Diploma Thesis

Added value of the S100B protein in the radiological assessment of traumatic brain injury?

submitted by

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Graz, October 29, 2021

Statutory Declaration

I hereby declare that I have authored this thesis independently, that I have not used other than the declared sources/resources, and that I have explicitly marked all material that has been quoted either literally or by content from the used sources.

Graz, October 29, 2021 Michael Johannes Singer eh

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Abbreviations

5-HT1A	serotonin 1A
BMI	body mass index
cCT	cranial computed tomography
CCTHR	Canadian CT head rule
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
DAMPs	damage-associated molecular pattern molecules
EDH	epidural hematoma
GCS	Glasgow coma scale
GI	gastro intestinal
GOS	Glasgow outcome scale
GRE	gradient-echo
ICH	intracerebral hemorrhage
IVH	intraventricular hemorrhage
kDa	kilodalton
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
NEXUS II	National Emergency X-Radiography Utilization study II
NO	nitric oxide

NOC	New Orleans Criteria
PNS	peripheral nervous system
RAGE	receptor for advanced glycation end-products
ROS	reactive oxygen species
RTAs	road traffic accidents
SAH	subarachnoid hemorrhage
SDH	subdural hematoma
SHT	Schädelhirntrauma
SNC	Scandinavian Neurotrauma Committee
SWI	susceptibility-weighted imaging
TBI	traumatic brain injury
TLR	toll-like receptor
TNF-α	tumor necrosis factor-alpha
tSAH	traumatic subarachnoid hemorrhage

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** with courtesy of the Division of General Radiology, Department of Radiology, University Hospital Graz, Medical University of Graz, Austria.*

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Zusammenfassung

Einleitung: Es herrscht eine große Diskrepanz bezüglich der Praktikabilität von S100B-Serumwerten zur Diagnostik, Überwachung und Prognose von Patient*innen mit Schädelhirntrauma (SHT). Aktuell liegt das Augenmerk vor allem darauf, ob S100B-Serumwerte unter einem definierten Cut-Off-Wert geeignet sind, um Patient*innen eine kraniale Computertomographie (cCT) mit damit verbundener Strahlenexposition zu ersparen. Andere Einflussfaktoren von S100B-Werten stellen hierbei eine große Hürde dar. Das Scandinavian Neurotrauma Committee (SNC) veröffentlichte 2013 erstmals Leitlinien mit Berücksichtigung von S100B-Werten.

Methoden: Als Basis dieser Studie diente eine retrospektive Datenanalyse im Zeitraum von 1.1.2017 bis 31.1.2020 von Patient*innen mit SHT, die am LKH Universitätsklinikum Graz behandelt wurden, bei denen eine cCT-Untersuchung und eine Bestimmung der S100B-Werte durchgeführt wurden (n = 110). Es wurden unterschiedliche CT-Klassifikationen (Marshall, Rotterdam, Stockholm, Helsinki) sowie mögliche Einflussfaktoren wie extrakranielle Verletzungen oder die Dauer bis zur S100B-Abnahme erhoben und mit den S100B-Werten verglichen.

Ergebnisse: Bei einem Cut-Off-Wert von 0,100 µg/L zeigte sich eine Sensitivität von S100B zur Vorhersage von Pathologien in der CT von 94,7% (100% für die in den SNC guidelines definierte Gruppe) und eine Spezifität von 17,6% (21,2% nach SNC guidelines). Die Spezifität für Polytrauma-Patient*innen (n = 11) lag bei 0%, für jene mit sonstigen extrakraniellen Verletzungen (n = 41) bei 5,3%. Alle erhobenen CT Klassifikationen korrelierten signifikant (n = 110, p < ,01, R = ,376 bis R = ,468) zu den S100B-Werten. Ebenso korrelierten die Zeiten zwischen Hospitalisierung und S100B-Abnahme (n = 91, p = ,006, R = -,287), jedoch nicht die Zeiten zwischen Trauma und S100B-Abnahme (n = 23, p = ,429, R = -,173) mit den S100B-Werten von Patient*innen ohne Pathologien in der CT.

Schlussfolgerung: Extrakranielle Verletzungen haben einen großen Einfluss auf S100B-Werte. Es muss geschlussfolgert werden, dass der Cut-Off-Wert von 0,100 µg/L für Patient*innen mit multiplen Verletzungen ungeeignet ist und es diesbezüglich weiterer Forschung bedarf. Angepasste Cut-Off-Werte je nach Zeitverzögerung bis zur S100B-Abnahme könnten die Spezifität potenziell erhöhen, jedoch gibt es noch zu viele Unklarheiten bezüglich der genauen Kinetik von S100B.

Abstract

Introduction: The potential use of the S100B protein regarding diagnosis, monitoring and outcome estimation of traumatic brain injury (TBI) in daily clinical practice is still a matter of discussion. Currently, the focus lies especially on the fact whether S100B serum values can predict pathological cranial computed tomography (cCT) findings and whether cCT scans (along with radiation exposure) can be avoided for certain patients. In this regard, a big challenge arises by other influence factors, like extracranial injuries, of S100B serum values. In 2013, the Scandinavian Neurotrauma Committee (SNC) added S100B serum values for the first time to official guidelines.

Methods: This study was based on retrospective data analysis from 01/01/2017 to 31/01/2020 of patients, who suffered TBI and sought medical help at the Hospital of the Medical University of Graz, receiving both a cCT scan and S100B sampling (n = 110). Different CT classifications (Marshall, Rotterdam, Stockholm, and Helsinki) were compared with S100B serum values. Additionally, the impact of important influence factors like extracranial injuries or times between trauma and S100B sampling on S100B serum values has been analyzed in detail.

Results: At a cut-off value of 0,100 µg/L sensitivity of S100B predicting pathologies in CT was 94,7% (100% for the group defined by SNC guidelines), while specificity was 17,6% (21,2% regarding SNC guidelines). Specificity for patients suffering polytrauma (n = 11) was 0%, for patients with multiple injuries (n = 41) it was 5,3%. All the four CT classifications correlated significantly (n = 110, p < ,01, R = ,376 to R = ,468) with S100B serum levels. Time from trauma to S100B sampling did not significantly correlate to S100B serum levels for patients without pathologies in CT scan (n = 23, p = ,429, R = -,173). However, time from hospitalization to S100B sampling did show a significant correlation (n = 91, p = ,006, R = -,287).

Conclusion: Extracranial injuries have a major influence on S100B serum values. Therefore, it must be concluded that a cut off value of S100B ≥ 0,100 µg/L is not suitable for patients with multiple injuries and further research is necessary for this group. Adjusted cut off values depending on the length of time between trauma and S100B sampling may potentially increase the specificity, however there are still too many uncertainties about the detailed kinetics of the S100B protein.

1. Introduction

Traumatic brain injury (TBI) is a common consequence of various accident types, potentially resulting in death or lasting severe damage. Therefore, a valid diagnostic pathway regarding the diagnosis, treatment, and monitoring of TBI is indispensable. In this context, the S100B protein represents one of the most promising biomarkers.

In the following section, we will look at the features of TBI, the characteristics of the S100B protein, and briefly examine the current state of relevant studies regarding the role of S100B in TBI.

1.1. Anatomical overview of the brain and its meninges

The human brain (encephalon) is located in the neurocranium. It is roughly divided into three major parts: the forebrain or prosencephalon (consisting of diencephalon and telencephalon), the midbrain or mesencephalon, and the hindbrain or rhombencephalon (consisting of the medulla oblongata, pons, and the cerebellum). Each of these parts is further subdivided into numerous structural and functional formations. (1)

To provide adequate blood supply and protect sensitive structures, the brain and the spinal cord are covered by the meninges, formed by three different integuments, as displayed in *Figure 1*. As the outermost layer, the cranial dura mater is located between the skull and the arachnoid mater. The dura mater can be divided into a periosteal and meningeal layer, which - as a result of separating these layers at specific locations - form several partitions like the falx cerebri, falx cerebelli, or tentorium cerebelli, as well as the cranial venous sinuses. The primary function of the firm and tough dura mater is to ensure mechanical stability and embed the meningeal arteries. The subtle and avascular arachnoid mater is located between the dura mater and the pia mater. The name of the arachnoid stems from the fact that its inward-facing trabeculae form a cobweb-like network. Like the dura, the arachnoid mater skips the brain's fissures, except the longitudinal fissure separating the two hemispheres. Finally, the pia mater is the innermost layer of the meninges and covers all the contours and fissures of the brain as a tightly fitting, soft, and thin membrane. (2)

As a result of this arrangement of meningeal layers, it is possible to differentiate between clinically highly relevant spaces. The epidural space, also known as extradural or peridural space, between the cranial bone and the periosteal layer of the dura mater, is typically closed by the strong attachment of these layers and may evolve into a blood-filled compartment in case of TBI. The virtual cavity between the meningeal layer of the dura mater and the arachnoid mater is called subdural space. In this context, the term “subdural hematoma” is misleading because this type of hemorrhage is caused by a dissection of the innermost part of the dura mater. (3) In classical literature, however, this discrepancy is hardly ever mentioned. (4) By the fact that the pia mater follows the contours of the brain, while the arachnoid

mater does not, a physiologically existing space between these layers, called “subarachnoid space,” can be described. The subarachnoid space contains blood vessels and cerebrospinal fluid (CSF), which is produced in the ventricles of the brain and drains off into the venous system through arachnoid villi. (3)

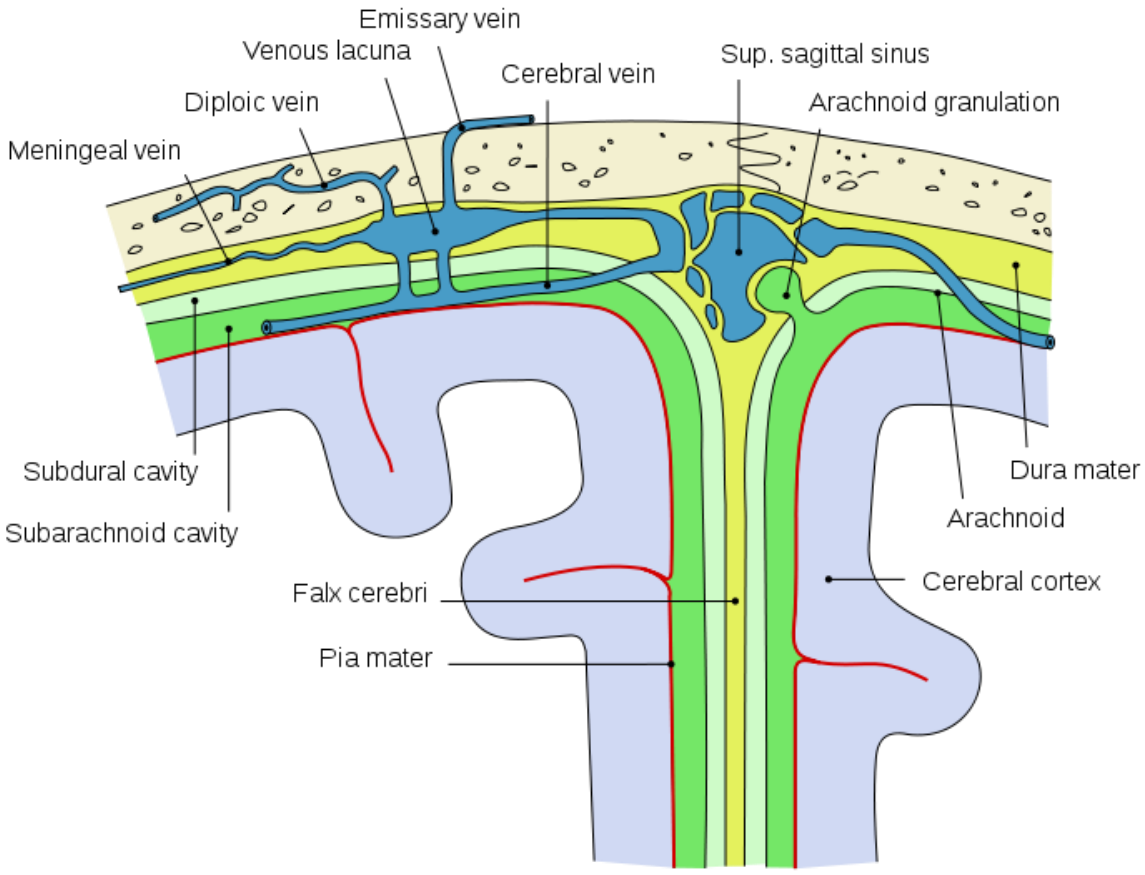

***Figure 1**: Schematic representation of the meninges and the spaces deriving of these.* (5)

1.2. Traumatic brain injury

The effect of externally applied force on the head can range from minor contusions without any neurological impairments to life-threatening bruises of the brain, which often end fatally. The loss of consciousness and amnesia (retro- and antegrade) are the main symptoms, which are often used to get an impression about the severity of the injury. Feared complications in the form of intracranial bleeding and neurological failures have to be monitored carefully. (6)

1.2.1. Epidemiology and causes

With a total estimated number of 2'095'353 hospital discharges and 82'546 deaths due to TBI per year in whole Europe (calculated by data of the year 2012), TBI represents one of the most frequent and, therefore, most important physical injuries. (7) By the fact that these numbers are calculated just based on cases who received medical care, it has to be assumed that total numbers are much higher, which is also reinforced by a recently published review. (8) TBI often results in permanent disabilities of young and older persons, which significantly impacts socioeconomic status. (9,10) While about 10% of all TBIs end fatal, 5-10% result in permanent severe disabilities and up to 40% lead to moderate neurological deficits. (11)

Depending on the source, the incidence of TBI in Europe ranges between 300 to 1'000 per 100'000 people, while the mortality rate is about 12 per 100'000 people. (7,8) However, there are notable changes between different countries, age groups, and genders (see *Figure 2*). Nearly two-thirds of TBI-related hospital discharges and deaths in total are related to men. In contrast, women are affected significantly more often at the age of 65 years or older. However, this must be explained by the gender distribution in this age group and not a higher risk of females at that age. Deaths caused by TBI make up 37% of all injury-related deaths in Europe. (7)

According to the age distribution of hospital discharges due to TBI, two peaks can be identified: The first high appears in the group of underage patients and young adults, the second one in the age group of 80 years and older. While the number of deaths within the group of minors is shown to be the lowest (about 6% of all TBI-

related deaths), patients over the age of 80 account for nearly one-third of all deaths associated with TBI. (7)

