Diplomarbeit

Risk Factors contributing to the Progression of Traumatic Brain Injury

eingereicht von

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zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Orthopädie und Traumatologie Graz

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Graz, am 10.09.2021

Eidesstattliche Erklärung

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Graz, am 10.09.2021 *Jasmin Helena El-Shabrawi, eh.*

Preface

During medical school, I started working voluntarily in the field of prehospital medical care. My intention was to acquire basic skills in the management of medical emergencies and to apply them when needed in the professional setting. In the course of my training I started taking great interest in emergency medicine, especially in trauma and trauma management. Eventually, in third year of medical school, we had lectures about orthopaedics and traumatology, which attracted my attention. I asked if there was any possibility to write my thesis at the department of orthopaedics and trauma. Fortunately, I was offered the opportunity to collaborate in a study about traumatic brain injury, and to use the results for my thesis in return. In the process of this study I had the chance to learn a lot not only about traumatology, but also about scientific working.

As my interest and commitment in emergency medicine has not ceased but rather increased ever since I can consider myself lucky to have written my thesis at the department of orthopaedics and trauma. The knowledge I gathered has great value for me, and will influence my future decisions as medical doctor for the better.

Acknowledgements

First and foremost, my sincere gratitude goes out to Priv.-Doz. Dr. Lukas Leitner, my supervisor. I want to thank him for his relentless support in every aspect, and for his incomparable patience regarding all of my concerns and requests. As a matter of fact, he surely became one of my role models regarding professional commitment and expertise.

I also want to thank my second supervisor Priv.-Doz. Dr. Paul Puchwein, who offered me the opportunity to do scientific research, and to write my thesis at the department of Orthopaedics and Trauma.

Furthermore, I would also like to express special thanks to Prof. Dr. Andreas Leithner, Head of the Department of Orthopaedics and Trauma, who provided valuable insights in the fields of good scientific practice.

Last but certainly not least, I want to thank my family for their unwavering faith in me, and for always reminding me that no one was born a master.

List of Contents

Glossary and Abbreviations

ADP	adenosine diphosphate
ARCM	American Congress of Rehabilitation Medicine
CBF	cerebral blood flow
CCHR	Canadian CT Head Rule
COX-I	cyclooxygenase I
COX-II	cyclooxygenase II
CPP	cranial perfusion pressure
CVR	cerebrovascular resistance
DAI	diffuse axonal injury
DOAC	directly acting oral anticoagulant
DVT	deep vein thrombosis
EDH	epidural hematoma
GCS	Glasgow Coma Scale
GOSE	Glasgow Coma Outcome Scale
GSC	German Society of Neurosurgery
ICB	intracerebral bleeding
ICH	intracranial hemorrhage
ICI	intracranial injury
ICP	intracranial pressure
LOC	loss of consciousness
MAP	mean arterial pressure
NOC	New Orleans Criteria
PBI	primary brain injury
SAH	subarachnoid hemorrhage
SBI	secondary brain injury
SDH	subdural hematoma
TBI	traumatic brain injury
VKA	vitamin K antagonist
WHO	World Health Organization

List of Figures

List of Tables

List of Equations

Zusammenfassung

Einleitung: Schädel-Hirn-Trauma (SHT) zählen zu den häufigsten Ursachen für das Aufsuchen der chirurgischen Notaufnahme. Ein Großteil der PatientInnen mit diagnostiziertem SHT erhält zumindest ein Schädel CT und wird zur weiteren Observanz stationär aufgenommen. Der Grund dafür ist, eine neurologische Verschlechterung sofort zu erkennen und therapeutische Maßnahmen einzuleiten.

Das Ziel dieser Diplomarbeit war, Risikofaktoren zu identifizieren, die maßgeblich an einer Progression von SHT beteiligt sind.

Material und Methoden: Es wurde eine Studie durchgeführt, die in Summe 2036 PatientInnen einschloss, welche im Zeitraum von 2008-2018 die chirurgische Notaufnahme der Abteilung für Orthopädie und Trauma an der Medizinischen Universität Graz aufsuchten. Alle PatientInnen mussten zumindest ein Schädel CT erhalten haben und/ oder stationär aufgenommen worden sein, um in dieser Studie berücksichtigt zu werden. Folgende Parameter wurden im Anschluss erhoben; Alter, Geschlecht, Einnahme blutverdünnender Medikamente, Vorerkrankungen (koronare Herzkrankheit, Niereninsuffizienz, Diabetes, Vorhofflimmern und Zustand nach ischämischem Insult), Alkoholabusus (akut und chronisch), Fraktur des Neurokraniums und intrakranielle Blutungen im Zuge des SHT.

Progression von SHT wurde definiert als entweder intrakranielle Blutung im initial durchgeführten Schädel CT und/ oder die Progression von intrakraniellen Blutungen in Verlaufs-CTs und/ oder das Versterben des Patienten/ der Patientin 30 Tage nach Aufnahme ins Krankenhaus.

Ergebnisse: Von 2036 PatientInnen waren 1170 Männlich (57.4%) und 863 Weiblich (42.4%). Das mittlere Alter betrug 57.6 Jahre (SD 22.6 Jahre, min. 16.3 Jahre, max. 103.7 Jahre). 96.6% der PatientInnen (n=1968) erhielten initial ein Schädel CT und in 48.5% der Fälle (n=988) wurde eine radiologische Verlaufskontrolle durchgeführt. Von allen Variablen, die erfasst wurden, stellten sich folgende als Risikofaktoren heraus; in Bezug auf Blutung im initialen Schädel-CT: Alter über 65 Jahre ($p<0.001$), blutverdünnende Medikamente ($p<0.001$), Fraktur des Neurokraniums ($p<0.001$), Alkoholmissbrauch ($p=0.002$) und Niereninsuffizienz ($p<0.001$); in Bezug auf Blutungsprogression in Verlaufs-CTs: Alter über 65 Jahre ($p=0.025$) sowie Fraktur des Neurokraniums ($p<0.001$); in Bezug auf 30-Tage-Mortalität: Alter über 65 Jahre ($p<0.001$), Fraktur des Neurokraniums ($p<0.001$), blutverdünnende Medikamente ($p<0.001$) und chronische Niereninsuffizienz ($p<0.001$).

Diskussion: PatientInnen, die mit obengenannten Risikofaktoren aufgrund eines SHT die chirurgische Notaufnahme aufsuchen, sollten sorgfältig observiert werden, da die Wahrscheinlichkeit einer SHT Progression wahrscheinlicher ist als bei anderen PatientInnen. Vor allem ältere PatientInnen sind gefährdet, da bei diesen meistens mehr als nur ein Risikofaktor zu finden ist (zum Beispiel, Alter über 65 Jahre, Einnahme blutverdünnender Medikamente, chronische Niereninsuffizienz). Daher sollte nicht nur auf eine engmaschige Observanz zur Prävention einer SHT Progression geachtet, sondern bereits schon auf die Prävention von Unfallgeschehen eingegangen werden.

Abstract

Introduction: Traumatic brain injuries (TBI) are among one of the most common reasons for visits to the emergency department. The majority of patients with diagnosed TBI receive at least one cranial CT scan (CCT) and are hospitalized for observation. The ulterior motive of this strategy is to detect neurological deterioration, and initiate therapy if necessary. The aim of this thesis was to identify risk factors, which increased the likelihood of TBI progression.

Material and Methods: We conducted a retrospective study, which comprised 2036 patients that were admitted to the Level I Trauma Center of the Department of Orthopaedics and Trauma at the Medical University of Graz from 2008-2018. Patients had to receive at least one CCT scan, and/ or be hospitalized to be included in this study. Following variables were assessed; age, sex, intake of antiplatelet/ anticoagulant therapy, concomitant diseases (coronary heart disease, kidney insufficiency, diabetes, atrial fibrillation, and previous ischemic strokes), alcohol abuse (acute and chronic), fracture of the neurocranium and intracranial hemorrhage in the course of TBI.

Progression of TBI was defined as either intracranial hemorrhage on initial CCT scan, progression of hemorrhage on follow-up CCT scans, and/ or death 30 days after admission.

Results: Out of 2036 patients, 1170 were male (57.4%) and 863 were female (42.4%). Mean age was 57.6 years (SD 22.6 years, min. 16.3 years, max. 103.7 years). 96.6% of patients (n=1968) received an initial CCT scan, and in 48.5% (n=988) radiologic follow-up was performed. Amongst all variables that were assessed following risk factors could be identified; concerning hemorrhage on initial CCT scans: age over 65 years ($p<0.001$), anticoagulant/ antiplatelet therapy ($p<0.001$), neurocranial fracture ($p<0.001$) alcohol abuse ($p=0.002$) and chronic kidney disease ($p<0.001$); concerning progression of hemorrhage on follow-up CCT scans: age over 65 years ($p=0.025$), neurocranial fracture ($p<0.001$); concerning 30-day mortality: age over 65 years ($p<0.001$), neurocranial fracture ($p<0.001$), antiplatelet/ anticoagulant therapy ($p<0.001$) and chronic kidney disease ($p<0.001$).

Conclusion: TBI patients presenting to the ED with stated risk factors should be observed vigorously as progression of TBI is more likely than in other patients. Especially elderly patients seem to be at risk to develop TBI progression after trauma because they may obtain more than just one risk factor (e.g. age over 65 years, antiplatelet/ anticoagulant therapy, chronic kidney disease). Hence, attention should not only be stressed on close observation to prevent TBI progression, but also on prevention of trauma itself.

1 Introduction

1.1 Pathophysiology of traumatic brain injury

Traumatic brain injury (TBI) is a result of acceleration/deceleration trauma or blunt mechanical forces directed to the head. These injuries may lead to focal brain damages such as concussion and hemorrhage, or to diffuse brain damages like axonal damage and brain swelling. [1, 2]

Common symptoms, which follow traumatic incidents on the head can include headache, nausea, dizziness, amnesia and loss of consciousness (LOC). [3]

There are two different pathophysiological factors, which influence the course of TBI. They are referred to as primary and secondary brain injury.

