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Clinical and Biochemical Aspects of the Emergency Management of Traumatic Brain Injury

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Clinical and Biochemical Aspects of the Emergency Management of Traumatic Brain Injury

Clinical and Biochemical Aspects of the Emergency Management of Traumatic Brain Injury

Tomas Vedin



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DOCTORAL DISSERTATION

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Clinical and Biochemical Aspects of the Emergency Management of Traumatic Brain Injury		
<p>Abstract</p> <p>Background and aim: Traumatic brain injury is a common cause of mortality and morbidity worldwide. Several guidelines for its emergency management are available. One guideline incorporates the use of the brain-biomarker serum protein S100B. This dissertation aimed to evaluate the usage of guidelines in the emergency department, delineate the epidemiology of traumatic brain injury, explore the assay precision of S100B in capillary-sampled serum and urine instead of venous-sampled serum, and study these assays' ability to rule out intracranial hemorrhage after head trauma.</p> <p>Methods: In Paper I, questionnaires were used to assess physicians' attitudes toward and adherence to guidelines for managing traumatic brain injury in the emergency department, as well as the effect of changing the guidelines. Paper II employed a retrospective review of medical records to explore the current epidemiology of adult traumatic brain injury in a large Scandinavian emergency department. In Paper III, a retrospective review of medical records was used to apply the proposal from Paper II to amend the current guidelines for managing traumatic brain injury. Paper IV assessed the concordance between capillary- and venous-sampled S100B around the clinical cut-off currently used to rule out intracranial hemorrhage. Paper V prospectively researched the precision of S100B in urine and the urine-assay's ability to rule out intracranial hemorrhage in adult patients with head trauma.</p> <p>Results: Paper I showed that physicians trusted their own judgment more than the guidelines and that guideline adherence was 60% before the guidelines were changed and declined to 40% afterward. Paper II demonstrated a shift in epidemiology toward older patients and falls instead of motor vehicle accidents as the most common trauma mechanism and identified a large cohort of patients with low-energy trauma where no intracranial hemorrhages were found (low-risk proposal). Paper III showed a 13% decrease in the head-computerized tomography (CT) rate with maintained safety after the current guidelines from the Scandinavian Neurotrauma Committee were amended with the low-risk proposal. Paper IV established a low concordance between capillary and venous serum S100B protein samples and suggested an inaccuracy of capillary S100B in ruling out intracranial hemorrhage at the clinical cut-off defined for venous samples because of too much intersample variation. Paper V found that urine S100B had slightly lower performance in ruling out intracranial hemorrhage but that the arithmetic difference between serum and urine S100B had better performance than both venous protein S100B assay and urine S100B assay.</p> <p>Conclusions: Physicians trust their own judgment more than the guidelines but order a CT-head scan even when they rate the pathology probability as low. A shift in epidemiology has taken place as the patients have increased in age and the main trauma mechanism is a low-energy force from falling on the ground. Capillary S100B cannot be recommended to rule out intracranial hemorrhage with the current methods of sampling and analysis. The performance of urine S100B is almost similar to that of serum S100B, but a way of improving performance of S100B in ruling out intracranial hemorrhage might be to prospectively measure both urine S100B and serum S100B and use the arithmetic difference to rule out intracranial hemorrhage. Amending the guidelines with a tentative low-risk proposal might result in a lower head-CT ratio but should be tested prospectively.</p>		
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Contents

Contents.....	8
List of scientific papers	10
Populärvetenskaplig sammanfattning	11
(Summary in Swedish)	11
List of abbreviations and acronyms	14
Dissertation at a glance	15
Chapter 1 Background.....	17
Guideline implementation and adherence	18
Protein S100B and other biomarkers	20
Guidelines for management of traumatic brain injury	22
Management of traumatic brain injury from the clinical perspective	23
Chapter 2 Aims of the dissertation	25
Chapter 3 Methods and study design.....	27
Ethical aspects	27
Statistical analysis	27
Definitions of degrees of traumatic brain injury	28
Paper I – Quantitative questionnaire-based survey of traumatic brain injury guidelines	29
Papers II and III – Retrospective review of medical records and amendment of current guidelines.....	30
Papers IV and V – Biomarker analysis	32
Chapter 4 Results.....	35
Paper I – Questionnaire-based analysis.....	35
Paper II – Retrospective review of medical records.....	39
Paper III – Proposed amendment of current guidelines	43
Paper IV – Capillary and venous S100B.....	47
Paper V – Urine and venous S100B.....	52

Chapter 5 Methodological considerations	61
Introduction to methodological considerations	61
Paper I	62
Paper II	65
Paper III.....	67
Paper IV	69
Paper V	71
Chapter 6 Discussion	75
General aspects of guideline adherence	75
Implementation of brain biomarkers for traumatic brain injuryt.....	77
Specific aspects of guidelines for traumatic brain injury	78
Epidemiology and clinical features of traumatic intracranial hemorrhage ..	80
Potential amendment of present guidelines.....	81
S100B in venous, capillary, and urine samples.....	82
Summary and main conclusions.....	84
Acknowledgments.....	85
Grants	87
Chapter 7 References.....	89

List of scientific papers

This dissertation is based on the following scientific papers:

- I. Vedin T, Edelhamre M, Karlsson M, Bergenheim M, Larsson PA. *Management of Traumatic Brain Injury in the Emergency Department: Guideline Adherence and Patient Safety*. Qual Manag Health Care. 2017;26:190-195.
- II. Vedin T, Svensson S, Edelhamre M, Karlsson M, Bergenheim M, Larsson PA. *Management of mild traumatic brain injury-trauma energy level and medical history as possible predictors for intracranial hemorrhage*. Eur J Trauma Emerg Surg. 2018
- III. Vedin T, Karlsson M, Clausen L, Edelhamre M, Svensson S, Bergenheim M, Larsson P-A. *A proposed amendment to the current guidelines for mild traumatic brain injury: reducing computerized tomographies while maintaining safety*. Submitted for publication.
- IV. Vedin T, Karlsson M, Bergenheim, M, Edelhamre M, Larsson P-A. *Prospective comparison of Capillary and Venous Brain Biomarker S100B: Capillary Sampling not accurate enough to rule out Intracranial Hemorrhage in Patients with Trauma to the Head*. Submitted for publication.
- V. Vedin T, Karlsson M, Bergenheim, M, Edelhamre M, Larsson P-A. *Features of Urine S100B and Its Ability to Rule Out Intracranial Hemorrhage in patients with head trauma: A Prospective Trial*. Submitted for publication.

Populärvetenskaplig sammanfattning

(Summary in Swedish)

Hjärnskada som orsakas av olyckor är en vanlig orsak till både handikapp och död bland vuxna. För 30 år sedan var majoriteten av de som drabbades yngre eller väldigt gamla. Ålderssammansättningen av de som drabbas har skiftat under de senaste 20 åren och nu är det ungefär lika vanligt i alla åldrar. Dessutom är den vanligaste olycksorsaken inte längre fordonsolyckor utan fall i samma plan.

För läkare som handlägger skullskadade patienter på akutmottagningar finns det flera olika riktlinjer. Dessa skiftar i olika länder och kan vara utfärdade av enskilda forskargrupper eller nationella organ. De är ofta baserade på forskning som är äldre än 15 år vilket kan medföra att de inte är helt aktuella.

En riktlinje som ofta används i Skandinavien rekommenderar att man mäter nivån av S100B i blodet på vissa grupper av skullskadade patienter. Detta är en så kallad biomarkör som kan hjälpa till att utesluta att patienten som drabbats av skullskadan har hjärnblödning. Det finns ett antal sådana biomarkörer men S100B är den enda som används i klinisk praxis. Flera andra biomarkörer håller på att testas och nyligen har användning av två andra biomarkörer godkänts för kliniskt bruk i USA.

Det finns två säkra sätt att utesluta allvarlig hjärnblödning efter skullskada: observation på sjukhus eller skiktröntgen av skallen. Fördelen med observation är att det inte innebär att patienten utsätts för strålning som kan vara skadlig och nackdelen är att man tar vårdresurser i anspråk. Skiktröntgen kan både utesluta och påvisa hjärnblödning med i det närmaste fullständig säkerhet men kräver att man utsätter patienten för strålning.

Riktlinjerna för handläggning av skullskada har testats i flera vetenskapliga studier och det råder inga tvivel om att när de följs förbättrar de kvaliteten på handläggningen, dels genom att göra den mer konsekvent men också genom att minska antalet skiktröntgenundersökningar och därmed också kostnaderna. Dock efterföljs inte alltid riktlinjer och trots omfattande forskning på området har vi inget bra recept för att utveckla och införa en riktlinje så att den efterlevs av majoriteten av de som den riktar sig till.

För att kunna mäta S100B måste man ta ett blodprov från en ven och detta sker vanligtvis i armvecket. Att mäta det i ett blodprov som tas från kapillära blodkärl (genom ett stick i fingret) eller i urin som insamlas genom att patienten kissar i en

provbuk skulle ha uppenbara fördelar men det finns inte tillräckligt med kunskap om S100B i dessa kroppsvätskor för att det ska kunna rekommenderas.

Denna avhandling baserar sig på fem olika delarbeten som utforskar olika aspekter av handläggning av patienter med skallskada och det övergripande syftet är att bidra med kunskap som ska kunna förbättra omhändertagande av skallskadade patienter på akutmottagningar.

Delarbete 1 genomfördes med frågeformulär som delades ut till läkare på en akutmottagning efter att de handlagt en patient med skallskada. Syftet var att kartlägga läkarnas attityder till skiktröntgen av huvudet, att se hur väl de efterlevde riktlinjerna och hur införandet av nya riktlinjer påverkade användning av riktlinjer. Det visade sig att läkarna litade mer på sitt eget omdöme än riktlinjerna men att de ofta beställde skiktröntgen trots att de värderade risken för hjärnblödning som låg. Införandet av en ny riktlinje resulterade i en sänkning av användning från 60%-40%, trots en informationskampanj som bedrevs för att befrämja användandet av den nya riktlinjen.

Delarbete 2 genomfördes som en journalgenomgång, Vi granskade journalerna för alla patienter som sökt med skallskada på en akutmottagning under ungefär 1 år. Det framgick att den vanligaste åldern var 56 år och att den vanligaste orsaken till huvudskada var fall i samma plan, precis som modern forskning på skallskada visar. En grupp som motsvarande ungefär hälften av patienterna, som alla hade fallit i samma plan och var under 59 år, befanns vara fria från hjärnblödning oavsett hur de mådde när de undersöktes på akutmottagningen. Konsekvensen av detta skulle kunna vara att man kan skriva hem betydligt fler patienter från akuten än man gör idag utan mer omfattande medicinsk undersökning och utan risk för allvarliga konsekvenser. Det fanns också indikationer på att risken för hjärnblödning om man behandlas med Trombyl 75mg var högre än om man behandlas med starkare blodförtunnande medel såsom Waran, något som traditionellt anses medföra högre risk för hjärnblödning i dessa sammanhang.

