)	0.63
Midline shift (median; IQR)	0; 0	0;0	0; 0	0.10
Skull fracture (N(%))	12 (34.3)	3 (21.4)	4 (21.1)	0.64
Admission ICU (N (%))	8 (22.9)	5 (35.7)	5 (26.3)	0.66
Brain surgery (N (%))	6 (17.1)	3 (21.4)	2 (10.5)	0.70
Rehabilitation (N (%))	6 (17.1)	3 (21.4)	5 (26.3)	0.73

IQR=inter-quartile range; ICU=intensive care unit

Cognitive outcomes

The patients included in the telephone evaluations performed the TICS a mean of 4.2 years post-TBI (range 1-11). Although patients presented slightly lower mean TICS scores than controls (32.0/41 SD=5.1 vs 34.0/41 SD=3.8), the differences among groups were not statistically significant (p=0.34).
The patients included in the written evaluation performed the TYM a mean of 4.9 years post-TBI (range 1-13) and had a mean score of 44.9/50 (SD 6.9), which is higher than the cut-off associated with dementia (≤42) (296). Moreover, caregivers completed the AD8 Dementia Screening Interview 6.7 years post-TBI (range 2-14) and the mean AD8 score was 2.7 (SD 2.9), which can be considered as an impairment in cognition (297).

Sleep quality

Patients reported a poorer sleep quality, indicated by a higher mean PSQI score 1-11 years post-TBI, than the control group (6.6 vs 3.5, p<0.01).

Quality of life

Patients had lower cognition, self, daily life and autonomy, social relationships and physical problems score than the control group in QOLIBRI. The mean total QOLIBRI score in the patient group was 72.4/100 (SD 15.7), and the mean score in the control group was 85.9/100 (SD 9.3, p=0.01) [Table 5.3].

Table 5.3 QOLIBRI scores for the patients and control group

	Patients included in the telephonic and written evaluations (N=49)	**Control group (N=19)**	**t-test p value**
Years between TBI and evaluation (mean; range)	4.2;1-11	-	-
QOLIBRI			
Cognition score (mean ± SD)	3.9± 0.8	4.4± 0.5	<0.01
Self score (mean ± SD)	3.8± 0.8	4.3± 0.5	<0.01
Daily Life and Autonomy score (mean ± SD)	3.9± 0.8	4.7± 0.4	<0.01
Social Relationships' score (mean ± SD)	4.0± 0.6	4.2± 0.5	0.02
Emotions' score (mean ± SD)	4.3± 0.8	4.5± 0.7	<0.01
Physical Problems' score (mean ± SD)	3.7± 1.0	4.4± 0.6	<0.01

Total score (mean ± SD)	72.4±15.7	85.9± 9.3	0.01
QOLIBRI-OS			
Physical condition (mean ± SD)	3.6± 1.4	4.5± 0.7	<0.01
Cognition (mean ± SD)	3.6± 1.2	4.4± 1.0	<0.01
Emotions (mean ± SD)	4.0± 1.1	4.6± 0.6	<0.01
Function in daily life (mean ± SD)	4.0± 1.1	4.7± 0.5	<0.01
Personal and social life (mean ± SD)	4.1± 1.1	4.7± 0.6	<0.01
Current situation and future prospects (mean ± SD)	3.6± 1.2	4.5± 0.6	<0.01
Total score (mean ± SD)	70.3± 22.9	88.8±11.1	<0.01

QOLIBRI=Quality of life after Brain Injury; QOLIBRI-OS=Quality of Life after Brain Injury Overall Scale

Correlations between injury types and outcomes and between outcome components

In this cohort, no associations between injury types and any of the outcome scores were found. However, lower cognitive scores (TICS) correlated with worse sleep quality (higher PSQI scores) (r=-0.27, p=0.05) and worse QoL (worse QOLIBRI-OS total score) (r=0.28, p=0.04). Furthermore, higher PSQI scores correlated with worse QoL (worse QOLIBRI-OS total score) (r=-0.32, p=0.02).

5.1.5 Discussion

This study assessed cognitive function, sleep quality and QoL 1-20 years post-TBI in patients ≥65 years old admitted to a single tertiary hospital and in a group of healthy volunteers with similar demographic characteristics. The results show that older patients that had sustained mild TBI had a poorer sleep quality and lower QoL than healthy volunteers. The patients that sustained a TBI were also more frail in terms of cardiovascular history and polypharmacy. Cognitive function did not differ between both groups that were able to perform a telephone interview. Frailty increased when patients were not able to perform a telephone interview or were not able to either perform a telephone interview or fill a questionnaire. Cognitive decline was only found in those that had difficulties with both telephone and written interrogation.

It is a striking finding that even though the TBI was classified as mild, QoL and sleep continued to be disturbed several years later. And while TICS was not significantly different between patients and controls and TYM scores were above the cut off for cognitive decline, the scores in ex-mild-TBI patients were lower than normal.

Shorland et al. reported in 2020 that patients with TBI over 55 years old have a higher deterioration and lower scores for speed of processing and attention, verbal and visual memory, executive function and working memory at 5 years or more post-injury than younger patients (298). A poorer sleep quality following TBI has also been reported in previous studies (290,299). It is known that patients with TBI often have difficulty falling asleep after getting to bed (299) and have excessive daytime sleepiness (299,300). In addition, the rate of insomnia seems much higher in older than in younger patients with TBI (290). This could be due to an alteration in melatonin production (301) or to a higher susceptibility for post-traumatic stress syndrome (PTSD) (302), among other causes. Sleep quality plays an important role in functional outcome. The significant correlation between sleep disturbances and depression (303), anxiety (304), pain (303), functional impairment (305,306) and poor QoL (307) has been previously reported and is confirmed by the association between PSQI and QoL in our results.

A correlation between lower cognitive performance and reduced QoL was seen in the present study. TBI has a considerable impact on patients' QoL. This has also been reported previously by other authors (308–311). It is important to take into account that QoL is a very broad concept in which many factors, which are not only health-related, can play an important role (312). Up to date, older age, more severe injuries and female sex have been reported as risk factors for worse QoL post-TBI (308–311). However, we believe that the multifactorial nature of QoL needs better understanding. Evidence expliciting changes in QoL in older adults is rather limited and future studies investigating the influence of pre-injury function and medical history on post-TBI QoL seem desirable (313).

We believe that the present study will add useful information to the evidence on long-term outcomes following TBI in older patients. However, the present study has limitations and the obtained results should be carefully interpreted. First, the sample size of the included patients is rather low. This was due to the difficulty perceived by the researchers in recruiting older patients in the study. Older patients usually have many health issues and do not always want to participate in non-essential clinical procedures, such as research studies. Future studies with bigger sample sizes would be desirable in order to draw more consistent conclusions. Also, the written evaluations of patients and caregivers was performed without the researchers' supervision, which was done for practical reasons. Furthermore, a formal frailty assessment was not performed in the patients nor volunteers. This could have helped to substantiate bias.

Despite its limitations, we think that our results contribute to the better understanding of the long-term outcomes after TBI in patients aged ≥65 years. We have found that TBI in older adults can lead to some cognitive impairment (although not significantly different from healthy controls), sleep problems and QoL deterioration. Previous research has found that individualized support is very important for these patients' functioning and QoL, even in mild TBI, so that they can maintain their previous life roles (314). Therefore, sufficient focus on early rehabilitation strategies and long-term support seems warranted.

5.1.6 Conclusion

At long term follow up, mild TBI in patients ≥65 years old was associated with poorer sleep quality, lower overall QoL. Poorer sleep quality was associated with poorer cognitive function and reduced QoL in these patients.

5.2 Profound prospective assessment of radiological and functional outcome 6 months after TBI in older patients

This section has been adapted from:

Gavrila Laic R.A., Verheyden J., Bruyninckx D., Lebegge D., Vander Sloten J., Depreitere B. Profound prospective assessment of radiological and functional outcome 6 months after TBI in elderly. [Manuscript submitted for publication to Acta Neurochirurgica].

5.2.1 Abstract

Background: Recovery after Traumatic Brain Injury (TBI) in older adults is usually affected by the presence of comorbidities, leading to more severe sequelae in this age group than in younger patients. However, there are only few reports that prospectively perform in-depth assessment of outcome following TBI in older adults.
Objective: This study aims at documenting structural brain characteristics and functional outcome and quality of life in older patients 6 months after TBI and comparing these data with healthy volunteers undergoing the same assessments**.**
Methods: 13 patients ≥ 65 years old, admitted to the University Hospitals Leuven (Belgium), between 2019 and 2022 due to TBI, including all injury severities, and a group of 13 healthy volunteers with similar demographic characteristics were prospectively included in the study. At admission, demographic, injury and CT scan data were collected in our database. Six months after the accident, a brain MRI scan and standardized assessments of frailty, sleep quality, cognitive function, motor function and quality of life were conducted.
Results: A total of 13 patients and 13 volunteers were included in the study, with a median age of 74 and 73 years, respectively. 9 out of the 13 patients presented with a mild TBI. The patient group had a significantly higher level of frailty than the control group, presenting a mean Reported Edmonton Frailty Scale score of 5.8 (SD 2.7) vs 0.7 (SD 1.1) ($p<0.01$). No statistically significant differences were found between patient and control brain volumes, fluid attenuated inversion recovery white matter hyperintensity volumes, number of lesions and blackholes, and fractional anisotropy values. Patients demonstrated a significantly higher median reaction time in the One Touch Stockings of Cambridge (22.3 s vs 17.6, $p=0.03$) and Reaction Time (0.5s vs 0.4s, $p<0.01$) subtests in the Cambridge Neuropsychological Test Automated Battery. Furthermore, patients had a lower mean score on the first Box and Blocks test with the right hand (46.6 vs 61.7, $p<0.01$) and a significantly higher mean score in the Timed-Up & Go test (13.1 s vs 6.2 s, $p=0.02$) and Timed Up & Go with cognitive dual task (16.0 s vs 10.2 s, $p<0.01$). Substantially lower QOLIBRI total score (60.4 vs 85.4, $p<0.01$) and QOLIBRI-OS total score (53.8 vs 88.5, $p<0.01$) were also observed in the patients' group.
Conclusion: In this prospective study, patients ≥65 years old with TBI, when compared with controls, showed slightly worse cognitive performance and poorer motor function, higher fall risk, but a substantially reduced QoL at 6 months FU, as well as significantly higher frailty, even when the TBI is classified as mild. No statistically significant differences were found in structural brain characteristics on MRI. Future studies with larger sample sizes are needed to refine the impact of TBI versus frailty on function and QoL in older adults.

5.2.2 Introduction

Older patients have an increasing risk of sustaining a traumatic brain injury (TBI) (4,5), mainly due to the increasing life expectancy (223) and more active lifestyle in this population (81,82,105). As a consequence, TBI has become an important cause of mortality and long-term disability for the older population worldwide (4,85,315).

The ageing process is associated with physiological and functional changes, such as deterioration in the balance system, muscle weakness, joint problems, visual and cognitive decline as well as increased frailty and polypharmacy, among others (4,73,81,82,190).
The recovery process after TBI in older adults is frequently affected by the presence of comorbidities (316). This results in a higher risk for secondary medical complications (8), psychosocial changes (6), disability (7), dependency (8) and depression (193). Therefore, the older population suffer from worse outcomes after TBI than young patients (153,154), despite being mostly classified as ''mild TBI'' cases (81,87,152).

Older patients following TBI often arrive in the hospital in a rather good neurological status and deteriorate subsequently due to lesions that only progressively exert mass effect (74). They have a higher risk of sustaining intracranial hemorrhages (ICH)(5,227), which have previously shown to increase in-hospital mortality and disability (225,226). Furthermore, they often have more prolonged hospitalizations, long-term morbidity, permanent disability at several domains, sleep disturbances and low quality of life (QoL) than younger patients (4,5,317).

Up to date, older adults, especially those with pre-existing psychiatric and neurological problems, have been excluded from TBI research studies (318,319). Moreover, no validated outcome prediction models exist, the impact that TBI has on older patients' wellbeing is still unclear (9) and there are no clinical guidelines specific to this population (194,195). Better understanding of the patient characteristics related to poor outcomes in older patients is necessary to improve these patients' clinical care. Therefore, this study aims at prospectively assessing the nature of post-TBI brain damage on MRI, its sequelae in terms of sleep quality deterioration, cognitive and motor impairment, and the impact on quality of life in older patients 6 months after TBI**.**

5.2.3 Methods

This is a prospective study in which 13 patients ≥ 65 years old, admitted to the University Hospitals Leuven (Belgium) between 2019 and 2022 due to TBI, including all injury severities, and a group of 13 healthy volunteers with similar demographic characteristics were recruited.

Patients were excluded if they had a chronic subdural hematoma, a neurodegenerative disease before the TBI, cognitive and motor disturbances caused by any other pathology, or previous alcohol/drugs abuse. Volunteers were selected based on the same exclusion criteria.

When included after informed consent, the clinical records and CT scans of the patients were screened and relevant clinical information was collected in our database. Six months after the accident, a brain MRI scan was performed using a Siemens 1.5 T Magnetom Vision system. High-resolution T1 and T2 weighted imaging sequences, Diffusion Tractography Imaging (DTI) and Susceptibility Weighted Imaging (SWI) sequences were taken. The results were interpreted with the ico**brain** TBI report (320), provided by ico**metrix**.

Intracranial lesions, fluid attenuated inversion recovery (FLAIR) white matter hyperintensity areas and black holes were quantified. White matter hyperintensities were defined as hyperintense areas seen on T2 weighted imaging sequences (321) and black holes as hypointense areas in T1 weighted imaging sequences (322).

Frailty, sleep quality, cognitive and motor function, fall risk and quality of life were assessed using the Reported Edmonton Frail Scale (323), Pittsburgh Sleep Quality Index (PSQI) (294), Cambridge Neuropsychological Test Automated Battery (CANTAB) (324), Box and Blocks test (325), Berg Balance Scale (BBS) (326), Timed Up and Go (TUG) (327), TUG with cognitive dual task (328), Quality of Life after Brain Injury (QOLIBRI) (329), and Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS) (329).

In CANTAB (324), the Motor Screening (MOT), Multitasking (MTT), One Touch Stockings of Cambridge (OTS), Paired Associated Learning (PAL), RTI (Reaction Time), RVP (Rapid Visual Information Processing) and Spatial Working Memory (SWM) tests were used.

The healthy volunteers underwent exactly similar assessments.

Descriptive statistical analyses, t-tests and Pearson correlations were obtained using Python, in order to find relations between input and outcome to the best extent possible. The impact of brain injury, sleep quality deterioration and cognitive and motor impairment on QoL was also studied using Pearson correlations of the studied variables.

5.2.4 Results

A total of 127 patients were screened for this study and 49 fulfilled our in-/exclusion criteria and were invited to participate. 27 patients and 13 controls signed the ICF to participate in the study. In the patients group, 5 patients died, due to TBI and/or associated co-morbidities, before performing the evaluation and 9 were lost to follow-up before they could be assessed. Finally, a total of 13 patients and 13 controls participated in the study. The recruitment process is detailed in Figure 5.2.

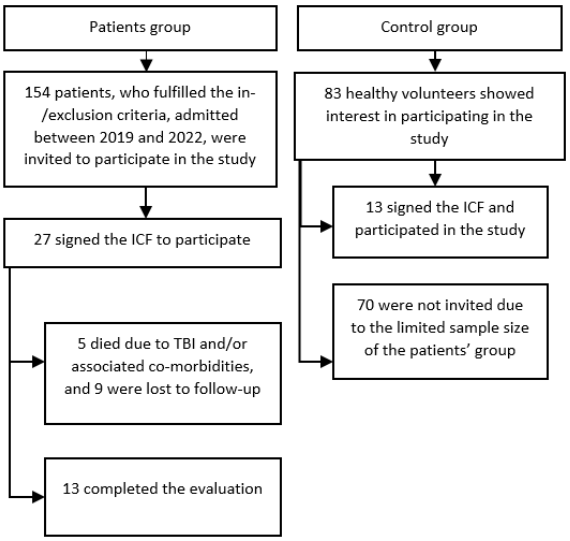


Figure 5.2 Patient and control screening and selection process

Demographic and injury characteristics

The patients had a median age of 74 years (IQR=6) and the volunteers of 73 years (IQR=7) (p=0.43). Patients had a higher polypharmacy rate (46.2% vs 0.0%, p<0.01) than controls, while no statistically significant differences were observed for cardiovascular history (p=0.45) nor for antithrombotic intake (p=0.20) between both groups.
The main cause of TBI in the patients consisted of fall accidents (61.5%) and the median GCS was 15 (IQR=0). 46.2% of the patients were admitted to the Intensive Care Unit (ICU), 23.1% underwent brain surgery and 69.2% received rehabilitation after injury.
Regarding CT findings on the first CT scan at admission, skull fractures were the most common injury type (53.8% of the cases), followed by acute subdural hematoma (aSDH) (46.2%) and subarachnoid hemorrhages (SAH)(38.5%).
The patient group had a significantly higher level of frailty 6 months post-TBI than the control group at the moment of evaluation, presenting a mean Reported Edmonton Frailty Scale score of 5.8 (SD 2.7) vs 0.7 (SD 1.1) (p<0.01). Pre-injury frailty levels were not available in the patient group.

Brain MRI results

MRI scans of the brain were performed at 6 months in all 13 patients and 13 controls. Patients had a mean whole brain volume of 1033.6 cm^3 (SD 127.9), while the mean volume in controls was 1115.1 cm^3 (SD 120.6) (p=0.11). When comparing volumes, although patients had lower whole brain, white and grey matter, lateral ventricles, parietal and temporal cortex, brainstem and thalamus volumes, these differences were not statistically significant [Table 5.4 and Appendix 5A]. Regarding FLAIR white matter hyperintensity for both groups, patients also presented higher volume than controls (10 ml vs. 5 ml), but the difference was not statistically significant (p=0.20) [Table 5.4 and Appendix 5A].

Table 5.4. Brain volume, FLAIR white matter hyperintensity volume and FA values comparison between the patient and control group

	Patient group (N=13)	**Control group (N=13)**	**t-test p value**
Whole Brain volume (cm3) (Mean ± SD)	1033.6±127.9	1115.1±120.6	0.11
White Matter volume (cm3) (Mean ± SD)	398.7±50.2	434.0±52.9	0.09
Grey Matter volume (cm3) (Mean ± SD)	634.9±84.3	681.1± 72.4	0.15
Lesions volume (cm3) (Mean ± SD)	12.1±13.6	6.7±6.2	0.20
Black Holes volume (cm3) (Mean ± SD)	8.6±10.0	4.7±4.3	0.21
FLAIR white matter hyperintensity volume (ml) (Mean ± SD)	10±8	5±5	0.20
Whole brain white matter FA (mean ±SD)	0.4±0.0	0.4±0.0	0.11

ROI=region of interest; SD=standard deviation; FLAIR=fluid attenuated inversion recovery; FA=fractional anisotropy

Regarding the mean number of lesions and blackholes, also no statistically significant differences were found between patients and controls (61.8 vs. 69.8, p=0.57 and 43.2 vs. 50.3,p=0.53, respectively).

When considering diffusion data, fractional anisotropy in the patient group was not significantly different than in controls [Table 5.4 and Appendix 5A].

Cognitive outcomes

The 13 patients and 13 controls completed the CANTAB test. The Motor Screening (MOT), Multitasking (MTT), One Touch Stockings of Cambridge (OTS), Paired Associated Learning (PAL), RTI (Reaction Time), RVP (Rapid Visual Information Processing) and Spatial Working Memory (SWM) tests were used.

A significantly higher median latency of response in the OTS test (OTSMDLFC) was seen in patients (22.3 s; SD 6.5) than in controls (17.6 s; SD 4.6) (p=0.03). Furthermore, patients had a significantly higher median reaction time in RTI test (RTIFMDRT) (0.5s vs 0.4,s p<0.01).

In the patient group there was also a tendency towards a higher median latency of response in the MTT test (MTTLMD) (0.9 s vs 0.8s, p=0.07) and lower mean of correct answers on the first attempt in the OTS test OTSPSFC (8.6 vs 9.8, p=0.09). Nevertheless, those differences, and the differences between groups for the other CANTAB measures, were not statistically significant [Appendix 5B].