1.1.1 Primary brain injury

Injuries that directly result from the traumatic incident itself are described as primary brain injury (PBI). This includes direct damages of brain tissue, its coverings and blood vessels. Primary injuries often occur as focal contusions of the cerebral cortex or as vascular trauma causing intracranial hemorrhage. [2, 3]

As neuronal tissue has little capacity for recovery, neurons that were damaged in the course of primary brain injury will irreversibly lose their function. [4] As a result, the extent of injuries that are linked to the trauma itself can merely be affected by therapeutic interventions. Nonetheless judicious initial medical treatment is crucial to prevent any further pathological changes, referred to as secondary brain injury (SBI).

1.1.2 Secondary brain Injury

SBI occurs in the course of TBI, and is no direct consequence of the trauma itself. This means that primarily non-involved neural cells can be harmed in the course of TBI, causing severe neurological deficiencies. In contrast to PBI, SBI can be prevented, when pathologies are identified early enough.

SBI can be generated by intracranial causes such as increased intracranial pressure (ICP), as well as extracranial causes like hypotension and hypoxemia.

When it comes to intracranial causes of SBI, the ratio of volume of different brain compartments plays an important role. In the literature this is also described as Monro-Kellie doctrine or mass effect. [4, 5]

According to the doctrine of Monro-Kellie, under physiological circumstances, intracranial volume is comprised of three different compartments, namely brain parenchyma (83%),

cerebrospinal fluid (11%) and blood (6%). If there is an increase of volume in one of these compartments (due to e.g. hemorrhage or cerebral swelling), the volume of the other compartments decreases. This allows changes in volume size without any increase in ICP for a long time. ICP increases not until all three compartments have been replaced by one compartment only. [4, 5]

In regards to TBI, cerebral contusions are often followed by perifocal edemas leading to increased permeability of the surrounding blood vessels. The increased permeability of blood vessels generates diffuse cerebral swelling resulting in changes of volume ratio.

Whilst cerebrospinal fluid as well as blood are extruded from the brain, the volume of brain parenchyma, due to brain swelling, increases. If all three compartments are fully replaced by brain parenchyma only, ICP increases leading to brain compression, loss of brain stem reflexes and finally brain death. [1, 6, 7]

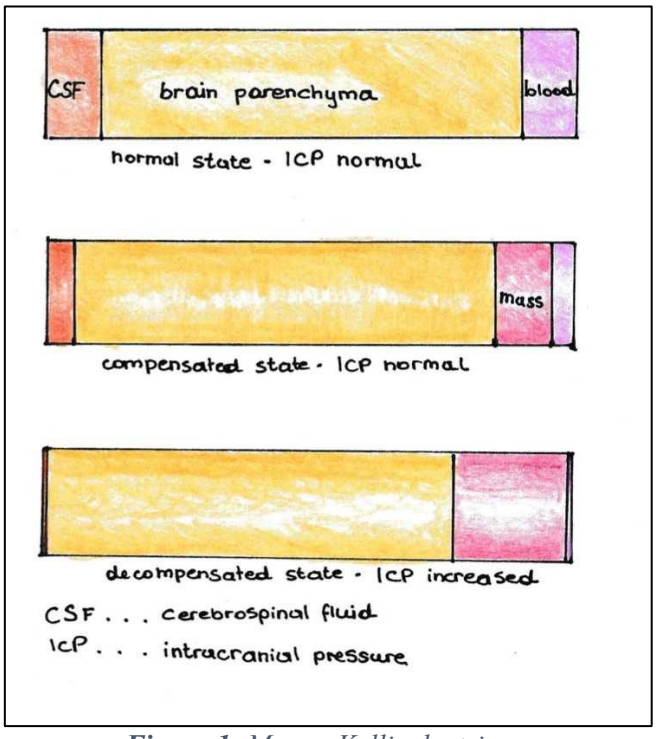

***Figure 1**: Monro-Kellie doctrine*

Extracranial causes, especially hypoxemia and hypotension, also have an impact on the development of SBI and progression of TBI. Impairment in oxygen supply of the brain induces complex biochemical, neurochemical and inflammatory mechanisms that result in tissue hypoxia and apoptosis. Hypotension, as systemic blood pressure might not be able to exceed increased intracranial blood pressure, aggravates the mismatch of oxygen supply and demand. This leads to an impaired cranial perfusion pressure, and to persistency of cranial blood flow and hence oxygen supply. [8]

$$CPP = MAP - ICP$$

***Equation 1: CPP** = cranial perfusion pressure, **MAP** = mean arterial pressure, **ICP** = intracranial pressure*

$$CBF = \frac{CPP}{CVR}$$

***Equation 2: CBF** = cerebral blood flow, **CVR** = cerebrovascular resistance*

Moreover, especially rotational acceleration and deceleration trauma can lead to shearing mechanisms, which are responsible for damage of white brain matter. This type of traumatic brain damage is referred to as diffuse axonal injury (DAI). Coma without increase of intracranial pressure can result from DAI and is associated with worsening outcome and higher mortality. [7]

SBI occurs within hours to days after the primary incident.

1.2 Clinical and Radiologic assessment

Especially mild TBI has a very low risk of progression and symptoms resolute in short time. Hence, the majority of patients does not require any radiological assessment or in-hospital observation.

However, in some cases deterioration of neurologic status and complications such as ICH are observed. These patients often obtain certain risk factors which increase the possibility of injury progression.

Studies suggest that evidence of skull fracture as well as posttraumatic seizures highly correlate with the occurrence of intracranial bleeding. Other clinical symptoms such as persistent vomiting, focal neurologic deficiencies and decreased Glasgow Coma Scale (GCS) are also linked to an adverse outcome. [9]

1.2.1 Clinical assessment

Clinical evaluation of symptoms is an important tool to assess severity grade of head trauma and to predict any possibility of progression. One of the most commonly used tools in clinical stratification and prediction of TBI is the GCS. It is comprised of three components: best motor response, best verbal response, and eye opening.

Studies suggest that, out of these three components, motor response seems to have the best predictive value. [10]

A persistent lower GCS correlates with the severity of intracranial injury (ICI) findings on cranial CT (CCT), and the requirement for neurosurgical intervention. If GCS scores declines from 15 to 14, ICI on CCT and need for surgical intervention doubles. On the contrary, a normalization of GCS score (from 13 to 15) within two hours is not linked to any ICI or adverse outcome. [11]

Other parameters such as pupillary reaction and pupil size are also important for prediction of TBI progression in general. However, pupil reactivity in mild TBI does not play a prognostic role, as pupillary abnormalities are often due to other etiologies than TBI. [12]

GCS score	eye opening	verbal response	motor response
6 points	-	-	obeys command
5 points	-	oriented to time, person and place	moves to localized pain
4 points	spontaneously	confused	flex to withdraw from pain
3 points	to speech	inappropriate words	abnormal flexion
2 points	to pain	incomprehensible sounds	abnormal extension
1 point	none	none	none

Table 1: *Glasgow Coma Scale: mild TBI: 13-15, moderate TBI: 12-9, severe TBI: <9*

1.2.2 Radiologic assessment

To detect any morphological brain damages, non-contrast CT head scans are commonly used for TBI. Decision rules such as the Canadian CT Head Rule (CCHR) or the New Orleans Criteria (NOC) help to identify in which cases performance of CT scans is required.

According to the CCHR there are two groups, high-risk and medium-risk group, where CT scans are indicated. [13, 14]

Patients in the high-risk group have a high possibility to require neurosurgical intervention due to ICI. These patients may either present with GCS < 15 over 2 hours and/or suspected open, depressed or basal skull fracture and/or vomiting for more than two times and/or age over 65 years. [13, 14]

The medium-risk group includes patients, who show any sort of ICI on CCT. Symptoms of these patients are retrograde amnesia over 30 minutes before impact and/ or dangerous mechanism of injury (such as pedestrian struck by motor vehicle or fall from > 1 meter). [14]

The New Orleans Criteria recommends CT scans if the patient is older than 65 years or if any of the following symptoms appear in mild TBI: headache, vomiting, seizures and persistent anterograde amnesia. Furthermore, CT scans are advised if there are signs of alcohol or drug intoxication or if there is any visible trauma above the clavicle.

Both of these criteria guarantee high sensitivity in detection of intracranial injuries. However, according to studies, the CCHR shows higher reliability when it comes to specificity. This means that unnecessary use of CT scans on patients can be avoided if the CCHR is taken into consideration. [14]

Although ICI is one of the most dreaded complications of TBI, findings of injury-related lesions on CCT do not always require follow-up CT scans or neurosurgical intervention.

Such lesions are: solitary contusion < 5 mm in diameter, localized subarachnoid blood < 1 mm, smear subdural hematoma < 4 mm, isolated pneumocephalus, and closed depressed skull fracture not through the inner table. [15]

These ICI are labelled as clinically inconsequential, and have no relevant impact on the course of TBI.

1.3 Classification of TBI

Traumatic brain injuries are classified into three degrees of severity: mild, moderate and severe traumatic brain injury. The classification of TBI depends on clinical as well as radiologic examination. Common scores, such as the GCS and the Glasgow Coma Outcome Scale Extended (GOSE) are used for better prediction and outcome of TBI. [16]

Mild head injuries have a GCS of 13-15, patients may also experience LOC. In these cases, LOC should not exceed a time period over 30 minutes.

Moderate TBI is defined as GCS of 9-12 and LOC with up to 24 hours.

Severe TBI is classified as GCS < 9 and LOC over 24 hours. [7]

1.3.1 Mild Traumatic Brain Injury

Mild traumatic brain injury, also referred to as concussion in sports, is the mildest form of TBI. Definitions of mild TBI have been proposed by several working groups, such as the World Health Organization (WHO) or the American Congress of Rehabilitation Medicine (ARCM) and are equally used for citation.