Delarbete 3 gjordes på samma sätt som delarbete 2 med en journalgenomgång av alla patienter som sökt akutmottagningen för skallskada under 1 år för att testa den hypotes som framlades i delarbete 2 om att en stor grupp patienter med fall i samma plan som var under 59 år och inte tog blodförtunnande mediciner skulle kunna skickas hem utan mer omfattande medicinsk undersökning. Om dagens skandinaviska riktlinje för skallskada utökades med dessa villkor och skulle användningen av skiktröntgen minska med 13%. Ändå skulle alla hjärnblödningar som krävde någon form av kirurgisk åtgärd upptäckas, det vill säga alla allvarliga hjärnblödningar.

Delarbete 4 och 5 genomfördes med syfte att utreda om S100B som mättes i kapillärt blod samt urin kunde användas för att utesluta hjärnblödning efter skallskada. Kapillära prover tagna på samma patient vid samma tillfälle hade mycket stor spridning och lämpade sig därför inte att användas till detta syfte. Analysmetoden för S100B i urin visade sig vara mycket pålitlig men S100B i urin hade sämre förmåga än det blodprov för S100B, som idag är standard, att utesluta hjärnblödning. Däremot visade det sig att en differens mellan standardblodprovet och urinprovet verkade ha bättre förmåga än dagens blodprov att påvisa hjärnblödning och att pH i urin förefaller påverka koncentrationen av S100B i urin.


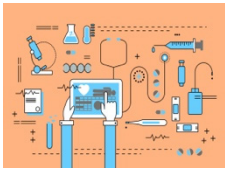

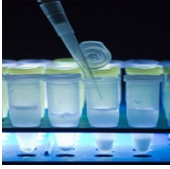
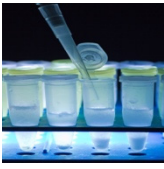
Avhandlingens slutsatser kan sammanfattas i följande punkter:

- Utvecklande och införande av riktlinjer måste ske på andra sätt än de traditionella om man ska få fler att efterleva dem.
- De riktlinjer som finns bör uppdateras med bakgrund i modernare forskning.
- Kapillärt S100B bör inte användas för att utesluta hjärnblödning men differensen mellan S100B mätt i blodprov från armen och i urin bör testas för att se om det kan ha bättre träffsäkerhet än något de enskilda proven har.

List of abbreviations and acronyms

CT	Computerized tomography
kDa	kiloDalton
S100B	Protein S100 B subunit
MSv	MiliSievert
SST	Serum-separating tube
ECLI	Electrochemiluminescence
ICU	Intensive care unit
NICE	National Institute for Health Care Excellence
P	Probability value
SNC	Scandinavian Neurotrauma Committee
SD	Standard deviation
GCS	Glasgow Coma Scale
ATLS®	Advanced Trauma Life Support
IQR	Interquartile range
RLS	Reaction Level Scale 85
NOAC	Novel oral anticoagulant
LMWH	Low molecular weight heparin
ROC	Receiver operational characteristics
N	Number
ASA	Acetylsalicylic acid
NPV	Negative predictive value
PPV	Positive predictive value
TBI	Traumatic brain injury
S	Serum
U	Urine
AGREE	Appraisal of Guidelines for Research and Evaluation

Dissertation at a glance

Paper	Research questions	Methods	Results and conclusions
<p>I</p> 	<p>What are emergency department physicians' attitudes toward head-computerized tomography (CT)? Are the guidelines for traumatic brain injury followed? How do the new guidelines impact their use?</p>	<p>Quantitative questionnaire study</p> <p>One study period before and one after new guidelines, including biomarker S100B, were introduced</p>	<p>Physicians trust their own judgment more than the guidelines but order a CT even when they rate the pathology probability as low. Changing the guidelines has decreased their usage from 60% to 40%.</p>
<p>II</p> 	<p>How does the current epidemiology of traumatic brain injury look in a Scandinavian emergency department?</p>	<p>Retrospective review of medical records over >365 days</p>	<p>Epidemiology is shifting with older patients and falling on the ground as the most common trauma mechanism instead of motor vehicle accidents. More than 50% of the patients have low-energy falls and no intracranial hemorrhage, regardless of signs and symptoms.</p>
<p>III</p> 	<p>Can the current guidelines for traumatic brain injury be amended and thus be improved with the recommendations from Paper II?</p>	<p>Retrospective review of medical records over 365 days</p>	<p>The retrospective amendment of the guidelines yields 13% fewer head-CTs, without missing any patients requiring neurological intervention.</p>
<p>IV</p> 	<p>Is concordance between capillary and venous S100B samples good enough to recommend capillary S100B to rule out intracranial hemorrhage at the current clinical cut-off for mild traumatic brain injury (TBI)?</p>	<p>Sampling of capillary and venous S100B at S100B-levels typical for mild TBI.</p>	<p>Capillary sampling has too much intersample variation and to little concordance with venous S100B samples to be used to rule out intracranial hemorrhage. New studies should be withheld until the sample volume can be reduced below 400 µl for a reliable analysis.</p>
<p>V</p> 	<p>Is an assay of urine S100B a reliable method? Is there a typical temporal profile of S100B in urine over 48 hours? Can urine S100B be used instead of venous S100B to rule out intracranial hemorrhage?</p>	<p>Sampling of patients with intracranial hemorrhage over 48 hours</p> <p>Sampling of patients with and without intracranial hemorrhage and who have had head trauma</p>	<p>The determination of urine S100B has good precision, but it performs slightly worse than serum S100B in ruling out intracranial hemorrhage. Arithmetic difference between serum and urine S100B performs better than either one of the assays alone.</p>

Chapter 1 Background

General introduction

In the era of modern medicine, multiple theoretical and practical adjuncts exist to help the clinician. Some of these include radiological methods, hematological analyses, and written guidelines.

Radiography, such as computerized tomography, magnetic resonance imaging, ultrasound, and other functional radiological methods, is incorporated in many clinical guidelines. It has provided an invaluable tool for cancer management, as well as trauma and emergency medicine.

Some blood analyses can also be called biomarkers, and similar to radiology, they have revolutionized medicine. The management of common diseases relies entirely on biomarkers. These ailments include chest pain (troponin), infectious diseases (C-reactive protein and white blood cells), and cancer (carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 15-3), to name a few [1–8].

Many clinical guidelines have emerged during the 21st century. They are often based on large amounts of research data and have been validated with high negative predictive values (NPVs). This is the case with current guidelines for managing TBI such as the New Orleans Criteria, the Canadian CT Head Rule, the Nexus Criteria, the Scandinavian Neurotrauma Committee (SNC) Guidelines, and NICE (National Institute for Health Care Excellence) Guidelines [9–13].

Undoubtedly, the intention of all clinical aids is to provide safer and more efficient care, but it is possible that despite their good intentions, they might do just the opposite. Guidelines are written to match the general patient and are not always readily applicable to the patient at hand. Sometimes, guidelines can be difficult to interpret or apply due to the circumstances or simply because of the lack of physician experience. Furthermore, biomarkers can lead a physician down the wrong diagnostic path because of a false positive or a false negative value, and a radiological workup can both be performed and interpreted erroneously. Especially for a young physician, it is probably very difficult to contest the result of a clinical workup—based on a guideline—that is stated in the patient’s medical record.

The clinician is ultimately responsible for providing each patient with the best possible care, regardless of what the adjuncts state. This is achieved by applying sound clinical judgment, and the judgment might force the clinician to make a decision that goes against guideline recommendations. All clinicians have

experienced this situation and hopefully handle it to the best of their abilities. Research has shown that guidelines for managing pediatric TBI might increase the rate of head-CT, without adding much diagnostic accuracy compared with physicians' judgment [14].

Guideline implementation and adherence

Many factors need to be taken into account if the aim is to convince clinicians to adhere to certain guidelines. A literature review has showed many different ways to develop and implement guidelines. Cabana et al. (1999) surveyed and published adherence barriers, including lack of awareness (clinicians do not know that the guidelines exist, up to 10%), lack of familiarity (do not know how to interpret and/or apply the guidelines, up to 10%), lack of agreement (disagree on the interpretation of the evidence, up to 10%), lack of self-efficacy (10%), lack of outcome expectancy (up to 25%), and inertia of previous practice (up to 40%) [15]. The other external barriers were that the guidelines "... [were] oversimplified or 'cookbook', would reduce autonomy, were not practical, were biased, would decrease physicians' self-respect, were not applicable to a practice population, would decrease flexibility, lacked credible authors or would make the patient-physician relationship impersonal" [15].

Wollersheim et al. (2005) identified features for a successful implementation of guidelines: "attention to the relevance of the topic, credibility (systematic development by rigorous transparent methodology), involvement of all relevant stakeholders and attention to the impact on resources, materials and facilities, accessibility and an attractive design and tools for application and monitoring in practice" [16].

It is not necessarily that difficult to successfully implement guidelines but understanding and overcoming the particular obstacles encountered at the implementation level (national, regional, or local) are instrumental. Chaillet et al. (2006) examined the factors affecting implementation in the obstetric setting and drew the following conclusion, which succinctly sums up the guideline implementation process: "Prospective identification of efficient strategies and barriers to change is necessary to achieve a better adaptation of intervention and to improve clinical practice guidelines implementation. In the field of obstetric care, multifaceted strategy based on audit and feedback and facilitated by local opinion leaders is recommended to effectively change behaviors" [17].

Another factor that has to be taken into account is that people currently take more doctor-prescribed drugs than in the past, and a significant amount of the population is prescribed some sort of anticoagulant (warfarin, low-molecular weight heparin injections, or novel oral anticoagulants [NOACs]) and/or thrombocyte inhibitors (aspirin, persantin, clopidogrel, ticagrelor, prasugrel, etc.). This situation poses a new challenge to the clinician, and different guidelines deal with this problem in various ways, indicating that the evidence is not completely clear [10, 12]. Furthermore, both NOACs and newer thrombocyte inhibitors, such as ticagrelor and prasugrel, have not been extensively studied with regard to the risk of traumatic intracranial hemorrhage. The guidelines largely have to rely on expert opinions and the risks extrapolated from experiences with similar drugs.

Considering how both epidemiology and the drug panorama have shifted over time, new epidemiological analyses are needed at regular intervals to ensure that the guidelines can be updated to fit the characteristics of the patients who currently frequent the emergency departments. For instance, in addition to the findings presented in Papers II and III, there is some evidence suggesting that traumatic intracranial hemorrhage might be as common or even more common in patients treated with thrombocyte inhibitors than in patients treated with some sort of anticoagulant [31]. Furthermore, the risk of intracranial hemorrhage after head trauma among patients treated with NOACs, which is presented in Paper III, might be as low as half the risk of patients on warfarin [32, 33]. It is feasible that aspirin could carry a higher risk of intracranial hemorrhage after trauma than NOACs.

Protein S100B and other biomarkers

In 1983, Bakay and Ward postulated the preferred properties of a brain biomarker: high specificity for the brain, high sensitivity for the injured brain, be released only upon injury, appear quickly in blood, and have a reliable temporal profile. It should have low variability with age and gender, use an easy and accessible method of analysis, and be clinically significant [34]. During the course of the research on the topic, brain biomarkers have come and gone (e.g., brain-specific creatine kinase, lactate dehydrogenase) [34, 35]. Protein S100B was first discovered in 1965, but it would be almost 30 years before it was studied as a brain biomarker and 38 years before it was adopted into a clinical guideline for TBI management [12, 36].