Motor outcomes and fall risk

In the motor assessment, poorer manual dexterity was found on the first B&B test with the right hand in patients (B&B RH1) (mean score 46.6 vs 61.7, p<0.01), while none of the differences were statistically significant for the left hand and second attempts. Moreover, patients had a significantly higher score in the TUG test (13.1 s vs 6.2 s, p=0.02) and TUG with cognitive dual task (16.0 s vs 10.2 s, p<0.01), indicating a higher fall risk and poorer gait. The motor outcome assessment scores are detailed in Appendix 5C.

Sleep quality and QoL outcomes

The PSQI test was only completed by 6 of the patients and 3 of the controls. No statistically significant differences were found for both groups [p=0.24].
The 13 patients and 13 controls completed the QOLIBRI and QOLIBRI-OS scales. Patients had a significantly lower QOLIBRI total score (60.4 vs 85.4, p<0.01) and QOLIBRI-OS total score (53.8 vs 88.5, p<0.01) than controls [Table 5.5].

Table 5.5. Sleep quality and QoL in patients and in controls

	Patient group (N=13)	**Control group (N=13)**	**t-test p value**
PSQI total score (Mean ± SD))	8.7±5.7	8.0±5.4	0.24
QOLIBRI			
Cognition score (Mean ± SD)	3.7±0.6	4.4±0.4	<0.01
Self score (Mean ± SD)	3.1±0.8	4.3±0.5	<0.01
Daily Life and Autonomy score (Mean ± SD)	3.4±1.0	4.7±0.4	<0.01
Social Relationships' score (Mean ± SD)	3.4±0.8	4.3±0.6	<0.01

Emotions' score (Mean ± SD)	3.6±0.9	4.4±0.5	0.01
Physical Problems' score (Mean ± SD)	3.2±0.9	4.2±0.8	<0.01
Total score (Mean ± SD)	60.4±14.7	85.4±7.7	<0.01
QOLIBRI-OS			
Physical condition (Mean ± SD)	2.9±1.1	4.5±0.5	<0.01
Cognition (Mean ± SD)	3.2±1.2	4.3±0.6	<0.01
Emotions (Mean ± SD)	3.2±0.9	4.5±0.7	<0.01
Function in daily life (Mean ± SD)	3.2±1.1	4.7±0.5	<0.01
Personal and social life (Mean ± SD)	3.2±1.2	4.8±0.4	<0.01
Current situation and future prospects (Mean ± SD)	3.2±0.9	4.5±0.5	<0.01
Total score (Mean ± SD)	53.8±18.1	88.5±10.6	<0.01

SD=standard deviation; QOLIBRI=Quality of Life after Brain Injury; QOLIBRI-OS=Quality of Life after Brain Injury Overall Scale

Many correlations were found in this study between the demographic and injury characteristics, sleep quality, and cognitive and motor outcomes. All the Pearson correlation results of the studied variables are shown in Appendix 5D-5G.

In this cohort, higher ages, higher Reported Edmonton Frailty Scores, polypharmacy, previous cardiovascular history and ICU admission correlated with worse CANTAB results (r=0.5–0.6, r=0.5–0.7, r=0.5, r=0.5 and r=0.6, respectively) and worse TUG scores (r=0.5, r=0.6 and r=0.8, respectively). Furthermore, antithrombotic intake prior to TBI correlated to worse CANTAB results (r=0.6) and worse B&B scores TBI (r=-0.5 – r=-0.6), and brain surgery with worse TUG scores (r=0.6).

Regarding the patients' clinical management, ICU admission correlated with worse CANTAB results (r=0.6) and brain surgery with worse TUG scores (r=0.6).

Some correlations between MRI findings and motor and cognitive outcomes, and sleep quality, were also found. Hematoma volumes positively correlated with PSQI scores (r=0.5) and worse CANTAB results (r=0.7). The presence of cerebral contusions, smaller white and grey matter volumes, and SDHs correlated with worse CANTAB results (r=0.5, r=-0.6, r=-0.5 and r=0.5–0.6, respectively) and worse TUG scores (r=0.6, r=-0.6, r=-0.6 and r=0.6, respectively).

Moreover, lower FA in the whole brain white matter, left corticospinal tract and right corticospinal tract negatively correlated with PSQI scores (r=-0.5), while lower FA in the whole brain white matter, left arcuate fasciculus and cingulum, and higher FA in the corticospinal tract, correlated with worse CANTAB results (r=-0.4 – -0.6 and r=0.5, respectively). Lower FA in the whole brain white matter, arcuate fasciculus, cingulum and inferior fronto-occipital fasciculus correlated to worse TUG scores (r=-0.5–-0.6).

Additionally, EDH correlated to worse CANTAB results (r=0.6) and worse B&B scores (r=-0.5); skull fractures and SAH correlated to worse CANTAB results (r=0.5–0.7 and r=-0.6, respectively); and the presence of midline shift correlated to worse CANTAB results (r=0.5), worse B&B scores (r=-0.5) and worse TUG scores (r=0.5).

Impact of brain injuries, sleep quality deterioration and cognitive and motor impairment on QoL

The presence of TBI, polypharmacy, ICU admission, SAH, EDH, skull fracture and higher frailty scores correlate with a lower QOLIBRI total score 6 m post-TBI (r=-0.7, r=-0.4, r=-0.6, r=-0.5, r=-0.5, r=-0.5, r=-0.7, respectively). Furthermore, lower B&B scores and higher TUG scores, higher reaction times and number of errors in CANTAB, and higher PSQI scores were also correlated to lower QOLIBRI total scores (r=0.3–0.5, r=-0.3, r=-0.1 – -0.5, r=-0.2 – -0.4 , and r=-0.4, respectively) [Appendix 5D and 5E].

5.2.5 Discussion

This study assessed the sequelae of TBI in older patients in terms of level of changes on MRI imaging of the brain, sleep quality deterioration, cognitive and motor impairment, and quality of life decline in older patients 6 months after TBI**.**

We found that patients had a substantially poorer QoL than controls. They also showed a poorer cognitive and motor performance, although this difference was less pronounced, and there were no statistically significant structural differences in MRI brain characteristics, which might be due to the low sample size of the patients and control group. Importantly, although the age of patients and controls did not differ, patients had higher frailty levels, including higher rates of polypharmacy, than the control group. Therefore, this raises the question whether the patients were also frailer pre-injury and had the TBI because they were frailer.

Previous studies have reported that frailty levels and pre-injury function are better variables to assess outcome than age (330–332), being associated with several adverse outcomes (331,332). Nevertheless, obtaining an answer to the question on the precise cause of lower QoL is rather difficult, as the monitoring of frailty levels in healthy older patients is not routinely performed and pre-injury frailty levels are not available. An option could be to compare outcomes between older patients that sustained a TBI and patients that sustained a major fracture and with similar estimated frailty levels. It has been previously reported that patients with hip fracture are also frailer and at higher risk of poor functional outcomes (333) and mortality (333,334).

Similar results on low QoL in older patients following TBI were found by the authors in a systematic review and meta-analysis, where they found that almost one quarter of the patients aged ≥65 years that sustained mild TBI became dependent for daily life activities (ADL) and that QoL scores were ''far below'' the average scores in the general population (103). In previous studies Haller et al., Kinsella et al. and Thompson et al. found that health-related QoL was impaired to the same extent in mild as in severe TBI (98,115,143). Moreover, a recent study published in 2022 by Van der Vlegel et al. reported that health-related QoL and mental health symptoms were comparable between older patients with mild or moderate/severe TBI (316). Nevertheless, until now, there is a lack of age-specific QoL measures for older TBI patients (335), which impairs obtaining sufficiently specific information (336,337).

Our results indicate that patients with poorer QoL presented polypharmacy, had injuries such as SAH, EDH and skull fracture, were admitted to the ICU and were frailer. Furthermore, they had worse manual dexterity and poorer gait, performed worse in the cognitive assessment and presented a worse sleep quality.

Some studies have also shown correlations between sleep quality, cognitive and motor outcomes and QoL (305–311). However, the impact that post TBI cognitive deterioration has on QoL is still unclear. It is known that severe cognitive impairment is usually associated with impaired self-awareness (338) and could paradoxically lead to higher reported QoL scores (339), while milder cognitive impairments affecting daily life activities could be associated with a worse perceived QoL by the patients. On the other hand, sleep disturbances also contribute to cognitive dysfunction (340) and poorer functional status (341), leading to a reduced QoL.
Most likely, QoL in older adults depends on a large amount of variables in the patients' lives and not only the patients' status after TBI.

In our cohort, subtle differences in cognitive and motor outcomes were seen between patients and controls. Regarding cognitive outcomes, patients presented a higher latency of response and a lower mean of correct answers in some CANTAB subtests. However, these differences were not statistically significant for all subtests. It has been previously reported that TBI can lead to cognitive decline, or even dementia (342,343). However, up to date, the published information regarding this issue is still contradictory and not entirely clear. Future studies with larger sample sizes are necessary to better understand cognitive outcomes in older TBI patients. Patients also presented poorer manual dexterity and had significantly higher TUG scores than the control group, indicating a higher fall risk and poorer walking ability 6 months post-TBI. This needs to be taken into account during the patients' rehabilitation process to avoid recurrent fall accidents.

ASDH and SAH were the most frequent injury types upon admission. However, 6 m post-TBI, no statistically significant differences were found in MRI analyses between patients and controls. Previous studies on brain imaging after TBI have suggested that diffuse aspects of TBI contribute the most to functional outcomes, when compared to focal lesions (344). Furthermore, DTI analyses performed in adults were able to distinguish healthy controls from patients with TBI (345,346), with decreased FA in the frontal lobes highly correlating to deficits in attention (347), memory (348), and executive function (349). Nevertheless, our results did not show such changes, and up to date, brain imaging evidence for TBI in this specific older age group is rather scarce.

Currently, no specific clinical guidelines for the management of TBI in older patients exist (103) and the impact that TBI eventually has on the older patients' function is still insufficiently clear. Therefore, we believe that our results can be useful to better understand and characterize the phenomenon of TBI in older adults and ultimately improve clinical care. However, this study also has limitations. First, the studied sample was rather small, and this was negatively affected by the Covid pandemic. The continuation of the study, to achieve a higher number of patients, is planned by the researchers and necessary to draw more sound conclusions. Second, the patients' pre-injury frailty levels were unknown and the study did not assess causality. Therefore, it is impossible to identify whether the patients were frailer due to the TBI or had the TBI because they were frailer, nor was it possible to pinpoint whether poor QoL was due to pre-existing frailty or to the TBI. Having included a group of patients with hip fracture in the study would have helped us to better understand the effect of frailty of patients' outcomes. However, recruitment of this group of patients during the Covid pandemic was extremely difficult and we could not do it. Future studies including injured controls, such as hip fracture patients, could help to clarify this matter.

Finally, unfortunately, only one MRI scan per patient, at 6 months post-injury, was taken in the included cohort. It would have been an added value to also have the patients' MRI scan at admission to better understand the evolution of the lesions and make better comparisons. Moreover, no functional MRI (fMRI) was performed in this study. We believe that having additional functional data could help us to better understand differences in network capabilities and future studies should include it to better understand functional changes.

5.2.6 Conclusion

In this prospective study, patients with TBI aged ≥65 years, when compared with controls, showed slightly worse cognitive performance and poorer motor function, higher fall risk, but a substantially reduced QoL at 6 months FU, as well as significantly higher frailty, even when the TBI is classified as mild. However, a causal relation between TBI and poor outcome could not be established. No statistically significant differences were found in structural brain characteristics on MRI. Future studies with larger sample sizes are needed to refine the impact of TBI versus frailty on function and QoL in older adults.

Appendix 5

Appendix 5A. Brain volume and FA values comparison between the patient and control group

	Patient group (N=13)	Control group (N=13)	t-test p value
ROI volume (cm3) (Mean ± SD)			
Lateral Ventricles	42.9±12.4	44.2±26.3	0.87
Hippocampus	9.1±1.1	8.9±0.9	0.49
Frontal Cortex	235.3±16.14	230.0±11.4	0.34
Parietal Cortex	143.9±12.7	144.9±7.8	0.82
Temporal Cortex	144.8±10.6	149.8±7.2	0.17
Occipital Cortex	66.8±6.1	66.4±8.0	0.89
Brainstem	36.5±3.0	37.0±3.0	0.66
Cerebellum	146.7±11.8	146.3±6.8	0.91
Putamen	13.0±0.8	12.8±0.9	0.55
Caudate Nucleus	8.2±0.7	8.0±0.6	0.63
Thalamus	16.5±0.9	16.6±1.0	0.87
Globus Pallidus	4.1±0.3	4.0±0.3	0.53
FA (mean ±SD)			
Corpus callosum	0.6±0.1	0.6±0.0	0.23
Left corticospinal tract	0.4±0.1	0.4±0.0	0.51
Right corticospinal tract	0.4±0.0	0.4±0.0	0.14
Left arcuate fasciculus	0.3±0.0	0.3±0.0	0.09
Right arcuate fasciculus	0.3±0.0	0.3±0.0	0.23
Left inferior fronto-occipital fasciculus	0.3±0.0	0.3±0.0	0.14
Right inferior fronto-occipital fasciculus	0.3±0.0	0.3±0.0	0.15
Left cingulum	0.3±0.0	0.3±0.0	0.12
Right cingulum	0.3±0.0	0.3±0.0	0.11

ROI=region of interest; SD=standard deviation; FA=fractional anisotropy

Appendix 5B. CANTAB results in patients and in controls

CANTAB test	Specific CANTAB measure	Patient group	Control group	t-test p value
MOT	**MOTML (Mean ± SD)**	1.2±0.3	1.0±0.3	0.17
MTT	**MTTLMD (Median; IQR)**	0.9; 0.1	0.8; 0.1	0.07
OTS	**OTSMDLFC (Median; IQR)**	22.3;6.5	17.6;4.6	0.03
	OTSPSFC (Mean ± SD)	8.6±3.5	9.8±2.3	0.09
PAL	**PALFAMS28 (Mean ± SD)**	8.4±5.7	9.8±3.9	0.46
	PALTEA28 (Mean ± SD)	32.7±19.5	23.1±16.4	0.10
RTI	**RTIFMDMT (Median; IQR)**	0.3;0.1	0.3;0.1	0.20
	RTIFMDRT (Median; IQR)	0.5;0.0	0.4;0.1	<0.01
RVP	**RVPMDL (Median; IQR)**	0.7;0.3	0.6;0.1	0.38
	RVPPFA (Mean ± SD)	0.0±0.1	0.0±0.1	0.87
SWM	**SWMBE468 (Mean ± SD)**	20.4±9.0	19.1±5.9	0.67
	SWMS (Mean ± SD)	9.9±1.3	9.0±1.9	0.15

IQR=inter-quartile range; SD=standard deviation; MOT=Motor Screening Test; MTT=multitasking test; OTS=One Touch Stockings of Cambridge; PAL=Paired Associated Learning; RTI=Reaction Time; RVP= Rapid Visual Information Processing; SWM= Spatial Working Memory; MOTML= mean latency from the display of a stimulus to correct response (s); MTTLMD=median latency of response (from stimulus appearance to button press) (s); OTSMDLFC=median latency, measured from the appearance of the stocking balls until the first box choice was made by the subject (s); OTSPSFC=total number of assessed trials where the subject chose the correct answer on their first attempt; PALFAMS28=number of times a subject chose the correct box on their first attempt when recalling the pattern locations; PALTEA28=number of times the subject chose the incorrect box for a stimulus on assessment problems, plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach; RTIFMDMT=median time taken for a subject to release the response button and select the target

stimulus (s); RTIFMDRT=median duration it took for a subject to release the response button after the presentation of a target stimulus (s); RVPMDL=median response latency on trials where the subject responded correctly (s); RVPPFA= number of sequence presentations that were false alarms divided by the number of sequence presentations that were false alarms plus the number of sequence presentations that were correct rejections; SWMBE468=number of times the subject incorrectly revisits a box in which a token has previously been found; SWMS=number of times a subject begins a new search pattern from the same box they started with previously

Appendix 5C. Motor outcomes for the patients' and control group

	Patients group (N=13)	Control group (N=13)	t-test p value
Box and blocks test			
B&B RH1 (Mean ± SD)	46.6±11.4	61.7±13.2	<0.01
B&B LH1 (Mean ± SD)	49.2±10.2	61.6±12.3	0.09
B&B RH2 (Mean ± SD)	53.8±13.7	64.7±13.1	0.17
B&B LH2 (Mean ± SD)	51.9±12.5	63.2±11.9	0.13
Berg balance scale (Mean ± SD)	48.6±14.2	55.4±1.4	0.45
Timed-Up & Go test (s) (Mean ± SD)	13.1±10.1	6.2±1.7	0.02
Timed Up & Go with cognitive dual task (s) (Mean ± SD)	16.0±11.4	10.2±2.5	<0.01

SD=standard deviation; B&B=Blocks and Box; RH1=first attempt with right hand; LH1=first attempt with left hand; RH2=second attempt with right hand; LH2=second attempt with left hand

Appendix 5D. Pearson correlation coefficients for demographic characteristics, type of injury, sleep quality, motor functions' and QoL outcomes

	QOLIBRI Total	B&B RH1	B&B LH1	B&B RH2	B&B LH2	BBS	TUG	PSQI
Presence of TBI	-0.7	-0.5	-0.3	-0.3	-0.3	-0.2	0.4	-0.2
Age	-0.1	-0.2	0.0	-0.1	-0.1	0.1	0.5	0.2
C.H.	-0.1	-0.1	-0.1	-0.2	-0.1	-0.2	0.4	-0.1
Ant. Intake	-0.2	-0.3	-0.5	-0.6	-0.5	-0.5	0.4	-0.1
PoI	-0.4	-0.4	-0.2	-0.3	-0.3	-0.3	0.8	-0.2
ICU	-0.6	-0.3	0.1	0.1	0.2	-0.1	0.3	0.3
Surg	-0.1	-0.4	0.2	0.1	0.2	-0.1	0.6	0.2
Rehab	-0.4	-0.4	-0.2	-0.4	-0.3	-0.2	0.4	0.1

Contusion	0.2	-0.4	0.7	0.6	0.6	0.6	0.6	0.3
SAH	-0.5	-0.3	0.2	0.2	0.2	0.3	0.1	-0.2
SDH	0.0	-0.7	-0.2	-0.4	-0.3	-0.2	0.6	0.3
EDH	-0.5	-0.2	-0.3	-0.2	-0.3	-0.5	0.3	-0.4
Skull Fr	-0.5	-0.3	0.0	-0.2	-0.1	-0.1	0.4	-0.2
Midline shift	-0.3	-0.4	-0.2	-0.1	-0.1	-0.5	0.5	0.1
Hem. Vol.	-0.2	-0.4	0.2	0.2	0.3	0.1	0.4	0.5
Frailty	-0.7	-0.6	-0.3	-0.4	-0.3	-0.2	0.6	-0.2
QOLIBRI Total Score	-	0.5	0.5	0.3	0.4	0.4	-0.3	-0.4

C.H.=cardiovascular history; Ant. Intake=antithrombotic intake; Pol=polypharmacy; ICU=admission to Intensive Care Unit; Surg=brain surgery; Rehab=rehabilitation; SAH=subarachnoid hematoma; SDH=subdural hematoma; EDH=epidural hematoma; Skull Fr=skull fracture; Hem. Vol= hematoma volume; Frailty=Reported Edmonton Frailty Scale score; B&B=Blocks and Box; RH1=first attempt with right hand; LH1=first attempt with left hand; RH2=second attempt with right hand; LH2=second attempt with left hand; BBS=Berg Balance Scale; TUG=Timed Up & Go test; PSQI=Pittsburgh Sleep Quality Index; QOLIBRI=Quality of Life after Brain Injury; QOLIBRI-OS=Quality of Life after Brain Injury Overall Scale

Appendix 5E. Pearson correlation coefficients for demographic characteristics, type of injury, QoL and CANTAB outcomes