The ARCM defines mild TBI as, “traumatically induced physiological disruption of brain function” that presents with (at least) one of the following symptoms: LOC - not exceeding a time period of 30 minutes - any mental alteration, focal neurological signs (e.g. seizures) and posttraumatic amnesia. [17]

Posttraumatic amnesia can include events prior to trauma (retrograde amnesia) as well as events after trauma (anterograde amnesia), but should not last longer than 24 hours. Furthermore, mild TBI is often accompanied by nausea and vomiting.

GCS score of patients is between 13-15.

1.3.2 Moderate Traumatic Brain Injury

Moderate TBI is seen in patients with GCS scores from 9-12. CT scans often show intracranial damages in these patients (60%) and neurosurgery for decompression and/ or evacuation is performed in 15% of cases. [18]

Early symptoms include impaired consciousness or focal neurologic deficits such as hemiparesis, cranial nerve deficiencies and focal seizures. [7]

In the population of patients suffering from moderate TBI, neurological outcome varies from full recovery to severe neurological compromise.

Studies suggest that outcome and prediction of patients highly depend on individual factors, such as age, skull fracture, intracranial bleeding, coagulopathy and GCS score. Although

morbidity is not as high as in severe TBI patients, a lot of patients do not experience a favorable outcome. [18, 19]

1.3.3 Severe Traumatic Brain Injury

Severe TBI is defined as GCS < 9 and LOC of at least 24 hours.

Focal cranial damages as well as diffuse axonal injuries lead to severe neurological impairment. Additional complications including intracranial hemorrhage or hydrocephalus may aggravate the severity of cranial injury.

Symptoms of severe TBI such as cranial nerve deficiencies, hemiparesis and seizures are similar to the symptoms of moderate TBI. In contrast to moderate TBI, however, neurologic symptoms of severe TBI often persist or exacerbate.

Due to SBI, brain swelling and increase of ICP is often observed in severe TBI. Increased ICP can also lead to damages of different brain regions finally resulting in loss of brain stem reflexes and fixed pupils. [7]

1.4 Complications of TBI

TBI is often followed by intracranial hemorrhage (ICH). Depending on the localization, intracranial hemorrhage can be classified into four subgroups: epidural hematoma (EDH), subdural hematoma (SDH), subarachnoid hemorrhage (SAH) and intracerebral bleeding (ICB). Clinical presentation varies according to the localization of ICH.

1.4.1 Epidural Hematoma

EDH is located between the outer meninx, the dura mater, and the skull. These hemorrhages have a convex shape as the expansion of the bleeding is stopped by the skull and hence directed inward to the brain.

Epidural hematoma leads to a rupture of meningeal arteries, and in some cases to a disruption of the transversus sinus. [5]

The onset of clinical manifestation can either appear immediately after the traumatic incident or after a certain amount of time. After primary unconsciousness, some patients experience a time period free of neurological symptoms, described as lucid interval. This period is followed by secondary neurological deterioration. [7]

Symptoms range from headache and nausea to neurological deficits, somnolence and coma. Pupil abnormalities are seen in 20-30% of EDH cases. [20]

Ipsilateral mydriasis on the side of the hemorrhage is a sign of compression of the third cranial nerve, the oculomotor nerve, and is often accompanied by contralateral hemiparesis. If evacuated early enough (within 70 minutes after occurrence), ipsilateral mydriasis is reversible and not associated with worse outcome. [20, 21]

On the contrary, contralateral and bilateral mydriasis as well as fixed pupils are related with adverse outcome. [20]

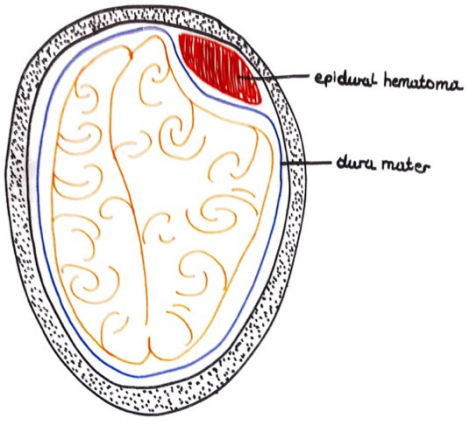

Figure 2: *scheme of epidural hematoma (EDH)*

1.4.2 Subdural Hematoma

SDH is a result of ruptured bridging veins and anatomically located between the dura mater and the arachnoid meninx. On CT-scans they appear as crescent-shaped bleedings that spread along the inside of the skull. SDH can be accompanied by Increase of ICP and ischemia. [22]

SDH is also classified into two categories: acute SDH and chronic SDH.

Acute SDH develops due to traumatic incidents. It is commonly caused by acceleration/ deceleration trauma on the head. In these cases, acute SDH presents with severe neurologic symptoms, such as compromised vigilance, LOC, ipsilateral mydriasis and contralateral hemiparesis. Acute SDH can be a life-threatening condition as it is often ensued by cerebral edema, deviation of the midline and cerebral herniation. [5] Thus, early detection and treatment are crucial to avoid adverse neurologic outcome and death.

On contrary, chronic SDH is commonly seen in the elderly population or in individuals with chronic alcohol abuse. Antiplatelet and/or anticoagulant agents are also contributing factors to the manifestation of chronic SDH.

Symptoms are non-specific and tend to develop over a long period of time. Clinical presentation of individuals suffering from chronic SDH may vary from headaches and dizziness to deteriorated mental status or unconsciousness. Due to increased cerebral pressure and ischemia, occurrence of isolated third nerve palsy is also observed in chronic SDH. [23]

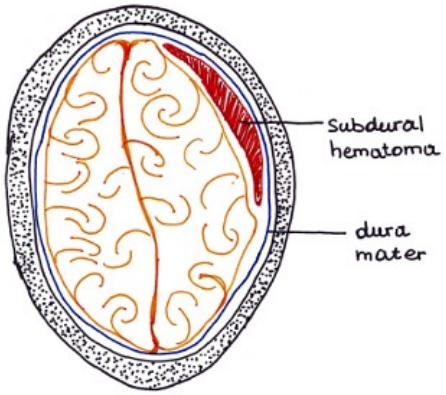

Figure 3: *scheme of subdural hematoma (SDH)*

1.4.3 Subarachnoid Hemorrhage

SAH is located between the arachnoid meninx and the pia mater. Under physiological circumstances, this space, called subarachnoid space, is filled with cerebrospinal fluid. SAH often occurs due to coup and contrecoup injuries on the head, which lead to tearing of small

vessels in the pia mater. In these cases, cerebral contusions do not exceptionally appear on the side of the traumatic impact (coup) but also on the opposite side (contre-coup).
Clinical presentation and severity of SAH depends on the severity of TBI. Vomiting, nausea and altered mental status can be seen in patients suffering from traumatic SAH. Sometimes, patients even present with meningism and back pain as the hemorrhage spreads along the spinal meninges. [7]
Contrary to other intracranial bleedings such as SDH, neurological deterioration is rarely seen in patients with traumatic SAH after the primary onset of symptoms. [24]

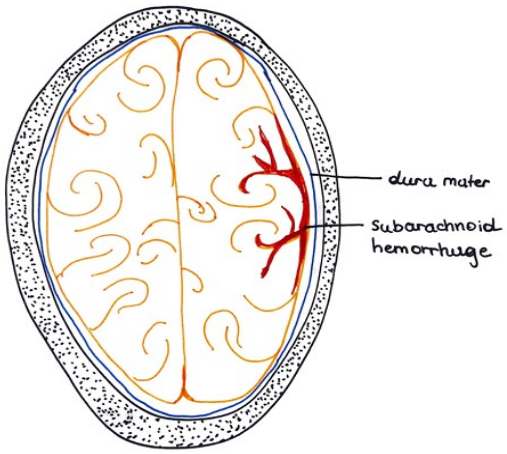

Figure 4: *scheme of subarachnoid hemorrhage (SAH)*

1.4.3.1 Intracerebral Bleeding

Bleedings occurring in the ventricles or brain parenchyma, namely contusions, are defined as ICB. It has been reported, that out of all intracranial hemorrhages, contusions are the most likely to progress, leading to an increase in mortality and morbidity. [25] Intracerebral bleedings most often occur near to the cortical area of the brain. They lead to edema and ischemia in the approximated brain tissue causing neural cell destruction and necrosis. [26] Possible complications of ICB can be seizures, hydrocephalus, coma, or neurological deficiencies and severe disabilities. [26]

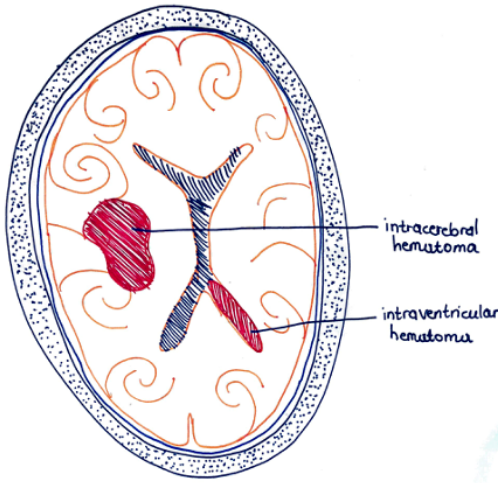

Figure 5: *scheme of intracerebral hematoma (ICB)*

1.5 Antiplatelet/ Anticoagulant Therapy

Preinjury use of antiplatelet and/or anticoagulation therapy is very common amongst elderly patients. Adverse drug effects such as coagulopathies vary depending on substance class, amount of intake, and underlying condition that is being treated with such medication (i.e. atrial fibrillation, coronary heart disease).

1.5.1 Antiplatelet Therapy

Antiplatelet drugs are effective in the arterial circulation and inhibit aggregation of platelets and thrombus formation. Therefore, they are commonly used for prevention of arterial thrombosis and therapy of diseases affecting the arterial circulation, such as coronary heart disease or peripheral vascular disease.

The main goal of all antiplatelet drugs is to decrease calcium-dependent activation of platelet aggregation.

Release of intracellular calcium through different prothrombotic cascades precipitates an activation of GPIIb/IIIa receptors. Activated GPIIb/IIIa receptors have a high affinity to fibrinogen. Through cross-links of platelets, formed by fibrinogen, platelet aggregation is achieved.