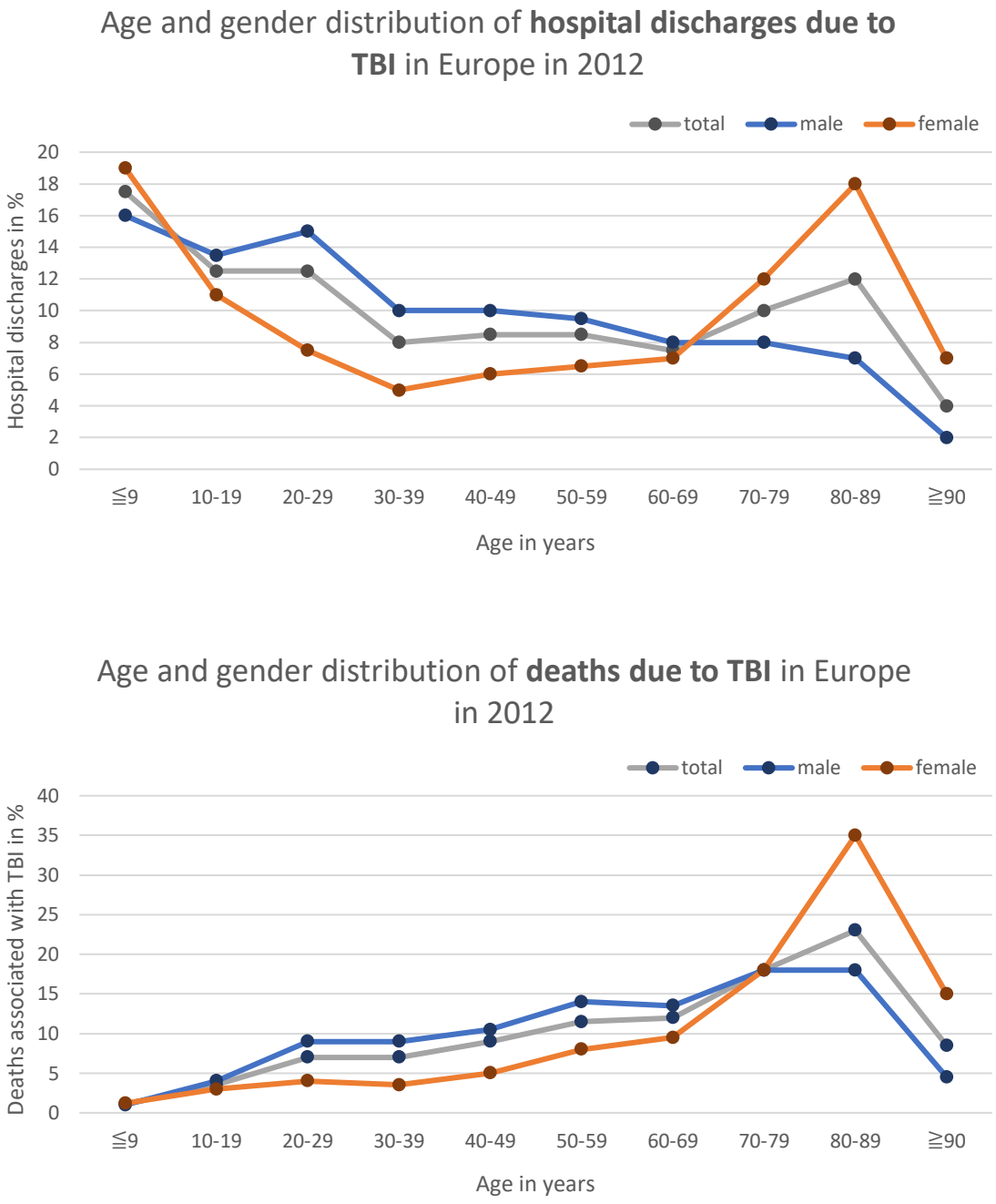

Figure 2: *Schematic illustration of age and gender differences regarding TBI constructed by data of 25 European countries. [Own representation based on Majdan et al. 2016, e78.* (7)*]*

Especially in wealthy countries like, e.g., Norway or Belgium, there is a temporal trend of decreasing incidence in children. In contrast, the incidence in older adults

appears increasing. (12,13) The reasons behind this course of events may be explained by effective prevention programs to protect children from injuries caused by falling. (12) In contrast, increased risk of falling and insufficient fall prevention measures along with higher life expectancy in the elderly generation are factors that may lead to the increase of incidence in that age group. (13) About 80% of all TBIs are classified as mild, whereas moderate and severe injuries have an approximately portion of 10% each. (14)

The leading causes of TBI can be divided into four main mechanisms: falls, road traffic accidents (RTAs), being struck by or against an object, and assault. (15) Despite significant differences between different countries, studies conclude that falls have replaced RTAs as the most frequent cause of TBI almost everywhere in Europe in the last decades. (7,16) In Austria, for example, during 2009 to 2011 80% of all hospital discharges and 43% of all deaths due to TBI were related to falls, whereas RTAs only accounted for 7% of hospital discharges and 17% of deaths. (17) The reverse trend is noticed if only moderate-to-severe and severe TBIs are being considered. In these cases, RTAs remain the leading mechanism of injury. (16) Regarding age-dependent correlation, children and older adults tend to suffer TBI most frequently by falls. At the same time, RTAs represent the leading cause of TBI in the age group of young adults. (16)

1.2.2. Classification

TBI can be classified by various criteria. The most common types are the characterization by mechanism, morphology, and severity (see *Figure 3*).

Mechanism

Foremost, a distinction can be made between *closed* or *penetrating head injury*. Closed head injury is characterized by an intact dura mater and is mostly caused by falls, RTAs, and assault. In contrast, penetrating head injury is accompanied by damage of the dura mater, usually due to gunshot and stab injuries. Intracranial air inclusions and CSF leak are confident signs of a penetrating injury. Furthermore, due to unavoidable infection of these open wounds, inflammatory processes like brain abscess, meningitis, encephalitis, or empyema are common complications of penetrating head injuries. (18,19)

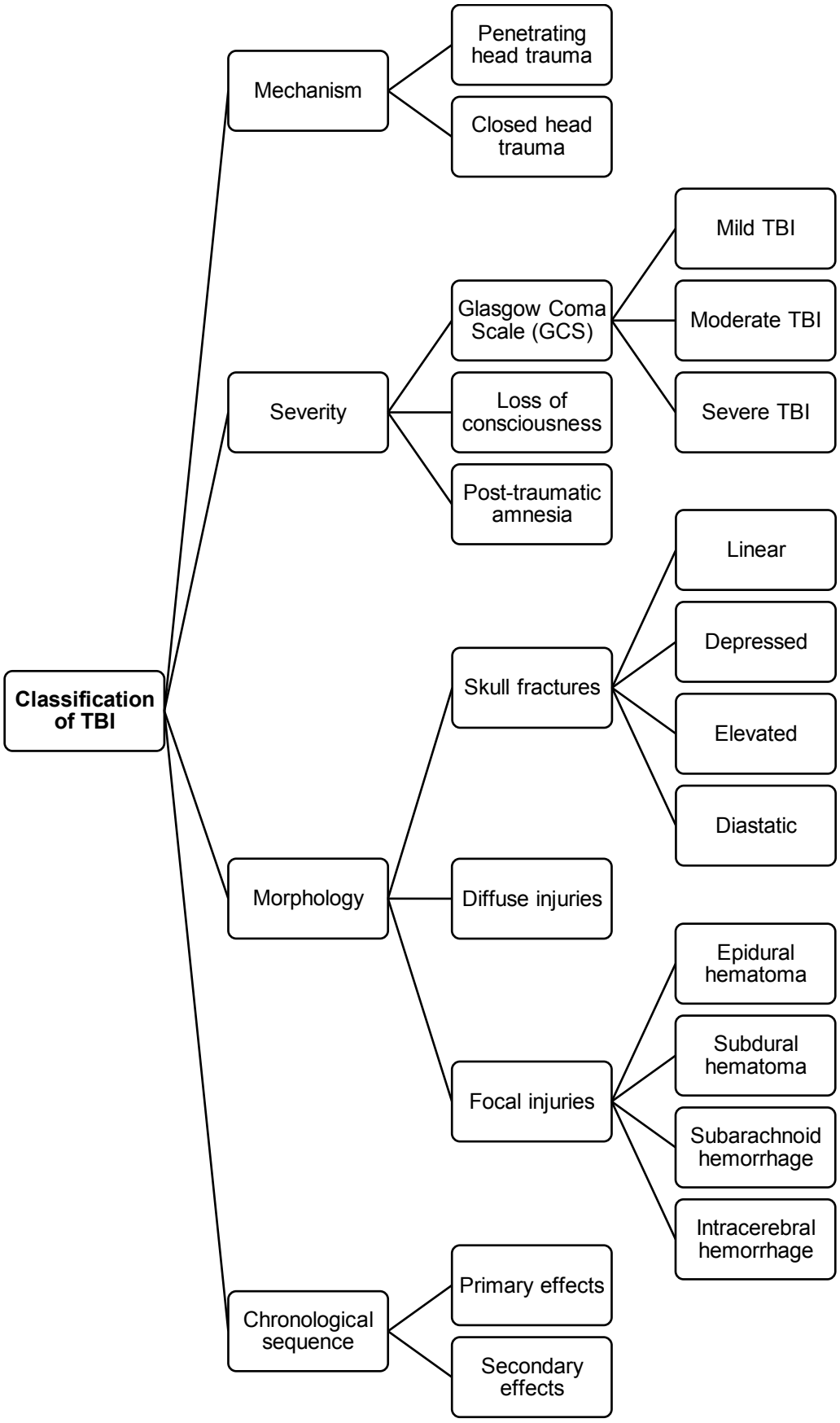

Figure 3: *Schematic overview of TBI classifications. [Own representation based on Bales et al. 2018, 368 added by information of Osborn 2017, 6.* (11,18)*]*

Some researchers suggest adding *blast-induced head injury* as another distinguished type of injury mechanism because of its specific properties. This makes sense, especially for institutions specialized in the treatment and follow-up care of veterans and victims of war related injury. (18)

Severity

The *Glasgow Coma Scale* or Glasgow Coma Score (both abbreviated “GCS” and used in the same context), published in 1974 (20), has meanwhile evolved into the international state-of-the art method of determining the degree of severity of TBI in the first place. (14) The GCS combines the examination of three components: Verbal, motor, and eye response. For each component, up to 6 points are assigned and added up to obtain a Score between 3 and 15 points. 3 points correspond to a fully comatose patient who neither opens eyes nor speaks nor reacts to pain stimulus. In comparison, a score of 15 points represents patients opening eyes spontaneously, being fully oriented, and obeying commands. (For a detailed description of the GCS, see *Table 1*) (18)

Although it is an undemanding procedure to perform, some specific score characteristics must be kept in mind. Firstly, it is important always to use the best responses when assigning points of the three components. Situations in which the score is not meaningful or even not possible to be determined are: intubated patients, who cannot be evaluated for a verbal response, or patients under sedation induced by medical drugs, which results in false low scores. Furthermore, it must be noted that the GCS depends heavily on the moment of determination and, therefore, can change rapidly within hours. As a result of this volatility, the value of the GCS regarding outcome prediction has to be considered with precaution. (14)

Besides these downsides, the GCS is a reliable tool to evaluate TBI severity and detect both worsening and improvement. Particularly, the decisions in the early phase of treatment can be supported by the GCS. (21) Easy and fast handling, as well as the simple information transfer between physicians and departments, supported the GCS as a popular evaluation method during the past few decades. (22)

***Table 1**: Glasgow Coma Scale*

Feature	***Response***	***Points***
Best eye response	Open spontaneously	4
	Open to sound	3
	Open to pressure	2
	No response	1
Best verbal response	Oriented to time, place, person	5
	Confused	4
	Inappropriate words	3
	Makes sounds	2
	No response	1
Best motor response	Obeying commands	6
	Localizing to pain	5
	Normal flexion to pain	4
	Abnormal flexion to pain	3
	Extension to pain	2
	No response	1
GCS = [Best eye response] + [Best verbal response] + [Best motor response]		
Worst Score = 3. Best Score = 15.		

The most common way to initially classify TBI is by applying the GCS and thereby differentiating between three degrees of severity:

- ***Severe TBI: (GCS 3-8)***

  With a GCS < 8, this category represents comatose patients, which have a high mortality and risk of severe, long-lasting damages. Therefore, comprehensive management concepts are indicated for these patients to achieve the best possible outcome.

- ***Moderate TBI: (GCS 9-13)***

  About 10% of TBI patients can be assigned to this group. They are typically not intubated and must be monitored carefully due to the risk of deterioration. Computed tomography (CT) scan is a standard tool in the diagnostic work-up of moderate TBI.

- ***Mild TBI: (GCS 14-15)***

  The vast majority of TBIs are considered mild, mostly simple concussions. Often these cases do not seek medical care. The need for CT scans is discussed within this group.

[Classification based on Bales et al. 2018. (18)*]*

Patients with a GCS of 13 are classified variably, either into the group of moderate or mild TBI, depending on the source. It is also a matter of discussion about whether it is useful to distinguish between mild and moderate head injury. Current trends aim to fuse these two groups. (18)

In some parts of Europe, especially in the German-speaking area, another similar classification system based on the timely length regarding the presence of symptoms exists, differentiating between 1st (concussion), 2nd (contusion), or 3rd (compression) degree of severity. This approach comes with several downsides and is considered obsolete and recommended to be replaced with the internationally recognized classification based on the GCS. (14)

Pathological features

Traumatic intracranial bleeding can occur in different morphological ways depending on the location of injured blood vessels. These types of bleedings can be classified by the affected tissue layer. (See *chapter 1.1* for the anatomical description of these spaces.)