	MOTML	MTTLMD	OTSMDLFC	OTSPSFC	PALFAMS28	PALTEA28	RTIFMDMT	RTIFMDRT	SWMBE12	SWMBE4	SWMBE468	SWMBE6	SWMBE 8	SWMS	RTISMDMT	RTISMDRT	RVPA	RVPMDL	RVPPFA
Presence of TBI	0.3	0.4	0.4	0.3	0.2	0.3	0.3	0.5	0.3	-0.1	0.1	-0.3	0.3	0.3	0.2	0.5	-0.5	0.2	0.0
Age	0.1	0.6	0.6	0.5	-0.1	0.5	0.1	0.2	0.2	0.4	0.4	0.3	0.3	0.2	0.1	0.2	-0.6	0.3	0.2
C.H.	0.1	0.1	0.1	0.1	-0.2	0.1	0.3	0.5	0.1	0.1	0.2	0.3	0.2	0.1	0.3	0.5	-0.4	0.4	-0.1
Ant. intak	0.1	0.1	0.1	0.0	-0.2	0.2	0.1	0.6	0.3	0.1	0.4	0.2	0.4	-0.1	0.3	0.5	-0.3	0.5	-0.3
Pol	0.0	0.4	0.4	0.4	-0.1	0.2	0.0	0.5	0.1	-0.1	0.1	-0.1	0.1	0.2	-0.1	0.4	-0.6	0.3	-0.1
ICU	-0.4	0.6	0.6	0.6	0.3	0.3	0.1	0.3	0.3	-0.3	-0.2	-0.1	-0.2	0.6	0.0	0.2	-0.3	-0.2	-0.1
Surg	-0.3	0.1	0.1	0.2	-0.1	-0.3	0.1	0.4	-0.2	-0.1	0.1	0.2	0.0	0.6	0.3	0.4	-0.1	-0.1	0.0
Rehab	-0.2	0.4	0.4	0.4	0.2	0.2	-0.1	0.5	0.4	0.1	0.2	0.4	0.1	0.5	0.2	0.2	-0.5	0.2	-0.4
Contusion	0.0	0.5	0.5	0.5	-0.1	0.1	0.2	0.2	-0.2	0.0	-0.1	0.2	-0.2	0.5	0.0	0.1	-0.7	-0.3	0.2
SAH	-0.2	0.3	0.3	0.3	0.3	0.3	-0.1	0.3	-0.1	-0.6	-0.2	-0.3	-0.1	0.1	-0.4	-0.2	-0.2	-0.4	-0.1
SDH	-0.3	0.2	0.3	0.3	-0.2	-0.4	-0.2	0.3	-0.1	0.1	0.3	0.6	0.1	0.4	0.2	0.5	-0.3	0.3	-0.2
EDH	-0.2	-0.2	-0.2	-0.2	0.0	-0.3	0.2	0.6	0.4	-0.4	-0.3	-0.4	-0.1	0.0	0.2	0.1	0.0	0.1	0.0

Skull Fr	-0.2	0.1	0.1	0.1	0.3	0.2	-0.2	0.7	0.3	-0.3	0.1	0.1	0.1	0.5	0.0	0.2	-0.3	-0.1	-0.2
Midline shift	-0.4	0.0	0.0	0.0	0.1	-0.4	0.0	0.4	-0.1	-0.2	0.0	0.0	0.1	0.5	0.3	0.5	0.1	-0.2	-0.2
Hem. Vol.	-0.4	0.3	0.3	0.4	0.3	-0.2	0.1	0.3	-0.1	-0.2	-0.2	0.0	-0.2	0.7	0.3	0.3	-0.1	-0.4	-0.2
Frailty	0.0	0.6	0.6	0.6	0.3	0.3	0.1	0.6	0.3	-0.1	0.1	-0.2	0.2	0.4	0.1	0.4	-0.7	0.2	-0.1
QOLIBRI Total Score	0.0	-0.1	-0.1	0.0	0.1	-0.2	-0.1	-0.5	-0.4	0.2	0.1	0.4	-0.2	-0.2	0.0	-0.3	0.3	0.0	0.1

C.H.=cardiovascular history; Ant. Intake=antithrombotic intake; Pol=polypharmacy; ICU= admission to Intensive Care Unit; Surg=brain surgery; Rehab=rehabilitation; SAH=subarachnoid hematoma; SDH; subdural hematoma; EDH=epidural hematoma; Skull Fr=skull fracture; Hem. Vol= hematoma volume; Frailty=Reported Edmonton Frailty Scale score; MOTML= mean latency from the display of a stimulus to correct response (s); MTTLMD=median latency of response (from stimulus appearance to button press) (s); OTSMDLFC=median latency, measured from the appearance of the stocking balls until the first box choice was made by the subject (s); OTSPSFC=total number of assessed trials where the subject chose the correct answer on their first attempt; PALFAMS28=number of times a subject chose the correct box on their first attempt when recalling the pattern locations; PALTEA28=number of times the subject chose the incorrect box for a stimulus on assessment problems, plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach; RTIFMDMT=median time taken for a subject to release the response button and select the target stimulus (s); RTIFMDRT=median duration it took for a subject to release the response button after the presentation of a target stimulus (s); SWMBE=number of times the subject incorrectly revisits a box in which a token has previously been found; SWMS=number of times a subject begins a new search pattern from the same box they started with previously; RVPMDL=median response latency on trials where the subject responded correctly (s); RVPPFA= number of sequence presentations that were false alarms divided by the number of sequence presentations that were false alarms plus the number of sequence presentations that were correct rejections; QOLIBRI=Quality of Life after Brain Injury

Appendix 5F. Pearson correlation coefficients for brain MRI results and sleep quality, motor functions' and QoL outcomes

	QOLIBRI Total Score	B&B RH1	B&B LH1	B&B RH2	B&B LH2	BBS	TUG	PSQI
Whole Brain	0.3	0.4	0.3	0.3	0.3	0.3	-0.6	0.2
White Matter	0.3	0.4	0.3	0.3	0.3	0.3	-0.6	0.2
Grey Matter	0.3	0.4	0.2	0.3	0.3	0.3	-0.6	0.3
Cortical Grey Matter	0.3	0.3	0.2	0.3	0.3	0.3	-0.6	0.3
Deep Grey Matter	0.3	0.2	0.2	0.1	0.2	0.2	-0.4	-0.1
Lateral Ventricles	0.0	0.1	0.1	0.2	0.1	0.0	0.1	0.3
Hippocampus	-0.5	-0.1	-0.1	0.0	0.0	-0.2	-0.1	-0.1
Frontal Cortex	-0.1	0.1	-0.1	0.0	0.0	0.0	-0.2	0.0
Parietal Cortex	-0.1	-0.1	-0.3	-0.2	-0.3	-0.2	-0.4	0.0
Temporal Cortex	0.2	0.2	0.1	0.1	0.2	0.3	-0.6	0.3
Occipital Cortex	-0.1	0.3	-0.1	0.0	-0.1	-0.2	-0.3	-0.2

Brainstem	-0.1	0.0	-0.1	0.0	0.0	-0.2	0.0	0.1
Cerebellum	0.0	0.0	-0.1	0.0	0.0	-0.3	0.2	0.1
Putamen	-0.1	0.0	-0.1	-0.2	-0.2	-0.2	0.0	-0.3
Caudate Nucleus	0.0	-0.1	-0.3	-0.3	-0.3	-0.2	0.0	-0.3
Thalamus	-0.2	0.0	-0.1	-0.1	0.0	-0.2	-0.1	0.1
Globus Pallidus	-0.3	-0.2	-0.2	-0.2	-0.1	-0.1	0.0	-0.1
FA whole brain white matter	0.1	0.4	0.1	0.0	0.0	0.0	-0.5	-0.5
FA corpus callosum	0.0	0.3	0.1	0.1	0.1	0.0	-0.4	-0.4
FA left corticospinal tract	-0.3	0.1	0.0	-0.1	-0.1	-0.1	-0.1	-0.5
FA right corticospinal tract	-0.4	0.0	-0.1	-0.1	-0.1	-0.1	0.0	-0.5
FA left arcuate fasciculus	0.2	0.3	0.1	0.1	0.0	0.0	-0.5	-0.4
FA right arcuate fasciculus	0.1	0.3	0.1	0.0	0.0	0.0	-0.5	-0.4
FA left inferior fronto-occipital fasciculus	0.1	0.3	0.1	0.1	0.1	0.0	-0.4	-0.3
FA right inferior fronto-occipital fasciculus	0.1	0.4	0.1	0.1	0.1	0.1	-0.6	-0.4
FA left cingulum	0.1	0.3	0.0	0.1	0.0	0.0	-0.5	-0.3
FA right cingulum	0.2	0.3	0.1	0.1	0.1	0.0	-0.5	-0.4

FA=fractional anisotropy; QOLIBRI=Quality of Life after Brain Injury; B&B=Blocks and Box; RH1=first attempt with right hand; LH1=first attempt with left hand; RH2=second attempt with right hand; LH2=second attempt with left hand; BBS=Berg Balance Scale; TUG=Timed Up & Go test; PSQI=Pittsburgh Sleep Quality Index

Appendix 5G. Pearson correlation coefficients for brain MRI results and CANTAB outcomes

	MOTML	**MTTLMD**	**OTSMDLFC**	**OTSPSFC**	**PALFAMS28**	**PALTEA28**	**RTIFMDMT**	**RTIFMDRT**	**SWMBE12**	**SWMBE4**	**SWMBE468**	**SWMBE6**	**SWMBE8**	**SWMS**	**RTISMDMT**	**RTISMDRT**	**RVPA**	**RVPMDL**	**RVPPFA**
Whole Brain	0.0	-0.2	-0.2	-0.2	0.2	-0.2	-0.2	-0.6	-0.3	-0.1	-0.2	0.1	-0.3	-0.2	0.0	-0.4	0.5	-0.3	0.0
White Matter	0.1	-0.1	-0.2	-0.1	0.2	-0.1	-0.2	-0.6	-0.1	-0.1	-0.2	0.1	-0.3	-0.1	-0.1	-0.3	0.4	-0.3	0.1
Grey Matter	-0.1	-0.3	-0.3	-0.2	0.2	-0.3	-0.2	-0.5	-0.3	0.0	-0.2	0.1	-0.3	-0.1	0.1	-0.4	0.5	-0.3	-0.1
Lateral Ventricles	-0.2	0.1	0.2	0.1	0.3	0.1	-0.1	0.1	-0.3	-0.2	0.0	-0.2	0.1	-0.2	0.0	-0.1	0.0	-0.2	-0.2
Hippocampus	-0.1	0.1	0.0	0.1	0.2	0.0	-0.3	0.0	0.3	-0.1	-0.1	-0.2	-0.1	0.0	-0.3	0.2	0.2	-0.2	-0.1
Frontal Cortex	0.1	-0.4	-0.3	-0.4	0.2	-0.3	0.2	-0.1	-0.2	0.1	-0.2	-0.2	-0.2	0.0	0.5	-0.1	0.2	-0.2	-0.1

Parietal Cortex	0.0	-0.4	-0.4	-0.4	0.3	-0.2	-0.2	-0.4	0.0	-0.2	-0.2	-0.1	-0.1	0.0	0.1	-0.3	0.5	-0.3	0.2
Temporal Cortex	-0.1	-0.3	-0.4	-0.3	0.2	-0.2	-0.1	-0.4	-0.1	0.2	-0.1	0.1	-0.2	0.0	0.0	-0.4	0.5	-0.2	0.0
Occipital Cortex	-0.1	-0.3	-0.3	-0.3	0.1	-0.1	-0.5	-0.2	-0.2	-0.2	-0.1	0.0	-0.1	-0.1	-0.3	-0.4	0.3	0.1	-0.2
Brainstem	-0.1	0.0	0.0	0.0	0.0	0.0	-0.1	0.1	0.3	0.0	-0.2	-0.1	-0.2	0.0	-0.3	0.2	0.1	-0.1	-0.1
Cerebellum	-0.1	-0.1	-0.1	-0.1	-0.3	-0.2	-0.1	0.0	0.0	0.0	-0.3	0.0	-0.3	0.0	-0.1	0.1	0.2	0.1	-0.1
Putamen	0.2	0.2	0.2	0.2	-0.1	0.3	0.1	0.1	0.4	0.1	0.2	0.0	0.2	0.2	0.1	0.3	-0.2	0.4	0.2
Caudate Nucleus	0.0	0.0	0.0	0.0	-0.2	0.1	-0.1	0.2	0.2	-0.1	0.2	0.0	0.2	0.0	-0.2	0.2	-0.3	0.3	0.0
Thalamus	0.0	0.1	0.1	0.1	0.2	0.3	0.1	0.1	0.4	0.0	-0.1	-0.2	0.0	0.2	0.0	0.1	0.1	-0.1	0.2
Globus Pallidus	0.1	0.4	0.4	0.4	0.2	0.5	0.0	0.3	0.6	-0.1	0.1	-0.1	0.2	0.1	-0.2	0.3	-0.2	-0.1	0.0
FA whole brain white matter	0.0	-0.5	-0.5	-0.5	0.2	-0.3	0.0	-0.1	0.0	-0.2	-0.3	-0.2	-0.2	-0.3	0.0	-0.1	0.5	-0.3	-0.2
FA corpus callosum	0.0	-0.2	-0.2	-0.1	0.3	-0.1	0.0	-0.1	0.0	-0.3	-0.4	-0.2	-0.3	-0.1	-0.1	0.0	0.4	-0.4	-0.3
FA left corticospinal tract	0.1	-0.1	-0.1	-0.1	0.5	0.1	0.0	0.2	0.3	-0.3	-0.1	-0.4	0.1	-0.1	0.1	0.1	0.1	-0.3	-0.2
FA right corticospinal tract	0.2	0.0	0.0	-0.1	0.5	0.1	0.0	0.3	0.3	-0.2	0.0	-0.3	0.2	0.0	0.2	0.2	-0.1	-0.2	-0.2
FA left arcuate fasciculus	0.1	-0.5	-0.6	-0.5	0.1	-0.2	-0.2	-0.2	0.0	-0.2	-0.2	0.0	-0.3	-0.2	0.0	-0.3	0.5	-0.1	0.0
FA right arcuate fasciculus	0.0	-0.4	-0.4	-0.4	0.1	-0.1	-0.2	-0.2	0.1	-0.1	-0.2	0.0	-0.3	-0.1	-0.1	-0.2	0.5	-0.1	-0.1
FA left inferior fronto-occipital fasciculus	0.1	-0.4	-0.4	-0.4	0.1	-0.2	0.1	-0.1	-0.1	-0.2	-0.4	-0.2	-0.3	-0.3	0.2	-0.2	0.4	-0.2	-0.1
FA right inferior fronto-occipital fasciculus	0.1	-0.3	-0.3	-0.3	0.2	0.0	-0.1	-0.1	0.0	-0.2	-0.2	-0.1	-0.2	-0.2	0.0	-0.2	0.4	-0.2	-0.2
FA left cingulum	0.1	-0.5	-0.5	-0.5	0.1	-0.2	-0.1	-0.2	0.0	-0.2	-0.3	0.0	-0.3	-0.3	0.1	-0.2	0.5	-0.2	-0.1
FA right cingulum	0.1	-0.4	-0.5	-0.4	0.1	-0.2	-0.2	-0.2	0.0	-0.2	-0.3	-0.1	-0.2	-0.2	0.0	-0.2	0.4	-0.2	-0.1

FA=fractional anisotropy; MOTML= mean latency from the display of a stimulus to correct response (s); MTTLMD=median latency of response from stimulus appearance to button press (s); OTSMDLFC=median latency, measured from the appearance of the stocking balls until the first box choice was made by the subject (s); OTSPSFC=total number of assessed trials where the subject chose the correct answer on their first attempt; PALFAMS28= number of times a subject chose the correct box on their first attempt when recalling the pattern locations; PALTEA28=number of times the subject chose the incorrect box for a stimulus on assessment problems, plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach; RTIFMDMT=median time taken for a subject to release the response button and select the target stimulus (s); RTIFMDRT= median duration it took for a subject to release the response button after the presentation of a target stimulus (s); RVPMDL=median response latency on trials where the subject responded correctly (s); RVPPFA=

number of sequence presentations that were false alarms divided by the number of sequence presentations that were false alarms plus the number of sequence presentations that were correct rejections; SWMBE468=number of times the subject incorrectly revisits a box in which a token has previously been found; SWMS= number of times a subject begins a new search pattern from the same box they started with previously

Chapter 6

Development of a prognostic tool for 30-day mortality and 6- and 12-month functional outcome of TBI in older patients based on the international prospective CENTER-TBI core study

6.1 Abstract

Older patients with TBI have worse outcomes than younger patients. Outcome prediction in the older cohort would be highly welcomed to help clinical decision making and counseling of patients and their families. However, outcome prediction requires accurate and specific knowledge of the patient, injury and treatment characteristics, as well as outcomes in this population, which remains difficult. The Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) core study data repository provides a unique opportunity to model outcomes in the older population. Therefore, the goals of this study were to investigate clinical predictors of mortality within 30 days post-TBI and unfavorable functional outcomes, defined by a Glasgow Outcome Scale Extended (GOSE) ≤4, at 6- and 12-months follow-up and to establish prognostic tools specifically for patients with TBI aged ≥65 years. Furthermore, the association between patient demographics, injury characteristics, functional outcomes, and Quality of Life (QoL) 12 months after TBI was studied.

Data from patients with TBI aged ≥65 years, contained in the CENTER-TBI database, were statistically analyzed using Python. Using Machine Learning (ML) algorithms, two prediction models were built for each of the following outcomes: 30-day mortality, 6-month and 12-month functional outcomes. One model was built using admission data only, and the other using all available data on day 14 post-TBI.

A total of 932 patients with TBI were included in the study. The median age of the patients was 74 years (range 65-96 years). The main cause of TBI was fall accidents (67.1%) and the median GCS score upon admission was 15 (range 3-15). The most common traumatic intracranial pathologies on CT imaging were subarachnoid hemorrhages (51.3%) and acute subdural hematomas (37.2%). All patients were hospitalized for a median stay of 5 days (range 0-371 days), whereby 44.1% were admitted to the Intensive Care Unit (ICU). Neurosurgical interventions were performed in 15.8% of cases. At 30-days post-TBI, 34.1% of the overall cohort had died and at the 12-months follow-up, 32.4% of the followed-up patients had an unfavorable functional outcome (GOSE ≤4) and 40 reduced QoL (QOLIBRI <60). Patients with reduced QoL 12 months after TBI were older (median age of 76 vs. 72 years, p=0.02) and had higher rates of upper severe disability (GOSE ≤4 in 22.5% vs. 4.5%, p<0.01).

Using logistic regression, decision tree, random forest, XGBoost, and K-Nearest Neighbors algorithms, the ML models could predict mortality within 30 days post-TBI with an AUC of 0.88-0.89, unfavorable

functional outcomes (GOSE <5) at 6 months with an AUC of 0.85-0.88 and at 12 months with an AUC of 0.85-0.86.
Cisternal compression on early CT, total Injury Severity Score (ISS) and neuroworsening were the three most important parameters for predicting mortality within 30 days. Unconsciousness at admission, preinjury systemic disease, cisternal compression, and neuroworsening were the most important predictive factors for unfavorable functional outcomes 6 months post-TBI. For 12-month unfavorable functional outcomes, the most important predictors were total ISS and the presence of cisternal compression and mass lesions on early CT. Better model performance was obtained when clinical data available on day 14 post-TBI were added.
In conclusion, the present study demonstrates that it is possible to obtain good predictive performance for outcome in older TBI patients by using ML algorithms with AUCs ranging between 0.85-0.89. Accurate prediction of very poor outcomes may guide management decisions in this population, both at admission and at early reassessment.