Although the pharmacological pathway is very similar, there are a lot of different antiplatelet agents that target different keystones in the coagulation cascade. The following, acetylsalicylic acid as well as adenosine diphosphate receptor inhibitors (ADP inhibitors) are very common antiplatelet substance classes in Austria. They are indicated in the setting of cerebrovascular, cardiovascular and peripheral vascular disease and reduce the risk of stroke, unstable angina pectoris and myocardial infarction.

1.5.1.1 Cyclooxygenase Inhibitors (Acetylsalicylic Acid)

Acetylsalicylic acid (ThromboASS®) works as an irreversible inhibitor of the enzymes cyclooxygenase I and II (COX-1/ COX-2).

Through membrane damage, cyclooxygenase is activated and starts to convert arachidonic acid (AA) to thromboxane-A_2 (TXA_2). The conversion to TXA_2 happens entirely via COX-1, whereas COX-2 is responsible for the production of prostaglandins and for the inflammatory response. TXA_2 stimulates the release of intracellular calcium, which leads to the activation of GPIIb/IIIa receptors. Fibrinogen can know bind on the activated receptors and initiate primary hemostasis. [27]

In low dosages, acetylsalicylic acid inhibits the coagulation cascade via selective inhibition of COX-1, while COX-2 is merely affected. This pharmacological mechanism is used to

implement the antithrombotic effects of acetylsalicylic acid without activating the anti-inflammatory effects of this agent (which are achieved via inhibition of COX-2). [28]

1.5.1.2 ADP Receptor Inhibitors (Clopidogrel, Prasugrel, Cangrelor, Ticagrelor)

Physiologically, ADP (adenosine diphosphate), which is a purine nucleotide, binds on the ADP receptor, P2Y12, on thrombocytes. This leads to an activation of the GPIIb/IIIa receptor and induces aggregation of thrombocytes. ADP receptor antagonists bind on the ADP receptor, P2Y12, and lead to an inhibition of receptor action. Clopidogrel (Plavix®) and Prasugrel (Efient®) are irreversible inhibitors of P2Y12 receptor, whereas Ticagrelor (Brilique®) and Cangrelor (Kengrexal®) bind reversibly. Duration of action lasts longer in drugs with irreversible inhibition of thrombocytes than in reversible agents. This is due to the fact, that thrombocytes do not have a cell nucleus and are therefore not able to reproduce blocked cellular receptors. For regain of thrombocytic function, new thrombocytes have to be built, which takes 8-11 days. [27-29]

1.5.2 Anticoagulant Therapy

In contrast to antiplatelet agents, anticoagulants work as direct inhibitors of coagulation and prevent formation of thromboses. Anticoagulant agents are primarily effective in the venous system. They are used for treatment as well as prevention of recurrent venous thrombosis, such as deep vein thrombosis (DVT) and pulmonary embolism. Furthermore they are also used for prophylaxis of arterial thromboses (e.g. strokes) in the setting of atrial flutter or fibrillation. [28, 30]

Following substance classes, namely coumarins and directly acting oral anticoagulants (DOACs) are the agents the most frequently prescribed by general practitioners and/ or internal specialists.

1.5.2.1 Coumarins (Warfarin, Phenprocoumon)

Coumarins such as Acenocoumarol (Sintrom®), Phenoprocoumon (Marcumar®) and Warfarin (Coumadin®) are vitamin K antagonists (VKA). Vitamin K is a crucial substrate for the synthesis of certain clotting factors in the liver. VKAs inhibit an enzyme called vitamin K epoxide reductase, which is responsible for the reactivation of vitamin K_1. Without vitamin K_1, clotting factors II, VII, IX, X as well as protein C and S cannot be synthesized sufficiently, leading to an impairment of blood clotting. [28]

1.5.2.2 Directly Acting Oral Anticoagulants (Apixaban, Edoxaban, Rivaroxaban, Dabigatran)

There are currently four different agents of DOACs which are commonly used in Austria; namely Apixaban (Eliquis®), Edoxaban (Lixiana®) as well as Rivaroxaban (Xarelto®), which act as factor Xa inhibtiors and Dabigatran (Pradaxa®), which does not act as an inhibitor of factor Xa, but binds directly on the activated thrombin-molecule instead.

Factor X (also known as Stuart-Prower factor) is the first factor in the thrombin cascade and is responsible for the transformation of prothrombin (factor II) to thrombin (factor IIa).

Factor Xa inhibitors bind on factor Xa, making thrombin-mediated platelet aggregation impossible. [28, 30]

Dabigatran on the other hand, binds directly on the activated factor II, namely thrombin, This also causes an inhibiton of the coagulation cascade. [31] While the mechanism of action of Dabigatran differs from factor Xa antagonists, the result is the same.

2 Material and Methods

2.1 Objectives

This thesis was part of a study performed as retrospective analysis at the Level I Trauma Center of the Department of Orthopaedics and Trauma at the Medical University of Graz. Results that were obtained from this study were also recently published in a paper. [32]
The study was conducted for optimization of risk assessment in order to reduce unnecessary diagnostics and hospitalization and to improve clinical decision-making.
Primary endpoint of this study was to identify risk factors which could lead to a deterioration of TBI.
Deterioration of TBI was defined as development of intracranial hemorrhage on initial CCT scans and/or progression of intracranial hemorrhage in follow-up CCTs and/or death in patients 30 days after admission.
We included potential risk factors such as age, sex, intake of antiplatelet/ anticoagulant therapy, concomitant diseases (coronary heart disease, kidney insufficiency, diabetes, atrial fibrillation, and previous ischemic strokes), alcohol abuse (acute and chronic), fracture of the neurocranium and intracranial hemorrhage in the course of TBI.

2.2 Ethics

The study was submitted to the local Institutional Ethical Review Board (Reference Number: EK-Nr.: 19-534 ex 16/17) and was approved by it.

2.3 Study Population

We collected retrospective data of patients admitted to the Level I Trauma Center from 2008-2018 due to TBI. These patients got hospitalized and/ or received a minimum of one cranial CT (CCT) scan in the emergency department.

2.3.1 Inclusion Criteria

Patients included in this study had to receive a CCT scan and/ or be hospitalized after admission to hospital. All patients had to be older than 16 years.

2.3.2 Exclusion Criteria

There were no exclusion criteria as this study was strictly retrospective, and criteria of the study population were decided before conduction.

2.4 Acquisition of Data

Data was collected from the hospital's internal data system and included patients' past medical history, diagnostics, duration of hospitalization, therapy and follow-up as well as demographic characteristics.

Retrieved data of patients' past medical history included existence of comorbidities such as ischaemic heart disease, kidney disease, atrial fibrillation, ischemic strokes, chronic or acute alcohol abuse, diabetes and intake of anticoagulant or antiplatelet therapy.

Data of hospitalization included duration of hospital stay and requirement for neurosurgical intervention, and total number of CCT scans. Furthermore, findings on the CCT scans were assessed, which included findings such as intracranial hemorrhage (comprised of ICH, SDH, EDH), progression of ICH and fracture of the neurocranium.

Mortality data were acquired from insurance data and comprised 30-day mortality after discharge from hospital as well as overall mortality.

2.5 Stratification of Patients

After admission to our institution, severity of TBI was evaluated according to international standards.

TBI severity classification included duration of unconsciousness, alteration of mental state, post-traumatic amnesia and Glasgow Coma Scale (GCS). [33]

Following evaluation, further diagnostics as well as treatment was implemented according to guidelines of the German Society of Neurosurgery (GSN). [34]

2.5.1 Diagnostics

Cranial imaging was indicated in patients, who fulfilled CCT criteria according to guidelines of the GSN.

The guidelines of the GSN recommend cranial CT in patients with coma, alteration of consciousness, amnesia, neurologic deficiencies, seizures, repetitive vomiting, signs of cranial fracture, suspicion of depressed fracture or other penetrating injuries, suspicion of cerebrospinal fluid fistula or possible coagulopathy. Furthermore, CT imaging should be considered in patients with uncertainty of trauma mechanism, severe headaches, drug poisoning and/or high speed trauma. [34]

These recommendations were strictly followed by admitting physicians in the observed period.

2.5.2 Hospitalization

After radiologic imaging, it was decided whether patients had to be admitted for observation and if necessary for treatment or could be discharged home.

GSN guidelines recommend hospitalization in cases of cranial injuries requiring neurosurgical intervention, neurologic deficiencies, cranial fracture, leakage of liquor in combination with open cranial fracture and findings of injuries on CCT scans.[34]

These recommendations were generously followed by the admitting physicians in our institution. However, it could be observed, that some patients, who got admitted to hospital did not fulfil any of the requirements listed above. In these cases CCT scans revealed no posttraumatic alterations and GCS score was 15 throughout clinical observation. Patients did not show any signs of neurocognitive disorders.

Length of hospital stay as well as discharge had to be decided individually for each case by thy physician in charge, as there are no internationally accepted guidelines available, concerning this issue.

2.5.3 Neurosurgical intervention

Neurosurgical intervention following traumatic brain injury was strictly consistent to the GSN guidelines. These advise urgent surgical treatment in case of space-occupying lesions, such as massive intracranial hemorrhage. [34]

2.6 Statistical methods

After data were acquired, statistical analyses followed. Statistical analysis program by choice was *SPSS Statistics 20 (IBM, Armonk, NY)*.

Data were discerned into quantitative and qualitative/ categorical variables. Descriptive and explorative statistical analyses were performed.

According to type of variable different statistical test methods were applied.

Tables and figures were created, using MS Office Excel (Microsoft Excel 2013)

2.6.1 Quantitative variables

Continuous variables were described as mean value and standard deviation. All examined variables were independent sample sizes.

Levene's test for equality of variances was used for testing whether variances of sample sizes were equally distributed. Comparison of means and statistical significance could then be calculated with *independent samples t-test*. Alternate hypothesis was accepted, if p-value was 0.05 or below.