Other brain biomarkers that have been studied during the 21st century include total tau protein, myelin basic protein, neurofilament light polypeptide, neuron specific enolase, glial fibrillary acidic protein, spectrin breakdown products, ubiquitin carboxyl-terminal hydrolase isoenzyme L1, mononuclear small noncoding RNA structures in peripheral blood, fatty acid-binding protein, and oligodendrocyte-specific proteins [37–46]. Almost all of them have shown some promise, but researchers have chosen to bring forward S100B; by now, it is a fairly good match for Bakay and Ward’s ideal brain biomarker.

S100B is readily analyzed in serum, and the in-hospital cost is around US\$ 20. Several companies manufacture laboratory machines that offer S100B assays. The influence of hemolysis is low [47]. S100B is stable even after prolonged storage time and in room temperature [48]. Serum levels increase by increasing age but are not affected by intoxication [49]. Extracerebral trauma might give false high levels of serum S100B because of the release from peripheral cells [50].

In 1965, Moore coined the name S100 because the protein has solubility in 100% saturated ammonium sulfate at a neutral pH [36]. S100B is a small protein with a molecular weight of 21 kiloDalton (kDa). It is present in the body as a dimer composed of two subunits with α -chains and β -chains. The main sources of S100B are astrocytes, but it is also secreted from adipocytes, chondrocytes, malignant melanoma cells, and Schwann cells. It regulates calcium homeostasis [24]. In vitro tests have revealed S100B’s neurotrophic effects in the nano-molar range and neurotoxic effects in the micro-molar range. It induces inflammatory-mediated apoptosis by raising levels of Interleukin-6 and is mainly calcium dependent [51, 52]. It is secreted from astrocytes into the cerebrospinal fluid and transported into the blood, most likely through the glymphatic system. It is eliminated through the kidneys [53]. Its half-time is reported as 25–97 minutes [54–56]. In the adult population, the variability with sex and age is fairly low [57]. It can be detected in the cerebrospinal fluid, urine, amniotic fluid, and saliva, as well as in venous, capillary, and arterial blood [58–62]. The protein has many variations of subunits, but the β -subunit is the most specific to brain tissue; for this reason, the clinically

used protein is referred to as S100B. It has an NPV of more than 99% (CI 98–100%) and a 97% sensitivity in detecting intracranial hemorrhage that is visible on a head-CT scan when 0.10 µg/l is used as the cut-off and the sample is taken within 6 hours after the trauma. However, the specificity is approximately 30% [63–66].

The S100B brain-biomarker research in relation to TBI has focused on the S100B determination in plasma. Some studies have analyzed S100B in urine and in capillary blood [62, 67–69]. Most of the studies focusing on S100B determination in urine have involved pediatric populations and the role of S100B in infant hypoxic encephalopathy, and no studies have reported the precision of urine S100B analysis [60, 64, 70–76].

The brain-biomarker part of this dissertation is entirely focused on S100B as it is the best researched brain-biomarker and highly suitable for indicating brain damage, at least according to Bakay and Ward's tenets [34, 77].

All factors than can affect the results of a laboratory analysis and occur before the analysis itself are usually referred to as preanalytical errors. Depending on the sample, various errors can occur that will skew the results in some way. General examples include sampling the wrong patient, using the wrong test tube, not removing the venous compression before sampling, sampling from an arm that has ongoing intravenous fluid resuscitation and diluted blood because of this, storing the sample in a refrigerator when it is not supposed to be refrigerated or vice versa, exposing the sample to sunlight, and so on. In general, it can be assumed that venous samples are slightly less sensitive to preanalytical errors than capillary samples because of the low capillary blood flow and the risk that the blood would be diluted or tainted in the sampling process. To ascertain adequate blood flow, the fingertip usually needs to be preheated to ensure that the capillaries are dilated. Even after preheating, which is rather time consuming, it might be difficult to obtain good blood flow, and the sampler might be tempted to manipulate the fingertip to increase the flow. This could lead to a shift of molecular concentrations in the sample because the molecules that were supposed to be measured might be mechanically affected or simply because too much extracellular fluid was extracted, causing the sample to be diluted.

The most common application for adult capillary sampling is point-of-care assay because it is a fast and easy way to acquire important pieces of the clinical puzzle. However, due to the innate risk of preanalytical error associated with capillary sampling, the clinician must take into account the occurrence of an incorrect assay of the molecule in question.

Guidelines for management of traumatic brain injury

In the late 20th century, the guidelines for TBI management were starting to emerge. Most of them were local guidelines, and the need for well-researched and validated guidelines became clear. During the early 21st century, two monumental scientific research articles were published that would lead the way for guidelines for TBI management: the Canadian CT Head Rule and the New Orleans Criteria [9, 10]. Other guidelines, such as the NICE Criteria and NEXUS II, emerged during this time, but the aforementioned two gained the most international headway [11, 13, 78]. Of the two, the Canadian CT Head Rule has become the set of guidelines of choice for many clinicians worldwide, in use for well over 15 years. It is also the most researched set of guidelines [79]. However, when these guidelines were drafted, no brain biomarker was considered safe enough to be recommended in clinical praxis. Another 12 years would pass before the SNC put forth its guidelines with an algorithm incorporating the brain biomarker S100B [12].

The foundation of the current guidelines for TBI management is constituted by both prospective and retrospective studies. Most of these studies have been conducted in North America or Europe. However, it seems that the epidemiology has shifted over the past 30 years. During the 1980s, motor vehicle and work-related accidents were the prevailing mechanisms of trauma, and the age and the gender distributions showed two peaks: young male individuals around 20 years of age and older individuals, men and women alike. Starting in the 1990s and continuing well into the 21st century, the majority of the patients have become older, and the trauma mechanism has shifted toward low-energy traumas, such as falling on the ground [18–30].

Management of traumatic brain injury from the clinical perspective

The guidelines for TBI management focus on identifying patients who are at risk of intracranial hemorrhage and patients who are at risk of neurosurgical intervention because of their injuries. The majority of the patients (up to 95%) suffer only mild TBI and have little risk of suffering intracranial hemorrhage [80]. The risk of neurosurgical intervention in this group is very small.

Brain concussion is defined as the loss of consciousness and/or the occurrence of amnesia due to head trauma. The patients who are at risk of intracranial hemorrhage are almost exclusively those who have suffered a concussion, thus presenting with some degree of acute cognitive dysfunction. The guidelines are based on the patient history, as well as clinical signs and symptoms, and it often proves difficult to obtain a reliable history and sometimes to have the patient perform the necessary movements included in the basic neurological examination. This situation can make the guidelines difficult to apply, and the clinician's only choice might be a better-safe-than-sorry CT-head scan.

In order for guidelines to have a high NPV, they prescribe head-CT scans to more than 50% of the patients when the frequency of intracranial hemorrhage is only 4–8%, and very few of the patients with intracranial hemorrhage require neurosurgical intervention [81, 82]. A large discrepancy exists between the number of CTs performed and the number of intracranial hemorrhages found, and there are several problems with this, including radiation exposure, cost, and logistic problems in emergency departments.

An adult patient undergoing a head-CT scan using a modern machine is exposed to approximately 2 MiliSievert (MSv). The risk of cancer is difficult to ascertain, but it has been estimated at 1/2000–1/6000 adult head-CT scans, mainly depending on the patient's age on exposure [83, 84]. The risk is most likely inversely related to the age on exposure [85]. The risk may also increase exponentially with a cumulative radiation dose, and because of the large number of CTs performed each year, it is not negligible, at least not on the population level. In practical terms, this means that every CT-head scan should be prescribed after careful consideration of each case. A guideline that prescribes many head-CT scans might make it difficult for clinicians to reduce the number of CTs based on their judgment.

An external validation of the SNC 2013 Guidelines concluded that the correct use of the guidelines and S100B would decrease CT usage by 32%; another study showed that it reduced the cost by €39/patient at the researchers institution [12, 65]. Despite the favorable reduction in CT usage and cost, 67% of the patients underwent a head-CT scan in first study, and it can be argued that the number of CTs is too high, considering the low incidence of intracranial hemorrhage.

A valid alternative to a head-CT scan is in-hospital observation. This has proven safe but time-consuming and expensive [86–88]. The main advantage of observation is the absence of radiation exposure.

Chapter 2 Aims of the dissertation

Numerous studies have dealt with aspects of adult TBI. Overall, the available scientific data is satisfactory in safely ruling out intracranial hemorrhage in the clinical setting. However, issues still exist with guidelines not being followed and guidelines rendering a high number of head-CT scans for each intracranial hemorrhage diagnosed. One concern is the outdated epidemiological data that is the foundation of paramount guidelines, such as the Canadian CT Head Rule, and the guidelines might need to be changed to better match the characteristics of present-day patients with head trauma. There is still a need for further exploration of how to obtain better guideline adherence in the clinical setting. One way of doing so entails not only further improving the guidelines but also investigating the circumstances that guide the clinical decision of ordering a CT-head scan. Many studies have investigated the safety and the efficacy of S100B in the emergency management of TBI when determined in venous blood, but few have aimed to evaluate assays in capillary blood and urine. Such assays could potentially contribute to creating more applicable guidelines, possibly with fewer CTs being prescribed.

This dissertation's general aim was to scientifically evaluate TBI-management and contribute to the improvement of the clinical management of TBI in emergency departments.

This dissertation's specific aims were as follows:

- Study the attitudes towards CT of the head and the adherence to guidelines among emergency department physicians who manage patients with head trauma.
- Evaluate the characteristics of adults with head trauma in the emergency department to identify the clinical features of intracranial hemorrhage and outline the present epidemiology in Scandinavia.
- Study if capillary serum S100B and urine S100B can be used to rule out intracranial hemorrhage.
- Explore ways of improving the current guidelines for the emergency management of TBI.

Chapter 3 Methods and study design

Ethical aspects

All studies were approved by the Ethics Review Board at Lund University. For further ethical discussion, see Chapter 5: Methodological considerations.

Statistical analysis

The statistical analysis was performed with the Statistical Package for the Social Sciences for Mac, v. 21 and v. 25. Histograms, Q-Q-plots, and the Shapiro-Wilks formula were used to test for normal distribution. Central tendencies were presented as means ($\pm 1.96 \times$ standard deviation [SD]) when parametric and as medians (interquartile range [IQR]) when non-parametric. For more specific information on the statistical methods, refer to Chapter 5: Methodological considerations.

Definitions of degrees of traumatic brain injury

There are several definitions of the degrees of traumatic head injury, which are all similar. The most important part of each definition is the degree of consciousness according to the Glasgow Coma Scale (GCS). The SNC defines severe head injury as GCS <9, moderate as GCS 9–13, mild as GCS 14 or GCS 15 with suspected or confirmed loss of consciousness or 2 or more vomits, and minimal as GCS 15 without loss of consciousness and repeated vomiting [65]. Sometimes minimal and mild traumatic brain injury are commonly referred to as minor traumatic brain injury.