6.2 Introduction

Traumatic brain injury (TBI) is a major cause of mortality and long-term disability for the older population worldwide (315). It is known that older patients with TBI suffer from worse outcomes than younger patients. In this particular population, factors such as comorbidities and frailty not only interfere with the potential for recovery, but also increase the risk of secondary medical complications (8), psychosocial changes (6), and resulting disability (7). This leads to the need for longer hospitalization and rehabilitation, post-acute residential care and high economic costs for society (315).
One of the main goals of the clinical care for patients with TBI is to guarantee the patients' survival and to preserve the patients' functional status in the long term (350). Therefore, in order to facilitate optimal clinical decision-making, as well as patient and family counseling, outcome prediction in the early stages of treatment would represent a valuable good (351).
Studies on TBI have shown that variables such as age, lower admission Glasgow Coma Score (GCS), higher head abbreviated injury scores (AIS), absent pupillary reflexes, hypoxia, anemia, increased intracranial pressure (ICP), and tracheotomy, among others, are related to poor functional outcomes (352,353). Multiple prediction models, using different clinical parameters, have been proposed before to predict morbidity and mortality after TBI (354). In this context, tools such as machine learning (ML) and artificial intelligence (AI) provide the opportunity to handle high-quality validated data for large populations and to combine information to make predictions (355).
To date, the gold standard for TBI outcome prediction are the International Mission for Prognosis and Clinical Trial design in TBI (IMPACT) (356) and Corticosteroid Randomization After Significant Head Injury (CRASH) models (357). However, in these studies older patients were underrepresented and they lose reliability with older age (358). A performant prediction model for outcomes in older patients with TBI, based on routinely collected data which is applicable across all injury severities, is still lacking (354). Therefore, the goals of this study were to investigate clinical predictors for mortality within 30 days post-TBI and for unfavorable functional outcomes at the 6- and 12-month follow-up. Moreover, we sought to establish specific prognostic tools for these outcomes in patients with TBI aged ≥65 years based on data available upon admission and data available on day 14 post-TBI. Furthermore, the interactions between the patients' demographic characteristics, injury characteristics, functional

outcomes, and Quality of Life (QoL) 12 months after TBI were studied. This information could contribute to the development of clinical guidelines specific to TBI in the older population.

6.3 Methods

The analyses in this study were performed on data obtained in the framework of the international multi-center Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) project, which consists of a prospective observational longitudinal data collection of patients with TBI (registered at ClinicalTrials.gov: NCT02210221). In this project, patients were eligible for inclusion when presenting to one of the participating study centers with a clinical diagnosis of TBI, within 24h post-injury. The study was approved by the local ethics committees of its 65 centers in Europe and Israel (102). Approval was obtained from the CENTER-TBI proposal committee to access and analyze the data. Only data from the CENTER-TBI database on patients ≥65 years old with a diagnosis of TBI, including all injury severities, were used, and analyzed for this study. Patients with a penetrating TBI were excluded from the study.
A descriptive and multivariate regression statistical analysis was conducted using Python v 3.7 (Python Software Foundation) to find key outcome predictors specific for older TBI patients. These analyses were designed using the Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research (359) and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guideline (360). Furthermore, a descriptive analysis of the patients' Quality of Life (QoL) at the 12-months follow-up was performed, in which a Quality of Life after Brain Injury (QOLIBRI) score <60 was considered as reduced quality of life (361). Due to the low sample size of patients with available QOLIBRI scores 12 months post-TBI, no multivariate analyses could be performed and no ML models were used. In our models, unconsciousness at admission was determined by the AVPU- 'Alert, Voice, Pain, Unresponsive', neurological examination (362).

6.3.1 Outcome predictors

A forward selection of the predictive variables was performed. Predictors were selected based on their individual statistical influence on the chosen outcome variables using logistic regression models and clinical relevance by two investigators (RG and BD). Input variables were selected at three different time-points (hospital admission, 7 days post-TBI and 14 days post-TBI) due to the clinical relevance of those time points for clinical decision making. These variables included patients' sex, age, comorbidities and pre-medication, injury characteristics, cranial CT findings, clinical variables, treatment variables and complications. The list of input variables selected for each of the models are shown in Appendix 6A-6F.
The outcome variables chosen were mortality within 30 days post TBI and unfavorable functional outcome at 6 and 12 months post-TBI, defined as a GOSE ≤4.
GOSE is scored as: 1 (death), 2 (vegetative state), 3 (lower severe disability), 4 (upper severe disability), 5 (lower moderate disability), 6 (upper moderate disability), 7 (lower good recovery) to 8 (upper good recovery) (62). GOSE 1-4 are considered as unfavorable outcomes (62).

6.3.2 Data processing and ML model building

The first step in the analysis was the database cleaning and creation of dummy categorical variables from the available variables. Only dichotomous categorical variables were included in the models

(0=negative result and 1=positive result). Unknown values were presented in the database with a value of 88. Missing data or unknown values were not imputed in the models and patients with missing data in the selected input and output variables were removed from the analyses.

Variance Inflation Factor (VIF) values of the available variables were calculated to avoid multi-collinearity. VIF values ranging from 5-10 were considered as indicators of multicollinearity (363). In case of multicollinearity, we carefully assessed the nature of the variables and chose the best representative variables. The impact of each of the input variables in the predicted outcome variable was calculated through the SHapley Additive exPlanations (SHAP) values (364).

Six different prediction models were built with the selected variables using ML techniques: 1) A prediction model for mortality within 30 days post-TBI containing only input variables registered at admission to the emergency department (ED), which is intended to support decision making within the first hours post-TBI. 2) A prediction model for mortality within 30 days post-TBI containing all information available on day 14, which is intended to support decision making in the subacute phase post-TBI. 3) A prediction model for unfavorable outcomes at the 6-months follow-up (FU), based on input variables at admission. 4) A prediction model for unfavorable outcomes at the 6-months FU containing input variables on day 14 post-TBI. 5) A prediction model for unfavorable outcomes at the 12-months FU, based on input variables at admission. 6) A prediction model for unfavorable outcomes at the 12-months FU containing input variables on day 14 post-TBI.

A comparison of five different ML algorithms was performed for the six different models: logistic regression (365), decision tree (366), random forests (367), XGBoost (368) and K nearest neighbors (KNN)(369). All algorithms were implemented using the Scikit-learn package in Python (370).

The data were randomly divided into a training sample (70%) and a testing sample (30%). For each of the models, the precision, sensitivity, specificity, prediction accuracy and area under the curve (AUC) were calculated and compared in order to determine which ML algorithm had the best performance (371,372). AUCs were considered as follows: AUC of 0.7 as acceptable discrimination, 0.8 as good discrimination and 0.9 as excellent discrimination (373).

6.4 Results

6.4.1 Patient characteristics

A total of 932 patients with TBI, with a median age of 74 years (range 65-96 years), fulfilled the inclusion criteria. Comorbidities were present in 83.6%. Antithrombotic medication was taken by 41.0% of the patients prior to TBI and 20.6% took ≥ 6 medications prior to TBI.
Fall accidents were the main cause of TBI (67.1%), followed by road traffic accidents (23.7%).
The median GCS at admission was 15 (range 3-15). The most common (intra)cranial lesions on CT imaging were traumatic subarachnoid hemorrhage (51.3%), acute subdural hematoma (aSDH) (37.2%), skull fracture (33.7%) and brain contusion (33.4%). Furthermore, a mass lesion was observed in 25.5% of the patients and 15.1% had a midline shift > 5mm. 52.7% of the patients presented an extracranial AIS $\geq$3 at admission.

All patients were hospitalized with a median stay of 5 days, whereby 44.1% were admitted to the Intensive Care Unit (ICU) and 15.8% underwent a neurosurgical intervention. Within 30 days post-TBI 34.1% of the patients had died and at the 12-months FU 32.4% had an unfavorable outcome (GOSE ≤ 4).
The demographics, injury characteristics and outcomes are summarized in Tables 6.1 and 6.2.

Table 6.1. Injury cause, admission findings and CT results (n=932)

Injury cause	
Road traffic accident (N (%))	221 (23.7)
Fall accident (N (%))	625 (67.1)
Violence/assault (N (%))	10 (1.1)
Suicide attempt (N (%))	3 (0.3)
Admission findings	
GCS (median; IQR)	15; 2
Mild TBI (N (%))	570 (61.2)
Moderate TBI (N (%))	50 (5.4)
Severe TBI (N (%))	99 (10.6)
Unknown GCS (N (%))	213 (22.9)
Neuroworsening in ED (N (%))	115 (12.3)
Complicated event in ED (N (%))	157 (16.8)
Pupils non symmetric (N (%))	118 (12.7)
Extracranial AIS ≥3 (N (%))	491 (52.7)
Cranial CT results	
Brain contusion on early CT (N (%))	311 (33.4)
TAI on early CT (N (%))	67 (7.2)
aSDH on early CT (N (%))	347 (37.2)
Subarachnoid hemorrhage on early CT (N (%))	478 (51.3)
Epidural hematoma on early CT (N (%))	6 (0.6)
Skull fracture on early CT (N (%))	314 (33.7)
Midline shift on early CT (N (%))	141 (15.1)
Mass lesion on early CT (N (%))	238 (25.5)
Marshall CT score (median; IQR)	2; 2

GCS = Glasgow Coma Scale; IQR = Interquartile range; ED = Emergency Department; CT = Computed Tomography; TAI = Traumatic Axonal Injury; aSDH = Acute subdural hematoma

Table 6.2. Clinical management and outcomes (N=932)

Clinical management	
Admitted to ICU (N (%))	411 (44.1)
Total days hospitalization (median; IQR)	5; 11
ICP monitoring (N (%))	132 (14.2)

Cranial surgery (N (%))	147 (15.8)
Outcomes	
Mortality 30 days (N (%))	179 (34.1)
GOSE 12 m (mean; SD)	3.9;3
Unfavorable outcomes at 12m (N (%))	302 (32.4)
Favorable outcomes at 12 m (N (%)	223 (23.9)
Unknown GOSE at 12 m (N (%))	407 (43.7)

ICU = Intensive Care Unit; IQR = Interquartile range; ICP = Intracranial pressure; GOSE = Glasgow Outcome Scale Extended

6.4.2 Prediction of mortality

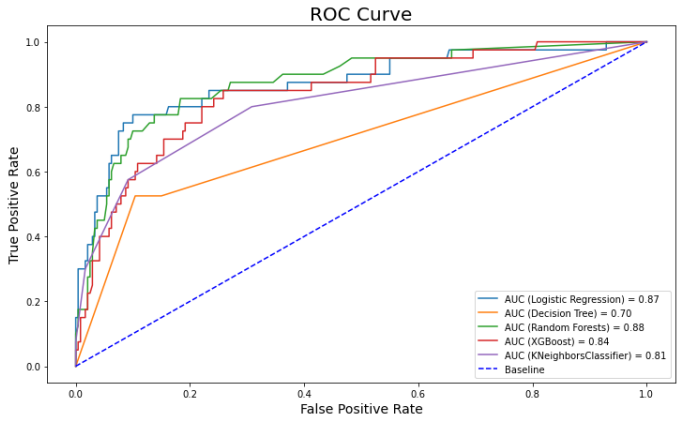
Data from all 932 patients were used for 30-day mortality prediction. Two models were created, in which data from 652 patients were used for training and data from 280 patients for validation.
First, a prediction model for mortality within 30 days post-TBI, containing variables registered at admission, was created. Outcome was predicted with an accuracy of 80.0-90.0%. The highest precision, specificity and prediction accuracy were achieved by logistic regression (92.0%, 53.0% and 90.0%, respectively). The highest sensitivity was achieved by the KNN model (98.0%) and the highest AUC was obtained by Random Forest (0.88) [Table 6.3 and Fig 6.1 a].

Table 6.3. Prediction performance of all ML models

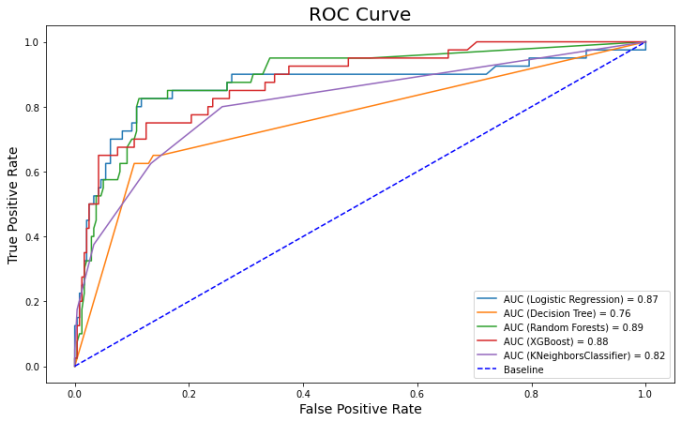
Input variables	Outcome variable	ML algorithm	Precision	Sensitivity	Specificity	Prediction accuracy	AUC
All available at admission	30-day mortality	Logistic regression	0.92	0.96	0.53	0.90	0.87
		Decision tree	0.91	0.88	0.48	0.82	0.70
		Random forest	0.90	0.96	0.38	0.80	0.88
		XGBoost	0.91	0.93	0.48	0.87	0.84
		KNN	0.89	0.98	0.30	0.89	0.81
All available on day 14	30-day mortality	Logistic regression	0.92	0.96	0.53	0.90	0.87
		Decision tree	0.93	0.90	0.58	0.86	0.76
		Random forest	0.93	0.95	0.58	0.90	0.89
		XGBoost	0.94	0.96	0.65	0.91	0.88
		KNN	0.90	0.97	0.38	0.88	0.82
All available at admission	Unfavorable outcomes at 6-months FU	Logistic regression	0.83	0.82	0.82	0.79	0.85
		Decision tree	0.79	0.64	0.71	0.68	0.65
		Random forest	0.78	0.82	0.80	0.75	0.80
		XGBoost	0.79	0.82	0.81	0.76	0.79
		KNN	0.77	0.75	0.76	0.71	0.79
All available on day 14	Unfavorable outcomes at	Logistic regression	0.86	0.80	0.83	0.80	0.88
		Decision tree	0.80	0.72	0.76	0.71	0.70

	the 6-months FU	Random forest	0.82	0.88	0.85	0.80	0.85
		XGBoost	0.83	0.83	0.83	0.78	0.86
		KNN	0.85	0.75	0.80	0.76	0.85
All available at admission	Unfavorable outcomes at 12 months FU	Logistic regression	0.71	0.65	0.83	0.76	0.85
		Decision tree	0.55	0.68	0.64	0.65	0.69
		Random forest	0.68	0.68	0.79	0.75	0.82
		XGBoost	0.68	0.71	0.78	0.75	0.78
		KNN	0.57	0.74	0.65	0.68	0.76
All available on day 14	Unfavorable outcomes at the 12-months FU	Logistic regression	0.70	0.74	0.79	0.77	0.86
		Decision tree	0.55	0.69	0.64	0.66	0.68
		Random forest	0.64	0.69	0.75	0.73	0.83
		XGBoost	0.64	0.66	0.76	0.72	0.79
		KNN	0.59	0.84	0.63	0.71	0.77

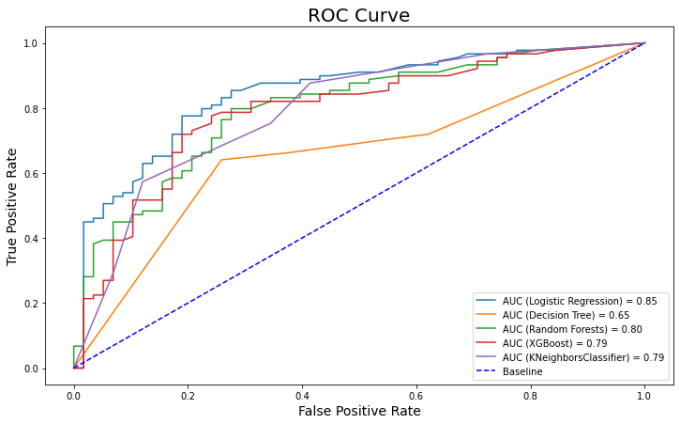
ML=machine learning; AUC=area under the curve; FU= follow-up; KNN= K-Nearest Neighbors

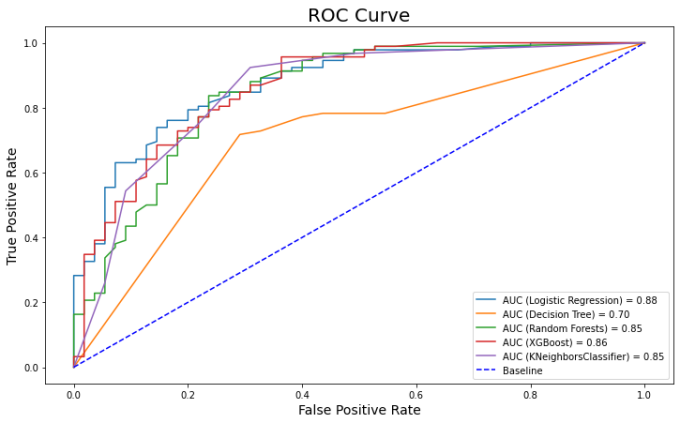


6.1 a) Prediction of mortality within 30 days post-TBI based on input variables at admission

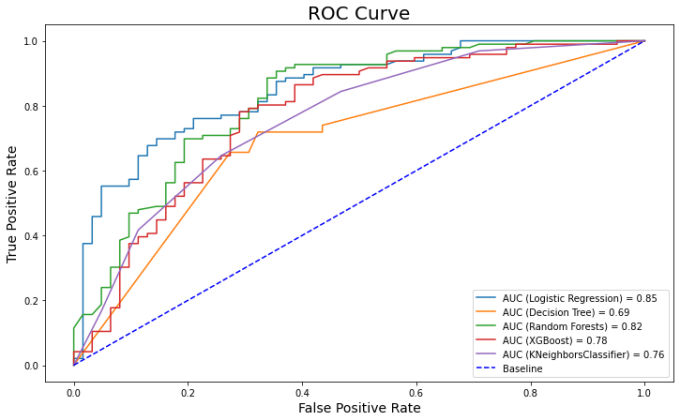


6.1 b) Prediction of mortality within 30 based on input variables on day 14 post-TBI

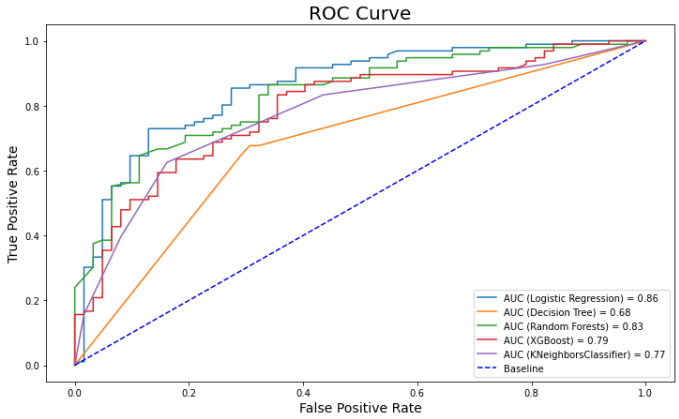




6. 1 c) Prediction of unfavorable outcomes at the 6-months FU based on input variables at admission



6.1 d) Prediction of unfavorable outcomes at the 6-months FU based on input variables on day 14 post-TBI



6.1 e) Prediction of unfavorable outcomes at the 12-months FU based on input variables at admission

6.1 f) Prediction of unfavorable outcomes at the 12-months FU based on all information available on day 14 post-TBI

ROC=receiver operating characteristic; AUC=area under the curve
Figure 6.1. Comparison of ROC curves in the different ML models

Second, modeling was performed for 30-day mortality prediction with all data available on day 14 post-TBI. Prediction accuracy was 86.0-91.0%. The highest precision, specificity and prediction accuracy were obtained by the XGBoost model (94.0%, 65.0% and 91.0% respectively). The highest sensitivity was obtained by the KNN model (97.0%) and the highest AUC was obtained by Random Forest (0.89) [Table 3 and Fig 1b].

Cisternal compression on early cranial CT, total ISS and neuroworsening were the three most important parameters to predict mortality within 30 days in the older TBI patients [Appendix 6G and 6H].

6.4.2 Prediction of unfavorable functional outcomes at 6 months FU

Data from 490 patients, in whom the GOSE at the 6-months FU were available, were used to create two prediction models for unfavorable functional outcome. The models were trained on data from 343 patients and validated on data from 147 patients.

Based on variables registered at admission, unfavorable functional outcome 6 months post-TBI was predicted with an accuracy of 68.0%-79.0%. The highest precision, sensitivity, specificity, prediction accuracy and AUC were achieved by logistic regression (83.0%, 82.0%, 82.0%, 79.0% and 0.85, respectively) [Table 6.3 and Fig 6.1 c].