Epidural hematoma:

The epidural hematoma (EDH), localized between the skull and the dura mater, can be either caused by arterial or venous bleeding mostly due to a skull fracture. More frequently, EDH is a result of an injury of the middle meningeal artery or one of its branches. Formation of the arterial EDH is usually fast and therefore, early detection is possible. About 10% of EDHs are due to dural venous sinuses damage. A delayed occurrence several hours after the injury is commonly seen especially in the venous EDH and its detection is of high importance, in order to prevent serious, life-threatening complications. Typical early symptoms include impaired consciousness, occurring with two peaks separated by a lucid, symptom-free time interval lasting several hours, headache, and vomiting. (14,19,23,24)

Aside from clinical examination and neurological assessment, which focuses on the appearance of anisocoria and hemiparesis, radiological diagnostics is the method of choice for diagnosing EDHs. (19) A cranial computed tomography (cCT) scan is primary performed in the acute stage, while magnetic resonance imaging (MRI) is recommended for the chronic stage. In cCT, the acute EDH presents as a biconvex, hyperdense expanding lesion, as seen in *Figure 4*, and is limited by cranial sutures except in case of the presence of sutural diastasis. However, the density of the hematoma on the cCT image decreases over time, so chronic lesions appear hypodense. EDH usually occurs unilateral and is mostly located in the temporoparietal region, along the middle meningeal artery pathway. Only rarely it is found frontally. Supratentorial hemorrhage are five times more frequent than infratentorial hematomas. (23,25)

About two-thirds of patients suffering EDH are younger than 40. Men are five times more frequently affected than women. (19)

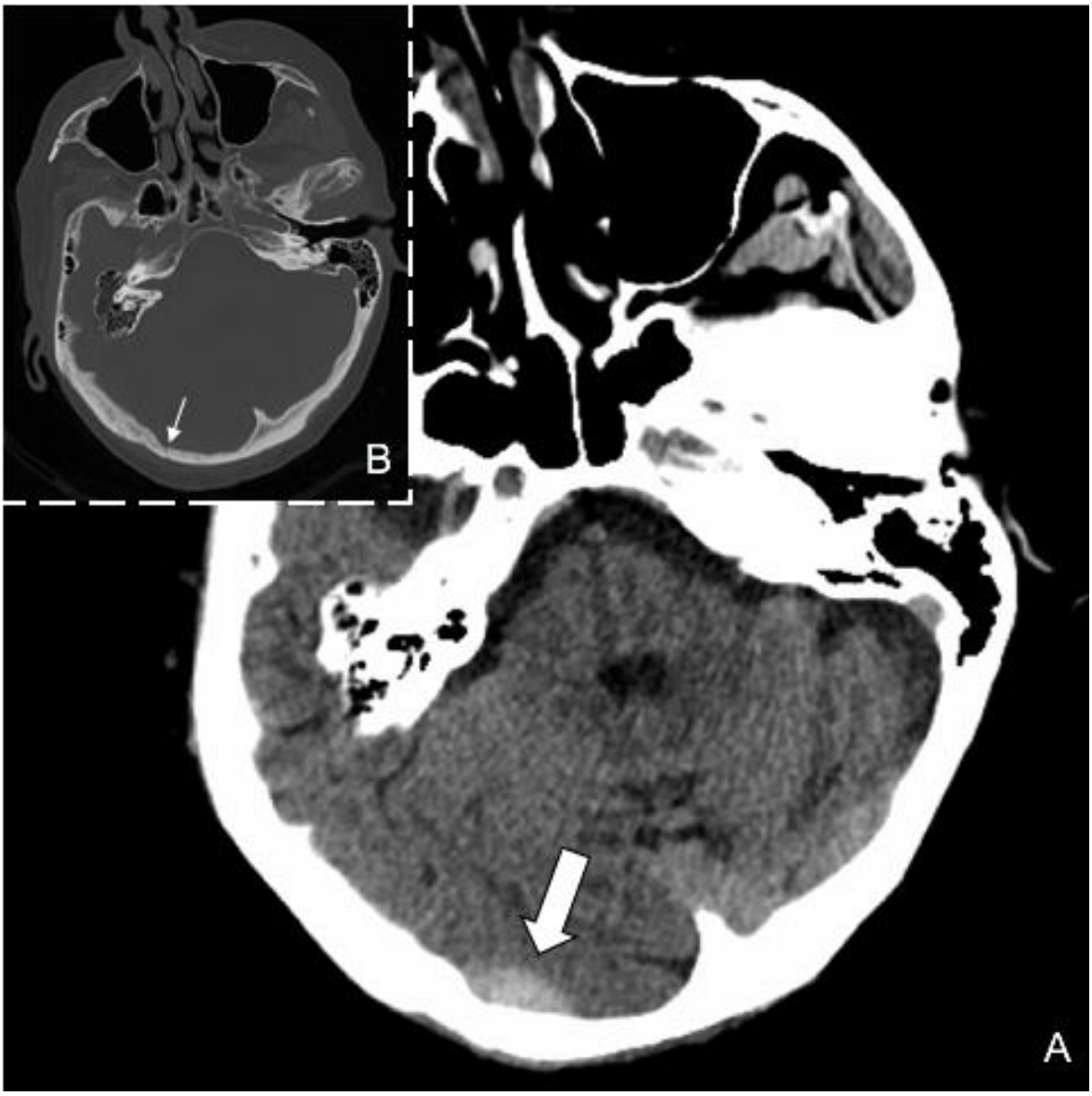

Figure 4*: An 83-year-old male with epidural hematoma of the posterior fossa.*

A) Axial CT image in “brain window” at the level of the posterior fossa on the right side shows convex, lens-shaped hyperdense structure in the epidural space corresponding to epidural hematoma (filled arrow).
B) Axial reconstruction in “bone window” shows nondisplaced “hairline” fracture of the occipital bone causing epidural hematoma (arrow).

Subdural hematoma:

In contrast to the EDH, the subdural hematoma (SDH) course can vary widely. The acute SDH is characterized by a development within a few hours up to days, while the chronic form may even occur several weeks after the initial injury. Progressive impaired consciousness, homolateral mydriasis, and contralateral hemiparesis are typical symptoms of an acute SDH. Contrarily, neurological signs of a chronic SDH

are often much more unspecific and can be easily misinterpreted as symptoms of a stroke or transitory ischemic attacks. The chronic SDH is in many cases caused by minimal traumas, which are often unrecognized by patients. (14,19)

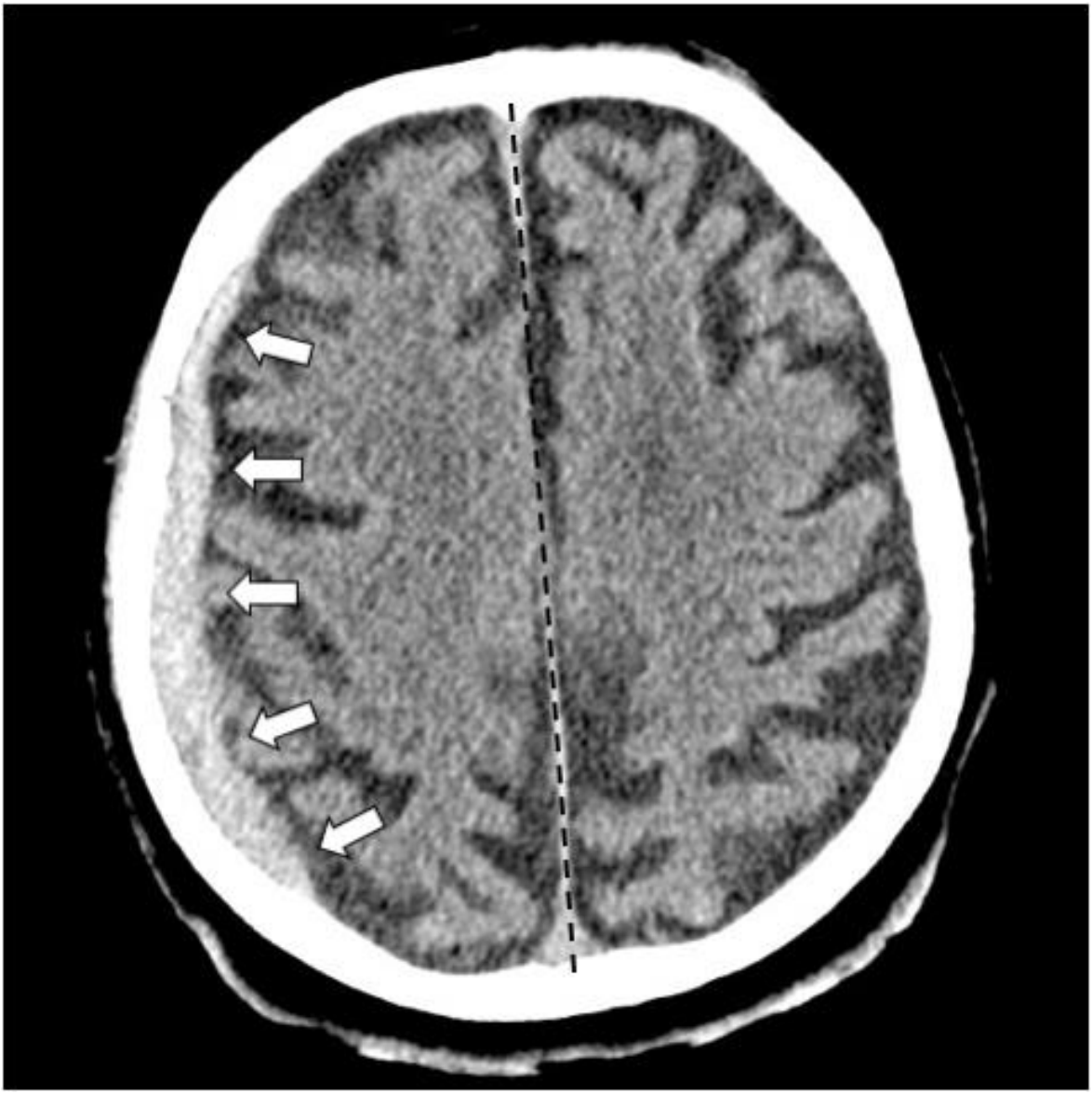

Figure 5*: A 93-year-old male with acute subdural hematoma.*

Axial CT image in “brain window” shows crescent-shaped homogenously hyperdense collection located in subdural space spreading diffusely over the right hemisphere (filled arrows) without midline shift (broken line).

The SDH is caused by tearing of bridging cortical veins, which lead to the accumulation of blood in the subdural space (a topic of controversy – see *chapter 1.1* for more information). Sometimes the arachnoid mater may also be affected, which results in additional leakage of CSF within. (4) The SDH is mostly located supratentorially, in the temporoparietal, or high parietal region. The majority of SDHs

in adults are located unilateral, while in infants, a bilateral occurrence is more frequent. In cCT, the SDH is characteristically crescent-shaped with an outer convex and inner concave shape (see *Figure 5*). Unlike the EDH, the SDH is not limited by sutures and may even stretch along the falx cerebri. In the acute stage the hematoma appears hyperdense in the cCT scan, whereas the chronic SDH is hypodense with potentially inhomogeneous density values caused by repeated hemorrhage. The use of contrast agents may help to detect subdural empyema or isodense, small lesions. MRI scans are rarely necessary and can be used to diagnose very narrow lesions or subacute SDHs without visible density changes in the cCT. (4,25)

SDH occurs in every age group and is present in 10 to 20% of all TBIs, with fatal outcomes in about a third of all cases. (4)

Subarachnoid hemorrhage:

Another important, differentiable type of bleeding in head trauma is the subarachnoid hemorrhage (SAH). SAH can be caused either non-traumatically mostly by a spontaneous rupture of an aneurysm, or traumatically. (26) 11 to 60% of patients suffering TBI sustain traumatic subarachnoid hemorrhage (tSAH). (27) Note that in the event of TBI, it sometimes appears unclear, whether SAH represents the trigger of the incident or whether it is the consequence of TBI. (28)

SAH is defined as an accumulation of blood within the subarachnoid space, synonymous with the outer cerebrospinal fluid space. Rarely, in a trauma setting, tSAH occurs isolated, while it is more commonly associated with contusions. tSAH can be often located in the cerebral sulci (as seen in *Figure 6*) or, less frequently, in the basal CSF cisterns or Sylvian fissure. Thunderclap headaches in combination with meningism are the typical leading symptoms of SAH. Thus, regarding the symptom resemblance, it is often necessary to rule out meningitis in the non-traumatic setting. (19,26,27)

Due to its availability worldwide, CT is the diagnostic tool of choice in TBI. However, due to a mixture of CSF with blood, higher blood density values are necessary to identify SAH in cCT scan. To categorize the amount of blood in cCT scan, the (modified) Fisher Scale is used to differentiate between four grades of SAH,

correlating with the risk of vasospasm. MRI is not only of higher sensitivity than cCT scan in detection of these hemorrhages, but also more capable in the detection of the causative injury. Besides the CT scan and MRI, a spinal tap can be used to prove the presence of SAH, especially in cases with unclear imaging. The digital subtraction catheter angiography poses the gold standard in the precise characterization of the underlying vascular pathology in non-traumatic SAH. (25,29)

Hydrocephalus formation and cerebral vasospasm are common complications of tSAH. The prognosis heavily depends on the degree of injury. (26,30)

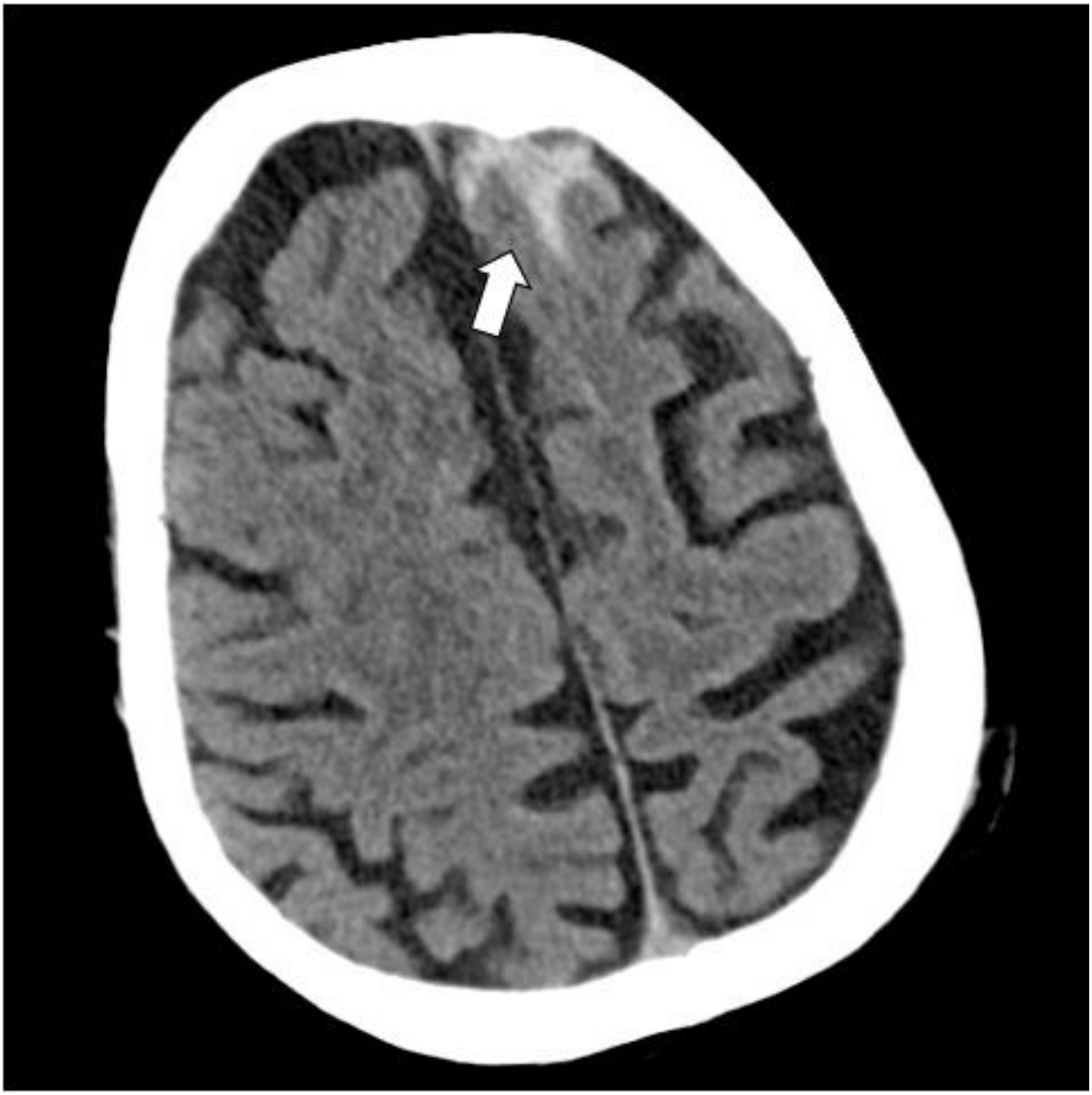

Figure 6*: A 99-year-old female with traumatic subarachnoid hemorrhage.*

Axial CT image in “brain window” shows hyperdense material filling the subarachnoid space along the left frontal lobe representing pooling of the blood (filled arrow).