2.6.2 Qualitative/ Categorical variables

For categorical variables (e.g. anticoagulation, sex, CT progression) crosstables were used preliminary to further statistical evaluation. This was done to calculate distribution frequency and to show interrelation between variables.

Pearson's chi square test was then used for explorative statistical analysis. Examined variables were tested for dependency. Results were accepted as significant if p-value was 0.05 or below, supporting alternate hypothesis. Null hypothesis was retained if p-value was above 0.05, concluding that there was no significant difference between two variables.

2.6.3 Analysis of variance (ANOVA)

When results revealed to be significant, we did testing of variance to determine if they were independently significant from another. If p-value was under 0.05, we accepted results to be independently significant and without any bias.

3 Results

3.1 Patient Characteristics

The total study population was comprised of 2036 patients, who were admitted to the Level I Trauma Centre of the Department of Orthopaedics and Trauma at the Medical University of Graz due to traumatic brain injury.

57.5% (n=1170) were males, 42.4% (n=863) were females. The mean age in years was 57.6 (SD 22.6) with a minimum of 16.3 years and a maximum of 103.7 years. Furthermore, the subgroup of patients with age at trauma greater than 65 years was 42.9% (n=873).

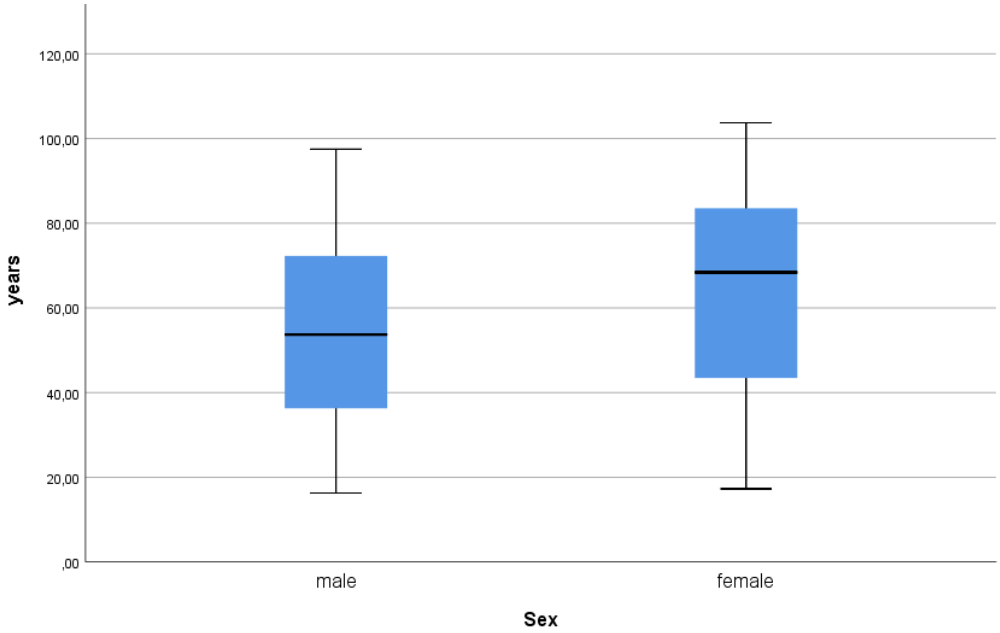

Figure 6: *Distribution of age at trauma in relation to sex*

Mild traumatic brain injury was diagnosed in 1788 patients (87.8%) who were admitted to hospital. The remaining 248 patients (12.2%) were diagnosed with moderate or severe TBI. Admission was followed by hospitalization in 89.9% (n=1831) of cases. Initial radiologic imaging of the neurocranium was performed in 96.6% (n=1968) of cases.

3.1.1 Radiologic imaging

As stated above, 96.6% (n=1968) received an initial CCT scan to screen for injuries of brain tissue and/or fracture of the skull. In 53.7% (n=1058) of those patients, intracranial hemorrhage could be identified. Type of intracranial hemorrhage fell into four categories: EDH, SDH, SAB and ICB.

EDH was detected in 5% (n=101), SDH in 24.1% (n=475) SAB in 36.4% (n=716) and ICB in 22.4% (n=441) of patients, initially receiving CCT. In some cases, more than one type of intracranial hermorrhage (e.g. SAB+SDH) could be found on CCT images.

Fracture of the neurocranium occurred in 379 (18.6%) of 2036 patients.

Follow-up CCT scans were performed in 988 cases (48.5%). A progression of intracranial hemorrhage was detected in 280 patients (13.7% overall; 28.3% in follow-up patients).

3.1.2 Comorbidities

Distribution of comorbidities in the study population was following.

11.2% (n=229) patients were diabetics, 13.9% (n=283) were diagnosed with coronary heart disease (CHD), 12.7% (n=258) with renal insufficiency. 9.9% (n=202) suffered from chronic or acute alcohol abuse. According to electronic patient files, 9.5% (n=193) of patients had atrial fibrillation. 5.6% (n=114) had a positive past medical history of ischemic or haemorrhagic stroke, as well as 1.9% (n=38), who had a positive medical history of transient ischemic attack (TIA).

For 30.7% (n=625) of patients, oral anticoagulant/ anti-platelet therapy was part of their long-term medication. Distribution of usage of different substance classes is shown in the figure below.

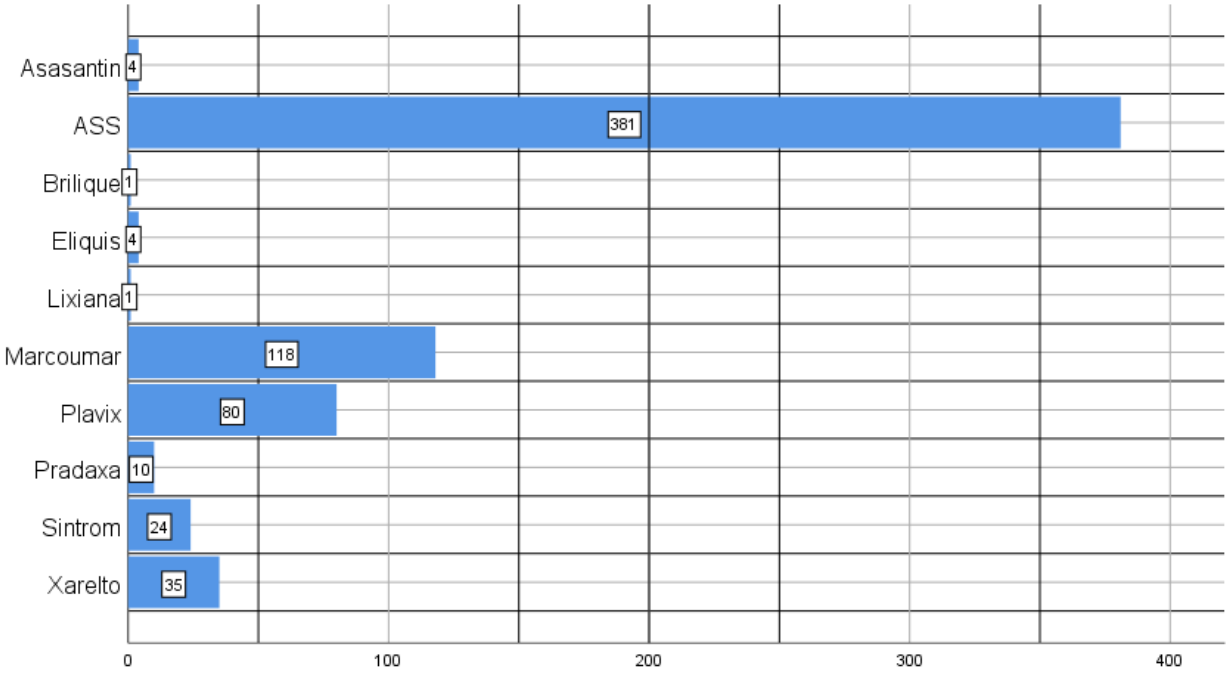

Figure 7: *Distribution of anticoagulant/ antiplatelet therapy in the study population (total numbers)*

3.1.3 Follow-up

Out of 2036 patients, 1831 patients (89.9%) got hospitalized. The other 205 patients (10.1%) were discharged home after clinical and radiological assessment in the emergency department. The mean duration of hospital stay was 8.9 days (SD 10.5). Hospitalization lasted at least for 1 day and went up to a maximum of 97 days.

To ascertain mortality of patients after admission, a follow-up of 30 days was conducted. Within this period of time, 4.4% (n=90) of patients died.

Overall mortality after completion of the study trial was 22.7% (n=482).

3.2 Identification of risk factors

Risk factors were defined as factors, which were significantly contributing to TBI progression.

Criteria for progression of TBI included 30-day mortality, intracranial hemorrhage in initial CCT scans as well as progression of intracranial hemorrhage in follow-up CCT scans. Following risk factors could be identified.

3.2.1 Age and sex

861 patients, who were at least 65 years old and 1112 patients, who were younger than 65 years received an initial CT scan. The older subgroup had a significantly higher risk for intracranial bleeding ($p<0.001$) with 587 cases (68.2%) showing positive CT findings of intracranial bleeding versus 469 patients under 65 years (42.2%) with positive CT findings. Progression in repeat CT scans was significantly more often detected ($p=0.029$) in the older patients' subgroup (173 out of 551 cases (31.4%) compared to 107 out of 439 cases (24.4%)).