Most definitions mention some extra conditions apart from the level of consciousness. These include history and duration of unconsciousness or other risk factors, such as repeated vomiting. It is mostly these extra conditions that differentiate the definitions from one another. Throughout this dissertation, the SNC's definitions are used if nothing else is stated in the text.

Paper I – Quantitative questionnaire-based survey of traumatic brain injury guidelines

There are several general studies regarding how to create, implement, and follow up the use of guidelines [15–17, 89–97]. The scientific literature investigating the use of guidelines for TBI management is somewhat scarcer in comparison to the corresponding number of studies testing the performance of guidelines [9, 10, 12, 65, 81, 98–107].

A study was therefore created using an adaptation of a preexisting, non-validated questionnaire to explore attitudes toward head-CT scans and guideline adherence among doctors working in the emergency department before and after the introduction of the SNC 2013 Guidelines [104].

The study was conducted as a prospective questionnaire-based survey in the emergency department of Helsingborg General Hospital. This hospital serves 75,000 emergency patients annually and has a catchment area of 350,000 people. It has trauma surgeons, general surgeons, orthopedic surgeons, emergency medicine doctors, anesthesiologists, and otorhinolaryngologists. The nearest neurosurgical clinic is 40 km away. Multitrauma patients are managed according to the Advanced Trauma Life Support (ATLS™) algorithm. The questionnaires were administered from November 12, 2013 to February 3, 2014; during this period, no intervention at all was performed. On February 4, 2014, the new guidelines were introduced. Due to the awareness of the difficulties in implementing new guidelines, repeated lectures were presented to the doctors in the emergency department during this time. The interventions were designed to increase knowledge of and improve attitudes toward the guidelines, according to Cabana et al. (1999) and Dean et al. (1997) [15, 95]. E-mail reminders were also sent to promote positive attitudes. From February 4 to September 1, 2014, no questionnaires were distributed or collected. This period was deemed sufficient to let the new guidelines settle and affirm positive attitudes and the desired behavior. The intention was that this long period of intermission would rid the study of the problems with the lack of awareness and the lack of familiarity [15]. The questionnaires were again administered from September 2 to November 30, 2014. Medical records were retrospectively reviewed to ensure that the questionnaire patients were similar to the entire cohort of head trauma patients. During this review, no record was kept of each physician's identity.

Papers II and III – Retrospective review of medical records and amendment of current guidelines

To further investigate if the foundation of the modern guidelines for TBI management rests on epidemiological data that might be somewhat outdated, a retrospective review of the medical records of adult patients with TBI was performed in the emergency department.

The setting for Papers II and III was Helsingborg General Hospital, as previously outlined (Chapter 3: Methods and study design, Paper I) The medical records of all patients with isolated head trauma were analyzed from November 11, 2013 to November 30, 2014 (Paper II) and from January 1 to December 31, 2017 (Paper III). Multitrauma patients were excluded from the analysis. The purpose of the unorthodox time period used for Paper II was to perform this review on all patients managed by the doctors who were included in Paper I. Paper III was designed as an improvement of Paper II. This improvement consisted of following the guidelines for retrospective review by Vassar et al. (2013) and performing a double review of 100 medical records to determine the degree of interrater-reliability so as to ascertain the highest possible reliability of the retrospectively obtained medical data [108].

The following parameters were manually extracted from the medical records:

1. Age (years)
2. Gender (M/F)
3. Head-CT scan performed (yes/no)
4. Head-CT outcome (hemorrhage/no hemorrhage)
5. Admission to general hospital ward (yes/no)
6. Admission to intensive care unit (ICU) (yes/no)
7. Admission to neuro-ICU (yes/no)
8. Neurosurgical intervention (yes/no)
9. Degree of head injury (minimal, mild, moderate, severe)
10. Level of consciousness using the Reaction Level Scale 85 (RLS) (1–8)
11. Level of consciousness using the GCS (15–3)
12. Blood pressure (systolic mm Hg/diastolic mm Hg)
13. Pulse rate (beats/minute)

14. Size of pupils (millimeter)
15. Body weight (kilograms)
16. Height (meters)
17. Past medical history (yes/no)
18. Anticoagulant treatment (no/warfarin/NOAC/injection)
19. Platelet inhibitor treatment (no/aspirin/clopidogrel/ticagrelor/other)
20. Other medication (yes/no)
21. Preexisting/new focal neurological deficits (yes/no)
22. Deterioration of neurological status during observation (yes/no)
23. S100B level ($\mu\text{g/l}$)
24. Nausea (yes/no)
25. Vomiting (yes/no)
26. Number of vomits (N)
27. Amnesia: type and duration (yes/no, antegrade/retrograde, time h:m)
28. Loss of consciousness (yes/no)
29. Peritraumatic seizure (yes/no)
30. Posttraumatic headache (yes/no)
31. Increasing intensity of headache (yes/no)
32. Trauma energy level (low, medium, high)
33. Clinical signs of basal skull fracture (yes/no)
34. Orthostatic hypotension (yes/no)
35. Cardiac dysrhythmia (yes/no)
36. Time from injury to medical examination in the emergency department (h:m)
37. Influence of any or multiple drugs/alcohol (yes/no)

Papers IV and V – Biomarker analysis

The S100B assay of serum has been introduced and validated as a means to help decide patients which do not need CT-head scans after head trauma. However, it needs to be analyzed no later than 6 hours post trauma, and venous blood has to be drawn [12].

All samples included in this dissertation were centrifuged for 10 minutes at 2200 G and analyzed using the Cobas e411 S100 electrochemiluminescence (ECLI) assay, (Roche Diagnostics) at the Helsingborg and Lund Hospital laboratories (accredited by the Swedish Board for Accreditation and Conformity Assessment). The assay had an 18-minute processing time, a lower detection limit of 0.005 µg/l, a within-assay coefficient of variability of 1.8%, and a total imprecision of 3.1% for concentrations between 0.08 µg/l and 2.13 µg/L.

The assay is a one-step immunometric sandwich method with ECLI assay. S100B from the sample (antigen), monoclonal mouse-anti-S100-antibodies conjugated with Biotin and monoclonal mouse-anti-S100-antibodies marked with Ruthenium react to form a sandwich complex. Paramagnetic particles covered with Streptavidin are added and through interaction between Biotin and Streptavidin, the sandwich complex binds to the paramagnetic particles. This causes it to shift state of aggregation from liquid to solid state, which in turn causes an electrochemical reaction resulting in light emission. The intensity of this light is measured, and it is directly proportional to the concentration of S100B in the sample.

To explore the versatility of S100B, two studies were designed to investigate if capillary blood or urine could be used instead of serum samples to rule out intracranial hemorrhage more effectively.

Paper IV was designed to study the agreement and the correlation between two capillary S100B samples drawn from one patient at the same time and the agreement and the correlation between the capillary samples and a venous sample of S100B that was also drawn at the same time. Only patients with traumatic intracranial hemorrhage and healthy volunteers were included. Other diagnoses that could theoretically result in elevated S100B were excluded. The capillary samples were drawn from separate fingers, with an effort to avoid manipulating the fingertips. A limited number of trained operators performed the blood sampling.

Paper V was designed to evaluate the precision of the S100B assay in urine, establish temporal profiles over 48 hours of serum S100B and urine S100B in patients with traumatic intracranial hemorrhage, and assess the ability of urine S100B to rule out intracranial hemorrhage. Further urine assays of osmolality, creatinine, Cystatin-C, and pH were performed to ascertain the effects of these parameters on urine protein S100B levels. The venous samples were obtained by venipuncture of the antecubital vein or by an indwelling infusion cannula. The urine

samples were obtained by micturition or by an indwelling catheter. The patients seeking medical attention because of head trauma were included in population 1. This population was used to investigate the ability of urine S100B to rule out intracranial hemorrhage. The patients with diagnosed traumatic intracranial hemorrhage were included in population 2, and the samples from this cohort were used to establish the temporal profile of urine S100B, ascertain the precision of the urine S100B assay and investigate if pH, osmolality etc. affected urine protein S100B levels.

Chapter 4 Results

Paper I – Questionnaire-based analysis

For 176 days, 161 completed questionnaires were collected, and 694 patients were registered. Of the 177 physicians working in the emergency department during this period, 69 (39%) filled out at least one questionnaire. See Table 1 for the distribution of the physicians' different levels of education and medical specialties.

Table 1.

Physicians working in the emergency department during the study period and their levels of education and medical specialties.

Level of education	Ear, Nose and Throat	Surgery	Emergency medicine	Internal medicine	Other	Total
Intern	0	39	2	1	0	42
Resident	4	27	26	0	2	59
Attending physician	20	20	13	4	19	76
Total	24	86	41	5	21	177

In 52% of the cases, no guidelines were applied. The most common set of guidelines to be used was the Canadian CT Head Rule, which was applied in 33.5% of the cases. In 12/38 (31.5%) cases where the Canadian CT Head Rule was applied to patients who had no loss of consciousness, CT was performed, in contrast to what the guidelines recommended. See Table 2 for the distribution of the guideline-usage and the levels of education.

Table 2.

Distribution per type of guidelines used, level of education of the physicians who used the guidelines, number of cases where CT was performed, and total number of cases.

Guidelines and level of education	N CTs/N total cases
Canadian CT Head Rule	27/54 (50%)
Intern	5/9 (55.6%)
Resident	15/33 (45.5%)
Attending/senior attending physician	7/12 (58.3%)
New Orleans Criteria	2/3 (66.7%)
Resident	2/3 (66.7%)
Local guidelines	5/12 (41.7%)
Intern	3/4 (75%)
Resident	2/8 (25%)
More than one set of guidelines used	4/6 (66%)
Intern	2/3 (66.7%)
Resident	2/3 (66.7%)
No guidelines used	57/84 (67.9%)
Medical student working under special license	0/1 (0%)
Intern	11/18 (61.1%)
Resident	31/47 (66.0%)
Attending/senior attending physician	15/18 (83.3%)
Total number of CTs/Total number of cases	97/161 (60.2%)

See Table 3 for the distribution of respondent-stated use of guidelines.

Table 3.

Respondent-stated use of guidelines, number of CTs, and total number of cases.

Guideline and Loss of consciousness	N CTs/N total cases
Loss of consciousness	39/46 (84.7%)
Canadian CT Head Rule	9/9 (100%)
New Orleans Criteria	1/1 (100%)
Local guidelines	3/4 (75%)
Other guidelines	1/1 (100%)
More than one set of guidelines	2/3 (66.7%)
No guideline	23/28 (82.1%)
No loss of consciousness	44/99 (44.4%)
Canadian CT Head Rule	12/38 (31.6%)
New Orleans Criteria	1/2 (50%)
Local guidelines	2/8 (25%)
Other guidelines	1/1 (100%)
More than one set of guidelines	1/3 (33%)
No guideline	27/47 (57.4%)
Unknown loss of consciousness	
Canadian CT Head Rule	14/16 (87.5)
No guideline	6/7 (85.7)

More than half of the respondents (54.1%) who prescribed a head-CT scan estimated the probability of intracranial hemorrhage as “low.” “Confirm or exclude diagnosis,” “fear of missing diagnosis,” and “expedite diagnosis” were the highest-rated reasons for ordering CT-scan of the head. See Table 4 for the full list of reasons for ordering CT and how they were rated to affect the decision of ordering the CT.