Intracerebral hemorrhage:

Traumatic intracerebral hemorrhage (ICH) is a bleeding within the cerebral parenchyma often associated with cerebral contusion. Penetration of the inner cerebrospinal fluid space may additionally occur. ICH is usually located in the cortical area of the frontal or temporal lobe. The formation of ICH is believed to be either due to a traumatic rupture of a distant blood vessel or increased vascular permeability in the region of contusion. (19)

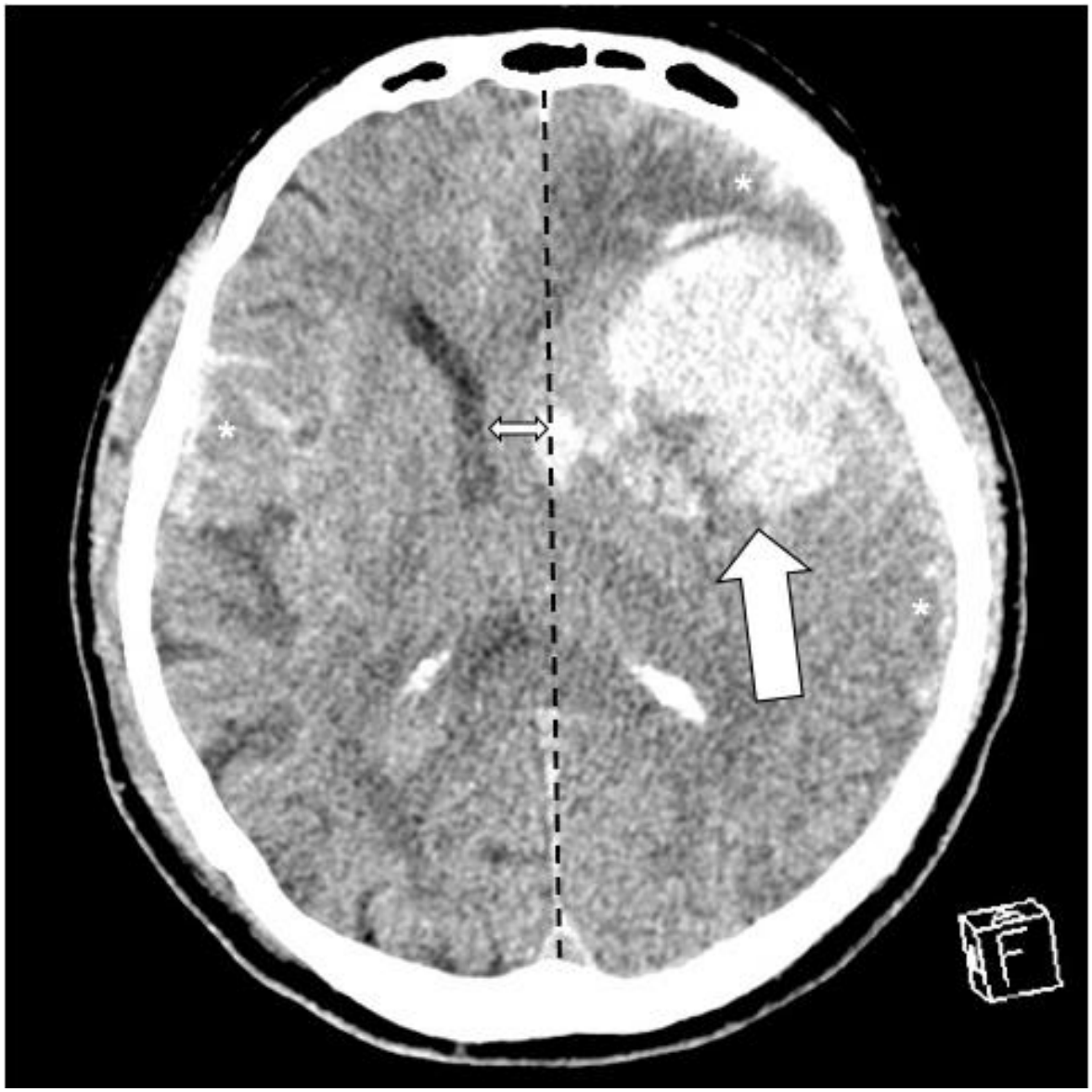

Figure 7*: A 79-year-old male with traumatic intracerebral hemorrhage.*

Axial CT image in “brain window” shows hyperdense collection of the blood in the posterior left frontal lobe (filled arrow) with edema of the surrounding parenchyma, compression of the ventricular system and contralateral midline shift of 9 mm. Diffuse subarachnoid hemorrhage (asterisks) is seen along both hemispheres.

Symptoms of ICH are strongly influenced by the extent and localization of the hemorrhage. Clinical signs suggesting ICH in varying degrees are headache, the loss of consciousness, or focal neurological failures like hemiparesis and aphasia. The extent of ICH may increase for up to four days, with a variety of imaging findings, in this period. (14,18,19) In cCT scans (see *Figure 7*), acute intracerebral bleeding is characterized by typical hyperdense areas in the coup or contrecoup region, often combined with perifocal or generalized edema. In case of ventricular rupture, blood levels in these inner cerebrospinal fluid spaces may be seen. MRI scan utilizes special sequences like susceptibility-weighted imaging (SWI) or gradient-echo (GRE) in the detection of small, punctiform bleedings, which are often not visible in the cCT scan. (31) Such minute lesions can be associated with significant clinical impairment and are therefore important to be diagnosed. In follow-up scans, weeks or months after the injury, the primary zone of contusion remains visible as a hypodense substance defect. (19,25,32)

The need for surgical treatment depends on factors like the hematoma size or increased intracranial pressure. ICH affects especially young males and older people and is lethal in up to 60% of all cases. (19)

Chronological sequence of injury, pathophysiology

Similar to the classification by morphology, it is possible to divide TBI chronologically between primary and secondary effects.

Primary head injuries:

Injuries, which emerge immediately after the initial head trauma - even if they are not detectable in the early examination - are defined as primary head injuries. The cause can be due to either direct or indirect trauma. Direct traumas like motor vehicle accidents or falls, which result in strong blows on the head, mostly lead to hematomas, skull fractures, or scalp lacerations. The pathomechanism behind these injuries often is the coup-contrecoup effect, which is described by a first hit on the brain at the region of impact and a second peak load exactly on the opposite side of the head. (18,33)

Effects of indirect trauma are characterized by rough distortion and deformation of the brain. This often comes from rapid deceleration or acceleration and strong linear

or rotational forces, which do not involve direct blows on the head. These forces may lead to damages of blood vessels, axons, or the cortex. In this way, severe, life-threatening brain injuries can occur even without fractures or visible outside lesions. (33)

In conclusion, the most common primary effects of head trauma are scalp and skull injuries, extra-axial hemorrhages (see chapter above: *Pathological features*), and parenchymal injuries like contusion or diffuse axonal and vascular injury. Another large group of primary injuries is associated with missile and other penetrating head injuries. (33)

Secondary head injuries:

After the initial effects of brain trauma, different pathophysiological processes may occur in the following days and months. Apart from the progression of hemorrhages, which usually occurs within the first hours after the trauma, other rapidly developing complications include brain swelling or all types of herniation syndromes. Additionally, CSF leaks or intracranial hypotension may appear after weeks or months. Finally, with a significant latency of years, different types of posttraumatic encephalopathic syndromes may arise as late consequences of TBI. (34)

The formation of secondary tissue damage, like necrosis of the parenchyma, is primarily explained by impaired venous and arterial circulation. Cerebral edema is a major contributing factor to this process. The exact mechanism behind traumatic brain edema is still not fully clarified but is considered to be caused by cytotoxic and not vasogenic effects in the early phase. As a result of the edema, the brain tissue is compressed, which leads to ischemia. This lack of oxygen can again boost the development of the edema – a vicious circle. Late effects (after about six weeks) of brain edema include a decrease of the brain marrow, which can be detected in CT as a hydrocephalus internus and coarsening of the cerebral folds. Other non-cerebral factors like systemic blood pressure or cardiac performance also greatly influence the progression of secondary brain injuries. (35)

While primary effects of head trauma cannot be therapeutically prevented or influenced, early recognition and sufficient treatment of secondary effects are essential to avoid severe, long-lasting damages. Teamwork between radiological evaluation and clinical treatment regarding the proper handling of elevated

intracranial pressure and oxygen deficiency is obligate in these cases of severe TBI. (34)

1.2.3. Therapy

The therapy of TBI strongly depends on the severity and morphology of the trauma. The treatment of mild TBI is usually based on pain management with analgesics like paracetamol. Inpatient admission is usually only necessary in patients older than 65 years or the presence of other risk factors like current anticoagulation or substantiated skull fracture. These patients should be at least observed for 24 hours with particular attention to the possible occurrence of impaired consciousness or suspicious reactions of the pupils. (19)

In contrast, the management of severe TBI requires all kinds of therapeutic interventions. The main objective of these measures is the prevention of cerebral hypoxia. The treatment begins with the emergency care at the place of the accident, where clear airways, adequate oxygen supply, and analgosedation are obtained as soon as possible. Moderate elevation (30-35 degrees) of the upper body supports venous drainage in the head and, therefore, can help avoiding brain edema. In the follow-up, monitoring body temperature, and blood glucose is of high significance because fever and hyperglycemia can worsen brain damage. Radiological imaging with cCT scan should be performed not only initially but also in the course to detect developing pathological changes of the brain. (19)

Lowering of the cerebral pressure can be obtained in the near term by moderate hyperventilation – note that the pressure should not fall below 30 mmHg, because this can result in dangerous cerebral vasoconstriction – or in the longer term via liquor drainage, which has to be controlled by pressure measuring with an intracranial probe. If these approaches are still insufficient in controlling high cerebral pressure, high-dose barbiturates or decompressive craniotomy are needed as instruments of last resort. The further treatment of TBI involves physiotherapy exercises, speech therapy, and other wide-ranging rehabilitation measures. Cerebral hemorrhages are primarily surgically treated. Exceptions are cases of very small hematomas without elevated intracranial pressure and tSAH, which is usually treated conservatively. (19)

1.2.4. Clinical practice guidelines regarding the diagnostic use of CT scan

Since minor head injuries characterized by GCS scores of 13 to 15 often present without clinically important findings in the cCT scan (36,37), useful decision-making tools to avoid those unnecessary CT scans are needed. Therefore, in this work, we will discuss some of the most established guidelines and give an overview of their characteristics:

Canadian Head CT Rule

The Canadian Head CT Rule (CCTHR), published in 2001 by Stiell et al., is a widely acknowledged clinical decision tool used for adult patients with minor head injuries. The CCTHR is based on a prospective study, carried out in 10 Canadian hospitals with a total of 3'121 patients. (37)

Inclusion criteria were head injuries within the last 14 hours, GCS scores of 13 to 15, blunt head traumas with at least amnesia, loss of consciousness or confusion, and a minimum age of 16 years. Exclusion criteria included the use of oral anticoagulants, bleeding disorders, or seizures after the injury. (37)

The CT Rule itself differentiates between high-risk criteria for neurosurgical intervention and medium-risk criteria for positive CT findings:

The high-risk factors include

- GCS scores below 15 at 2 hours after the injury,
- suspected depressed or open skull fracture,
- any signs of basal skull fracture (like hemotympanum, CSF rhinorrhea or otorrhea, raccoon eyes, or Battle's sign)
- 2 or more episodes of vomiting,
- or patients aged 65 or older.

These high-risk factors had 100% sensitivity and 68.7% specificity for identifying the need for neurological intervention. (37) Several studies showed similar reproducibility. (36,38–40)

To rule out important findings of brain injury in CT, medium-risk factors, including

- retrograde amnesia to the accident of at least 30 minutes,

- or dangerous injury mechanism (for instance, fall from height more than 3 feet or 5 stairs, a pedestrian struck by a motor vehicle, or ejection of occupants from a motor vehicle),

should additionally be assessed. The sensitivity of these medium-risk factors for clinically important CT findings was 98.4%, while the specificity was 49.6%. (37)

The consequent recommendation of the CCTHR is, that if any of the risk factors mentioned above are present, a CT scan should be performed.

New Orleans Criteria

In contrast to the CCTHR, New Orleans Criteria (NOC), as another clinical decision tool, only includes patients with GCS scores of 15. Further inclusion criteria of NOC are the age of at least 18 years and blunt head trauma within the last 24 hours associated with amnesia, loss of consciousness, or disorientation. (41)

NOC defines seven variables, whose presence advises a cCT scan: (41)

- age > 60 years
- headache
- vomiting
- seizure
- physical evidence of trauma above the clavicles
- drug or alcohol intoxication
- deficits in short-term memory

Several studies showed that on the one hand NOC has a similar level of sensitivity as CCTHR (82%-100%), but on the other hand, it has significantly lower specificity (3%-28%). (36,39,40,42) However, a recent study by Ro et al. questions these results, especially regarding sensitivity of CCTHR. (43)

National Emergency X-Radiography Utilization Study II

The National Emergency X-Radiography Utilization Study II (NEXUS II) was a multicenter study (21 emergency departments) in the United States of America and Canada based on data of 13’728 patients. NEXUS II demonstrated eight clinical

characteristics to predict the need of CT scans in patients who suffered from blunt head trauma. (44,45)

If any of the following criteria are present, a cCT scan is recommended: (45)

- Age ≥ 65 years
- evidence of significant skull fracture
- scalp hematoma
- neurologic deficit
- altered level of alertness
- abnormal behavior
- coagulopathy
- persistent vomiting

The sensitivity of these criteria for predicting substantial intracranial injuries was 98.3%, and specificity was 13.7%. (45)

Scandinavian Neurotrauma Committee guidelines

The Scandinavian Neurotrauma Committee (SNC) introduced evidence-based guidelines for managing patients with moderate, mild, or minimal head trauma in 2000. (46) After an update in 2013, SNC introduced S100B serum level into their guidelines, as a biomarker of brain injury and unique clinical decision-making tool. (47)

SNC guidelines provide criteria for CT scan requirement, admission, discharge, and monitoring of the patients. (47) In this work, we primarily focus on the principles pertaining to CT scan selection.

The most recent version of the SNC guidelines includes all adult patients with GCS scores of 9 to 15 within 24 hours after trauma. In patients with moderate TBI (GCS 9-13) it is always advised to perform cCT scan, initially and during consequent admission. Patients with GCS scores of 14 to 15 are divided into four groups with the following rules: (47)

High-risk patients (GCS 14-15) with:

- seizures after trauma
- focal neurological deficits

- signs of basal or depressed skull fracture
- hydrocephalus treated with a shunt
- coagulation disorders or therapeutic anticoagulation

cCT scan is advised with consequent admission regardless of radiological findings.

Medium-risk patients (GCS 14-15) with:

- no high-risk factors (mentioned above)
- age ≥ 65 AND medication with anti-platelet drugs

cCT scan is advised, but the patients are discharged only if CT is normal. Alternatively, observation is considered for at least 12 hours.