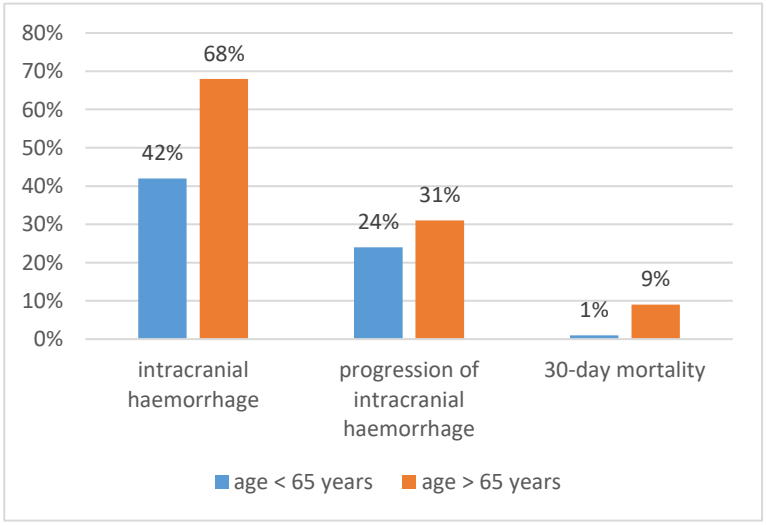

***Figure 8**: Progression in patients < 65 years versus > 65 years*

There was also a significantly higher risk concerning 30-day mortality ($p<0.001$) for the older population. 75 out of 869 patients (8.6%) over 65 years compared to 15 out of 1147 (1.3%) in the group of patients under 65 years died within this range of time.

Furthermore, patients who died after 30 days were significantly older with a p-value < 0.001 than those patients who survived. The mean age of patients who died 30 days after discharge from hospital was 78.0 years (SD 15.4) compared to patients who survived with a mean age of 56.7 years (SD 22.5).

There was no significant difference concerning female or male sex and TBI progression. 597 out of 1145 male patients (52.1%) and 459 out of 825 female patients (55.6%) showed an intracranial hemorrhage in initially performed CCT scans ($p=0.20$). Progression of bleeding was identified in 167 of 550 male patients (30.4%) and in 113 of 440 female patients (25.7%) ($p=0.17$). 49 out of 1168 males (4.2%) and 41 out of 860 females (4.8%) died within 30 days ($p=0.92$).

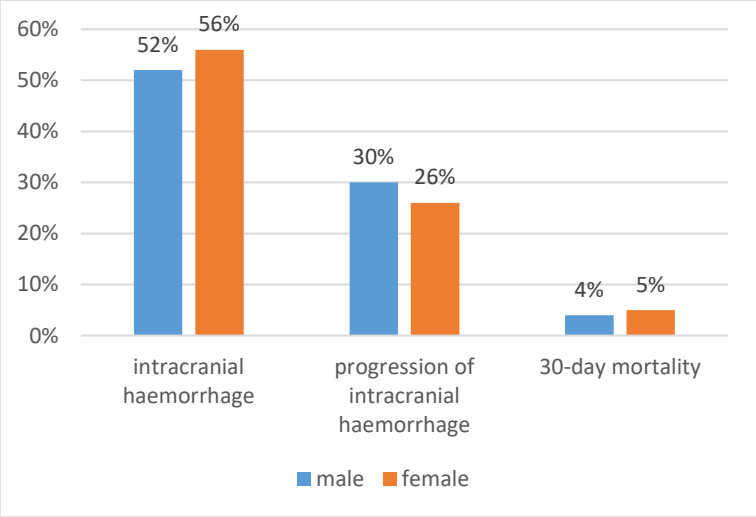

***Figure 9**: Progression of TBI in males versus females*

3.2.2 Neurocranial fracture

Radiologic imaging revealed that 322 out of 378 patients with fracture of the neurocranium (85.2%) and 734 out of 1595 patients with no fracture (46.0%) suffered from intracranial hemorrhage.

Follow-up CCT revealed bleeding progression in 41.5% (n=129 out of 311) of patients with fractured skull and in 22.2% (n = 151 out of 679) of patients without neurocranial fracture.

Death within 30 days amongst patients with neurocranial fracture was in 8.0% of cases (n=30 out of 379) and only in 3.6% of patients (n=59 out of 1651) without neurocranial fracture.

Chi-square test showed a significant increase of intracranial hemorrhage ($p<0.001$), as well as progression in repeat CT scans ($p<0.001$) and death within 30 days ($p<0.001$) in patients with fracture of the neurocranium.

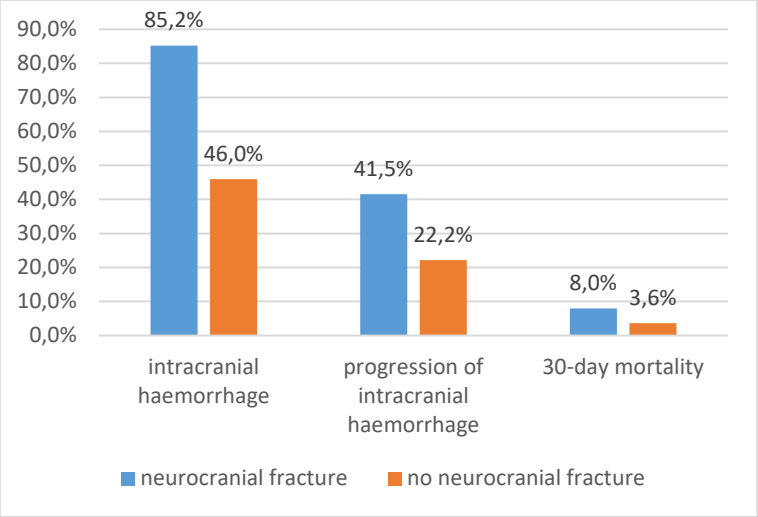

Figure 10: *Progression of TBI with and without neurocranial fracture*

3.2.3 Antiplatelet/ Anticoagulant therapy

Antiplatelet/ anticoagulant therapy revealed to be a significant risk factor with a p-value < 0.001 concerning intracranial hemorrhage on initial CCT scans as well as 30-day mortality. In this subgroup of patients, bleeding was found on initial CCT in 433 out of 621 cases (69.7%) and 51 out of 621 patients (8.2%) died within 30 days. Whereas initial CT findings of patients without intake of oral anticoagulation or antiplatelet therapy showed intracranial hemorrhage in 622 out of 1351 cases (46.0%). In the 30-day follow up we found a mortality of 2.8% (n=39 out of 1408) in this subgroup.

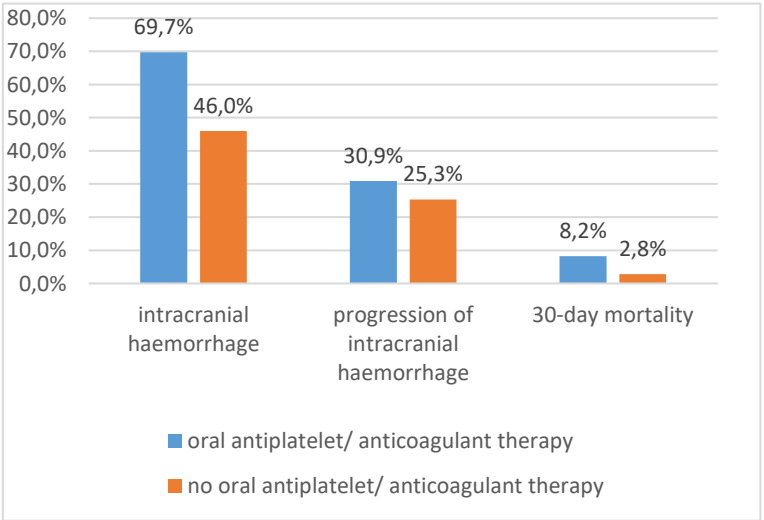

Figure 11: *Progression with and without antiplatelet/ anticoagulant therapy*

There was no statistical significance in terms of bleeding progression in follow-up CCT with a p-value of 0.195 (25.3% vs. 30.9%).

3.2.4 Comorbidities

Positive findings of intracranial bleeding were detected in 128 of 196 patients with a positive history of alcohol abuse (65.3%) and in 930 of 1775 patients with a negative history (52.4%). In patients with alcohol abuse, progression was found in 34 of 104 patients (32.7%) and 7 of 202 patients died within 30 days (3.5%).

On contrary 28.0% of patients (n=246 of 885) without abuse of alcohol showed progression of intracranial hemorrhage and 4.5% (n=83 of 1827) died.

255 patients suffering from chronic kidney disease received an initial CCT scan. 188 of them showed signs of intracranial bleeding (73.7%) versus 50.5% (n=868 of 1718) without CKD. Progression was found in 58 of 180 CKD patients (32.2%) and in 222 of 810 patients (27.4%) without renal insufficiency. Death within 30 days occurred in 10.5% (n=27 of 256) of CKD patients, and in 3.5% (n=63 of 1775) without CKD.

Chronic or acute alcohol abuse ($p=0.002$) as well as renal insufficiency ($p<0.001$) turned out to be significantly related to intracranial bleeding in initial radiologic imaging.

Furthermore, renal insufficiency could be identified as risk factor concerning 30-day mortality ($p<0.001$).

There was no significant correlation between progression of intracranial hemorrhage and alcohol consumption ($p=0.548$) or renal insufficiency ($p=0.39$) as well as 30-day mortality and alcohol abuse ($p=0.480$),

Any other comorbidity, including CHD, AF, stroke, TIA did not correlate with TBI progression.