Table 4.
Respondent-stated reasons for ordering computerized tomography.

Reason for ordering CT	n	Modus (min/max)	Mean (\pmSD)
Confirm/exclude diagnosis	161	8 (0–10)	5.3 (\pm 4.7)
Expedite diagnosis	70	5 (0–10)	4.6 (\pm 3.9)
Lack of in-hospital beds	66	0 (0–10)	0.3 (\pm 1.3)
Consultant request	67	0 (0–10)	0.9 (\pm 2.6)
General practitioner request	67	0 (0–10)	0.5 (\pm 1.9)
Colleague request	69	0 (0–10)	1.1 (\pm 2.7)
Pressure from patients/relatives	68	0 (0–8)	0.3 (\pm 1.3)
Fear of missing diagnosis	79	5 (0–10)	4.7 (\pm 3.18)
Fear of being reported	70	0 (0–10)	1.3 (\pm 2-1)
Elusive medical history	72	1.5 (0–10)	3.7 (\pm 4.1)
Other	10	10 (0–10)	7.7 (\pm 3.7)

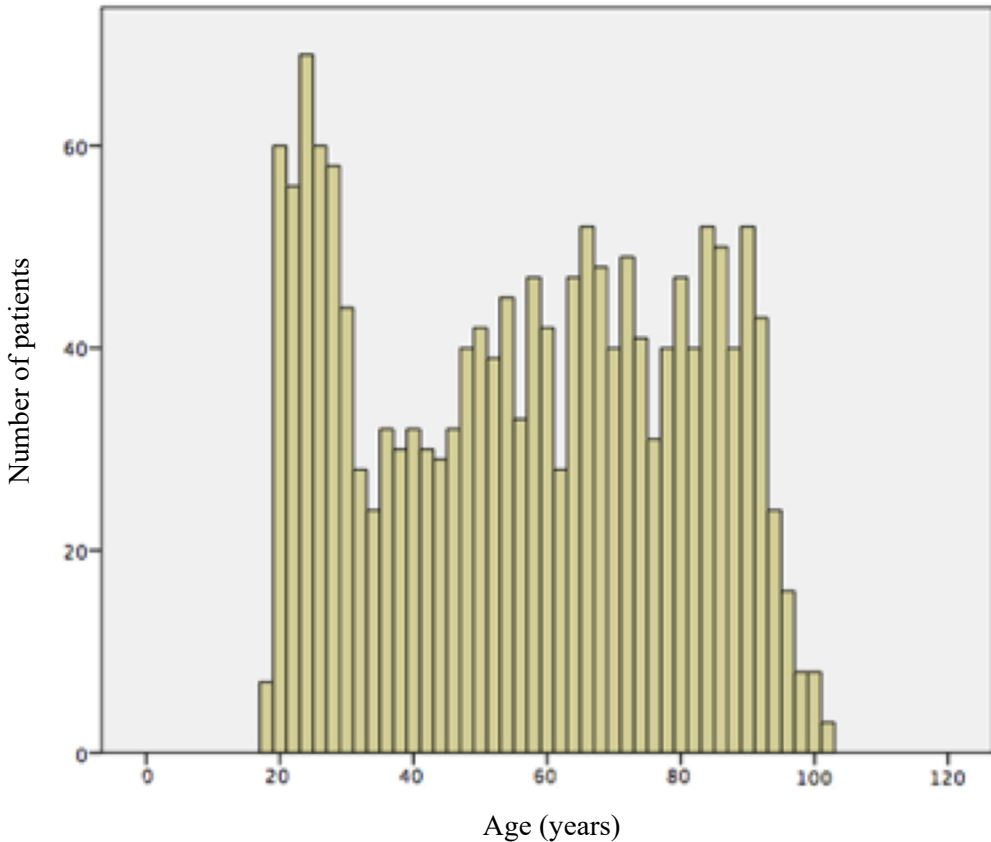
Modus and Mean represent how much the reason affected the respondent’s decision to order CT.

The “doctor’s notion that there is intracranial pathology” was significant in the logistic regression of both the “decision to order CT” and “what would make the doctor worry if CT could not be performed.”

Paper II – Retrospective review of medical records

The inclusion criteria were met by 1,638 patients, of whom 54.5% were male and 45.5% were female. The median age was 58 years (IQR: 35–77), with a slight peak at age 24. See Figure 1 for the age distribution.

Figure 1.
Age distribution in total cohort.



The CT-rate totaled 51.4%; of the CTs, 69.8% were performed on patients with low-energy trauma. The incidence of intracranial hemorrhage in the entire cohort was 4.3%. See Table 5 for the distribution of intracranial hemorrhage, age, and energy level.

Table 5.

Intracranial hemorrhage divided by age groups and levels of trauma energy.

		Age group				Total number of patients
		<i>18–39</i>	<i>40–55</i>	<i>56–79</i>	<i>80–100</i>	
		N Intracranial hemorrhage/N Total number				
Energy level	Low	0/328	0/251	16/349	27/323	1251
	Medium	0/47	3/28	5/17	2/2	94
	High	2/11	1/3	0/0	2/2	16
	n/a	1/93	1/65	6/79	5/44	277
Patients with intracranial hemorrhage		3/479 (0.6%)	5/347 (1.4%)	26/441 (5.9%)	36/371 (9.7%)	70

The age group cut-offs were selected at middle age (40 years), the first occurrence of intracranial hemorrhage in the low-energy trauma group (59 years), and age when intracranial hemorrhage was much more common (80 years).

Binary logistic regression to ascertain the effects of different parameters on intracranial hemorrhage rendered four significant parameters: increasing age, mild head injury, new neurological defects, and trauma-energy level. See Table 6 for the entire regression.

Table 6.

Binary logistic regression performed with intracranial hemorrhage as the dependent parameter and signs and symptoms commonly associated with intracranial hemorrhage as the independent parameters.

Parameter	Simple regression	Multiple regression 1	Multiple regression 2
	p-value	p-value	p-value
Age	<0.001	<0.001	<0.001
Gender	0.094	0.003	0.091
Degree of head injury	<0.001	<0.001	<0.001
Level of consciousness (RLS)	0.016	0.469	n/a**
Past illness	0.015	0.792	n/a**
Anticoagulation treatment	0.013	0.214	n/a**
Platelet inhibitor	<0.001	0.111	n/a**
Current medication	0.616	n/a*	n/a**
Preexisting neurological deficits	0.957	n/a*	n/a**
New neurological deficits	<0.001	0.007	<0.001
Trauma-energy level	<0.001	<0.001	<0.001
Intoxication	0.034	0.194	n/a**

*The value was marked n/a when the significance level in the previous analysis was too high for inclusion ($p > 0.4$).

**The value was marked n/a when the significance level in the previous analysis was too high for inclusion ($p > 0.05$).

Further subgroup analysis showed no intracranial hemorrhages among the patients under 59 years of age who were exposed to low-energy trauma and did not take anticoagulants or thrombocyte inhibitors (N = 826, 50.4%). The features of this cohort were used in Paper III in a proposed amendment to the current SNC guidelines and were collectively referred to as the low-risk proposal.

Intoxication was found in 25% of the patients. Most of these were influenced by alcohol. The incidence of intracranial hemorrhage in patients who took thrombocyte inhibitors was 11.8%, and in patients who took anticoagulants, it was 8.6%. S100B was measured in 198 cases, with an NPV of 98.9%. One patient with intracranial hemorrhage presented with a normal S100B.

Paper III – Proposed amendment of current guidelines

In total, 1,671 patients met the inclusion criteria. The median age was 64 years (IQR: 39–80), 887 (53.1%) of the participants were male, and 784 (46.9%) were female. Of these 1,671 patients, 756 (46.1%) had minimal head injury, 894 (53.5%) had mild head injury, 11 (0.7%) had moderate head injury, and 10 (0.6%) had severe head injury. The trauma-energy level was low in 1,033 (61.8%) patients, 38 (2.3%) patients had a medium trauma-energy level, and 9 (0.5%) had a high trauma-energy level. Of the remaining patients, 500 (29.9%) had classifiable trauma mechanisms without a pre-defined trauma-energy classification, and 89 (5.3%) had an unclear trauma mechanism.

During the study period, 1,039 (62.2%) patients underwent a head-CT scan. The rate of admission to the surgical ward was 21.5% (360 patients), and 11 (0.7%) patients were admitted to the ICU. Neurological intervention was performed on 8 (0.5%) patients. The mortality rate was 0.5% (8/1,671).

The SNC guidelines recommended 860/1,671 (51.5%) CT scans, correctly diagnosed 82/93 intracranial hemorrhages (89.2%), and missed 11 intracranial hemorrhages in the 179 patients who underwent a CT scan against the guideline recommendations. The SNC guidelines that were amended based on the low-risk proposal recommended 748/1,671 (44.8%) CT scans, correctly diagnosed 74/93, and missed 19 intracranial hemorrhages diagnosed with CT performed according to or against the SNC guidelines. Neither the original nor the amended version of the guidelines missed any intracranial hemorrhages that required neurological intervention (Tables 7–8).

Table 7.

Scandinavian Neurotrauma Committee guidelines applied to entire cohort.

Degree of head injury	Total number (N)	Computerized tomographies (N)	Intracranial hemorrhages (N)	Interventions (N)	Missed intracranial hemorrhages (N)	Missed intracranial hemorrhages with intervention (N)
Severe injury	10	10	7	2	0	0
Moderate injury	11	11	5	2	0	0
Mild injury, high risk	433	433	29	3	0	0
Mild injury, medium risk	142	142	14	1	0	0
Mild injury, low risk (RLS 2)	41	36	2	0	0	0
Mild injury, low risk (RLS 1)	278	228	25	0	0	0
Minimal injury	756	0	11	0	11	0
Total number	1,671	860	93	8	11	0

Table 8.

Amended Scandinavian Neurotrauma Committee guidelines applied to entire cohort.

Degree of head injury	Total number (N)	Computerized tomographies (N)	Intracranial hemorrhages (N)	Interventions (N)	Missed intracranial hemorrhages (N)	Missed intracranial hemorrhages with intervention (N)
Severe injury	10	10	7	2	0	0
Moderate injury	11	11	5	2	0	0
Mild injury, high risk	433	392	29	3	3	0
Mild injury, medium risk	142	142	14	1	0	0
Mild injury, low risk (RLS 2)	41	29	2	0	0	0
Mild injury, low risk (RLS 1)	278	164	25	0	5	0
Minimal injury	756	0	11	0	11	0
Total number	1,671	748	93	8	19	0

See table 9 for evaluation of the SNC guidelines' and the amended SNC guidelines' performance with regards to sensitivity, specificity, NPV and positive predictive value (PPV).

Table 9.