Low-risk patients (GCS 14-15) with:

- no high-risk or medium-risk factors
- Loss of consciousness confirmed or suspected
- vomiting ≥ 2 episodes

Performing S100B-sampling (see *chapter 1.3*) is advised if the event of trauma was not more than 6 hours ago and no extracranial injury is clinically apparent (in these cases: cCT scan is advised). If S100B is < 0.100 µg/L, discharge of the patient with written and oral instructions is advised. If S100B is ≥ 0.100 µg/L, a cCT scan is mandatory, and the patient can be discharged only if CT is normal, or observation for at least 12 hours is considered.

Patients with minimal head injury (GCS15) with:

- no high, medium, or low risks

Discharge is advised with written and oral instructions.

A validation study presented a sensitivity of SNC guidelines for predicting traumatic CT abnormalities of 97% and specificity of 34%. (48)

To conclude, there is a wide range of decision-making tools regarding CT use for patients with moderate, mild, or minimal TBI. Various studies showed similar results for sensitivity and specificity of CCTHR, NOC, NEXUS-II and SNC guidelines despite their different structures - concluding no tool to be superior. (49–51)

1.2.5. Radiological Interpretation Systems

In the assessment of cCT, different scores can be used to score TBI radiologically. In this work, we evaluated the efficacy of four popular scores, described in the following section:

Marshall CT Classification

The Marshall CT classification, published in 1992 and still used widely today, is a tool to differentiate between six classes of TBI based on certain features in cCT. (52) While the classification initially was not intended for prognostic purposes, several studies showed that the Marshall CT classification could predict the outcome of patients suffering TBI. Although, more current scoring systems are meanwhile considered to be more accurate in that sense. (52–55)

Structure of the Marshall CT classification: (52)

- Diffuse injury I:
    - No intracranial pathology seen on CT scan
- Diffuse injury II:
    - No high- or mixed-density lesion > 25 cm^3
    - Cisterns remain visible
    - Midline shift ≤ 5mm
- Diffuse injury III:
    - No high- or mixed-density lesion > 25 cm^3
    - Cisterns compressed or absent
    - Midline shift ≤ 5mm
- Diffuse injury IV:
    - No high- or mixed-density lesion > 25 cm^3
    - Midline shift > 5mm
- Evacuated mass lesion (often labeled “V”):
    - Any surgically evacuated mass lesion
- Non-evacuated mass lesion (“VI”):
    - High- or mixed-density lesion > 25 cm^3
    - Not surgically evacuated

Rotterdam CT Score

The Rotterdam CT score was published in 2005. It was generally based on the principles of the Marshall CT classification with additional features like the presence of intraventricular hemorrhage and tSAH. Unlike its predecessor, the Rotterdam CT score comes as an ordinal score and was intended to be used as a prognostic tool from the beginning. (56)

To calculate the Rotterdam CT score (1-6), the following scoring items – plus 1 to the total – are added up: (56)

- Basal cisterns:
    - 0: normal
    - 1: compressed
    - 2: absent
- Midline shift:
    - 0: shift ≤ 5mm
    - 1: shift > 5mm
- Epidural mass lesion:
    - 0: present
    - 1: absent
- Intraventricular blood or tSAH
    - 0: absent
    - 1: present

Multiple studies showed that the score is helpful to predict short-term mortality and the overall prognosis of patients suffering TBI. (56–58)

Stockholm CT Score

Introduced in 2010, the Stockholm CT score focuses more precisely on the presence and extent of tSAH or intraventricular hemorrhage (IVH) visible in cCT scan by obtaining a separate tSAH score. (59) In contrast to the Marshall CT classification and Rotterdam CT score, it makes use of the midline shift as a continuous variable and furthermore adds diffuse axonal injury to its score. Compared to its predecessors, the overall result is a score that makes possible a better prediction of outcome of patients with TBI. (55,59)

Calculation of the Stockholm CT score: (55)

- Tally = [midline shift (in mm) / 10] + [*tSAH score* (range: 0-6) / 2] - [1 if EDH] + [1 if diffuse axonal injury (brain stem, splenium, or basal ganglia)] + [1 if dual-sided SDH] + [1]
- *tSAH score*: [SAH in convexities (1 if 1-5 mm, 2 if > 5 mm)] + [SAH in basal cisterns (1 if 1-5 mm, 2 if > 5 mm)] + [IVH (2 if present)]

Helsinki CT Score

One of the latest (published in 2014) scoring tools regarding TBI is the Helsinki CT score. Based on Marshall CT classification and Rotterdam CT score, the Helsinki CT score differentiates between more types of mass lesions. (60) It was developed to allow a more accurate long-term prediction for patients suffering TBI than older scoring tools, which was confirmed by several validation studies. (55,60–62)

The Helsinki CT score (sum score: -3 to 14) is structured as follows: (60)

- SDH:
  - 0: absent
  - +2: present
- ICH:
  - 0: absent
  - +2: present
- EDH:
  - 0: absent
  - -3: present
- Hematoma volume:
  - +2: > 25 cm^3
- IVH:
  - 0: absent
  - +3: present
- Basal cisterns:
  - 0: normal
  - 1: compressed
  - 5: absent

1.3. S100B

1.3.1. Characteristics and functions of S100 proteins

The S100B protein is part of the S100 family, first detected in three animal species by Moore in 1965. (63) S100 proteins were initially found both in the central (CNS) and in the peripheral nervous system (PNS) but were meanwhile proven in other organ systems like, e.g., striated muscle tissue or adipocytes. (63–65) The name “S100” was given since the protein is soluble even in 100% saturated ammonium sulfate. (63) Counting to the calcium-binding EF-hand proteins (helix-loop-helix structural motif), we currently know 24 members of the S100 protein family. (66,67)

With an atomic mass between 9 and 13 kDa per monomer, the majority of the proteins of the S100 family are present as homodimers (see *Figure 8*) or, more rarely, as heterodimers. Each monomer, formed by two EF-hands, can bind two calcium ions or, as studies have shown, even zinc or copper ions. (68–71) There are several variations of alpha and beta subunits, leading to the wide range of the S100 family. (72–74)

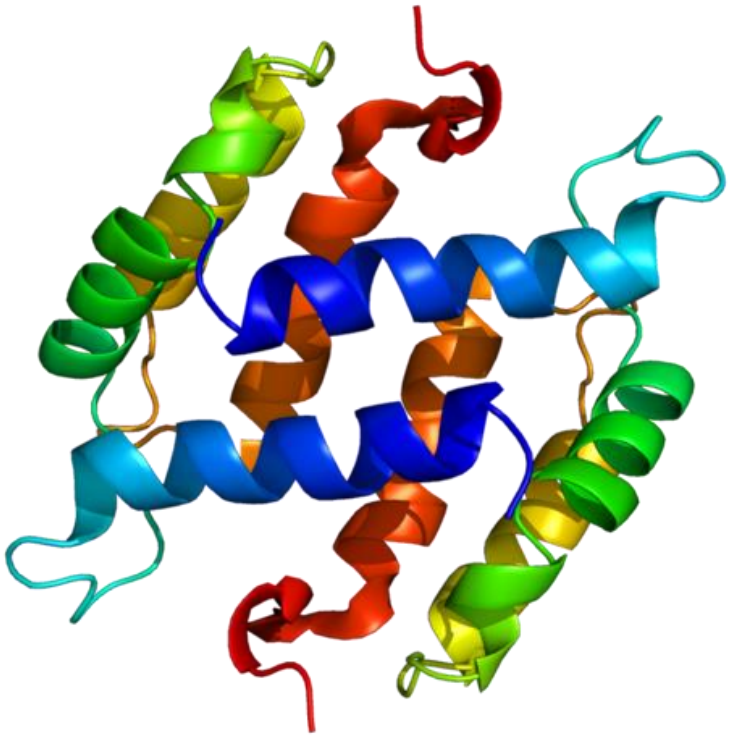

***Figure 8**: The dimer structure of the S100B protein.* (75)

Calcium-binding S100 proteins play a significant role in intracellular and extracellular processes. Although there is still a lot of research ongoing, it is already known that S100 proteins regulate calcium homeostasis and diversity of important cell functions like differentiation and proliferation. (66) Certain S100 proteins are actively involved in inflammatory responses and tissue injury reactions and therefore regarded as damage-associated molecular pattern molecules (DAMPs). They can even operate as growth factors in the regeneration after tissue damage. (66,76–79)

S100 proteins act on several surface receptors by executing these extracellular functions like different types of toll-like receptors (TLRs), receptors for advanced glycation end-products (RAGE), or scavenger receptors - either by direct transmittance or indirectly via signal potentiation of receptor ligands. (66,79–81)

A fact of clinic interest is that certain S100 proteins are overexpressed in the case of pathologies such as neurodegenerative diseases or tumor development. Especially when it comes to the role of individual S100 proteins in tumor suppression or progression, there will be a lot of research in the upcoming years relating to potential new therapeutic options by inhibiting or stimulating the activity of exactly these proteins. (66,70)

1.3.2. The S100B protein

S100 calcium-binding protein B, earlier called S100β, is a homodimer consisting of two beta subunits with a total atomic mass of 21 kDa. (82) However, in today's usage, the term "S100B" also includes the S100αβ heterodimer. (83) The beta subunit gene is located in the chromosomal region 21q22 unlike the other S100 proteins, which are located within a cluster in the 1q21 region. (84,85)

For a long time, it was a misbelieve that S100B is strictly present in nervous tissue (63) until studies in the 1980's discovered that the protein could also be found in the skin and other tissues. (86,87) As reviews showed, S100B is specifically high concentrated in glial cells with mature astrocytes as main representatives. Other neural cells in which S100B was repeatedly proved are oligodendrocytes, Schwann cells, ependymocytes, pituicytes, and enteric glial cells. Beyond the nervous system, the protein has been determined in many different cell types such as

Langerhans cells, melanocytes, chondrocytes, adipocytes, or skeletal muscle satellite cells. (65,86)

On the one hand, S100B is released by cells affected by tissue damage, which is the mechanism we are particularly looking at in this thesis. On the other hand, S100B is considered to act as a signal molecule both intracellularly and extracellularly. (65)

Although the intracellular functions are not finally concretized, it seems to be proven that S100B plays an important role in processes like differentiation and proliferation. (65) The complexity of its intracellular functions is underlined because S100B interacts with several target proteins in either calcium-dependent or calcium-independent manner. (88)

The extracellular effects of the protein are transmitted in an autocrine, paracrine, and - still discussed – endocrine way. (65,86) Low (nanomolar) concentrations of S100B are associated with trophic processes like securing neuron survival or regulating muscular regeneration. On the contrary, higher (micromolar) concentrations lead to toxic effects like the release of nitric oxide (NO) from astrocytes resulting in NO-dependent death of neurons and astrocytes or the production of increased reactive oxygen species (ROS) in neurons. (86,89–92) Released S100B is considered to operate primarily via RAGE receptors, but recent publications showed that non-RAGE receptors might also have high relevance in signal transduction. (81,93)

The release of S100B by astrocytes is additionally triggered by different stimulators such as serotonin 1A (5-HT1A), glutamate, and tumor necrosis factor-alpha (TNF-α). Other situations under which astrocytes release S100B are the acute phase of brain damage, growth phase, metabolic stress, and high cytosolic calcium. Some drugs and other agents, including MPTP, risperidone, and natural antioxidants, can lead to increased release by astrocytes. (65,94–103)

However, studies showed that there are several non-neural influencing conditions, which also result in higher blood levels of the S100B protein, for instance, melanoma, dilated cardiomyopathy, heart ischemia, non-brain traumas, and even strenuous physical exercises like running a marathon. (104–108) Interestingly, it

was also demonstrated that darker skin color is related with higher S100B serum concentrations. (109)

1.3.3. S100B as a biomarker

The history of the S100B protein as a potential biomarker goes back to 1979 when the protein was detected for the first time in human biological fluids by Michetti et al. (110). Increased levels of S100B were proven in the CSF of patients with multiple sclerosis in the exacerbation phase. In contrast, the levels of the protein in the stationary phase seemed to be significantly lower. Thus, the idea of S100B as a biomarker of neuronal cell damage was born. (110–112) Many other biofluids aside from CSF, such as peripheral blood (113) or urine (114), were found also to indicate higher S100B-levels in the case of neurological disorders. (111) Regarding brain injury, the serum is today used as the sample material of choice most of the time. (115) However, it's worthwhile to keep in mind that CSF levels are around 100 times higher than serum levels - depending on the type of the injury and the temporal evolvement. (116) The half-life of S100B ranges from 30 to 120 minutes but increases significantly with the degree of the injury. (83,117)

There is a wide range of neurological diseases in which increased S100B levels were found, including TBI, neurodegenerative disorders, or mental diseases (For a detailed list, see *Table 2* below). Since S100B levels are influenced by such a large variety of pathologies, the specificity of this biomarker is considered to be low. (111) However, it was shown that with the correct cutoff value, the sensitivity and negative predictive value of S100B concerning neuronal cell damage is high. (48) This means that the potential of S100B as a biomarker seems to lie much more in monitoring the trend of mentioned diseases and predicting the clinical outcome (111) than in making the correct initial diagnosis.

One of the fields where these characteristics come into effect is perinatal medicine. The S100B level in CSF, cord blood, and amniotic fluid gains increased importance regarding the detection of brain damage in risk events and the prediction of the outcome. S100B is a useful tool for evaluating potential dangerous conditions such as intraventricular hemorrhage, asphyxia, or post hemorrhagic ventricular dilatation. (86,111,118–120)

Additionally, since S100B was also isolated from melanocytes – which are of neuroectodermal origin - in human skin (87), the S100B serum level is described as a valuable biomarker of malignant melanoma. Studies demonstrated that the protein could be practically used to reflect the tumor load, staging, and prognosis of this malignant disease. (121)

Other non-neural pathologies, in which the role of S100B as a potential biomarker is not yet clarified, are dilated cardiomyopathy, ischemic heart disease, or non-brain traumas. (105–107) However, the possible influences of S100B release by the brain in these cases should not be neglected.

Table 2: *Pathologies which influence S100B protein serum levels*
("+" standing for increased, "-" for decreased S100B serum levels)

Organ	***Pathology***	***S100B level***	***Reference***
CNS	Acute brain injury	+	(122)
	Brain metastases	+	(123)
	Neuromyelitis optica	+	(124)
	Multiple sclerosis	+	(125)
	Amyotrophic lateral sclerosis	-	(126)
	Alzheimer's disease	-	(127)
	Schizophrenia	+	(128)
	Bipolar disorder	+	(129)
	Neonatal intraventricular hemorrhage	+	(120)
	Intrauterine growth retard	+	(130)
Skin	Malignant melanoma	+	(131)
Adipose tissue	Obesity	+	(132)

Heart	Ischemic heart disease	+	(106)
	Dilated cardiomyopathy	+	(105)
Breast	Breast cancer	+	(133)
GI tract	Inflammatory bowel disease	-	(134)
Other/ Unknown	Intense physical exercise	+	(108)
	Trauma without head injury	+	(107)
	Stressful activity	+	(135)

1.3.4. The use of S100B in traumatic brain injury

From the first detection of the S100B protein until today, the focus of number of studies was to find out if the protein would be a reliable marker to diagnose, grade, monitor and/or predict the outcome of acute brain injury. Therefore, the challenge arises from the still existing lack of knowledge concerning the exact pathological and physiological roles of S100B.