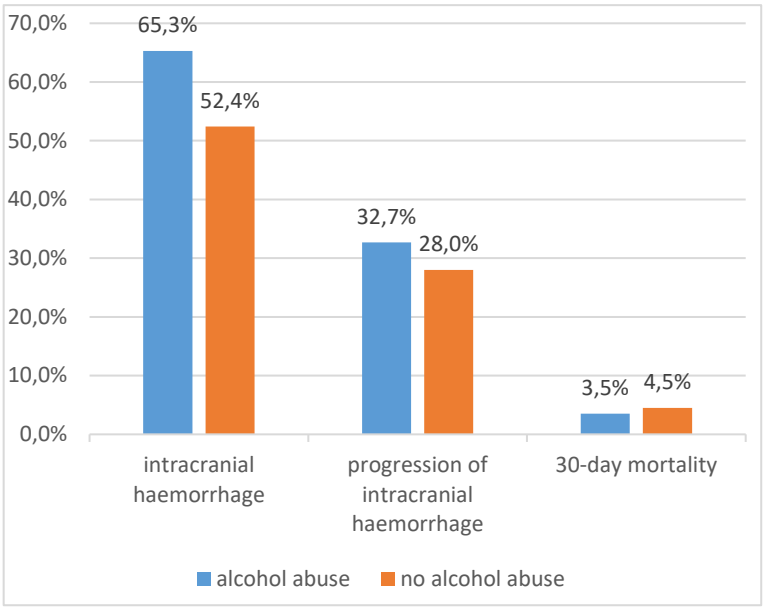

Figure 11: *Progression of TBI in patients with versus without alcohol abuse*

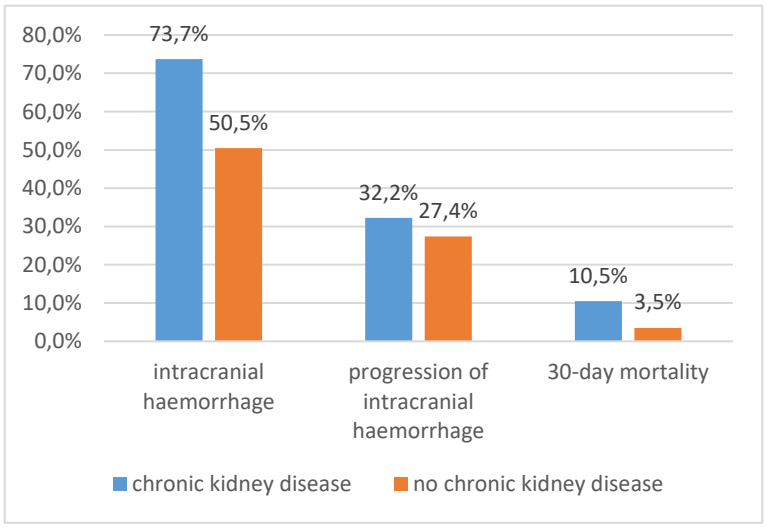

Figure 12: *Progression in patients without CKD versus with CKD*

3.3 Analysis of variance (ANOVA) of risk factors

ANOVA testing showed, that following patients' characteristics were significant independent risk factors for the progression of TBI; patients older than 65 years ($p<0.001$), chronic kidney disease ($p<0.001$), antiplatelet/ anticoagulation therapy ($p<0.001$), alcohol abuse ($p<0.001$) and fracture of the neurocranium ($p<0.001$).

3.4 Hospitalization

The mean duration of hospitalization was significantly longer in patients who underwent surgery with a p-value < 0.001. The mean duration of hospital stay in these patients was 18.0 days (SD 13.4 days) compared to patients who did not need any surgery. In these cases, duration of hospital stay was only 4.8 days (SD 4.5 days).

Patients with mild TBI spent only 6.9 days (SD 8.3) in hospital, whereas patients who suffered from moderate or severe TBI spent 20.0 days (SD 16.4) on average. These patients stayed significantly longer in hospital than those with mild TBI ($p<0.001$).

Furthermore, patients who suffered from intracranial bleeding on CCT scans got hospitalized significantly longer (10.4 days, SD 10.6) than those not displaying any pathological findings on CCT scans (6.6 days, SD 10.27) ($p<0.001$).

There was no significant difference concerning duration of hospital stay in patients over 65 years and younger patients ($p=0.060$).

4 Discussion

According to our statistical analyses, several risk factors could be identified, that influenced the clinical course of TBI. As to the complexity of the human organism, interaction of assessed variables had to be considered. Hence, concerning the identification of individual risk factors, univariate as well multivariate statistical analyses were performed, allowing scientifically founded statements as to whether certain patients' characteristics could predict a considerably unfavourable course of TBI.

In a time period of 10 years a total of 2036 patients were admitted to the Level 1 Trauma Centre. Admission, clinical course and discharge of these patients were retrospectively observed. Data of patients' past medical history and comorbidities were collected. Considering the amount of patients' data and changes in digitisation of documented case files all-encompassing observation was not feasible in all patients. In some statistical calculations, patients with missing data had to be removed.

Nonetheless, with a total study population of 2036 patients, statements that could be retrieved from statistical analyses were still well-evaluated and mostly in line with previous topic-related studies. We were also able to submit and publish our obtained results in a journal ("*Risk adapted diagnostics and hospitalization following mild traumatic brain injury"*). [32]

4.1 Radiologic imaging

Almost every patient, who got admitted to hospital received an initial CT scan (96.6%). In 53.7% ICH was detected. Interestingly only 48.5% of all patients received follow-up CT scans, missing out at least 5.2% of patients with initially positive signs of ICH.

Whereas this might seem surprising, radiologic findings should always be evaluated in the context of clinical presentation and presence or lack of symptoms. As a meta-analysis by *Reljic and colleagues* showed, strategy of treatment (ICP monitoring, neurosurgical intervention) only changed in 11.4% of patients in prospective studies and in 9.6% of patients in retrospective studies receiving repeat CCT scans. [35]

In our study population, progression of ICH in patients with initially ICH positive CCT scans was 28.3%. Leaving out 71.7% with no change of intracranial hemorrhage or even regression of bleeding. Although the majority of patients do have a favourable outcome concerning bleeding regression, caution is advised in patients with larger haemorrhagic lesions on initial CCT scans. According to *Carnevale and colleagues*, patients with larger bleeding volume

on initial CCT tend to develop bleeding progression more often. Moreover, expansion volume of bleeding is significantly higher. [36]

4.2 Identification of risk factors

4.2.1 Age

We found that 42.9% of admitted patients were older than 65 years. This subgroup of the study population was also significantly more prone to ICH, progression of ICH and mortality within 30 days after admission. These findings were in line with studies investigating the correlation between age and unfavourable outcome following TBI. [37-39]

In a study by *Garza and colleagues,* mean age of admitted patients with TBI gradually increased by 4.4 years per year in an observed time period of 7 years (2009-2016). [37] This allows the interpretation that the occurrence of TBI is becoming a greater concern for the aging population.

Studies have also shown that mortality and adverse outcome is increasing in the older population. [38-41]. *Hawley and colleagues* postulated a doubling of mortality rate after TBI in the age group ≥ 85 years compared to patients aged between 65-74 years (17% in age group 65-74 vs. 32 % in the age group ≥ 85 years). In our statistical analyses, there was an 8-fold increase in mortality comparing patients < 65 years to patients > 65 years. Although cause of death was not always solely due to TBI in our study population, this increase in mortality should still be considered.

Several theories exist as to why patients with increasing age tend to develop more complicated courses of TBI than younger patients. Some authors suggest that the capability of regeneration of brain tissue decreases in the course of aging. [42] Furthermore, multimorbidity in elderly patients has a negative influence on the healing process of TBI. This is due to the fact that physiological responses of coagulation and immune system as well as autoregulation of cerebral blood vessels may be impaired. Brain atrophy also allows greater expansion of intracranial bleeding leading to delayed altered mental status and an initial underestimation of injury. [40]

The main trauma mechanism of TBI in elderly patients is due to low level falls at home. [41] Increasing age can be considered as a very high-risk factor contributing to TBI progression. This should be thought of when diagnostic and therapeutic steps are planned and executed.

4.2.2 Sex

Gender distribution was very homogenous in our study population. With slightly but not significantly more males being admitted to hospital due to TBI than females. Moreover, we could not ascertain any statistically significant differences in terms of initial ICH, progression of ICH or mortality. Interestingly, this finding was not consistent with previous studies.

Oertel and colleagues found that the likelihood of ICH progression was significantly increased in the male sex. With 48% of men and only 18% of women showing a progression of bleeding in follow up CCT scans. In our study, findings were more evenly distributed with 30% of men and 26% of women showing ICH progression. [43] This disaccord of study findings may be due to different sample sizes (142 vs 2036 patients).

Another explanation might be, that in the population of adolescences, males are more likely to be exposed to sports-related injuries, motor vehicle accidents or violent disputes, leading to emergency department visits with higher frequency. [44, 45] With increase in age this difference of male-dominant hospital admission ceases to exist. [44] Although our sample size also included younger patients, 42.9% of our patients were older than 65 years, which could also explain the even distribution between males and females.

However, *Oertel and colleagues* also refer to the potential neuroprotective effects of oestrogen as explanation for their results. [43] The positive effects of oestrogen and progesterone on neuroprotection have been reviewed in a paper by *Brotfain and colleagues.* Hormonal mechanisms of protection include an increase of neural cell survival, reduction of free oxygen radicals, reduction of proinflammatory mediators, decrease of brain oedema and improvement of cerebral blood flow. [45, 46]

In contrary to age being a scientifically proven risk factor for TBI progression, the literature is still unsure about gender-related influences on the course of TBI. Nonetheless, female sex hormones seem to have a beneficial, neuroprotective effect.