In the model predicting outcome with all information available on day 14 post-TBI, unfavorable outcome at the 6-months FU was predicted with an accuracy of 71.0-80.0%. The highest precision and AUC were obtained by logistic regression (86.0% and 0.88, respectively), while the highest sensitivity and specificity were obtained by random forest (88.0% and 85.0%, respectively). Regarding prediction

accuracy, the highest values were given by logistic regression and random forest (80.0%) [Table 6.3 and Fig 6.1 d].
Unconsciousness at admission, preinjury systemic disease, cisternal compression and neuroworsening were the most important predictive factors for unfavorable functional outcomes 6 months post-TBI found in our cohort [Appendix 6I and 6J].

6.4.3 Prediction of unfavorable functional outcomes at 12 months FU

Data from 525 patients in whom GOSE at the 12-months FU were available were used to create two prediction models for unfavorable functional outcome. The models were trained on data from 368 patients and validated on data from 157 patients.
Based on variables registered at admission, unfavorable functional outcome 12 months post-TBI was predicted with an accuracy of 66.0-75.0%. The highest precision, specificity, prediction accuracy and AUC were achieved by logistic regression (71.0%, 83.0%, 76.0% and 0.85, respectively). The highest sensitivity was achieved by the KNN model (74.0%) [Table 6.3 and Fig 6.1 e].
In the model predicting outcome with all information available on day 14 post-TBI, unfavorable outcome at the 12-months FU was predicted with an accuracy of 66.0-77.0%. The highest precision, specificity, prediction accuracy and AUC was obtained by logistic regression (70.0%, 79.0%, 77.0% and 0.86, respectively). The highest sensitivity was obtained by the KNN model (84.0%) [Table 6.3 and Fig 6.1f].
The total ISS, the presence of cisternal compression and mass lesions on early cranial CT were the most important predictive factors for unfavorable functional outcomes 12 months post-TBI found in older TBI-patients [Appendix 6K and 6L].

6.4.4 The relation between patient and injury characteristics, clinical management, functional outcomes and Quality of Life

QOLIBRI results were available for 196 of the 932 patients at the 12-months FU.
Patients with a QOLIBRI <60 were older (median age 76 years) than patients with a QOLIBRI ≥ 60 (median age 72 years; p=0.02). Also, the gender distribution was different between groups with QOLIBRI <60 and ≥60 (67.5% female and 32.5% male vs. 35.9% female and 64.1% male; p<0.01). No statistically significant associations were found for any variable relating to patient history, injury, treatment or complications. [Tables 6.4 and 6.5].

Table 6.4. Demographic, previous clinical history and injury characteristics by QOLIBRI score categories

	QOLIBRI 12 m ≥60 (N=156)	**QOLIBRI 12 m <60 (N=40)**	**t-test p value**
Female/Male (N (%))	56 (35.9)/100 (64.1)	27 (67.5)/13 (32.5)	<0.01
Age (Median; IQR)	72;9	76; 10	0.02
Cardiovascular history (N (%))	95 (60.9)	30 (75.0)	0.53
Antithrombotics (N (%))	62 (39.7)	16 (40.0)	0.98

Intake of ≥6 medications (N (%))	33 (21.2)	10 (25.0)	0.60
GCS (median; IQR)	15;1	15;0	0.41
Neuroworsening in ED (N (%))	12 (7.7)	2 (5.0)	0.81
Loss of consciousness (N (%))	82 (52.6)	21 (52.5)	0.99
Post-traumatic amnesia (N (%))	60 (38.5)	11 (27.5)	0.20
Pupils non symmetric (N (%))	10 (6.4)	2 (5.0)	0.74
Brain contusion on early CT (N (%))	42 (26.9)	12 (30.0)	0.58
TAI on early CT (N (%))	12 (7.7)	2 (5.0)	0.57
aSDH on early CT (N (%))	50 (32.1)	17 (42.5)	0.60
Subarachnoid hemorrhage on early CT (N (%))	68 (43.6)	18 (45.0)	0.57
Epidural hematoma on early CT (N (%))	9 (5.8)	1 (2.5)	0.57
Skull fracture on early CT (N (%))	38 (24.4)	9 (22.5)	0.57
Midline shift on early CT (N (%))	15 (9.6)	3 (7.5)	0.57
Mass lesion on early CT (N (%))	25 (16.0)	5 (12.5)	0.56
Marshall CT score (median; IQR)	2;1	2;1	0.32

QOLIBRI=Quality of Life after Brain Injury; IQR=inter-quartile range; GCS=Glasgow Coma Scale; ED=emergency department; CT=computed tomography; TAI=traumatic axonal injury; aSDH=acute subdural hematoma

Table 6.5. Patients' clinical management by QOLIBRI score categories

	QOLIBRI 12 m ≥60 (N=156)	**QOLIBRI 12 m <60 (N=40)**	**t-test p value**
Intubation (N (%))	14 (9.0)	0 (0.0)	0.43
Ventilation (N (%))	11 (7.1)	1 (2.5)	0.34
Admitted to ICU (N (%))	82 (52.6)	9 (22.5)	0.17
Total days hospitalization (median; IQR)	4;7	7;13	0.70
ICP monitoring (N (%))	12 (7.7)	4 (10.0)	0.19
Cranial surgery (N (%))	21 (13.5)	4 (10.0)	0.56

QOLIBRI=Quality of Life after Brain Injury; IQR=inter-quartile range; ICU= intensive care unit; ICP=intra-cranial pressure

The highest proportion of upper good recovery (GOSE=8) was found in patients with QOLIBRI ≥ 60 (48.7% vs 15.0%, p<0.01), while the highest proportions of upper severe disability (GOSE=4) and lower severe disability (GOSE=3) were found in patients with QOLIBRI <60 (22.5% vs. 4.5% and 12.5% vs. 1.3%, respectively; p<0.01 each). No statistically significant differences were found between the two QOLIBRI score categories ≥60/<60 for the GOSE scores 5-7 (p=0.59, p=0.09 and p=0.39, respectively) [Table 6.6].

Table 6.6. Patients' functional outcomes at 12-months FU by QOLIBRI score categories

	QOLIBRI 12 m ≥60 (N=156)	QOLIBRI 12 m <60 (N=40)	t-test p value
Upper good recovery (GOSE=8) (N(%))	76 (48.7%)	6 (15.0)	<0.01
Lower good recovery (GOSE=7) (N(%))	50 (32.1)	10 (25.0)	0.39
Upper moderate disability (GOSE=6) (N(%))	16 (10.3)	8 (20.0)	0.09
Lower moderate disability (GOSE=5) (N(%))	5 (3.2)	2 (5.0)	0.59
Upper severe disability (GOSE=4) (N(%))	7 (4.5)	9 (22.5)	<0.01
Lower severe disability (GOSE=3) (N(%))	2 (1.3)	5 (12.5)	<0.01

QOLIBRI=Quality of Life after Brain Injury; GOSE=Glasgow Outcome Scale Extended

6.5 Discussion

In this study, data of 932 patients with TBI aged ≥65 years, with a median age of 74 years and a median GCS of 15, collected in the international multi-center CENTER TBI database, were analyzed and used for the creation of six prediction models for mortality and unfavorable functional outcome (GOSE ≤4). All six ML prediction models had good performance, based on precision, sensitivity, specificity, accuracy and AUC metrics, demonstrating that it is possible to accurately predict outcome in older TBI patients, which was previously questioned in the IMPACT and CRASH models (358).

The present ML models could predict mortality within 30 days post-TBI with an accuracy ranging from 90.0%-91.0% and AUCs between 0.88 and 0.89. Regarding unfavorable functional outcome, a prediction 6 months post-TBI could be obtained with accuracies of 79.0%-80.0% and AUCs of 0.85-0.88, while at 12 months post-TBI, an accuracy of 75.0%-77.0% and AUCs of 0.85-0.86 were achieved. Concerning the specific models used, decision tree was the underperformer, while logistic regression, KNN, XGBoost and Random Forest showed better results. Previous studies published by Gravesteijn et al (374) and Nourelahi et al (375) also reported a better performance of logistic regression methods in TBI outcome prognostication, compared to other machine learning algorithms. However, Gravesteijn et al (374) found an underperformance in Random Forest, which was not the case in the present analysis.

It is important to take into account that there is a large heterogeneity in input factors used for different ML models between different studies. Therefore, comparing results and deciding which ML model performs best in outcome prediction for older TBI patients is currently not possible.

In our study, cisternal compression on early cranial CT, the total ISS and neuroworsening were the three most important parameters to predict mortality within 30 days. Moreover, unconsciousness at admission, preinjury systemic disease, cisternal compression on early cranial CT and neuroworsening were the most important predictive factors for unfavorable functional outcomes 6 months post-TBI.

For 12-months outcomes, the total ISS and the presence of cisternal compression and mass lesion on early cranial CT were the most important predictors.

The presence of a midline shift on early cranial CT, a predictive variable according to all our 6 models, has also been reported to predict unfavorable outcome in the previous literature (376). Our finding that mass effect on early cranial CT imaging has predictive importance in older TBI patients might be attributable to the higher susceptibility to suffer from intracranial hematomas at higher ages (276).

The importance of extracranial injuries in outcome prediction is to be noted. In our study, 52.7% of the patients presented an extracranial AIS $\geq$3 at admission and our prediction models have shown a clear impact of the variable ISS in the studied outcomes. This has also been previously shown in the literature. According to Gravesteijn et al., extracranial injuries should be included in TBI classification systems (377). Refining the classification of TBI could be particularly important in the older population, as initial high GCS scores often mask the severity of the trauma, which renders the GCS less useful for prediction (51). Importantly, an initial high GCS score does not preclude poor outcome in older patients (8,106). In the present analysis, GCS was not an outcome predictor, which could be attributed to the predominance of mild TBI in the included patients and the fact that only 5.4% and 10.6% presented a moderate or severe TBI, respectively.

Previous studies have shown that an older age is a risk factor for higher mortality and worse functional outcome (110,154,315,378,379). This was also the case in our study. We confirmed that even within the older TBI population, age continues to have a negative association with outcome. This could be explained by the fact that older patients usually have high rates of comorbidities (190,198–203) and are more likely to suffer from emotional, psychosocial, cognitive and motor sequelae (6), leading to higher disability (7), dependency (8), medical complications (8), and depressions (193). Furthermore, in our analyses, we found additional age-related outcome predictors, such as antithrombotic pre-medication prior to TBI and a history of systemic disease, which need to be taken into account in prediction models for older patients.

The ability to predict mortality or very poor outcome with high accuracy may support clinical decision making such as treatment withdrawal, either at hospital admission or within the first two weeks post-TBI. The main goal of the clinical care for older patients with TBI is to guarantee their survival and preserve their functional status in the long-term (350). However, the patients' wellbeing or QoL has been relatively neglected in TBI research studies in the past (9). We initially hypothesized that a direct correlation would be found between functional outcomes and QoL. However, other previously published studies on the topic have shown that in reality the association between functional and QoL outcome measurements is more complex (103), which might be explained by the multi-factorial nature of QoL. Our study did not use ML algorithms to predict QoL, mainly due to the low sample size of patients with available QOLIBRI scores. We did not find a statistically significant correlation between the patients' previous clinical history, injury characteristics or clinical management and QoL. A reduction in QoL also occurred after mild TBI, especially at older age, and lower GCS did not significantly impact QoL. Similar findings were described in a previous systematic-review and meta-analysis, where only subtle differences in QoL were observed between patients with mild and severe TBI and, in some cases, the reported QoL scores were even lower for patients with mild TBI (103). Thus, patients with mild TBI could potentially perceive the injury's consequences as a serious burden, while patients surviving moderate and severe TBI may be rather positive, feeling happy to be still alive. The current study found that patients with lower QoL had higher rates of severe disability (GOSE 3-4) and patients with preserved QoL higher rates of complete recovery (GOSE=8). However, no statistically significant differences were found for the categories 5-7 of the GOSE. Future studies

reporting QOLIBRI results with larger sample sizes and with a higher proportion of patients with moderate and severe TBI are necessary to clarify this matter.

Nevertheless, previously published studies on outcome prognostication in patients with TBI have generally addressed the entire adult population and reported that, in many cases, the models lose reliability with age (358). In contrast, the present study demonstrates that specific prediction models for older patients are possible with the most important outcome predictors being mass effect on early cranial CT, neuroworsening during hospitalization, extracranial injuries and factors related with older age, such as antithrombotic pre-medication and a history of systemic disease. It is noteworthy that, to the authors knowledge, the current analysis for the first time specifically investigated such predictive factors and offered outcome prediction models for older patients with TBI.
While the relatively large number of included patients and variables as well as the prospective nature of this study can be rated as strengths, several limitations have to be noted: for the prediction of outcomes at 6 and 12 months post-TBI, the number of patients with available data was considerably reduced, which decreased the accuracy of the models. Furthermore, even though the attempt to introduce all information available on day 14 post-TBI was made for three of the applied models, the number of variables that could be included was rather limited, due to the high amount of missing data at this time point. Additional information including patients' vitals and clinical parameters in the first 2 weeks after their injury is likely to be useful in the future to improve the models' quality. In addition, the models were trained in a database where the number of patients with moderate and severe TBI was very low. Although the high amount of patients with mild TBI included in the database is representative of the TBI phenomenon in older patients (87), the interpretation of the model should be carefully performed in the case of moderate and severe injuries, as the prediction accuracy might be decreased in those cases. Lastly, although an internal validation of the model was done, the model has not yet been externally validated which is still necessary. Therefore, the model is still not ready for implementation in clinical practice. In order to do that, a big investment should be performed in the future to validate the models and create an user-friendly tool that could be used in a clinical setting (380).

6.6 Conclusion

TBI in the older population leads to high mortality rates within 30 days and high rates of unfavorable functional outcomes and reduced quality of life within 12 months. Cisternal compression and mass lesion on early cranial CT, total ISS and neuroworsening during hospitalization were the most important parameters for mortality and unfavorable functional outcome prediction. Specific prediction models using ML algorithms showed good performance in the prediction of 30-day mortality and 6- and 12-months unfavorable outcome, with AUCs ranging between 0.85-0.89.

Appendix 6

Appendix 6A. List of input variables at admission used for the 30 day mortality prediction

Input variables	
Sex	Is the patient older than 85 years old?
Prior intake of antithrombotics	Second insults and neuroworsening in ED
Comorbidities	Loss of consciousness and/or post-traumatic amnesia
Complicated event in ED	Presence of a lucid interval at admission
Intraventricular hemorrhage on CT at admission	Contusion on CT at admission
Extraaxial hematoma on CT at admission	GCS deterioration one hour after injury
Total ISS 51-75	Total ISS 26-50
Cisternal compression on CT at admission	Any intracranial traumatic abnormality on CT at admission
Skull fracture on CT at admission	Midline shift on CT at admission
Mass lesion on CT at admission	Extracranial AIS over 3
Pupils non symmetric	Preinjury mild systemic disease
Preinjury severe systemic disease	Traumatic axonal injury on CT at admission

ED=emergency department; CT=computed tomography; GCS=Glasgow Coma Score; ISS=Injury Severity Score; AIS=abbreviated injury score

Appendix 6B. List of input variables available on day 14 post-TBI used for the 30-day mortality prediction model

Input variable	
Sex	Is the patient older than 85 years old?
Prior intake of antithrombotics	Second insults and neuroworsening in ED
Comorbidities	Loss of consciousness and/or post-traumatic amnesia
Complicated event in ED	GCS deterioration one hour after injury
Presence of a lucid interval at admission	Pupils non symmetric
Skull fracture on CT at admission	Cisternal compression on CT at admission
Midline shift on CT at admission	Mass lesion on CT at admission
Contusion on CT at admission	Extraaxial hematoma on CT at admission
Marshall CT score over 3	Second insults and neuroworsening at day 7
Presence of any intracranial traumatic abnormality on CT at admission	Extracranial AIS over 3
Total ISS 51-75	More than 7 days of intubation, oxygen administration and/or mechanical ventilation
Tracheostomy performed within 14 days post-TBI	Cranial surgery performed within 14 days post-TBI
Extracranial surgery	Presence of a delayed hematoma
Presence of deep venous thrombosis	Presence of urinary tract infection

ED=emergency department; CT=computed tomography; GCS=Glasgow Coma Score; ISS=Injury Severity Score; AIS=abbreviated injury score

Appendix 6C. List of input variables at admission used for the 6-months unfavorable functional outcome prediction model

Input variable	
Extracranial AIS ≥3	Complicated event in ED
ISS of 0-25	Unconsciousness at admission
LOC_PTA_RGA_AOC	Raised ICP in ICU
GCS assessed while paralyzed	Pre-injury severe systemic disease

Mass lesion on early CT	Prior antithrombotic intake
Cisternal compression on early CT	ACE Focal NeuroDeficit
Second insults and neuroworsening in ED	Pupils non symmetric
ISS of 51-75	Contusion on early CT

AIS=abbreviated injury score; ED=emergency department; ISS=Injury Severity Score; LOC=loss of consciousness; PTA=post-traumatic amnesia; AOC=alteration of consciousness; RGA=retrograde amnesia; ICP=intracranial pressure; ICU=Intensive Care Unit; CT=computed tomography

Appendix 6D. List of input variables available on day 14 post-TBI used for the 6-months unfavorable functional outcome prediction model

Input variable	
Prior antithrombotic intake	GCS assessed while paralyzed
Mass lesion on early CT	More than 7 days of intubation, oxygen administration or mechanical ventilation
Second insults and neuroworsening in ED	CPR at arrival to ED
Extracranial AIS ≥3	More than 14 days of intubation, oxygen administration or mechanical ventilation
Pupils non symmetric	Contusion on early CT
Second insults and neuroworsening at day 7	Complicated event in ED
Raised ICP in ICU	ACE Focal NeuroDeficit
ISS of 0-25	Cisternal compression on early CT
Unconsciousness at admission	Intake of ≥6 medications
TAI on early CT	ISS 51-75
Pre-injury severe systemic disease	

CT=computed tomography; GCS=Glasgow Coma Score; ED=emergency department; CPR=cardiopulmonary resuscitation; AIS=abbreviated injury score; ICP=intracranial pressure; ICU=Intensive Care Unit; ISS=Injury Severity Score

Appendix 6E. List of input variables at admission used for the 12-months unfavorable functional outcome prediction model

Input variable	
Complicated event in ED	Is the patient older than 85 years old?
Prior intake of antithrombotics	Pupils non symmetric
Pupils not reactive	Extracranial AIS over 3
Comorbidities	Presence of focal neurological deficit
Mass lesion on CT at admission	Cisternal compression on CT at admission
Subdural collection mixed density on CT at admission	Epidural hematoma on CT at admission
Presence of any intracranial traumatic abnormality on CT at admission	Presence of skull fracture symptoms at admission
Total ISS 0-25	Second insults and neuroworsening in ED
Preinjury severe systemic disease	Preinjury mild systemic disease
Contusion on CT at admission	

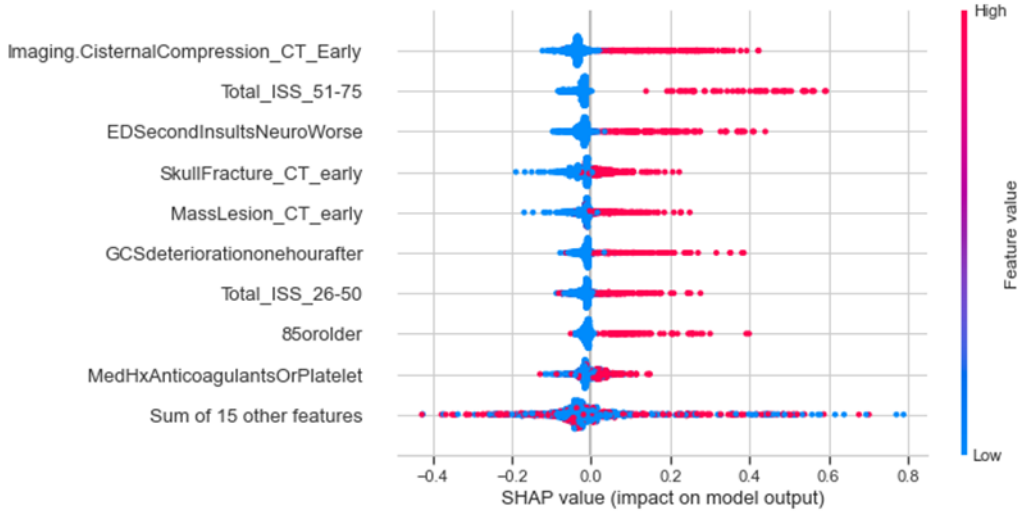
ED=emergency department; AIS=abbreviated injury score; CT=computed tomography; ISS=Injury Severity Score