Screening tool in mild TBI

Studies in the late 1990's and early 2000's showed that S100B serum levels in humans were significantly elevated in cases of all sorts of TBI and correlated with clinical severity, volume of contusion, and pathological CT findings. Many studies with similar conclusions followed. (122,136–139) Based on that growing evidence, the Scandinavian Neurotrauma Committee updated their guidelines for managing head injuries in 2013, which offer a tool to decide upon the further diagnostic procedure. It was the first time that S100B was included in official guidelines (see *chapter 1.2.4* for more information about the Scandinavian guidelines). (47)

As described in the section above, the specificity of S100B in case of neural injury is low. Though Stein SC et al. have shown, the sensitivity of S100B detecting an intracranial injury by applying the SNC guidelines is about 96%. (51) Furthermore,

the high negative predictive value (90-100%) of low S100B levels in minor head injuries (GCS 14 or 15) can potentially avoid unnecessary cCT scans, which paved the way for S100B to be incorporated into those guidelines. (139)

The avoidance of unneeded CT scans in case of mild TBI results in cost savings and reduces the risk of long-term radiation damages like the development of cancer or reduction of cognitive functions. This would take effect, especially in pediatric medicine, where avoiding unnecessary radiation exposure is of great importance. (140–142)

Use in pediatric medicine

Due to the fact that increased S100B levels are also related to the ongoing growth of the CNS in children, it is challenging to establish useful cut-off values in a pediatric population, where in case of mild TBI, CT scan could be omitted. (136,143,144) The current data in this regard is still insufficient and therefore, the Scandinavian guidelines of head trauma in children (< 18 years) have not yet implemented the biomarker S100B. (145) However, S100B appears to be useful today in assessing and predicting the outcome of TBI in children. (136,146)

Outcome estimation in moderate and severe TBI

Regarding moderate and severe TBI, where cCT is undoubtedly necessary, it is intensively discussed whether S100B would be a trustworthy biomarker to predict the outcome of this severely affected patient group. The requirement for such a biomarker is reinforced by the fact that most patients with moderate or severe TBI cannot be sufficiently clinically assessed due to their poor state. (136) A review by Mercier et al. (147) showed a correlation between S100B serum levels and bad outcomes of these patients, based on mortality, brain stem death or Glasgow outcome score ≤ 3. However, due to the large variety of present study designs, there is still considerable uncertainty about the correct cut-off values and sample times. Thus, more research is still needed to embed S100B as a standard tool for prognostic models in moderate and severe TBI. (136,147) In addition, it must be remembered that S100B serum levels can be influenced by several circumstances (see *Table 1*), and therefore making too hasty predictions can be potentially risky.

Monitoring tool for inpatients

It was shown that serial measurement of S100B during in-patient stay at intensive care units could provide a valuable information about the course of the injury. Both absent decline and ongoing increase of S100B serum levels in the hours after TBI were proven to be associated with worse outcomes. (136,148,149) Furthermore, secondary peaks of S100B levels are discussed to point to relevant ongoing secondary injuries like the progression of hematomas or cerebral infarction – cases in which S100B could influence the further treatment. (136,150–152) Thelin et al. (136) suggested that, due to the short half-life compared to other neuronal biomarkers such as glial fibrillary acidic protein (GFAP), S100B is a very promising kinetic biomarker to monitor patients with TBI in the future. (136) Further research is necessary to establish reliable kinetic models of S100B, which may significantly impact the treatment of inpatients.

Marker for treatment success

Another promising field of research is the potential use of the biomarker S100B as a tool to evaluate the efficacy of TBI treatment. It has been shown that S100B levels correlate with intracranial pressure, which today represents the most commonly used value to determine the current condition of the brain. (136) But since very few clinical studies have analyzed this issue so far, future studies will show whether S100B can be practically used in this context or not.

2. Methods

This study is based on retrospective data analysis from 01/01/2017 to 31/01/2020 of patients, who suffered TBI and sought medical help at the Department of Orthopedics and Traumatology at the Hospital of the Medical University of Graz. The study was officially approved by the Ethics committee of the Medical University of Graz (EK 32-511 ex 19/20).

Patient data were pseudonymized by assigning consecutive numbers. Collected data was saved in a Microsoft Excel file under password protection and could only be accessed by few authorized members of the Department of Radiology, Medical University of Graz.

2.1. Data collection

The data was collected by a query of the local hospital information system "openMEDOCS". The search and selection of patients were based on following key terms: "traumatic brain injury", "fall on the head", "strike on the head", "accident with head injury", "fall with subsequent symptoms of concussion", or "accident with subsequent headache". Traffic accidents have only been included when head injury was explicitly mentioned as the main injury.

2.1.1. Inclusion criteria

Patients had to meet the following criteria to be included in this study:

- acute TBI (any degree of severity)
- age over 18 years
- cCT scan at hospitalization
- S100B sampling at hospitalization

2.1.2. Exclusion criteria

Following exclusion criteria have been determined:

- Cases in which the time of the event of trauma was documented in writing:
  - time between the event of trauma and S100B sampling > 6 hours (2 patients)
- Cases in which the time of the event of trauma was not precisely documented:
  - Patients who arrived directly from the place of trauma by ambulance: time between hospitalization and S100B sampling > 4 hours (1 patient)
  - Patients who came to the emergency department by themselves: time between hospitalization and S100B sampling > 3 hours (3 patients)
- time between hospitalization and CT scan > 5 hours (1 patient)
- presence of artifacts in CT scan making interpretation impossible (2 patients)

Another patient was excluded due to multiple postoperative changes after craniotomy years ago.

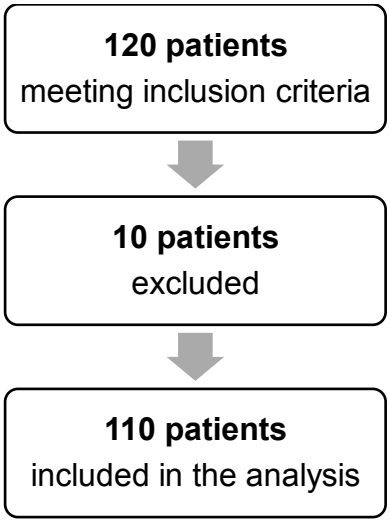

***Figure 9**: Flowchart of the recruiting process.*

2.1.3. Collected attributes

Via retrospective data analysis following features have been assessed for every patient:

- gender
- age [years]
- body mass index (BMI) [kg/m^2]
- presence of polytrauma or multiple injuries
- S100B serum level at hospitalization [µg/L]
- time between trauma and S100B sampling [hours: minutes]
- time between hospitalization and S100B sampling [hours: minutes]
- radiological CT scores (see *1.2.5 Radiological Interpretation Systems*), assessed by a radiology specialist with 9 years of experience in musculoskeletal and emergency radiology
    - Marshall CT classification, Rotterdam CT score, Stockholm CT score and Helsinki CT score
- time between hospitalization and CT scan [hours: minutes]
- presence of artifacts in CT scan
- GCS at hospitalization (see *1.2.2 Classification*)
- SNC guidelines low-risk criteria

- inpatient admission
- mortality
- pre-existing therapeutic anticoagulation
- pre-existing antiplatelet therapy

2.2. Laboratory analysis of S100B

S100B serum levels were measured by the Clinical Institute of Medical and Chemical Laboratory Diagnostics of the Hospital of the Medical University of Graz via electro-chemiluminescence immunoassay with Elecsys® technology by the company Roche. The used analytical unit “Cobas e 801” by Roche comes with measuring ranges from 0.015 to 30 µg/L and quantifies both the S100BB homodimer and the S100A1B heterodimer. (153)

According to the manufacturers' specifications, the cut-off value for elevated S100B serum level is stated at ≥ 0,105 µg/L. (154) However, in this study, we define values ≥ 0,100 µg/L as pathological, according to the SNC guidelines. (47)

2.3. Statistical analysis

Analysis has been done using IBM SPSS Statistics 26. For descriptive statistics, nominal and ordinal scaled variables have been described by absolute and relative frequencies. For metric scaled variables median, minimum, maximum, interquartile range (IQR) and for reasons of completeness mean with standard deviation (SD) have been calculated. In addition, cross tables were used to display relations of certain groups.

Normal distributions were tested both graphically with histograms and Q-Q plots and mathematically with Kolmogorov-Smirnov and Shapiro-Wilk test. Since in this study all metric variables were not normally distributed, Spearman's rank correlation coefficients were used to assess for correlations. In addition, Kruskal-Wallis and Mann-Whitney U tests have been performed to detect differences between certain groups regarding S100B serum levels. For all these tests, p-values < ,05 were defined as significant.

Additional to in 2.1.3 mentioned collected variables, patients have been grouped by the following features:

- “elevated S100B” if S100B was ≥ 0,100 µg/L
- “pathologies visible in CT scan” if Marshall CT classification was > 1
- the severity of TBI:
    - “mild TBI” if GCS was 14 or 15
    - “moderate TBI” if GCS was 9 to 13
    - “severe TBI” if GCS was 3 to 8
- “SNC low-risk“: See *1.2.4 Clinical practice guidelines regarding the diagnostic use of CT scan* for a detailed description of SNC guidelines
- “blood thinners” if patients had pre-existing therapeutic anticoagulation and/or antiplatelet therapy

3. Results

3.1. Descriptive statistics

***Table 3**: Overview of descriptive statistics*

		count	median	min.	max.	(IQR)	mean	SD
gender	male	50 (45,5%)						
	female	60 (54,5%)						
age [years]			42	19	99	(30-70)	50	23
body mass index [kg/m²]			23,81	17,09	44,98	(22,31-27,01)	25,21	4,89
blood thinning medication	no	98 (89,1%)						
	yes	12 (10,9%)						
type of trauma	isolated head injury	58 (52,7%)						
	multiple injuries	41 (37,3%)						
	polytrauma	11 (10,0%)						
severity	mild	104 (94,5%)						
	moderate	4 (3,6%)						
	severe	2 (1,8%)						
admission	no	43 (39,1%)						
	yes	67 (60,9%)						
lethal	no	106 (96,4%)						
	yes	4 (3,6%)						
time from trauma to S100B sampling [minutes]			86	39	335	(71-164)	127	85

time from hospitalization to S100B sampling [minutes]			31	6	264	(18-74)	56	57
time from hospitalization to CT scan [minutes]			68	4	292	(33-112)	80	56
pathologies in CT scan	no	91 (82,7%)						
	yes	19 (17,3%)						
S100B serum level [µg/L]			0,189	0,047	8,320	(0,123-0,400)	0,539	1,052

3.1.1. Demographic data

In this study population (n = 110) 50 patients (45,5%) were male and 60 (54,5%) female. The age distribution (*Figure 10*) of patients suffering TBI showed two peaks. Median age was 41,50 years. While the youngest patient had an age of 19 years, the oldest patient was 99 years old. IQR was 40,50 (29,75-70,25) years. The mean age was 50,39 (SD 23,25) years.

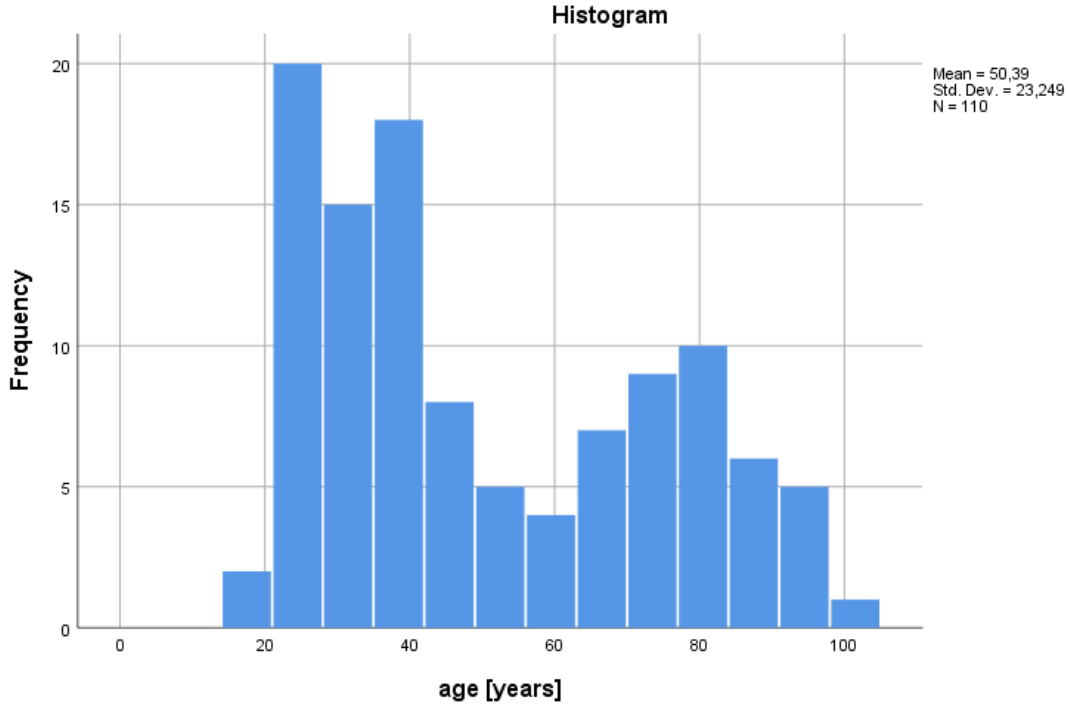

***Figure 10**: Age distribution*

BMI was documented in n = 63 (57,3%) cases (*Figure 11*). The median BMI was 23,81, the minimum BMI was 17,09, and the maximum BMI 44,98. IQR was 4,70 (22,31-27,01) and the mean BMI was 25,21 (SD 4,89).