4.2.3 Neurocranial fracture

Results concerning deterioration of TBI in patients with skull fracture were unanimous with previous studies. We were able to confirm, that fractures of the neurocranium were followed by a progression of TBI. [47-49]

One possible explanation of this finding could be that bone fracture is mainly due to more severe and high impact trauma mechanisms. High-energy trauma is accompanied by more severe TBI (moderate or severe), and has therefore a higher prevalence of TBI progression

and intracranial hemorrhage. Skull fracture could therefore act as an indicator for high-energy injury, and in conclusion, as a predictor for severity of TBI.
Skull fracture of specific anatomical regions are associated with a higher probability of SDH and EDH. Especially fractures of the temporal lobe are often accompanied by ICH as bridging veins and meningeal arteries are in close proximity to this anatomical area. [50]

4.2.4 Antiplatelet/ Anticoagulant therapy

So far, a number of studies has shown that there is a significant correlation between the intake of certain oral antiplatelet/ anticoagulant agents and the occurrence of intracranial bleeding as well as progression of hemorrhage and mortality after trauma. [36, 51-54] In our retrospective study results regarding initial hemorrhage as well as mortality were in-line with these previous postulations. Interestingly though, we did not find any significant difference in progression of hemorrhage in our study. This inequality in outcome might be due to the acquisition of our data, as we did not take closer evaluation concerning each substance class of anticoagulant/ antiplatelet therapy and progression of TBI.
Further studies, however, have peremptorily denied occurrence as well as progression of hemorrhage in association with intake of anticoagulant agents and especially antiplatelet agents. [55, 56]
Whilst other study results, though showing TBI progression in the context of oral antiplatelet/ anticoagulant therapy, did not reach statistical significance. [57-59]

4.2.4.1 Antiplatelet Agents

Several studies have already examined possible adverse outcomes in patients with TBI and preinjury use of antiplatelet therapy. The results of these studies have been counterintuitive so far. [51, 55-58]
In a retrospective study by *Brewer and colleagues*, positive CCT findings of hemorrhage could be depicted more often in patients taking antiplatelet agents. Even though these findings were non-specific, the authors argued that the lack of specificity was mainly due to the small sample size (n=141). [51] Similar to these findings, a meta-analysis by *Batchelor and colleagues* could identify a slight increase of mortality in patients with antiplatelet therapy, although the results did not reach statistical significance. [57] Another retrospective study by *Ronning and colleagues* could not find an increase in 30-day mortality in patients with antiplatelet therapy alone. But they were able to identify a significantly increased risk of 30-day mortality, when there was combined use of antiplatelet and anticoagulant agents. [58]

Other studies were not able to identify antiplatelet therapy as individual risk factor for TBI progression. [55, 56]

4.2.4.2 Anticoagulant Agents

When it comes to anticoagulant agents, especially VKA, significant results concerning the progression of TBI tend to be more homogenous.

A study by *Collins and colleagues* showed, that there was a 40% increase in risk for elderly patients on VKA, namely Warfarin, to develop ICH after TBI. Furthermore, patients on Warfarin had a 2-fold increase of 30-day mortality. [53] *Savioli* and colleagues also identified a 2-fold increased prevalence for ICH in patients with mild TBI, who were on VKA (in this study Dicumarol) when compared to the control group. [54]

Although the results of these studies correspond to our findings, patients in our study population used different VKAs prior to TBI than patients in the studies cited above. The most frequently prescribed VKA in our study population was Phenprocoumon. There was no patient in our study population receiving either Warfarin or Dicuramol.

In fact, few studies have been released so far, that explicitly examine progression of TBI in patients with preinjury use of Phenprocoumon. One study by *Jentzsch and colleagues* investigated if there was any difference in mortality or morbidity in patients taking Phenoprocoumon (VKA), Rivaraoxaban (DOAC) or no anticoagulant agents. They did not come up with any significant findings concerning deterioration of TBI after intake of Phenprocoumon or Rivaroxaban. [59]

However, further research revealed, that there was a significant difference concerning progression of TBI and intake of different substance classes of oral anticoagulant agents.

Feeney and colleagues found that the preinjury use of Warfarin as VKA was associated with a higher risk of mortality after TBI than the preinjury use DOACs. [60] These findings were in line with other studies. [54, 55, 59] Another study by *Müller and colleagues* compared the prevalence of hemorrhage in patients > 65 years after falls from standing, who took either DOACs or VKAs. They identified a significant higher risk for patients in the VKA group to develop intracranial hemorrhage. [61]

Warfarin seems to be the agent with the highest probability of adverse outcomes, while DOACs appear to have a better safety profile. As there is only a small amount of studies investigating the progression of TBI after intake of Phenprocoumon, further studies are required to yield a more valid statement for this anticoagulant agent.

4.2.5 Alcohol abuse

Regarding progression of TBI in the context of alcohol consumption (either acute alcohol intoxication or chronic alcoholism) there were significant results concerning findings of intracranial hemorrhage on initial CT scans (65.3% vs. 52.4% in the control group). Progression of intracranial hemorrhage as well as 30-day mortality were not significantly increased. An explanation for these findings could be, that acute alcohol intoxication is more frequent in adolescences and younger adults. These patients have better chances of full recovery and are less likely to develop neurologic deficiencies than older patients. In our study, we did not differentiate between patients with acute or chronic alcohol abuse. So this theory mentioned above may not be valid for all of our results.

Several studies have been conducted, that investigated the correlation between acute alcohol consumption and TBI progression. [62-65] Results retrieved from these studies were congruent with our findings. Acute alcohol intoxication was less likely to have any significant effect on bleeding progression and/or outcome of TBI. [62-65]

Another explanation for the good outcome of intoxicated patients in conducted studies could be, that as a result of the direct effects of alcohol on the nervous system and the neurocognitive behaviour of patients, applicability of the GCS score was limited. Making it difficult for physicians to discern between injury- or alcohol-related neurological impairment. Intoxicated patients hence tended to be assessed with a lower GCS on admission as a result of overestimation of TBI severity. In logical consequence they had better chances of full recovery when compared to patients classified with the same GCS score in the non-alcohol group, as part of their compromised GCS was due to alcohol and not due to the brain injury itself. [62-64]

Although there are many studies that cover acute alcoholism and TBI, effects of chronic alcohol consumption on the course of TBI have not been investigated as thoroughly in the literature so far. One experimental study by *Lai and colleagues* observed the effect of ethanol on the synapses of the medulla oblongata in a rat model. One group of rats was given ethanol for two weeks in advance, while the other was not (EtOH vs. non-EtOH). Some of the rats then received a minor strike on the head to imitate the injury mechanism of TBI (EtOH-TBI vs. non-EtOH-TBI). The EtOH-TBI group showed a significant loss of synapses, axonal impairment and an increase in mortality was noticed. [66] Other animal studies came to similar results. [67, 68] These studies suggest, that patients with alcohol induced brain damage could be more susceptible to an unfavourable outcome after TBI.

For better understanding of the interaction between chronic alcoholism and TBI progression more research is needed.

4.2.6 Chronic kidney disease

The last risk factor, which we identified was CKD. Patients with renal insufficiency had a higher rate of intracranial hemorrhage on initial CCT scans. Also mortality was significantly increased in this subgroup of patients. A large retrospective multicentre study (n=23877) by *Shibahashi and colleagues* was in line with our findings, also showing that 30-day mortality was significantly increased in patients with renal insufficiency. [69]

Renal insufficiency can cause many comorbidities which lead to a deterioration of TBI. CKD can lead to accumulation of uremic toxins which induce hemolysis. Hemolysis includes depletion of thrombocytes and results in thrombocytopenia. In the setting of TBI, thrombocytopenia causes progression of hemorrhage and also increases mortality. Furthermore, impaired renal clearance may cause accumulation of certain drugs, which also interfere with recovery after TBI.

Nevertheless, these are only hypotheses as to why CKD may have a negative impact on the outcome after TBI. Further research is required to explain the pathophysiological correlation between CKD and TBI.

Limitations

Although this study was well-planned and executed, the presence of limitations cannot be denied. As this is a retrospective study acquisition of data was limited in some cases. We had to rely on the quality of medical records and patient files from the hospital's internal data system. While the majority of patient files entailed all the necessary information some did not contain all variables that were needed.

In this context, especially the intake of oral antiplatelet and anticoagulant therapy was dependent on the compliance of the patient. The admitting physician had to rely on patients' honest statement concerning regular intake of prescribed medication. Furthermore, laboratory parameters, such as INR and aPTT, which could have reflected the effect of certain drugs, were not obtained. This would have allowed us to find out if there was any correlation between TBI progression and the bioavailability of certain drugs.

Another limitation of this study was that interpretation of TBI severity as well as GCS classification was dependent on the judgement of the physician in charge. Moreover, GCS was only assessed on admission and not on the day of discharge. Concerning clinical follow-up and neurological outcome this might have been an interesting parameter.

When it comes to radiologic imaging, we did not assess correlation of ICH progression on CCT scans and impact on the clinical course of TBI. As progression on CCT scans does not necessarily mean a deterioration of mental status or worsening of GCS in clinical context. Also, the bleeding size on initial CCT and the change in volume size on follow-up CCTs were not considered. These parameters could have helped us to determine if larger bleedings would rather increase mortality and morbidity than smaller ones.

Although 30-day mortality and overall mortality were assessed cause of death might not always have been related to TBI itself. Especially multimorbid or polytraumatised patients may have died due to causes other than TBI.

Conclusion

Traumatic brain injury is one of the leading causes for emergency department visits with tendency to rise. Many of these patients are older than 65 years. The presence of certain diseases such as coronary heart disease or atrial fibrillation imply the intake of anticoagulant/ antiplatelet agents and are not uncommon in this age group.

As demographics show, the aging population is currently increasing at high speed and there will not be any decline in the nearest future. Healthcare systems and providers will hence see themselves challenged with multimorbid elderly patients as capacities of diagnostic and therapeutic means may reach or even exceed limits.

In the context of our study, we could identify certain individual risk factors, such as age, antiplatelet/ anticoagulant agents or chronic kidney disease, that contribute to the progression of TBI. All of these risk factors might most certainly be present in elderly individuals, probably multiplying the likelihood of TBI progression. Deterioration of TBI may require intensified medical care, including repetitive CCT scans, clinical observation, admission to intensive care units (ICU) and surgical interventions.

To reduce ED visits and admissions due to TBI, a solution could be to optimize primary as well as secondary prevention. This means training of fall hazard recognition to avoid trauma and TBI in the first place. Also, optimal adjustment of oral-intake medication, especially all sorts of blood-thinning agents (introduction DOACs instead of VKAs) and judicious primary care to prevent the occurrence of secondary brain injury could minimize progression of TBI.

In conclusion, identifying risk factors for TBI might have the greatest potential to reduce extensive medical treatment and avoid overstraining of health care systems and providers.

The identification of risk factors as well as clinical implementation of economically efficient TBI management were also well-reflected in our study-related paper*: "Risk adapted diagnostics and hospitalization following mild traumatic brain injury".* [32]

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Appendix

Publications that were connected to this thesis:

Risk adapted diagnostics and hospitalization following mild traumatic brain injury

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Published in:

Archives of Orthopaedic and Trauma Surgery.

Volume 144, Issue 4, 619-627

DOI: 10.1007/s00402-020-03545-w

PMID: 32705384