Appendix 6F. List of input variables available on day 14 post-TBI used for the 12-months unfavorable functional outcome prediction model

Input variable	
Is the patient older than 85 years old?	Pupils not reactive
Complicated event in ED	Extracranial AIS over3
Previous history of musculoskeletal condition	Prior intake of antithrombotics
Previous history of neuro-psychiatric condition	Loss of consciousness and/or post-traumatic amnesia
Pupils non symmetric	Cisternal compression on early CT
Total ISS 0-25	GCS 13-15 on day 14
GCS 9-12 at day14	GCS_3-8 on day 14
Comorbidities	Cranial surgery performed within 14 days post-TBI
Epidural hematoma on CT at admission	Contusion on CT at admission
Skull fracture on CT at admission	Second insults and neuroworsening in ED
Midline shift on CT at admission	Mass lesion on CT at admission
Second insults and neuroworsening at day 7	Focal neurological deficit
Raised ICP in ICU	More than 14 days of intubation, oxygen administration and/or mechanical ventilation
CPR at admission	Systemic cardiovascular complication
Presence of subdural collections/mixed density hematomas on CT at admission	Preinjury mild systemic disease
Preinjury severe systemic disease	Presence of any intracranial traumatic abnormality on CT at admission
Presence of skull fracture symptoms at admission	Neuroworsening on day 14

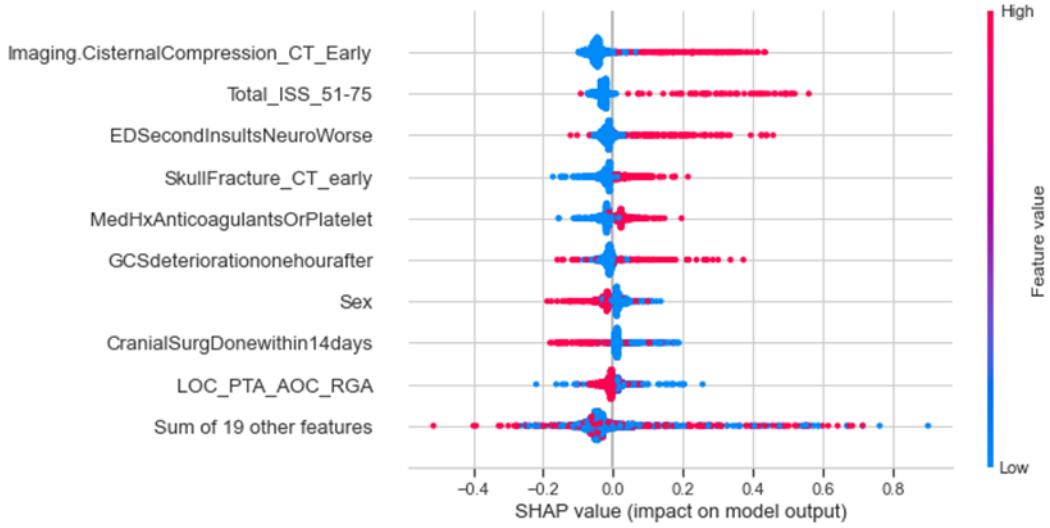
ED=emergency department; AIS=abbreviated injury score; CT=computed tomography; GCS=Glasgow Coma Score; ISS=Injury Severity Score; ICP=intracranial pressure; ICU=Intensive Care Unit; CPR=cardiopulmonary resuscitation

Appendix 6G. SHAP values for the different input variables used for the ML models for 30-day mortality prediction at admission



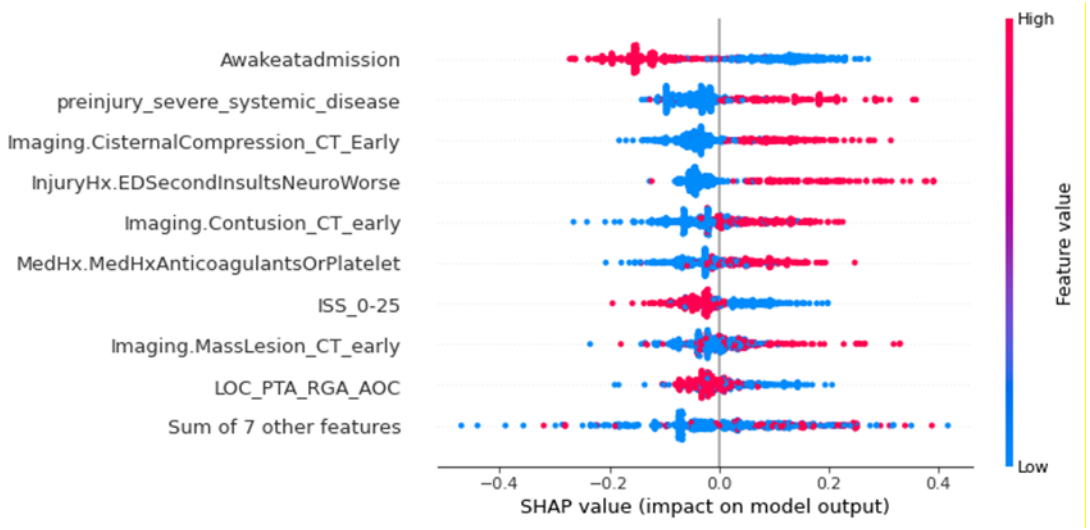
SHAP=Shapley Additive Explanation; CT=computed tomography; ISS=Injury Severity Score; ED=emergency department; GCS=Glasgow Coma Score

Appendix 6H. SHAP values for the different input variables used for the ML models for 30-day mortality prediction on day 14 post-TBI



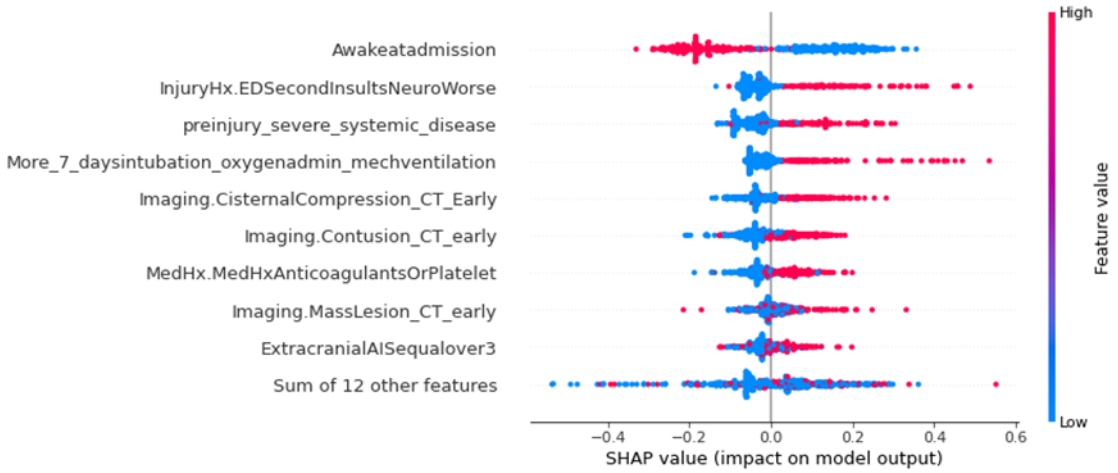
SHAP=Shapley Additive Explanation; CT=computed tomography; ISS=Injury Severity Score; ED=emergency department; GCS=Glasgow Coma Score; LOC=loss of consciousness; PTA=post-traumatic amnesia; AOC=alteration of consciousness; RGA=retrograde amnesia

Appendix 6I. SHAP values for the different input variables at admission used for the ML models for unfavorable outcomes at the 6-months FU



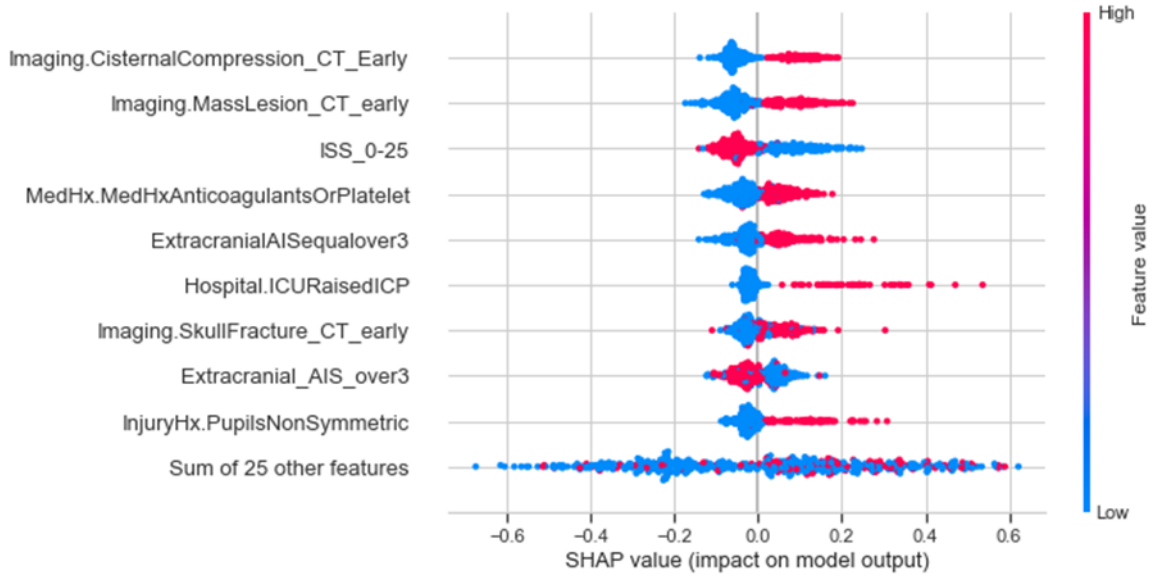
SHAP=Shapley Additive Explanation; CT=computed tomography; ED=emergency department; ISS=Injury Severity Score; LOC=Loss of Conciousness; PTA=post-traumatic amnesia; RGA=retrograde amnesia; AOC=alteration of consciousness

Appendix 6J. SHAP values for the different input variables on day 14 post-TBI used for the ML models for unfavorable outcomes at the 6-months FU



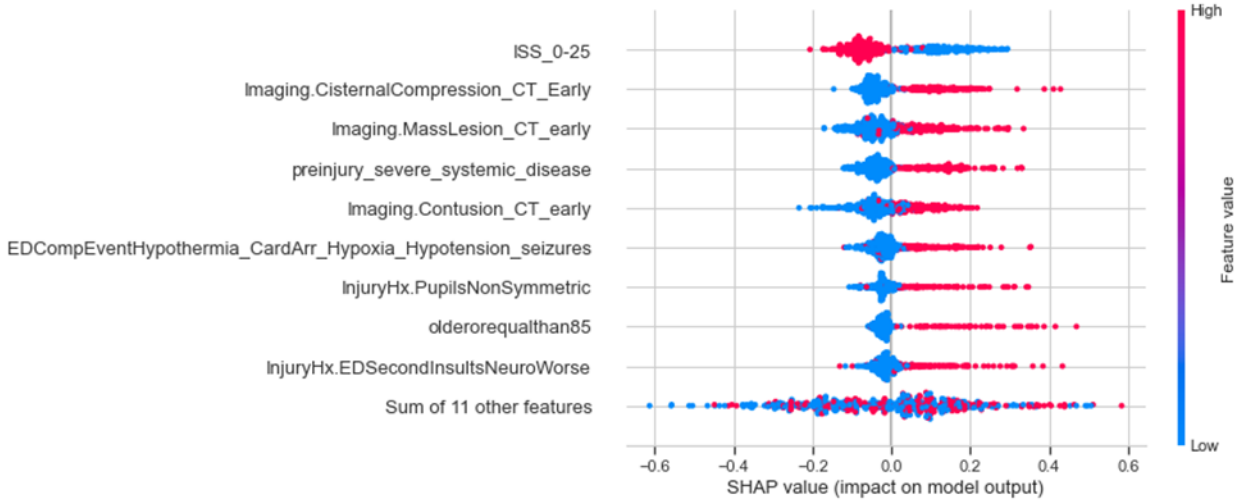
SHAP=Shapley Additive Explanation; CT=computed tomography; AIS= Abbreviated Injury Score

Appendix 6K. SHAP values for the different input variables at admission used for the ML models for unfavorable outcomes at the 12-months FU



SHAP=Shapley Additive Explanation; CT=computed tomography; ISS=Injury Severity Score; AIS=Abbreviated Injury Score; ICU=Intensive Care Unit; ICP=intracranial pressure

Appendix 6L. SHAP values for the different input variables used for the ML models for unfavorable outcome prediction on day 14 post-TBI



SHAP=Shapley Additive Explanation; ISS=Injury Severity Score; CT=computed tomography; ED=emergency department

Chapter 7

In-depth assessment of quality of life and real life impact of mild TBI in older patients by means of a focus group study

This chapter is based on:

Gavrila Laic R.A., Vander Sloten J., Depreitere B. In-depth assessment of Quality of Life and real life impact of Mild Traumatic Brain Injury in elderly by means of a focus group study. [Manuscript submitted for publication to Brain and Spine].

7.1 Abstract

Introduction Traumatic Brain Injury (TBI) in older patients leads to more severe consequences than in young patients. However, the impact that TBI has on older patients' Quality of Life (QoL) remains still unclear.
Research Question The main objective of this study is to qualitatively investigate changes in QoL after mild TBI in older patients.
Material and Methods A focus group interview was conducted with 6 patients with mild TBI, with a median age of 74 years old, admitted to the University Hospitals Leuven between 2016 and 2022. The data analysis was performed following the guide provided by Dierckx de Casterlé et al in 2012, using Nvivo software.
Results Three themes emerged from the analysis: functional disturbances and symptoms, daily life after TBI, and life quality, feelings and satisfaction. The most reported factors that deteriorated QoL 1-5 years post-TBI in our cohort were lack of support from relatives, changes in self-perception and social life, tiredness, balance, speech and sensory disturbances, headaches, cognitive deterioration, changes in physical health, changes in sexual life, sleep problems and dependence for daily life activities. The acceptance of the situation and hope for improvement were shown to be the most important coping mechanisms for these patients.
Discussion and Conclusion In conclusion, mild TBI in older patients frequently leads to changes in self-perception, daily life activities and social life 1 to 5 years after the injury, which could contribute to a loss of independence and QoL deterioration. The acceptance of the situation and a good support network seem to be protective factors for these patients' well-being after TBI.

7.2 Introduction

Traumatic Brain Injury (TBI) is a life changing event and one of the main causes of disability worldwide (381), frequently leading to long-term physical, cognitive, emotional, behavioral and social problems, and Quality of Life deterioration (QoL) (382–386).
It has been acknowledged that in older patients sequelae of TBI result in more severe consequences for the patient than in younger people, even when the TBI is classified as mild (8,387,388). The ageing process results in a deterioration of molecular and cellular functions (389), limiting physiological reserve and leading to higher comorbidities (390). Therefore, recovery in older patients can be more complicated and potentially compromised (391–393), while on the other hand the older population has the highest emergency department admission, hospitalization and mortality rates following TBI (394).
Following TBI, patients can experience anxiety (395), depressive symptoms (395), posttraumatic stress disorder (PTSD) (395) or even a self-identity disruption (396), that can last for months or years after the accident (397). Also in mild TBI, cognitive symptoms, such as reduced concentration and memory function, and experiencing lack of energy are frequently reported (398).
Patients with TBI usually report significantly variable ratings for QoL assessments following their injury, most probably due to the high amount of variables on which a person's QoL depends (193,300,399–404).
The main contributing factors for QoL after TBI have shown to be mental health, emotional and neurobehavioral status, cognitive functions, sleep quality, autonomy, energy levels, relationships, employment, and higher levels of independence and social participation, among others, which are usually affected in these patients (193,300,399–404).
Previous studies have shown that patients with longer hospital stays or who need more medical care are usually less satisfied with their general health and recovery after TBI and report lower QoL (405). Nevertheless, up to date, little is known about how patients cope with the long-term sequelae of TBI (406) and the impact that TBI has on older patients' QoL is still unknown, mainly due to the lack of a standard QoL measure for older adults (407). Furthermore, in early rehabilitation several of the patients' heterogeneous symptoms are usually not the focus of therapy and, to date, have not been included in TBI clinical guidelines (408). Therefore, the main objective of this study is to qualitatively investigate the difficulties that older patients suffer after mild TBI and how they affect their QoL, in order to better understand the impact of TBI on older patients' lives.

7.3 Methods

In order to perform a qualitative in-depth investigation of the QoL changes that older patients experience after mild TBI, a focus group study was designed and approved by the UZ Leuven/KU Leuven Ethics Committee.
For this study, patients older than 65 years, admitted to the University Hospitals Leuven (UZ Leuven) between 2016 and 2021, with the diagnosis of mild TBI were eligible to participate in the study. Patients were excluded if they had a diagnosis of any concomitant disease already affecting the patients' QoL, suffered cognitive disturbances caused by any other pathology, had previous substance abuse, or had communication difficulties. Only patients who were fluent in Dutch were eligible for the study.
The eligible participants were recruited from the UZ Leuven TBI registry and contacted by telephone or e-mail. After the study was explained, patients that provided informed consent were included in the study. These patients were contacted by telephone or e-mail to schedule a focus group interview

where several patients could attend. The sample size for a group interview was set at a minimum of 6 and a maximum of 10 patients. The interview could only take place in a Covid safe period.
The interview took place in UZ Leuven in May 2022 and lasted a total of 90 min. An interview guide was constructed with topics that would encourage the participants to describe experienced problems in their daily life after the TBI, in order to understand how those problems affected their QoL. The English translation of the used interview guide, originally in Dutch, can be read in Appendix 7.
During the interview, two moderators were present (BD and RG). The first moderator (BD) conducted the meeting and led the discussion. The second moderator (RG) recorded the interview and took notes of the conversation.
The session started by asking the participants to provide a brief autobiography and to share with the group how the injury had happened. Then, the interview guide was used to steer the conversation. Follow-up questions to specific comments, not present in the initial guide, were also asked in order to stimulate the conversation flow and obtain interesting details to answer the researchers' main research question.
The interview was digitally recorded using a smartphone and transcribed verbatim in a Word document. The patients' data was pseudoanonymized and data analysis was performed following the QUAGOL qualitative data analysis guide designed by Dierckx de Casterlé et al in 2012 (409), using paper methods and Nvivo software.

7.4 Results

For this study, one interview was performed with 6 patients (4 males and 2 females), with a median age of 74 years old (range 66-82 years old). The patients' age at the moment of the accident ranged between 65 and 77 years old and 2 patients had a GCS of 14 at admission, 2 of 15 and for the other 2 patients the GCS was unknown. The patients' median hospitalization length was of 10 days (range 5-30 days) and 1 of the patients was admitted to the Intensive Care Unit for 6 days (with initial GCS of 14).
From the two patients with a GCS of 14, one had a temporal contusion and frontal subarachnoid/subdural blood on the first CT scan taken at admission, while the other presented with a parietal subarachnoid haemorrhage. One of the patients with a GCS of 15 presented at admission with a frontal subdural hematoma and the other with an occipital skull fracture and underlying cerebellar contusion and subarachnoid blood. In the patients with unknown GCS, one had a normal CT scan at admission and the other a small intracerebral hematoma in the left superior frontal gyrus with limited surrounding edema. None of the patients underwent a neurosurgical intervention.