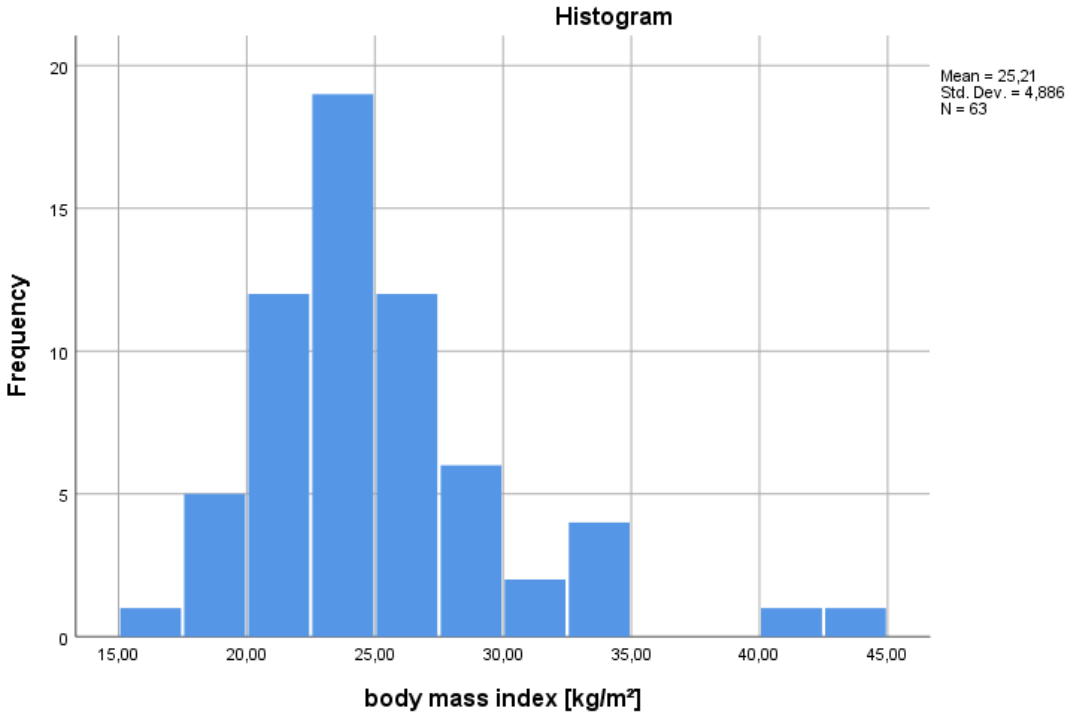

***Figure 11**: BMI distribution*

Regarding blood-thinning medications, in total, 12 (10,9%) patients took anti-clotting medication at the time of injury. Of these, 9 (8,2%) patients had antiplatelet therapy such as acetylsalicylic acid or clopidogrel and 3 (2,7%) patients had therapeutic anticoagulation with phenprocoumon or so-called direct oral anticoagulants like apixaban.

While 66,7% of patients with either antiplatelet therapy or therapeutic anticoagulation showed pathologies in the CT scan, only 11,2% of patients without blood-thinning medications had pathological findings, as displayed in *Table 4*.

***Table 4**: Frequency of blood-thinning medication related to pathologies in CT scan*

		pathologies in CT scan					
		no		yes		Total	
		Count	Row %	Count	Row %	Count	Row %
antiplatelet therapy	no	88	87,1%	13	12,9%	101	100,0%
	yes	3	33,3%	6	66,7%	9	100,0%
therapeutic anticoagulation	no	90	84,1%	17	15,9%	107	100,0%
	yes	1	33,3%	2	66,7%	3	100,0%
blood thinners	no	87	88,8%	11	11,2%	98	100,0%
	yes	4	33,3%	8	66,7%	12	100,0%

3.1.2. Classification, clinical course

In this study, we grouped patients concerning the type of trauma. 58 (52,7%) patients suffered an isolated head injury, 41 (37,3%) patients sustained multiple injuries like localized fractures of extremities or bruises and 11 (10%) cases were classified as polytraumas (see *Figure 12*).

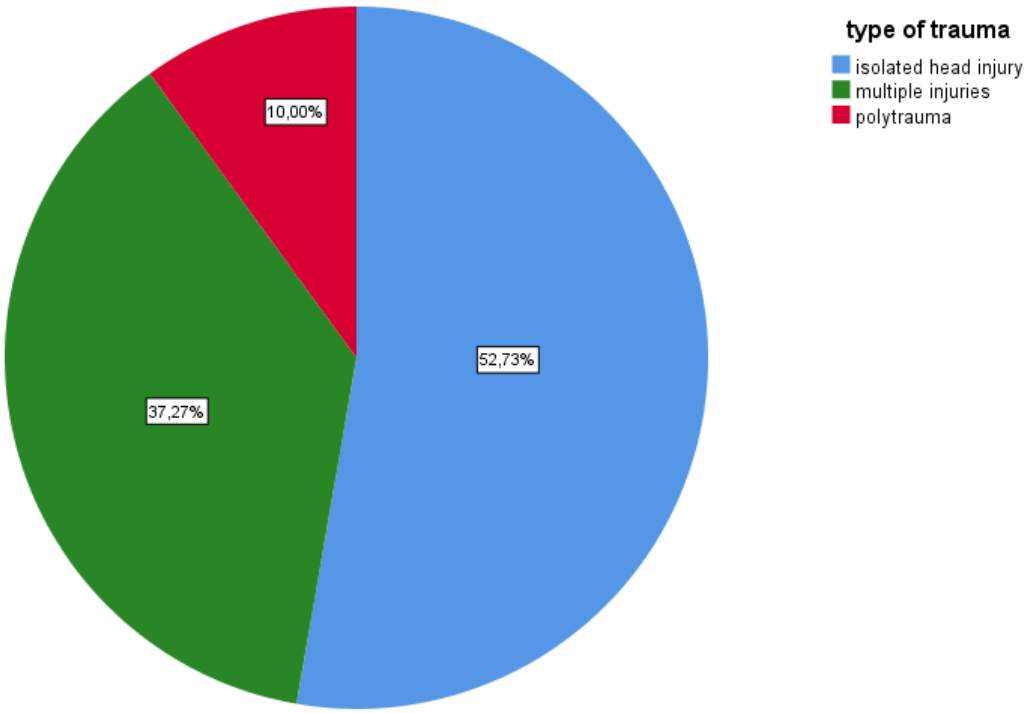

***Figure 12**: Type of trauma*

36,4% (4/11) of patients suffering polytrauma, 7,3% (3/41) of patients with multiple injuries, and 20,7% (12/58) of patients with isolated head injury had pathologies in CT scan.

According to common international practice, the clinical degree of severity of TBI in this study was divided into mild (GCS 14-15), moderate (GCS 9-13), and severe (GCS 3-8) TBI. In total, 104 (94,5%) patients suffered mild TBI, 4 (3,6%) patients moderate TBI and 2 (1,8%) patients severe TBI. Of patients within the group of mild TBI, 61 (55,5%) could be assigned to the low-risk group of SNC guidelines, for which S100B sampling is explicitly recommended (see *1.2.4 Clinical practice guidelines regarding the diagnostic use of CT scan*).

All patients with moderate and severe TBI showed pathologies in CT scans. By contrast, only 12,5% of patients with mild TBI had pathological CT findings (see *Table 5*).

***Table 5**: Frequencies of degrees of severity regarding pathologies in CT scan*

			pathologies in CT scan		
			no	yes	Total
severity	mild	Count	91	13	104
		Row %	87,5%	12,5%	100,0%
	moderate	Count	0	4	4
		Row %	0,0%	100,0%	100,0%
	severe	Count	0	2	2
		Row %	0,0%	100,0%	100,0%
Total		Count	91	19	110
		Row %	82,7%	17,3%	100,0%

In total, 19 (17,3%) patients showed pathologies in CT scan. Four different radiological scores have been assessed to classify these findings, namely Marshall CT classification, Rotterdam CT score, Stockholm CT score and Helsinki CT score, as shown in *Table 6*.

***Table 6**: Distribution of CT scores*

		Count	Column %
Marshall CT classification	I	91	82,7%
	II	11	10,0%
	III	3	2,7%
	V	4	3,6%
	VI	1	0,9%
Total		110	100,0%
Rotterdam CT score	2	94	85,5%
	3	8	7,3%
	4	5	4,5%
	5	2	1,8%
	6	1	0,9%
Total		110	100,0%
Stockholm CT score	1,0	93	84,5%
	1,5	5	4,5%
	2,0	4	3,6%
	2,3	1	0,9%
	2,5	1	0,9%
	3,0	1	0,9%
	3,9	2	1,8%
	4,0	2	1,8%
	4,5	1	0,9%
Total		110	100,0%
Helsinki CT score	0	98	89,1%
	2	4	3,6%
	3	4	3,6%
	5	3	2,7%
	7	1	0,9%
Total		110	100,0%

Regarding further handling after hospitalization at the emergency department, 67 (60,9%) patients were admitted as inpatients, of which 4 (3,6% of all patients) passed away subsequently. The mean age of patients who died was 71,25 (SD 31,03) years. All of them showed pathologies in CT scan.

3.1.3. Time until clinical diagnostics

Patients with delayed CT scan or S100B sampling have been excluded from this study, as described in *2.1.2 Exclusion criteria*. For this study population mean time from hospitalization to CT scan (n = 110) was 1:20:07 [hours: minutes:seconds] (SD 0:56:18), mean time from hospitalization to S100B sampling (n = 110) was 0:55:47 (SD 0:57:13) and mean time from trauma to S100B sampling (n = 32) was 2:06:51 (SD 1:24:40).

Due to a lack of documentation, in *Figure 13* the "time from trauma to S100B sampling" group (n = 32) does not include all patients. By the fact that the time of trauma was mostly read from the protocol of rescue, it is expected that the mean time from trauma to S100B sampling is slightly higher for the whole study population.

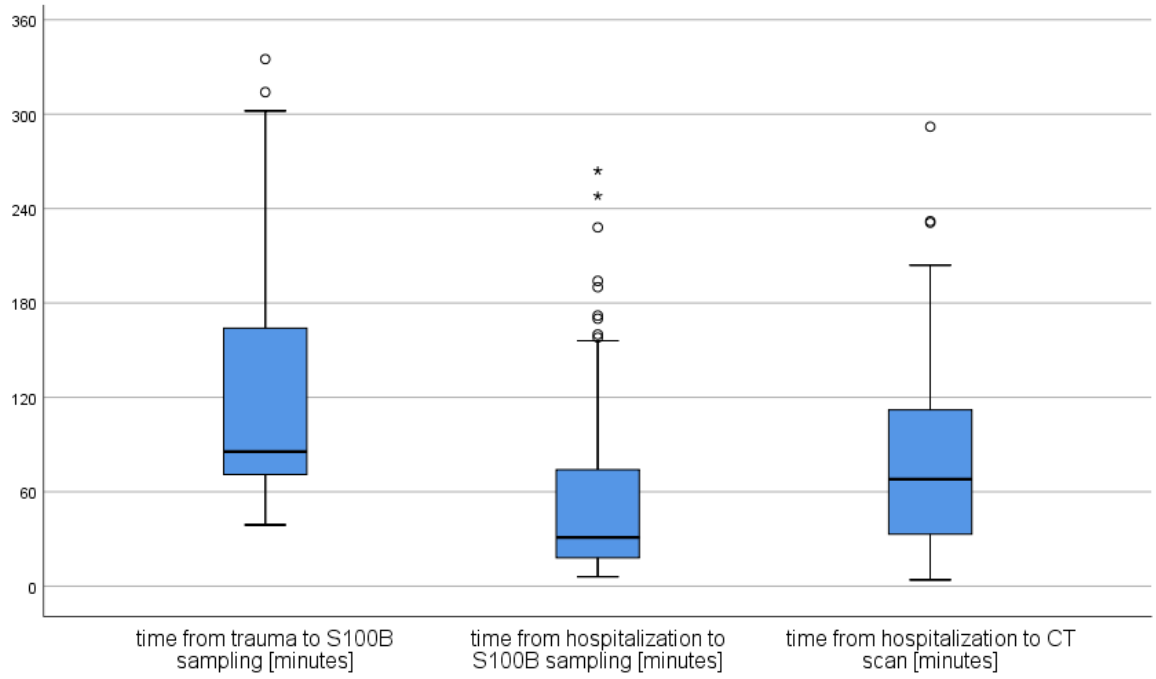

Figure 13: Distribution of times until clinical diagnostics

3.1.4. S100B

The distribution of S100B serum levels presented right-skewed, as displayed in *Figure 14* and *Figure 15*, with a median of 0,189 µg/L. The minimum S100B serum level was 0,047 µg/L and the maximum 8,320 µg/L. IQR was 0,302 (0,121-0,423) µg/L. The mean was 0,539 µg/L (SD 1,052). Kolmogorov-Smirnov ($p < ,001$) and

Shapiro-Wilk test (p < ,001) confirmed that S100B serum levels were not normally distributed.