Performance of Scandinavian Neurotrauma Committee guidelines, not amended and amended.

Type of performance measurement	Scandinavian Neurotrauma Committee guidelines	Amended Scandinavian Neurotrauma Committee guidelines
Sensitivity	88.2% (95% CI, 79.8–94.0%)	79.6% (95% CI, 70.0–87.2%)
Specificity	50.7% (95% CI, 48.2–53.2%)	57.3% (95% CI, 54.8–59.8%)
Negative predictive value	98.6% (95% CI, 97.7–99.2%)	97.9% (95% CI, 97.0–98.6%)
Positive predictive value	9.5% (95% CI, 8.8–10.3%)	9.9% (95% CI, 8.9–11.0%)

CI - Confidence Interval

The application of the low-risk proposal resulted in a relative 13% reduction of the head-CT scans (112 CT scans). The reduction of the CT scans was statistically significant ($p < 0.001$). The intracranial hemorrhage incidence was 11.9% (23/194) in the thrombocyte inhibitor cohort and 6.0% (13/215) in the anticoagulant cohort. In the remainder of the cohort, who did not take thrombocyte inhibitors, anticoagulants, or low molecular weight heparins (LMWHs), there were 58/1,254 (4.6%) intracranial hemorrhages.

Cohen's kappa coefficient varied between 0.167 and 0.857, corresponding to good and very good agreement in most of the parameters, except "new neurological deficits" and "LMWH treatment" (Table 10) [109].

Table 10.

Cohen's kappa coefficient for signs and symptoms associated with intracranial hemorrhage.

Parameter	Cohen's kappa	95% CI lower	95% CI upper
Trauma mechanism	0.641	0.521	0.761
Previous disease	0.717	0.580	0.854
Intoxication	0.857	0.739	0.975
Loss of consciousness	0.763	0.594	0.932
Amnesia	0.686	0.512	0.860
Two or more vomits after trauma	0.756	0.648	0.864
Posttraumatic seizure	*		
New neurological deficits	0.347	0.186	0.508
Thrombocyte inhibitor	0.825	0.702	0.948
Anticoagulant	0.799	0.697	0.901
LMWH treatment	0.167	-0.168	0.502

*The parameter is a constant; therefore, it is not possible to calculate the Kappa coefficient.

Paper IV – Capillary and venous S100B

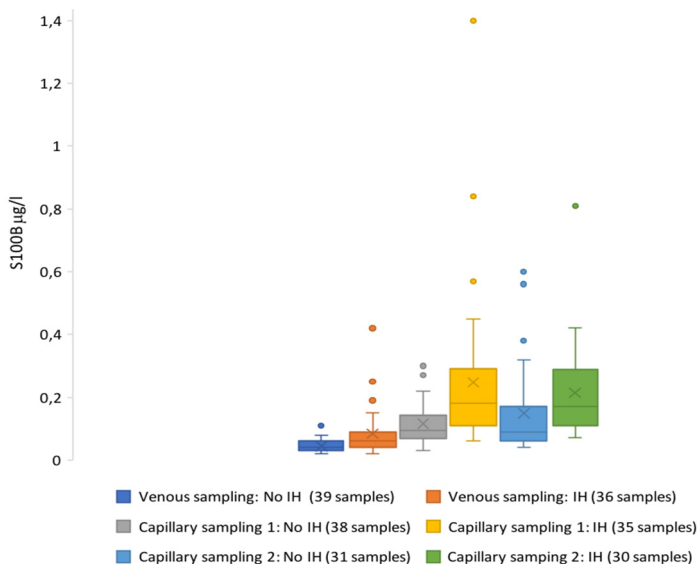
In total, 18 patients with intracranial hemorrhage were included, and 39 healthy volunteers without head trauma within the past 7 days were recruited. The 39 volunteers (18 females and 21 males) had a median age of 28 years (IQR: 26–32.75), and the 18 patients (9 females and 9 males) with intracranial hemorrhage had a median age of 53 years (IQR: 34.5–70). In total, 78 sampling events of 1 venous and 2 capillary samples were performed. Of the samples, 3/78 (4%) venous and 21/155 (13.5%) capillary samples were rejected, resulting in the analysis of 209 samples (75 venous and 134 capillary).

The mean S100B of capillary sampling 1 was 0.18 (± 0.371) $\mu\text{g/l}$, and the mean S100B of capillary sampling 2 was 0.18 (± 0.266) $\mu\text{g/l}$. The mean S100B of capillary sampling 1 in the volunteers was 0.12 (± 0.130) $\mu\text{g/l}$, and the mean S100B of capillary sampling 1 in the patients with intracranial hemorrhage was 0.25 (± 0.502) $\mu\text{g/l}$. The mean S100B of capillary sampling 2 in the healthy volunteers was 0.15 (± 0.289) $\mu\text{g/l}$, and the mean S100B of capillary sampling 2 in the patients with intracranial hemorrhage was 0.23 (± 0.291) $\mu\text{g/l}$ (Figure 2).

The mean S100B of all venous samples was 0.06 (± 0.112) $\mu\text{g/l}$. The mean S100B of the venous samples in the volunteers was 0.05 (± 0.034) $\mu\text{g/l}$. The mean S100B of the venous samples in the patients with intracranial hemorrhage was 0.08 (± 0.148) $\mu\text{g/l}$ (Figure 2).

Figure 2.

Box-and-whiskers plot of venous and capillary S100B samples.



Venous and capillary samplings of S100B with and without intracranial hemorrhage (IH).

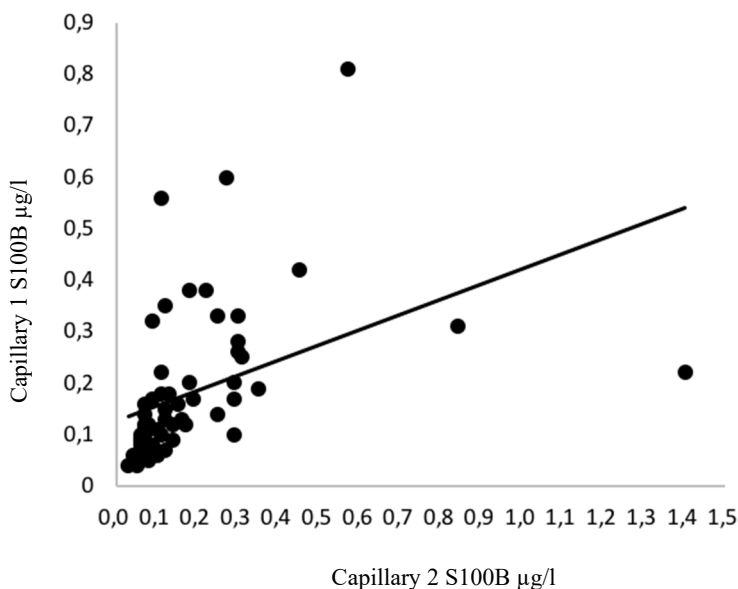
In four of the analyses, the venous samples were higher than capillary sample 1; in 2 of these cases, capillary sample 2 was missing, 1 was equal to the venous sample, and 1 was less than the venous sample. In the remaining 206 samples, the capillary samples were equal to or higher than the venous samples.

Wilcoxon's signed rank test results showed that the difference in S100B between capillary sampling 1 and the venous sampling was statistically significant ($z = -7.0$, $p < 0.001$), and so was the difference between capillary sampling 2 and the venous sampling ($z = -6.72$, $p < 0.001$). However, there was no statistically significant difference between capillary sampling 1 and capillary sampling 2 ($z = -0.99$, $p = 0.32$).

The correlation plot of capillary 1 and capillary 2 showed Spearman's $\rho < 0.8$ (Figure 3). The line of regression in the Bland-Altman plot of the capillary samples showed a slight negative slope. The limits of agreement were $-0.271 \mu\text{g/l}$ and $0.239 \mu\text{g/l}$ (Figure 4).

Figure 3.

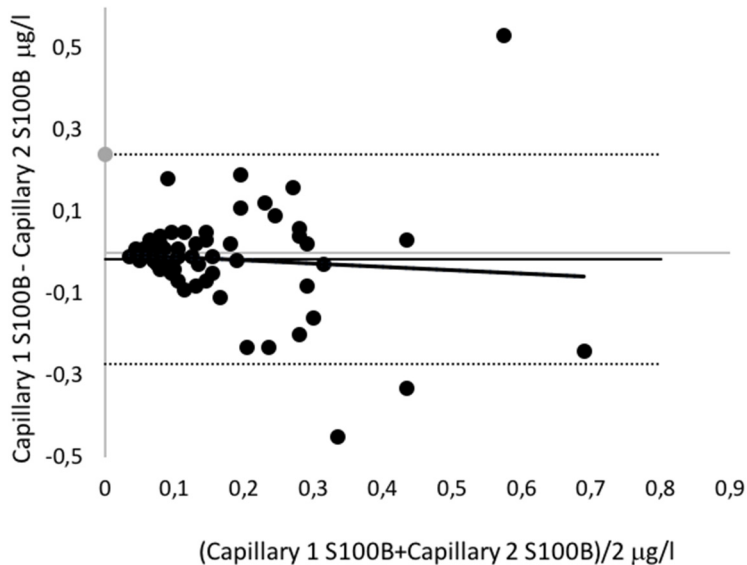
Correlation plot of capillary 1 serum protein S100B and capillary 2 serum protein S100B.



Sixty-one matched samples. Spearman's $\rho = 0.754$ ($p < 0.001$). Regression line: intercept = 0.127 (95% confidence interval [CI], $0.082-0.173$); slope = 0.295 (95% CI, $0.131-0.459$); $R^2 = 0.180$

Figure 4.

Bland-Altman plot of capillary 1 serum protein S100B versus serum capillary 2 serum protein S100B.

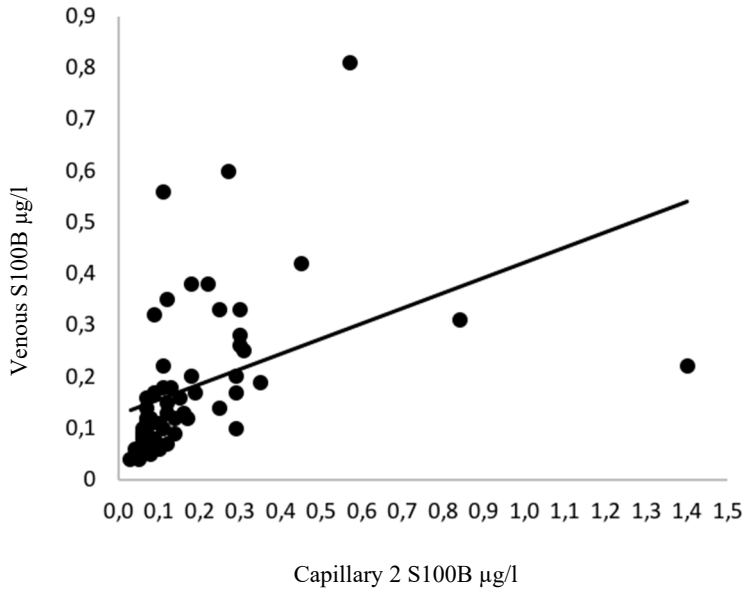


Sixty-one matched samples. Regression line: intercept = -0.0023 (95% CI, -0.058 to -0.053); slope = -0.081 (-0.344 to -0.181); $R^2 = 0.006$

The correlation plots of the capillary and the venous samples showed Spearman's $\rho < 0.5$ (Figure 5). The Bland-Altman plots of capillary sampling 1 and 2 versus the venous sampling showed a large dispersion of the samples and a steep positive slope of the line of regression (Figure 6). The limits of agreement for capillary sampling 1 and the venous sampling were -0.083 $\mu\text{g/l}$ and 0.269 $\mu\text{g/l}$. The limits of agreement for capillary sampling 2 and the venous sampling were -0.140 $\mu\text{g/l}$ and 0.391 $\mu\text{g/l}$ (Figure 6).