Four of the patients had the TBI due to a bicycle accident, one had a fall accident and one an accident with a horse. Two of the patients reported remembering very little or nothing about the accident itself and three described having experienced the trauma as being serious or having been picked up from the accident scene for near dead.

The analysis resulted in 17 codes, which were organized in 3 categories and 14 sub-categories [Table 7.1].
Three interrelated themes emerged from the analysis: (1) physical and cognitive symptoms, (2) daily life after TBI, and (3) QoL, feelings and satisfaction.

Table 7.1. Categories and subcategories that emerged from the qualitative analysis.

Categories (n=3)	**Subcategories (n=14)**
Physical and cognitive symptoms	Balance problems Headache Cognitive deterioration Physical health Senses' disturbances Sexual life Sleep problems Speech disturbances
Daily life after TBI	Daily life activities Support and help
QoL, feelings and satisfaction	General life satisfaction Changes in social life Self-perception Acceptance

7.4.1 Physical and cognitive symptoms

The patients reported having suffered physical and cognitive symptoms after the injury. The most common ones were balance problems, headaches, cognitive deficits, changes in physical health, sensory disturbances, changes in sexual life, and sleep problems. The most common cognitive alterations in this cohort were short-memory deficits and speech disturbances.
These symptoms were, in most of the cases, still present at the moment of the interview, 1 to 5 years post-TBI.

This can be observed in the following examples:

''I have the impression that I'm a bit, not steady enough, when I have to do something. Sometimes I'm just treading water on the plants and I have to hold on to it to keep my balance. That is a bit less, I think, than before.'' (Patient 4, GCS 15, 2 years after TBI)

''That headache…I'm constantly in pain, and even combing my hair, going to the shop…'' (Patient 5, GCS 15, 1 year after TBI)
''To get something, I go to the kitchen, to the garage, for that bottle of milk or water and then all disappears. Yes, I went to get something, but what…and then I turn back.'' (Patient 5, GCS 15, 1 year after TBI)

7.4.2 Daily life after TBI

Patients reported difficulties in their daily life after the TBI. Although they reported to be currently independent and active in their daily lives and thought they were lucky during their recovery process to achieve their current status, they still continued to experience some changes in their daily lives.
Activities such as cleaning or driving were the most affected ones in these patients and external cleaning help or transportation help was needed. This can be seen in the following example:

''Yes, absolutely, less independent...I can't drive my car anymore...now I have a driver, and yes, that means less independence.'' (Patient 5, GCS 15, 1 year after TBI)

However, the most important difficulty these patients reported was the lack of support and understanding of the patients' situation by partners and family, which was a big source of discomfort. Some of the patients' reports were:

''That I have this…I accept that to myself, I know it is like this, but my husband doesn't. I don't dare to say I'm tired, I don't dare to sit down, I cannot go to rest because he starts to bother me. He's always going to say what I'm forgetting, or what I have to change. He thinks I'm demented after the fall. I can't believe it. I don't get any support.'' (Patient 5, GCS 15, 1 year after TBI)

''I don't have a very cooperative husband either. That support is not always there. I think that for all of us...that understanding of people who are outside is completely different.'' (Patient 6, GCS of 14, 1 year after TBI)

Therefore, lack of support and understanding, and the continued inability to perform certain tasks, perceived to be important to them, were reported to be major elements affecting QoL in our cohort.

7.4.3 Life quality, feelings and satisfaction

The patients reported to be generally satisfied with their lives and to feel good at the moment of the interview:

''My quality of life is good, actually. I feel loved by a lot of people. And yes, I do get upset when certain things go less well, but globally I'm happy.'' (Patient 4, GCS 15, 2 years after TBI)

However, despite the general satisfaction, they reported some changes in their life that were referred as QoL-disturbing. Importantly, many patients reported not being the same person as before, mainly attributing those changes to higher irritability levels and a reduced interest in social life post TBI. This usually made the patients feel uncomfortable, very emotional, with difficulties to cope and/or unhappy:

''I am very irritable. I am not the same person as before...I used to be calm and quite easy going, but now I react very often to everything. I am very irritable, and I have never been like this.'' (Patient 5, GCS 15, 1 year after TBI)

''I used to be social, but I am not interested anymore…after I fell, that actually broke. So that social isn't... anymore. I had these friends, that used to be real friendship, but then I don't feel at home there anymore.'' (Patient 3, unknown GCS, 3 years after TBI)

Despite these difficulties, most patients reported having accepted their current situation and seemed optimistic and with hope for an improvement of the situation and none of the patients reported feelings of shame or depression when specifically asked.

7.5 Discussion

TBI is widely known to be a life changing event in all its severity categories (410). This luxating nature is particularly true and probably even more striking in older adults, that have reduced recovery potential and may find themselves already in a delicate premorbid situation with slowly increasing comorbidity and decreasing functionality. Even in mild TBI, older patients more often than not continue to be confronted with several post-traumatic difficulties affecting their lives after the

accident (391–394). In the present focus group study on QoL following mild TBI, this is confirmed, and insight into the underlying causes is deepened.
We qualitatively analyzed changes in QoL in 6 patients with mild TBI 1 to 5 years post TBI. The most important factors that were responsible for reduced QoL according to these patients were physical and cognitive sequelae (balance problems, headache, cognitive deterioration, changes in physical health, sensorial disturbances, changes in sexual life, sleep problems, speech disturbances), changes in self-perception and social life, tiredness, dependence for daily life activities, and lack of support and understanding. These symptoms and experiences have been reported previously in studies considering reporting on reduced QoL in adults with TBI (399,411–415).
Most striking in our cohort was that multiple patients reported on the heavy impact of their impaired social life, but particularly referred to the lack of support and understanding from their immediate environment as a heavy burden. Brown et al. (413) already showed that social participation is a key factor for improving and sustaining QoL in patients with TBI (399). A correlation between social support and higher levels of QoL was also shown in reports by Jones et al (411) and Kalpakjian et al. (412).

Our participants reported on a perceived strong association between impaired social interactions and reduced self-perception. Patients experienced a lack in social interest and reported to not recognize themselves anymore. They said they were ''not the same as before''. That patients report the perception of not having the same capabilities or feelings as they had in the pre-injury situation, was described in previous reports (414).

Insomnia was another consistent and persisting complaint. Sleep disturbances are a well-known challenge following TBI (415). However, the additional influence of a lack of sleep on other reported symptoms is still unclear and further investigation to clarify it would be very helpful.

Despite consistent ongoing complaints affecting their lives 5 years post-TBI, none of the patients reported symptoms of depression and all of them described being globally satisfied with their lives. A previous systematic review and meta-analysis published by the authors in 2021, showed that 2.6-4.8% of the older patients with mild TBI develop depressive symptoms (103). This was not the case in the present cohort. Even those patients who reported more complaints and worse support networks described using the acceptance of the situation and hope for improvement as mechanisms to cope.

It is important to take into account that in this study we only included patients that sustained a mild TBI. Therefore, the results cannot be extrapolated to more severe TBI categories. Although a direct correlation between GCS and QoL has not been found (416,417), we should consider that the group of patients that were included in the present study was quite homogeneous in terms of functional outcomes and favorable recovery. If patients with mild TBI with worse recovery or patients with more severe TBI would have been interviewed, this could potentially have led to a different study outcomes. In previous studies considering more severe TBI, Brown and Vandergoot (418) found that patients with lower GCS eventually had higher subjective QoL decades post-injury. Furthermore, Kalpakjian et al. (412) found that, whilst the mean QoL score in patients with severe TBI was lower than the average and significantly lower than in non-disabled patients, nearly half of the patients scored in the average or high range 5 years post-injury. Therefore, the literature regarding a possible association between the severity of TBI and QoL is still controversial and unclear (419). To date, no direct correlation

between GCS and QoL scores has been established (416,417). However, it is also acknowledged that admission GCS might not be as reliable for TBI injury classification in older as in younger patients, since older patients have an increased risk for intracranial injuries presenting with a delayed mass effect, leading to secondary deterioration of GCS (88–90). Thus, the correlation between QoL and other clinical parameters should be further investigated in older patients.
Regarding changes over time post-injury, we did not find big differences between patients interviewed 1 and 5 years post-TBI. Previous studies have shown that patients with TBI adapt over time and present a better QoL in the long-term after injury (420). Nevertheless, it would be interesting for future studies to consider shorter and longer times post-injury to better understand changes in QoL over time.

This study is, to the authors knowledge, the first qualitative study on QoL after mild TBI specific for older patients. However, it is important to consider that it has some limitations. First, the included sample size is quite low. This has to do with the fact that the group of interest is composed of patients with high age and frequently a high comorbidity rate, which made the interest for participation low. Furthermore, the recruitment fell in the covid-19 pandemic and patients were afraid to come to the hospital for non-essential procedures. Therefore, the number of performed interviews was limited to one. Second, only patients with mild TBI were included in the study. Although 80% of the older patients are classified as mild (81) and the included cohort could be representative of the TBI phenomenon in patients $\geq$ 65 years old, there is a lack of representation in our cohort of patients with moderate and severe TBI, and our results cannot be extrapolated to them. Future studies considering all injury severities in this population would be helpful to better understand the QoL and factors affecting poor QoL by injury severity. Third, patients were included in the study from 1 to 5 years after TBI. This may potentially induce some bias as to whether the addressed problems were only caused by TBI or were exacerbated by the ageing process. However, the patients were strong in their opinion and message that the specific problems they were experiencing at the moment of evaluation were secondary to the TBI, and eg. not present in their partner. More homogenous follow up times can be addressed in future studies. We hope that the present pilot study may represent a trigger for such future research.

From the results obtained in this study we saw that, even though the patients were globally satisfied with their lives 1-5 years post-TBI, they suffered from multiple complaints that had a real impact on their life and self-perception after the injury.
We believe that these results can be very valuable in clinical practice. Up to date, evidence for QoL changes in older patients with TBI is rather scarce (313) and a qualitative approach is very useful to thoroughly understand the patients' experience.
In our cohort, the acceptance of the situation and a good support network were described as protective factors for the patients' well-being after TBI. Therefore, efforts should focus on providing psychological assistance and establishing support networks for these patients. Patients should not have the feeling of being left alone and should be followed-up after hospital discharge and receive rehabilitation (414). Finally, more studies are required to identify treatable reasons for poor QoL in all injury severities in older patients. Remarkably, the patients participating in the present study all had such identifiable treatable reasons for reduced QoL, but had given up on the idea that medical care would help them.

7.6 Conclusion

Mild TBI in older patients frequently leads to changes in self-perception, daily life activities and social life 1 to 5 years after the injury, which could contribute to a loss of independence and QoL deterioration. The lack of support and inability to perform certain daily tasks are important factors for QoL deterioration in older patients with TBI. The acceptance of the situation, optimism, and a good support network seem to be protective factors for these patients' well-being after TBI. Future studies with bigger sample sizes, considering all injury severities and with more specific follow-up times are necessary to better understand changes in QoL after TBI in the older population.

Appendix 7

This interview is about the consequences you have suffered after the Traumatic Brain Injury that you had some time ago. We are investigating how such brain trauma affects the lives of older people. The following questions aim to address your experiences, but above all our main goal is to initiate a group discussion from which we hope to learn as much as possible.

-Do you remember the accident? What happened? Where were you? Were you alone?

-Do you remember how you were brought to the emergency department? Did you come by ambulance?

-Do you remember your stay in the emergency department or in the hospital? How long were you hospitalized? How did you find the care in the emergency department or in the hospital? Was there something missing?

-Where did you go after you were discharged from hospital (home, care institution...)?

-How did you find the care and follow-up after your discharge from hospital? Were there any shortcomings? Were you adequately helped and advised?

-Is your life after brain trauma different from life before? Can you describe it? In your opinion, is this due to the brain trauma?

-Are you now independent in your daily activities? Which activities do you need help with? Who helps you?

-Which of these changes make your life more difficult? Is there enough help for this?

-Has your social life changed since your accident?

-Is there any additional clinical care or help that you would like to have and that you have not received?

-Has the brain trauma affected your quality of life? In what way and to what extent?

-Do you often feel sad or depressed? Or anxious?

-Are you satisfied with your current situation? Why/why not?

-What would you need at this moment to improve your quality of life?

Chapter 8

Conclusion

In this final chapter, a brief summary of the research performed in the framework of this PhD is provided in Section 8.1, followed by a description of the contributions of this dissertation in section 8.2 and its general conclusions in section 8.3. Finally, the future research perspectives are discussed in section 8.4.

8.1 Summary

In this dissertation, chapter 1 started by providing the necessary background information to understand the main research questions of this thesis.
First, in section 1.1, we showed an overview of the anatomy of the human head. Then, the TBI condition was thoroughly described in section 1.2. Section 1.3 explained the most common changes observed in the ageing brain and their consequences. Afterwards, the main particularities of TBI in the older patients were discussed in section 1.4. The final section of this chapter, section 1.5, presented the research gaps that lie at the origin of this dissertation. There we described the current need to investigate the lifelong impact of TBI on older patients' wellbeing and, more specifically, the need to investigate how different types of injury mechanisms, clinical presentations and clinical management strategies influence older patients' outcomes.
In this PhD, a main objective was to, first of all, assess injury patterns, injury severity, the nature of brain damage, its sequelae in terms of level of dependency, cognitive and motor disturbances, and their impact on quality of life after TBI. Secondly, it aimed at creating specific prediction tools for mortality and unfavorable functional outcome after TBI in the older population, in order to help decision making and counseling of families. These general research objectives, together with their underlying specific objectives, were described in Chapter 2 and they will be further recapitulated in section 8.2 in this chapter, where they will be presented together with the main contributions of this dissertation.

In chapter 3, section 3.1 presented the results obtained from a systematic review and meta-analysis on risk factors for and incidence of post-TBI functional decline and dependency, nursing home admission, depression and poor Quality of Life (QoL) in the older population. Then, in section 3.2, the results from a systematic review and meta-analysis on outcomes after neurosurgical treatment in older patients with TBI were described. Both systematic reviews and meta-analyses showed that TBI in older adults has a major impact on patients' lives, often leading to significant functional decline, dependency, nursing home admission and poor QoL, even in mild TBI cases. After neurosurgery, outcomes on older patients are also less favorable than in younger patients, leading to high mortality rates. However, these results indicated that neurosurgery should not be denied in all older patients, since it could improve the functional outcomes and reduce mortality in selected patients.

In chapter 4, the results obtained from a clinical retrospective database, based on the clinical records of patients with TBI aged ≥65 years, admitted to UZ Leuven between 1999 to 2019, were described. First, section 4.1 provided an overview on patients' clinical history, injury severity, clinical presentation, clinical management and outcome and how this evolved over a 20 year period. Second, the results obtained from an analysis of injuries and outcomes in a sub-group of patients who were under antithrombotic treatment prior to TBI, were shown in section 4.2. Finally, section 4.3 reported on the investigation of the effect of early versus late evacuation of acute subdural hematomas (ASDH) on outcome. In this chapter we showed that TBI is a very heterogeneous and complex condition, which leads to serious consequences for older patients, even in mild TBI. We also reported the risks of vitamin K antagonist (VKA) intake prior to TBI for the development of acute subdural hematomas (ASDH) and worse outcome. Furthermore, we described that early neurosurgical treatment in the older ASDH cohort resulted in higher 30-day mortality rates than delayed surgery, while also patients treated conservatively had worse outcomes than patients who underwent delayed surgery.
Over the 20 year study period, we reported an increase of age and comorbidities, and a marked reduction in neurosurgical interventions and ICU admissions. Together with these changes, there was a trend to less severe injuries, but higher proportion of treatment withdrawals, while at the same time mortality rates decreased. This may indicate a recent change towards better patient-tailored decision making in clinical practice.

In chapter 5, section 5.1 showed the results obtained from a telephone and written cognitive, sleep quality and Quality of Life assessment performed 1 to 13 years post TBI. Then, Section 5.2 presented the results obtained from a prospective in-depth outcome study that assessed TBI sequelae in terms of level of dependency, cognitive and motor disturbances, quality of life and brain MRI changes in older patients 6 months after TBI. These studies showed that mild TBI in older patients often leads to poorer sleep quality, worse cognitive performance, poorer motor function, higher fall risk and reduced QoL 6 months and 1 to 13 years post-TBI.
Next, in chapter 6, the development of a prognostic tool for 30 day mortality and unfavorable functional outcome at 6 and 12 months following TBI in the older population, based on the international prospective CENTER-TBI data repository, was described. Up to date, no specific prognostic tool for older patients' mortality and functional outcome is available in clinical practice, while it is also known that older age reduces the accuracy of generic prognostic tools. Therefore, we developed specific prediction models for patients aged $\geq$ 65 years old using ML algorithms. The results reported good performance of the models, as mortality within 30 days post-TBI was predicted with an AUC of 0.88-0.89, unfavorable outcomes at 6 months with an AUC of 0.85-0.88 and unfavorable functional outcomes at 12 months with an AUC of 0.85-0.86. Cisternal compression on early CT, total Injury Severity Score (ISS) and neuroworsening were the three most important parameters to predict mortality within 30 days. Furthermore, awakeness at admission, preinjury systemic disease, cisternal compression and neuroworsening were the most important predictive factors for unfavorable functional outcomes 6 months post-TBI, while the total ISS and the presence of cisternal compression and mass lesion on early CT were the most important predictors for 12-month outcomes.
Finally, chapter 7 reported the results obtained from a qualitative assessment of quality of life and real life impact after mild TBI through a focus group interview in 6 patients. With this study we showed that mild TBI in older patients can lead to changes in self-perception, daily life activities and social life 1 to 5 years after the injury, which may potentially contribute to a deterioration of independence and QoL. Protective factors were the acceptance of the situation, optimism, and a good support network.

8.2 Main contributions

In this section, we revisit the specific research objectives that were stated in chapter 2, in order to summarize the contributions of the present research for the TBI research field.

Contribution 1: Characterization of the mechanisms, injuries, clinical presentation, co-morbidities, clinical management and outcomes of TBI in older patients

Despite the fact that the incidence of TBI in the older population is increasing very fast in the last decades (3,4,85), older patients have been relatively neglected in the TBI research field until the recent years (3,4,9). Therefore, knowledge about these patients' injury mechanisms, brain damage, clinical presentation, co-morbidities, clinical management and outcomes was rather scarce.

In order to contribute to this research gap, we first assessed co-morbidities, accident mechanisms, injury patterns, clinical management and outcomes in a retrospective cohort of 1480 patients with TBI aged ≥65 years admitted to a single tertiary hospital. Then, we assessed these variables in a sub-group of 1443 patients with TBI aged ≥65 years who were under different types of antithrombotic treatment and without pre-injury antithrombotic treatment. Finally, we assessed outcomes in a subgroup of 149 patients who underwent acute subdural hematoma evacuation after TBI.

This was, to the best of the authors' knowledge, the first time that such a big clinical database, based on clinical data from a national reference center and specific for older patients with TBI, was published. This led to the representation of a very detailed snapshot of TBI in older patients, indicating that with the high proportion of older patients nowadays presenting with TBI, patterns have been changing over time and patients are now frailer and at the same time present with less severe injuries, likely due to changing patterns in accident causes. However, although most of the older patients present with so-called, these patients' outcomes are not that mild. We have reported mortality, nursing home admission, cognitive and motor decline and quality of life deterioration in these patients. Therefore, we need to be especially careful in clinical practice with the ''mild TBI'' classification in older patients. We believe that this classification could have a negative impact on the patients' treatment intensity, since it has been demonstrated that outcomes are negatively impacted by the lack of intensive rehabilitation strategies (282). In that way, the high mortality and morbidity among older patients with TBI could be a self-fulfilling prophecy (107).

Furthermore, the subgroup analyses yielded useful information for clinical practice. First, we showed the poorer outcome associated with VKA use prior to TBI, which might be mitigated by a switch to DOACs in clinical practice, as they have a safer profile that has been previously reported in literature (246). Moreover, we presented data supporting the relative safety profile of aspirin in TBI situations. In this way, we highlighted the importance of selecting the right antithrombotic treatment in older patients, in order to minimize risks. Second, we provided useful preliminary results on outcomes of early vs. late surgery for ASDH, in comparison with outcomes after conservative treatment, showing that even though conservative treatment is the most often selected treatment strategy for older patients, those patients had worse outcomes than patients who underwent late surgery. The best timing of surgery for ASDH in older patients is still debated. In a recent comparative effectiveness analysis on ASDH treatment in the CENTER-TBI database, it was found that more aggressive centers did not produce better outcomes than more conservative centers treating similar patients. Our results seem to confirm that early surgery for ASDH is not always the best in the older population.