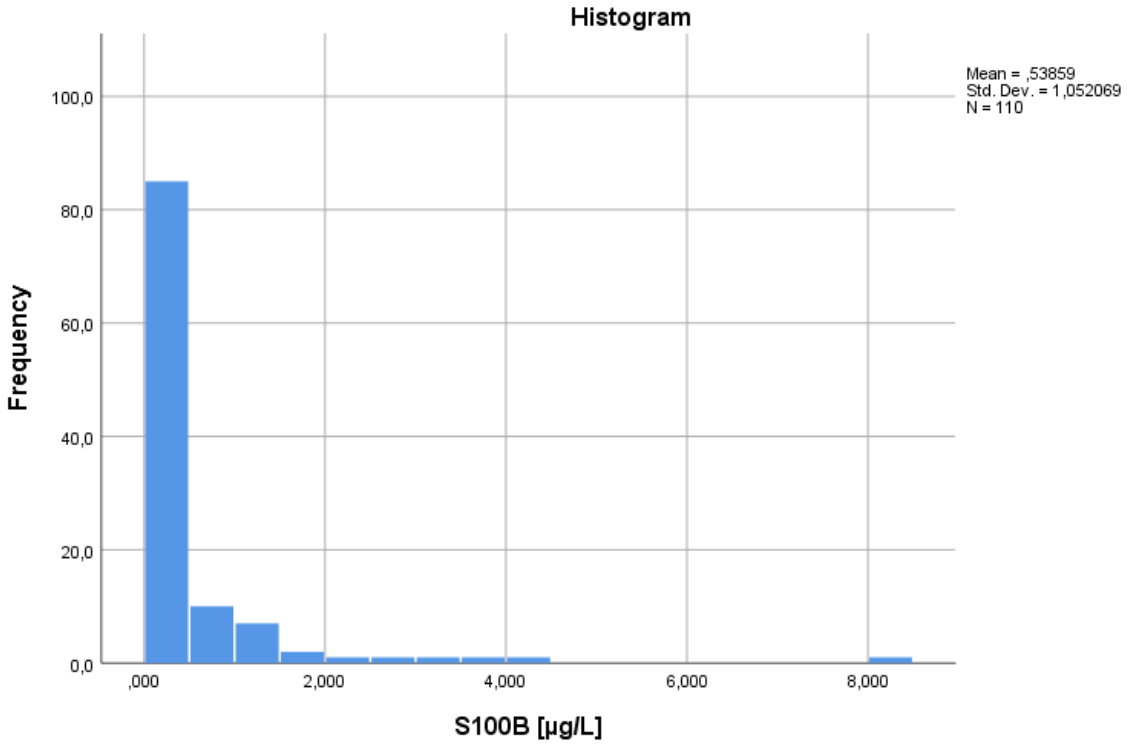

***Figure 14**: Distribution of S100B serum levels*

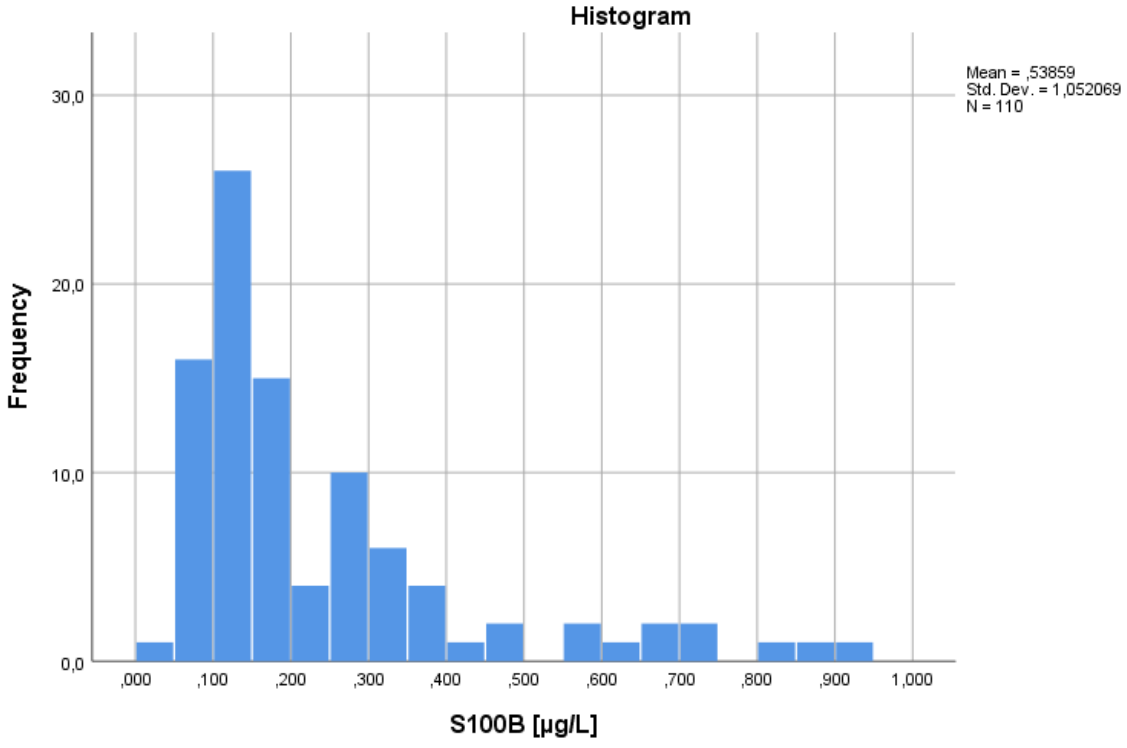

***Figure 15**: Additional view of the distribution of S100B serum levels*

Because of this right-skewed distribution, logarithmic scaled axes were chosen to present S100B serum levels in diagrams, to receive a better visual representation in this analysis.

In total, 93 (84,5%) patients had elevated S100B serum levels greater than/equal to 0,100 µg/L. In 17 (15,5%) cases S100B serum levels were under this cut-off value. Sensitivity of S100B predicting pathologies in CT scan in the whole study population (n = 110) was 94,7%, specificity was 17,6%. For the “low-risk” group defined by the SNC guidelines (n = 61) sensitivity was 100,0% and specificity 21,2%. (see *Table 7*)

***Table 7**: Elevated S100B serum levels regarding pathologies in CT scan*

				pathologies in CT scan		
				no	yes	Total
Total	S100B ≥ 0,100 µg/L	no	Count	16	1	17
			Column %	17,6%	5,3%	15,5%
		yes	Count	75	18	93
			Column %	82,4%	94,7%	84,5%
	Total		Count	91	19	110
			Column %	100,0%	100,0%	100,0%
SNC “ low-risk” group	S100B ≥ 0,100 µg/L	no	Count	11	0	11
			Column %	21,2%	0,0%	18,0%
		yes	Count	41	9	50
			Column %	78,8%	100,0%	82,0%
	Total		Count	52	9	61
			Column %	100,0%	100,0%	100,0%

3.2. Relationships and correlations

3.2.1. Type of trauma

Kruskal-Wallis Test showed a significant difference (p < ,001) of S100B serum levels between patients suffering an isolated head injury, multiple injuries or polytrauma, as visually displayed in *Figure 16 (S100B presented on a logarithmic scale)*. Pairwise comparisons between isolated head injury and multiple injuries (p = ,001), isolated head injury and polytrauma (p < ,001), and multiple injuries and polytrauma (p = ,015) all showed significant differences. For these post hoc tests significance values have been adjusted by the Bonferroni correction for multiple tests.

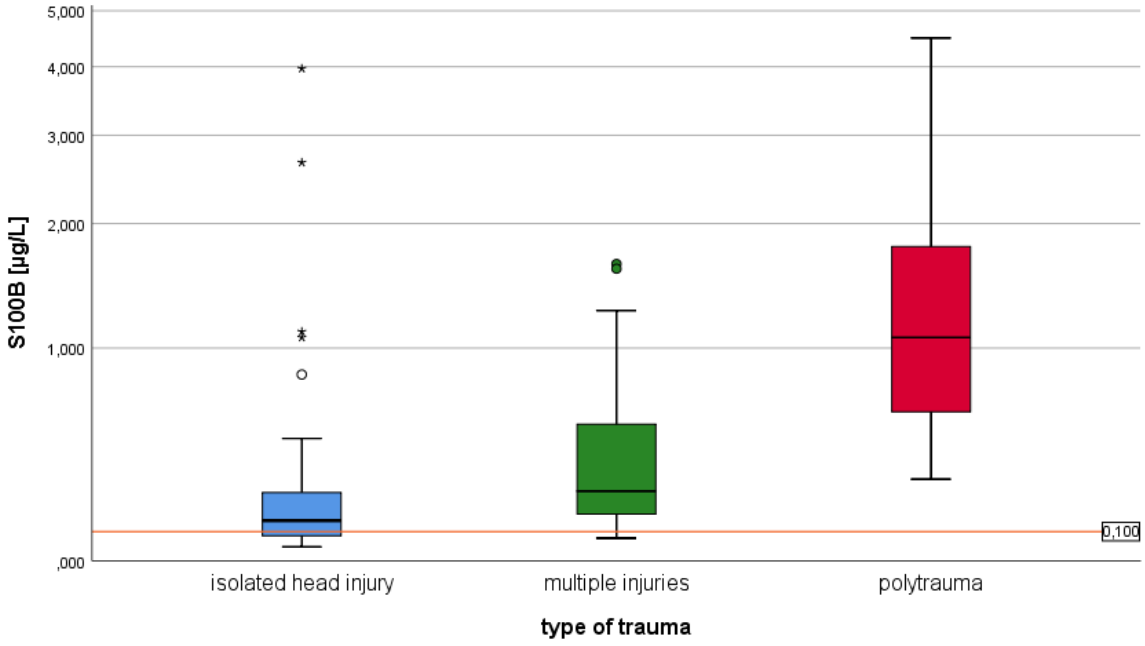

***Figure 16**: Visual comparison between types of injury regarding S100B serum levels*

100% (11/11) of patients suffering polytrauma, 95,1% (39/41) of patients with multiple injuries, and 74,1% (43/58) of patients with isolated head injury had elevated S100B serum levels. Consequently, while the sensitivity of S100B predicting pathologies in CT scan for patients with multiple injuries or polytrauma was 100%, specificity was only 5,3% for the group “multiple injuries” and 0% for polytraumas. See *Table 8* for detailed figures of S100B serum levels within these groups.

***Table 8**: Key figures of S100B serum levels related to the type of trauma*

		S100B [µg/L]					
		median	min.	max.	(Q_1; Q_3)	mean	SD
type of trauma	isolated head injury	0,140	0,047	3,970	(0,085; 0,249)	0,309	0,624
	multiple injuries	0,255	0,077	8,320	(0,165; 0,561)	0,600	1,295
	polytrauma	1,070	0,305	4,490	(0,597; 2,230)	1,522	1,326

3.2.2. Radiological scores and GCS

In the group of isolated head injury S100B serum levels significantly correlated with all radiological scores obtained, as well as with GCS ($p < ,01$). However, there were no significant correlations in the groups of multiple injuries and polytraumas, as shown in *Table 9*.

***Table 9**: Spearman's rank correlation coefficients (R) of radiological scores and GCS to S100B serum levels*

		Isolated head injury	**Multiple injuries**	**Polytrauma**
		S100B [µg/L]	S100B [µg/L]	S100B [µg/L]
Marshall CT classification	R	,446	,242	,359
	p-value	,000	,127	,278
	n	58	41	11
Rotterdam CT score	R	,424	,242	,359
	p-value	,001	,127	,278
	n	58	41	11
Stockholm CT score	R	,468	,244	,327
	p-value	,000	,124	,326
	n	58	41	11
Helsinki CT score	R	,376	,288	,075
	p-value	,004	,067	,826
	n	58	41	11
GCS at hospitalization	R	-,487	-,241	-,482
	p-value	,000	,130	,134
	n	58	41	11

3.2.3. Time until S100B sampling

In this study, time from trauma to S100B sampling did not correlate to S100B serum levels, neither for all patients for which time of trauma was documented (n = 32, p = ,571) nor for the selected group of patients without pathologies in CT scan (n = 23, p = ,429), nor for the group of patients with pathologies in CT scan (n = 9, p = ,732). However, time from hospitalization to S100B sampling showed a significant correlation for patients without pathologies in CT scan (n = 91, p = ,006), but not for the group of patients with pathologies in CT scan (n = 19, p = ,225). Correlation coefficients are displayed in *Table 10*.

***Table 10**: Spearman's rank correlation coefficients (R) of time from trauma and hospitalization to S100B sampling to S100B serum levels*

		No pathologies in CT scan	**Visible pathologies in CT scan**
		S100B [µg/L]	S100B [µg/L]
time from trauma to S100B sampling [minutes]	R	-,173	,133
	p-value	,429	,732
	n	23	9
time from hospitalization to S100B sampling [minutes]	R	-,287	-,292
	p-value	,006	,225
	n	91	19

3.2.4. Demographic data

To examine if S100B serum levels correlate to age or BMI, we assessed Spearman's rank correlation coefficients for all patients solely with the following characteristics to exclude important influence factors:

- isolated head injury
- mild TBI
- no pathologies in CT scan

For this group (n = 46) there was no significant correlation for both age (n = 46, p = ,725) and BMI (n = 23, p = ,486). Mann-Whitney U test showed that there was also no significant difference (p = ,886) of S100B serum levels across genders for this specific group.

4. Discussion

The goal of this study was i) to analyze the reliability of the S100B protein predicting pathologies in cCT scan in daily clinical practice in the TBI setting and ii) to evaluate the extent of important influence factors regarding S100B serum levels.

The population of this study is considered to be representative regarding both the gender distribution (45,5% male, 54,5% female) and the age distribution with its two peaks, complying with the results of a larger European epidemiological study. (7)

Compared with other studies, the specificity of S100B in our study was significantly lower. Despite high sensitivity of S100B ≥ 0,100 µg/L in predicting pathologies in the cCT of 94,7%, specificity was low at 17,6%. Further, for the “low-risk” group, defined by the SNC guidelines, sensitivity reached 100,0%, however specificity remained low at 21,2%. (48,51,155)

The comparison of radiological scores (Marshall CT classification, Rotterdam CT score, Stockholm CT score, Helsinki CT score) showed that all of them correlate with S100B serum levels ($p < ,01$) with similar correlation coefficients (from $R = ,376$ to $R = ,468$) suggesting that all these scores are appropriate to be used along with S100B sampling in daily clinical practice.

The most prominent result of this study was the influence of extracranial injuries on S100B serum levels. 100% of patients suffering polytrauma and 95,1% of patients with multiple injuries had S100B serum levels ≥ 0,100 µg/L, leading to a specificity of S100B predicting pathologies in CT scan of just 5,3% for patients with multiple injuries and 0% for polytraumas. This emphasizes the results of an earlier study from Papa et al. (156)

In this study, time from trauma to S100B sampling did not significantly correlate to S100B serum levels for the group of patients without pathologies in CT scan ($n = 23$, $p = ,429$, $R = -,173$). However, time from hospitalization to S100B sampling did show a significant correlation for patients without pathologies in CT scan ($n = 91$, $p = ,006$, $R = -,287$). This has to be noted as a discrepancy, which may be caused by the fact that the time of trauma was not documented in all cases (see *4.1 Limitations*), but can also be interpreted as an indication that kinetics of the S100B protein are complex.

Unlike other studies, we could not show a significant correlation between S100B serum levels and BMI (p = ,486) for patients suffering isolated TBI without pathologies in CT scan. (132,157) However, in this study, the sample for this group was small (n = 23) and larger studies are needed to clarify this topic.

As shown in this study, the use of S100B as a biomarker in TBI comes with many challenges. First of all, the kinetics of the S100B protein are still in the early stages of research. (158) Therefore, it is still not clear at which exact point(s) in time S100B sampling should be performed and if S100B cut-off values could be even set higher in case of earlier sampling to reach higher specificity without forfeiting sensitivity. Further studies are necessary to explore this issue. Furthermore, in daily clinical practice the time of trauma often cannot be determined precisely, as seen in this study, which results in difficulties to set a valid cut-off value.

Secondly, in this study population, S100B serum levels were elevated in patients suffering trauma of other body regions or polytrauma. Similar results were shown by other studies. (156,159) The use of S100B beyond isolated head injuries should therefore be questioned.

Furthermore, S100B serum levels can be influenced by a great amount of other intracranial and extracranial pathologies (see *Table 2*) which are often unknown. In the acute setting at an emergency department, it is futile and not feasible to take a detailed medical history regarding all those influence factors.

SNC guidelines seem to be a step in the right direction as they are defining a specific “low-risk” group which is recommended to undergo S100B sampling. (47) However, by applying these guidelines specificity of S100B is still low. Defining an even more constrained group, e.g., by solely including patients with isolated head injury, could increase specificity of S100B without forfeiting sensitivity and therefore avoid useless S100B sampling, saving both money and time in the acute care.

4.1. Limitations

The limitations of this study primarily arise by its retrospective design. Since the exact time of injury was not documented in all included cases (32 of 110), it cannot be guaranteed that S100B sampling was always performed within 6 hours after the injury with absolute certainty. However, exclusion criteria regarding cut-off times were strictly defined to be as reliable as possible.

Despite no clinical decision tools regarding the use of cCT scan, such as SNC guidelines, were routinely applied at the Department of Orthopedics and Traumatology at the Hospital of the Medical University of Graz within the period of this study, it must be assumed, that a certain number of patients with low S100B serum levels were discharged without receiving a cCT scan. This may be a reason the number of patients with S100B serum levels < 0,100 µg/L in this study population was so low, which, as a result, also may have led to a poorer specificity of S100B ≥ 0,100 µg/L predicting pathologies in CT scan.

4.2. Conclusion

With this study we were able to confirm that the sensitivity of S100B ≥ 0,100 µg/L predicting pathologies in CT scan is extremely high, as already demonstrated in prior studies. (48,51,155) It was also shown that S100B serum levels correlated with all four of the most established cCT scores (Marshall CT classification, Rotterdam, Stockholm, and Helsinki CT score) as well as with GCS, indicating that S100B serum levels correlate with the severity of TBI. The use of S100B as a biomarker in TBI in daily clinical practice is still challenging and implementation of guidelines is mandatory in order to reach high specificity and sensitivity of the method.

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