Figure 5.

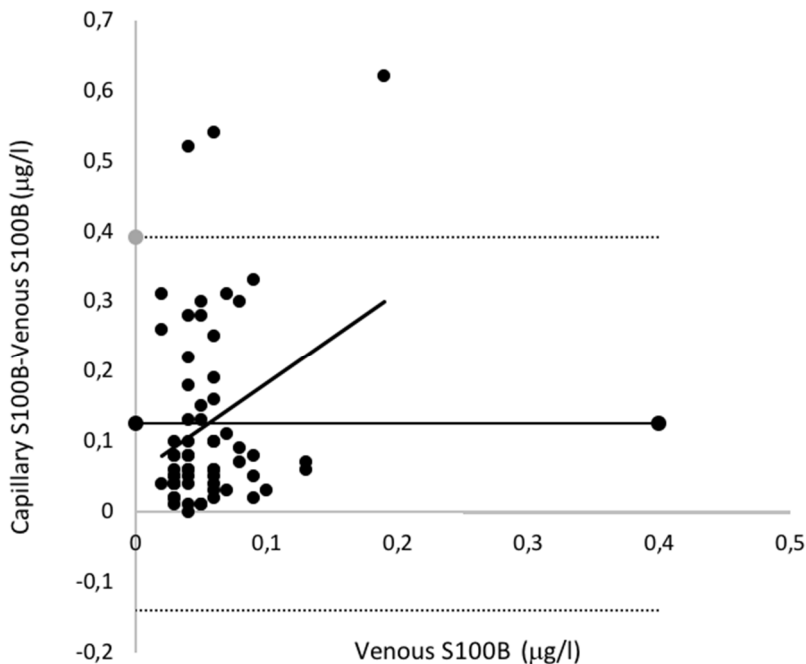
Correlation plot of venous S100B and capillary 2 S100B.



Sixty-one matched values. Spearman's $\rho = 0.461$ ($p < 0.001$). Regression line: intercept = 0.038 (95% CI, 0.027–0.049); slope = 0.095 (95% CI, 0.048–0.102); $R^2 = 0.219$

Figure 6.

Bland-Altman plot of venous serum protein S100B versus capillary 2 serum protein S100B.



Sixty-one matched samples. The venous sample is used on the y-axis because the true value is assumed to be that of the venous sample. Regression line: intercept = 0.047 (95% CI, 0.037–0.057); slope = 0.063 (95% CI, 0.008–0.118); $R^2 = 0.082$

The prediction equation classified 22/73 (30.1%) samples incorrectly over or under the clinical cut-off in capillary sampling 1, with a mean prediction error of 0.053 (0.353) $\mu\text{g/l}$. In capillary sampling 2, 22/61 (36.1%) samples were incorrectly predicted over or under the clinical cut-off of 0.1 $\mu\text{g/l}$, with a mean prediction error of 0.058 (0.251) $\mu\text{g/l}$. In capillary sampling 1, 8 corresponding venous samples were above the clinical cut-off, and 2/8 (25%) were predicted below the cut-off. In capillary sampling 2, 4 venous samples with corresponding capillary samples were above the clinical cut-off, and 1/4 (25%) was predicted below the cut-off. The prediction for the venous sample versus capillary sampling 1 showed a difference (in the prediction error) of 0.011 (0.064 - 0.053) $\mu\text{g/l}$ compared with the results of Åstrand et al. (2012) [62]. The prediction for the venous sample versus capillary sampling 2 showed a difference (in the prediction error) of 0.006 (0.064 - 0.058) $\mu\text{g/l}$ compared with the results of Åstrand et al. (2012) [62].

Paper V – Urine and venous S100B

Precision of S100B assay in urine

In all, 6 patients with intracranial hemorrhage and Serum(S)-S100B levels ranging from 0.083 µg/l to 0.301 µg/l were selected for precision analysis. The mean S100B concentration was 0.151 (±0.225) µg/l in serum and 0.067 (±0.200) µg/l in urine. The mean Coefficient of Variation % (CV%) in all 6 serum samples was 1.30 (±1.078). The mean CV% in the urine samples was 3.16 (±3.114) (Table 11).

Table 11.
Precision analysis of serum and urine S100B.

Sample #	Analysis	Mean (10 samples)	SD	CV% = (SD/Mean) x 100
1	S-S100B	0.292	0.004	1.35
	U-S100B	0.046	0.001	2.08
2	S-S100B	0.034	0.001	2.18
	U-S100B	0.030	0.001	2.47
3	S-S100B	0.095	0.001	0.66
	U-S100B	0.019	0.001	3.86
4	S-S100B	0.301	0.003	1.08
	U-S100B	0.274	0.004	1.34
5	S-S100B	0.083	0.001	1.65
	U-S100B	0.014	0.001	5.83
6	S-S100B	0.103	0.001	0.89
	U-S100B	0.022	0.001	3.37

Assay performed on 6 individual patient samples, with 10 within-day analyses on each sample

Comparison of ability of serum S100B and urine S100B to rule out intracranial hemorrhage

Population 1

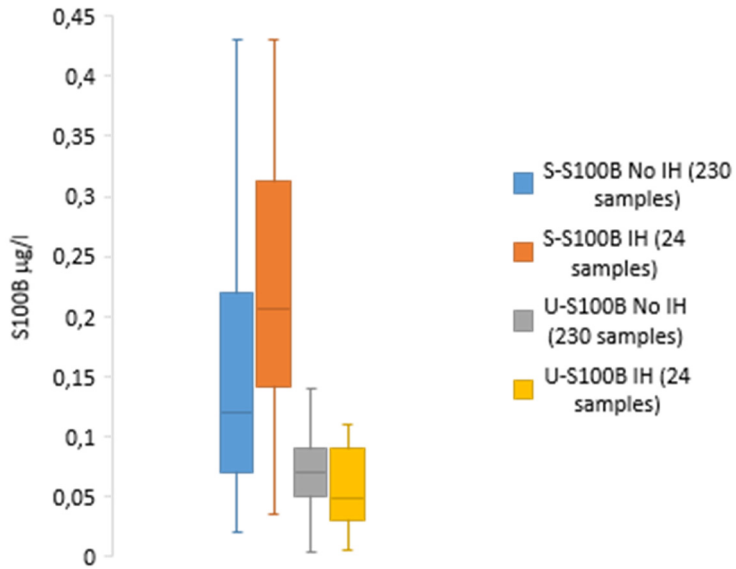
In total, 512 patients were included, and 73 of them were excluded because the time of trauma could not be ascertained. The laboratory rejected 8 urine samples because the wrong sampling tube was used, but no venous samples were rejected. Of the remaining 431 patients, 3 had missing venous S100B samples, and another 185 patients had no urine sample. Matching urine and blood samples were obtained from 243 patients.

In the cohort of 243 patients, the mean age was 60.8 years (± 44.96 years), and 13 patients had intracranial hemorrhage (5.4%). Loss of consciousness was recorded in 58/243 (23.9%) patients, and 38/243 (15.6%) patients could neither confirm nor deny any loss of consciousness. Amnesia was confirmed in 71/243 cases (29.2%). No patient arrived unconscious in the emergency department (RLS 1–3). Oral anticoagulants (Warfarin/NOAC) were taken by 37/243 (15.2%) patients, aspirin (75 mg) was taken by 24/243 (9.9%) patients, and 1/243 (0.4%) patient had a serious bleeding disorder.

The median S-S100B in the 230 patients without intracranial hemorrhage was 0.12 (IQR: 0.07–0.22) $\mu\text{g/l}$, and the median urine (U)-S100B was 0.07 (IQR: 0.05–0.09) $\mu\text{g/l}$ (41.7% lower than serum). The median S-S100B in the 13 patients with intracranial hemorrhage was 0.18 (0.05–0.42) $\mu\text{g/l}$, and the median U-S100B was 0.08 (IQR: 0.045–0.10) $\mu\text{g/l}$ (66% lower than serum). The median S-S100B in all 243 patients was 0.13 (IQR: 0.07–0.23) $\mu\text{g/l}$, and the median U-S100B was 0.07 (IQR: 0.05–0.09) $\mu\text{g/l}$ (46.2% lower than serum S100B) (Figure 7).

Figure 7.

Box-and-whiskers plot of patients with head trauma (from population 1) and patients with intracranial hemorrhage within 6 hours (from population 2).



All samples with and without intracranial hemorrhage (from population 1) and all samples within 6 hours from trauma (from population 2). IH – intracranial hemorrhage; S – serum; U – urine

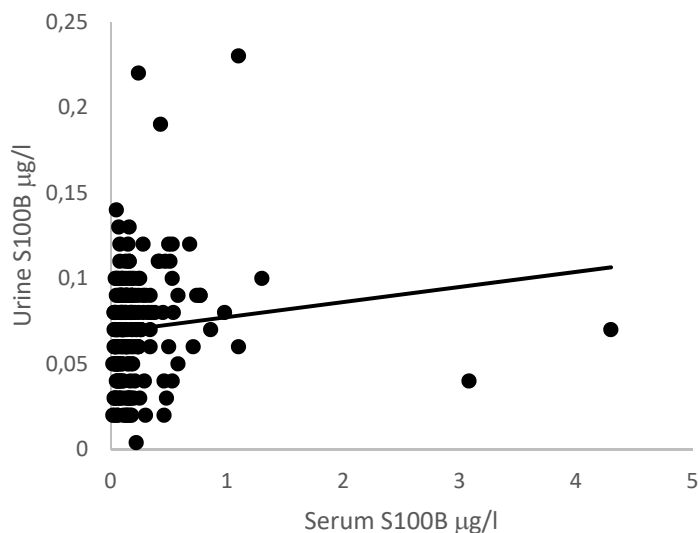
Populations 1 and 2, patients with intracranial hemorrhage

In total, 11 samples from population 2, drawn from 6 patients within 6 hours from trauma, were available for analysis. The median serum S100B was 0.22 (0.18–0.29) $\mu\text{g/l}$; the median urine S100B was 0.039 (0.0230–0.0435) $\mu\text{g/l}$. The difference in the median S-S100B in these 11 samples from population 2 compared with the 13 patients with intracranial hemorrhage from population 1 was 0.04 $\mu\text{g/l}$ (0.22 $\mu\text{g/l}$ - 0.18 $\mu\text{g/l}$, $p = 0.794$). The corresponding difference in the median U-S100B was -0.041 $\mu\text{g/l}$ (0.039 $\mu\text{g/l}$ - -0.08 $\mu\text{g/l}$, $p = 0.010$). The patients whose samples were drawn over time in the ICU (population 2) had serum S100B levels that did not statistically differ from those of population 1 and significantly lower levels of urine S100B.