We were also able to perform a detailed analysis of temporal changing patterns in injury characteristics, clinical care and outcomes on patients with TBI aged ≥65 years old from 1999 to 2019. We reported that, even though nowadays patients with TBI are older at the time of injury, have higher number of co-morbidities and receive less aggressive treatments and more treatment withdrawals, mortality rates have been decreasing since 2015. This study was necessary and very useful to self-reflect on the influences of policies on injury patterns and the influence of clinical management strategies on clinical outcomes. We showed, first, that the number of traffic accidents in the older population has significantly been reduced in the last years, probably due to the effect of traffic safety measures and campaigns. Therefore, these results could be a starting point for new fall accidents' prevention campaigns and the improvement of bicycle safety, which we believe are required to reduce the incidence of TBI in the older population. Then, we reported a substantial decrease in 30-day mortality for these patients in the last years. This might indicate that the quality of patient-tailored decisions has been improved and we have to continue working in this direction.

Contribution 2: Characterization of functional outcomes and impact on Quality of Life of TBI in older patients

Up to date, evidence reporting on TBI outcomes on older patients was relatively scarce (3,4). Therefore, the impact of TBI on these patients' functional outcomes and QoL was rather unclear.
We believe that understanding post-traumatic changes in the patients' functioning and wellbeing is necessary to aim at outcome improvement. Thus, we first performed two systematic reviews and meta-analyses: one describing post-TBI incidence of functional decline, dependency, nursing home admission, reduced quality of life and depression in older adults; and another one studying functional outcomes and mortality rates in older TBI patients who underwent neurosurgery.
Second, we performed two clinical studies to investigate outcomes in patients with TBI aged ≥65 years: one investigated cognitive functions, sleep quality and QoL 1-20 years post-TBI in patients ≥65 years old admitted to a single tertiary hospital and in a group of healthy volunteers with similar demographic characteristics. The other one assessed TBI sequelae in terms of brain MRI changes, level of dependency and sleep quality deterioration, cognitive and motor disturbances, and quality of life in older patients 6 months after TBI**.**

We initially hypothesized that TBI in older patients often results in significant functional decline and poor QoL, which was confirmed by the results of the systematic reviews. We described the important role of age and injury severity as predictive factors for unfavorable outcome. However, we showed how this was not the case for QoL, where only subtle differences were observed between patients with mild and severe TBI and, in some cases, the reported QoL scores were lower for patients with mild TBI. Furthermore, we showed specific data on cognitive impairment, motor alterations, sleep disturbances, dependency, nursing home admissions, QoL reduction and mortality rates in these patients, illustrating the major burden of TBI in older adults, even in mild TBI. This is primarily true for the patients and their families, but second, also for society, which is reflected in needs for outpatient supplies and residential care facilities and associated costs.
The results may be instructive to initiatives that aim at improving care in this specific population. E.g. more attention for posttraumatic sleep problems and more investment in occupational therapy to

accommodate ADL impairments, may already have a huge impact on the level of independence and subsequently, on quality of life. Also, more psychologic or psychiatric support may be at stake.

Contribution 3: Investigation of prognostic factors and creation of prognostic models for mortality within 30 days and outcomes 12 months post-TBI

In this dissertation, we have highlighted the importance of prognostication on clinical decision making and the improvement of these patients' clinical care. As previously mentioned, the main prognostic models for TBI, Corticosteroid Randomization After Significant Head Injury (CRASH) (357) and International Mission for Prognosis and Clinical Trial design in TBI (IMPACT) (356), lose reliability with age (358). Therefore, we aimed at investigating whether specific prediction models for mortality and unfavorable functional outcome in older adults post TBI were at all possible and we used ML algorithms to perform specific outcome modelling.

In order to achieve that objective we used data of 932 patients with TBI, with a median age of 74 years old, collected in the international and multi-center CENTER TBI database, and we created six prognostic models: two for the prediction of mortality within 30 days post-TBI, two for the prediction of unfavorable functional outcomes at 6 months and two for the prediction of unfavorable functional outcomes at 12 months post-TBI. In this study we provided with additional evidence for the fact that TBI in older patients, even the ''mild TBI'' classification, is a heterogeneous but very serious burden for patients and society, and should not be underestimated. Then, we reported that cisternal compression on early CT, total Injury Severity Score (ISS) and neuroworsening were the three most important parameters to predict mortality within 30 days. Furthermore, awakeness at admission, preinjury systemic disease, cisternal compression and neuroworsening were the most important predictive factors for unfavorable functional outcomes 6 months post-TBI, while the total ISS and the presence of cisternal compression and mass lesion on early CT were the most important predictors for 12-month outcomes. The variables predictive of outcome in older patients let themselves summarize as (delayed) mass effect and associated (delayed) neuroworsening, overall injury severity including extracranial injury and preinjury health condition. In younger adults, GCS and diffuse injury (higher Marshall score) have a higher weight in prediction (421), which is different in older patients because of their tendency to be admitted with high GCS and are more prone to contusions and intracranial hematomas with delayed mass effect.

For mortality within 30 days post-TBI prediction, including input variables registered at admission, outcome was predicted with a maximum accuracy of 90.0% and AUC of 0.88. When including input variables registered before day 14 after TBI, the performance of the model increased and outcome was predicted with a maximum accuracy of 91.0% and AUC of 0.89.

For unfavorable functional outcomes at 6 months post-TBI, outcome was predicted by admission variables with a maximum accuracy of 79.0% and AUC of 0.85. When including input variables available at day 14, the maximum accuracy was 80.0% and AUC increased to 0.88.

For unfavorable functional outcomes at 12 months post-TBI, when including only input variables at admission, outcome was predicted with a maximum accuracy of 75.0% and AUC of 0.85. When including input variables registered before day 14 post-TBI, outcome was predicted with a maximum accuracy of 77.0% and AUC of 0.86. Hence, we demonstrated that it is possible to design specific

outcome prediction models for TBI in older patients. Before the models can be used in clinical decision making, they will have to be validated in external cohorts.

Contribution 4: Qualitative description of quality of life and real life impact of TBI in elderly by means of a focus group study

QoL is multi-factorial in nature. Therefore, we aimed at better understanding the underlying factors below the reduced QoL levels that we observed in our patients. In order to do that, we qualitatively explored changes in QoL in these patients. Our results showed that the lack of support and understanding, changes in self-perception and social life, tiredness, balance disturbances, headache, cognitive deterioration, changes in physical health, senses' disturbances, changes in sexual life, sleep problems, speech disturbances and dependence for daily life activities were the factors that deteriorated QoL the most in our cohort. These results show the importance of incorporating psychological and psychiatric support in the care for older TBI patients.

The dissertations' contributions confirm the hypotheses that we formulated in Chapter 2.
TBI in older adults differs from TBI in younger people in terms of injury mechanisms, injury types, co-morbidities and outcomes (278,422). Moreover, TBI, including mild TBI, is a potential life changing event in older patients, including an underestimated risk of loss of independence and reduction of quality of life. It carries an increased risk for cognitive decline and dementias, and a substantial risk of functional loss and mortality. Finally, although different than in the general adult population, predictive factors for functional outcome and mortality after TBI in older adults exist and can contribute to a specific prognostic tool to aid decision making and family counseling.

8.3 General conclusions

TBI is known to be a life changing event in the overall population (59,103), whose specific consequences in the older population were, up to date, not very well known. The results presented in this thesis contribute to the better understanding of the impact that TBI has on the older population functioning and wellbeing. We showed that TBI is a heterogeneous and complex condition that can have a large impact on older patients' lives, as it very often leads to poorer sleep quality, cognitive and motor decline, higher fall risk, dependency, nursing home admission, poor QoL, and even mortality in patients with all injury severities, including mild TBI. We believe that the results can be used to create specific clinical guidelines for older TBI patients in the future.
From the qualitative assessment of the patients' QoL, we observed that TBI can also lead to changes in self-perception, daily life activities and social life 1 to 5 years after the injury. These results support the belief that early rehabilitation strategies, together with a short and long-term follow-up, are necessary in clinical practice to reduce the functional deterioration and improve these patients' QoL. Furthermore, as we observed that the acceptance of the situation, optimism, and a good support network seem to be protective factors for these patients' wellbeing after TBI, we believe that psychological and psychiatric interventions, and group support programs for these patients could provide an added value to these patients' recovery process.
From the results collected from the last two decades, we could see that there has been a change on these patients' injury mechanisms and clinical management, which has had an important influence on

the observed outcomes. Even though there was an increase of age and comorbidities, injuries tended to be less severe and there was a change towards less aggressive treatments, with a marked reduction in neurosurgical interventions and ICU admissions. The higher proportion of treatment withdrawals, associated to decreased mortality rates is an important sign of the improvement in patient-tailored decision making we have achieved in the last years. We believe that these changes are very positive and the paradigm should change, even more, in this direction, by the necessary improvement of quality prospective data collection and the prognostication modelling to support the best possible individual decision making.
The current dissertation already initiated the creation of specific prediction models for mortality at 30 days and functional outcomes at 12 months, which showed good performance. The validation of these models in the future could be a big step towards individualized design of treatment and rehabilitation programs to improve clinical outcomes in older patients with TBI.
We expect that all the presented results include the potential to contribute to the improvement of the clinical care of older patients with TBI, with the overall goal of maintaining independence for activities of daily living and a good QoL in these patients. In that way, we could reduce deterioration to dependency, which is associated to poor QoL and huge costs for society.

8.4 Future work

The work presented in this dissertation brings new information to the TBI research field, which helps to better understand injury mechanisms, clinical presentation, clinical management and changes in cognitive and motor functions, and QoL in older patients. This will be helpful for the establishment of specific protocols and clinical guidelines for these patients. Furthermore, we developed specific prediction models for mortality within 30 days and unfavorable functional outcomes at 12 months post-TBI that could potentially help to the improvement of patient-tailored decision making in the future. However, additional work needs to be performed in the future to prevent TBI in the older population, improve clinical care and validate the prediction models to implement them in clinical practice.

8.4.1 Injury prevention strategies

The results presented in this dissertation show that, while the incidence of traffic accidents in the older population has been decreasing in the last decades, there is an increasing incidence of fall and bicycle accidents in older adults (43,423). These accident types are increasingly associated with TBI (4,188,189). The reduction of traffic accident cases might be due to the implemented traffic safety policies and campaigns. Therefore, we believe that similar prevention strategies may be helpful to reduce the incidence of fall and bicycle accidents at the moment.
Previous studies have shown that the risk for falling can be reduced by 20%-40% after the implementation of different intervention strategies, such as exercise programs, home safety interventions, and interventions targeting medications, among others (424). Thus, although the current dissertation was not focused on prevention, our results should be taken as an alert sign and could be a starting point for the implementation of new measures.
As the older population is rapidly growing worldwide, future research studies are necessary to investigate the effectiveness of new prevention strategies for fall and bicycle accidents, in order to create effective policies that will help to reduce the incidence of TBI in older adults (425,426).

8.4.2 Injury severity classification in older patients

This dissertation has clearly demonstrated that, even though 80% of the TBI cases in the older population are classified as ''mild'' TBI (81,152), according to the GCS (44), these patients are particularly at risk for injuries with delayed mass effect and secondary deterioration (88–90) and do not have mild outcomes.
Patients diagnosed with a mild TBI very frequently experience sleep problems, cognitive and motor deterioration, reduced QoL, dependency, and in some cases, even mortality. Therefore, we believe that GCS on its own might not be an adequate classification system for TBI severity in older patients. The term "mild TBI" could be a misnomer for older patients (88–90) and new research studies should focus on investigating better severity classification systems for these patients, as a correct severity classification is necessary to provide the adequate treatment to the patients. In a previous study, Gravesteijn et al. already indicated that additional variables, such as the injury mechanism and major extracranial injuries, could improve TBI classification (377). Additionally, we believe that frailty scores could be a helpful variable for severity classification in older adults and future research studies considering these issues are necessary.

8.4.3 The importance of fragility levels on outcomes

Despite the fact that it is widely known that older patients have worse consequences after TBI than younger patients, (85,114–117), ageing is a very heterogeneous process. Previous studies have shown that older age alone is not sufficient to predict and understand outcomes in older patients with TBI, being frailty a better predictor than age (330).
Although frailty assessment was considered in one of our clinical studies from the beginning, it was implemented in a later stage in the other one. Therefore, frailty scores were not available for all the included patients in this thesis. Furthermore, pre-injury frailty levels were not available in the patients' clinical records and could not be included in our analysis. Thus, it is very difficult to certainly know whether patients were frailer after the accident or had the accident because they were already frailer. We think that this dissertation is a very interesting pilot work that could be used as a starting point to develop more complete studies in the future including pre-/post-TBI frailty scores, and also injured controls without TBI and similar degrees of frailty, to better understand the role of frailty in TBI outcomes.

8.4.4 Clinical data for the study of TBI in older patients

The work presented in this dissertation was based on patients' clinical data, collected through the patients' clinical records or through the assessments performed by the researchers. In this process, some difficulties were faced and we believe that important considerations could be learned from this thesis to minimize bias in future research studies.
First of all, when collecting data from patients' clinical records, we struggled with high amounts of missing data, especially for outcome measures. One solution for this problem could be the creation of standardized in-hospital registries, and the standardized registration of data in a daily basis in clinical practice, to facilitate data availability to researchers in the future.
Second, in our clinical studies, the main limitation was the small sample size of the studied groups, which depended on the number of admitted patients who fulfilled our in-/exclusion criteria. Although

this was out of the patients control, and aggravated by the COVID-19 pandemic, we believe that future multicenter prospective patient trials, including larger sample sizes, will be necessary to draw more consistent conclusions.

8.4.5 Outcome prognostication

The current dissertation already initiated the creation of specific prognostic models for mortality at 30 days and unfavorable functional outcomes at 6 and 12 months, which showed good performance. Our findings on the characteristics of this population can be valuable information to raise awareness and that can help patient and family counseling. However, although an internal validation of the model was done, the model has not yet been externally validated. Further external validation is necessary to validate the performance of our prognostic models, which could be a big step towards the individualized design of treatment and rehabilitation programs to improve clinical outcomes in older TBI patients.

8.4.6 Creation of specific clinical guidelines for older patients with TBI

The results obtained in this dissertation are very useful for the TBI research field, as we thoroughly described the functional and QoL changes that older patients suffer after TBI. Furthermore, we showed the temporal changes for injury patterns, clinical management and outcomes in these patients in the last two decades. We, therefore, hereby reduced the previously existing research gap to better understand the TBI phenomenon in older patients. However, there is still a lack of specific clinical guidelines for the treatment of older patients with TBI (10,11).

Previous studies have shown that presumed poor outcome in older adults leads to reduced treatment intensity because of fatalistic attitudes, which subsequently leads to worse outcomes (427). Furthermore, we have shown that the effect of neurosurgical interventions in these patients is still unclear. Therefore, clinical decisions are, in many cases, still difficult to make.

We believe that this paradigm needs to change. Future prospective patient trials, with large enough sample sizes, should focus on investigating the effects of neurosurgical treatments and early intensive rehabilitation strategies on older TBI patients' outcomes. The creation of specific clinical guidelines for older patients constitutes a real need. From the current research it is already clear that more attention should go to early sleep interventions, cognitive and motor rehabilitation, and psychologic or psychiatric support. However, one size will not fit all, and strategies that underpin patient-tailored approaches will be most beneficial.

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Personal contribution

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Conflict of interest

The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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Fundamental statistics KU Leuven (October 2018)

Science Communication Summer School Ghent University, University of Antwerp, University of Hasselt, University of Leuven and Vrije Universiteit Brussel (July 2018)

CONFERENCE PRESENTATIONS

Gavrila Laic, R.A., Vander Sloten, J., Depreitere, B. (2022). Traumatic Brain Injury in the elderly population: changes in injury patterns, management and outcome over a 2 decade period. Presented at EANS 2022, Belgrade (Serbia), 16-20 Oct 2022.

Gavrila Laic, R.A., Vander Sloten, J., Depreitere, B. (2022). Traumatic Brain Injury in elderly patients with pre-injury antithrombotic treatment: a retrospective study. Presented at the 15th International Neurotrauma Symposium, Berlin, 17 Jul 2022-20 Jul 2022.

Gavrila Laic, R.A., Bruyninckx, D., Lebegge, P., Vander Sloten, J., Depreitere, B. (2022). Functional outcomes and wellbeing after traumatic brain injury in elderly patients: a 6-month follow-up prospective study. Presented at the 15th International Neurotrauma Symposium, Berlin, 17 Jul 2022-20 Jul 2022.

Gavrila Laic, R.A., Vander Sloten, J., Depreitere, B. (2022). Injury patterns, clinical management and outcomes in elderly patients with Traumatic Brain Injury: changes over a 20 year period. Presented at the Annual Meeting of the Belgian Society of Neurosurgery, Leuven.

Gavrila Laic, R.A., Vander Sloten, J., Depreitere, B. (2021). Long-term outcomes after brain surgery in elderly patients with traumatic brain injury. Presented at the EANS 2021, Online.

Gavrila Laic, R.A., Bruyninckx, D., Vander Sloten, J., Depreitere, B. (2021). Are long-term consequences of Mild Traumatic Brain Injury in the elderly also mild? Presented at the International Neurotrauma Symposium, Online, 07 Feb 2021-11 Feb 2021.

Gavrila Laic, R.A., Bruyninckx, D., Lebegge, P., Vander Sloten, J., Depreitere, B. (2020). Mild Traumatic Brain Injury in the elderly: can it really be defined as "Mild"? Presented at the Frontiers in Traumatic Brain Injury 2020, Online.

Gavrila Laic, R.A., Kapeliotis, M., Musigazi, G., Famaey, N., Vander Sloten, J., Depreitere, B. (2019). Quantifying biovariability in position and diameter of bridging veins: a CT angiogram study. Presented at the Annual Meeting of the Belgian Society of Neurosurgery, Leuven.

Kapeliotis, M., Peñas, A.J., **Gavrila Laic, R.A**., Vander Sloten, J., Vanden Berghe, P., Famaey, N. (2018). End-to-end microscopic analysis of bridging veins: A microstructural investigation of the collagen structure as it unfolds throughout the complete length of the vessel. (Abstract No. 4178). Presented at the 8th World Congress of Biomechanics, Dublin, Ireland, 08 Jul 2018-12 Jul 2018

PUBLICATIONS

Laic, R.A G., Vander Sloten, J., Depreitere, B. with Laic, R.A G. (corresp. author) (2022). Traumatic brain injury in the elderly population: a 20-year experience in a tertiary neurosurgery center in Belgium. *ACTA NEUROCHIRURGICA*, *164* (5), 1407-1419. doi: 10.1007/s00701-022-05159-0

Gavrila Laic, R.A., Bogaert, L., Vander Sloten, J., Depreitere, B. with Gavrila Laic, R.A. (corresp. author) (2021). Functional outcome, dependency and well-being after traumatic brain injury in the elderly population: A systematic review and meta-analysis. *Brain and Spine*, *1*, Art.No. 100849. doi: 10.1016/j.bas.2021.100849 Open Access

Kapeliotis, M., **Gavrila Laic, R.A**., Penas, A.J., Vander Sloten, J., Vanden Berghe, P., Famaey, N., Depreitere, B. (2020). Collagen fibre orientation in human bridging veins. *BIOMECHANICS AND MODELING IN MECHANOBIOLOGY*, *19* (6), 2455-2489. doi: 10.1007/s10237-020-01349-w Open Access

Hocking DR, Farhat H, **Gavrila R**, Caeyenberghs K, Shields N. Do active video games improve motor function in people with developmental disabilities? A meta-analysis of randomized-controlled trials. Arch Phys Med Rehabil. 2019 Apr;100(4):769-781

LANGUAGES

Fluent in Spanish, English, Dutch, French, Italian and Portuguese