The correlation plot had Spearman's $\rho = 0.229$ ($p = 0.001$) (Figure 8). The Bland-Altman plot showed a mean bias of 0.12 (± 0.411) $\mu\text{g/l}$. The limits of agreement were -0.287 $\mu\text{g/l}$ and 0.536 $\mu\text{g/l}$ (Figure 9).

Figure 8.

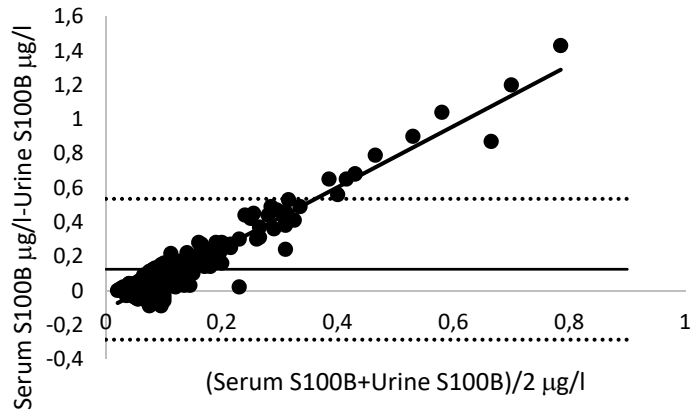
Correlation plot of serum and urine S100B samples within 6 hours or less between trauma and serum sampling.



This figure includes 199 matched samples and excludes 2 samples. Intercept = 0.069 (95% CI, 0.0633–0.0738); slope = 0.009 (95% CI, -0.003-0.020); $R^2 = 0.012$. Spearman's $\rho = 0.229$ ($p = 0.001$)

Figure 9.

Bland-Altman plot of serum and urine S100B.



This figure includes 239 matched samples and excludes 4 samples. Regression line: intercept = -0.114 (95% CI, -0.155-0.073); slope = 1.747 (95% CI, 1.628-1.865); $R^2 = 0.778$

One patient with intracranial hemorrhage had a serum S100B value of less than the clinical cut-off of 0.10 g/l when measured within the 6-hour limit. The performance of S-S100B, U-S100B, and S-S100B - U-S100B was similar with regard to NPV (95.8–97.09%). The PPV was much lower for U-S100B and S-S100B - U-S100B (37.31% versus 7.00% and 9.68%, respectively) (Table 11).

Table 11.

Comparison of serum and urine S100B assay performance up to 6 hours after trauma in populations 1 and 2.

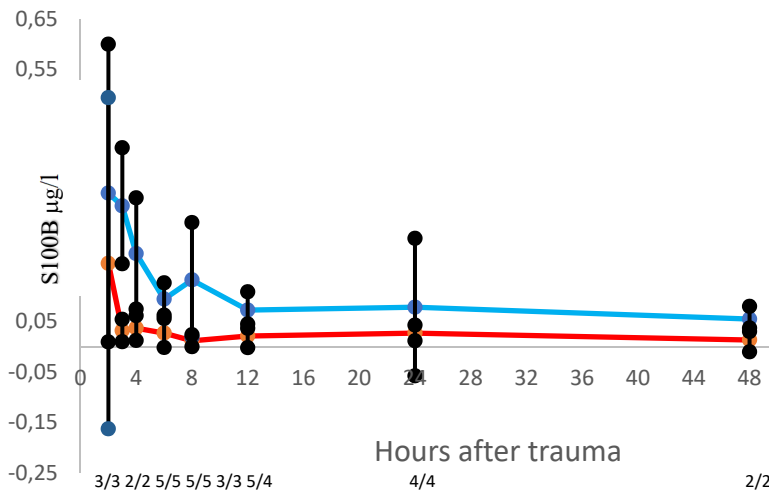
Assay	Sensitivity	Specificity
S-S100B \geq 0.10*	91.3% (95% CI, 71.96–98.93%)	34.4% (95% CI, 27.7–41.6%)
U-S100B \geq 0.09**	33.3% (95% CI, 14.6–57.0%)	67.1% (95% CI, 59.4–74.1%)
S-S100B - U-S100B \geq 0.15**	57.1% (95% CI, 34.0–78.2%)	71.8% (95% CI, 64.4–78.4%)
Assay	Negative predictive value	Positive predictive value
S-S100B \geq 0.10*	97.0% (95% CI, 89.5–99.2%)	14.5% (95% CI, 12.6–16.6%)
U-S100B \geq 0.09**	89.1% (95% CI, 85.5–91.9%)	11.1% (95% CI, 6.2–19.2%)
S-S100B - U-S100B \geq 0.15**	93.1% (95% CI, 89.1–95.8%)	20.0% (95% CI, 13.9–28.0%)
*212 samples. **191 samples.		

Temporal profile of serum and urine levels of S100B in patients with intracranial hemorrhage

There were 13 patients included in the cohort used for establishing the temporal profile of U-S100B and the analysis of the correlation and the agreement between serum and urine S100B levels over time (Population 2). Urine S100B levels dropped faster and had less variation than serum levels. There was no significant elevation of urine S100B compared with serum after the first 6 hours (Figure 10).

Figure 10.

Mean serum and urine S100B temporal profiles after CT-verified traumatic intracranial hemorrhage.

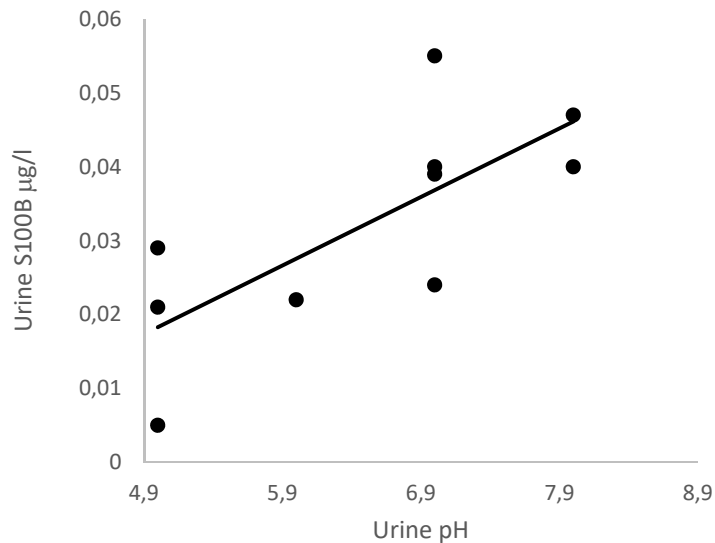


Forty-two matched serum and urine samples. 6 patients included in analysis. Median age = 68 years (IQR = 46–69). Blue line: serum S100B. Red line: urine S100B. The numbers at the bottom of the figure (e.g., 3/3) are the numbers of serum/urine samples included at each point in time.

Properties of kidney function and urine composition affecting S100B levels in urine

Plasma-creatinine, plasma-Cystatine C, estimated glomerular filtration rate, urine-osmolality, and urine-creatinine were not correlated with urine S100B levels. The only analysis of blood and/or urine that showed a correlation to urine S100B was urine pH measured within 6 hours after trauma. Spearman's $\rho = 0.778$ ($p = 0.008$) (Figure 11). After 6 hours from trauma, the correlation could not be observed.

Figure 11.
Correlation plot of urine pH and urine S100B within 6 hours after trauma.



One outlier excluded. Ten samples included in graph.

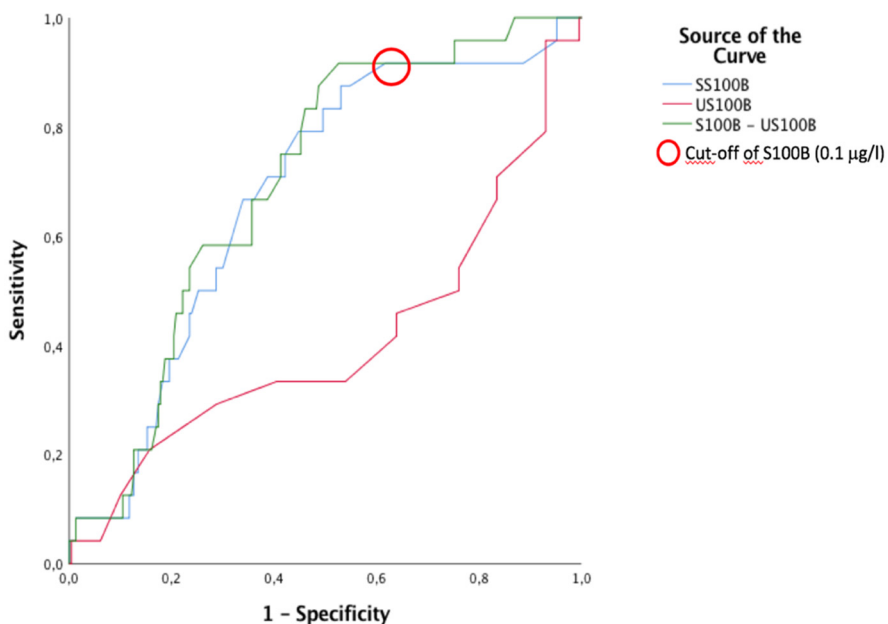
Regression line: intercept = -0.03 (95% Confidence Interval (CI), -0.07-0.02); slope = 0.009 (95% CI, 0.002-0.016); $R^2 = 0.551$. Spearman's $\rho = 0.778$ ($p = 0.008$)

Receiver operating characteristics of relationship between serum and urine samples and intracranial hemorrhage

The arithmetic difference, the ratio and the log-ratio between the paired serum S100B and urine S100B samples were tested. The arithmetic difference had a larger area under the curve than the urine and the serum samples, the ratio and the log-ratio when tasked to rule out intracranial hemorrhage. The receiver operating characteristics (ROC) of the trend analysis of S-S100B, U-S100B, and the arithmetic difference between serum S100B and urine S100B in populations 1 and 2 within 6 hours from trauma showed the largest area under the curve for the difference between SS100B and US100B (Figure 12).

Figure 12.

Receiver operator characteristics curve of population 1 and population 2 samples, maximum of 6 hours after trauma and urine sampling.



191 samples included in analysis. A total of 21/191 samples from patients with intracranial hemorrhage. Area under curve Serum (S)-S100B – Urine (U)-S100B = 0.686 (95% CI, 0.581–0.790, $p = 0.006$). Area under curve S-S100B = 0.657 (95% Confidence Interval [CI], 0.542–0.772, $p = 0.019$). Area under curve U-S100B = 0.386 (95% CI, 0.232–0.540, $p = 0.089$). Diagonal segments were produced by ties.

Chapter 5 Methodological considerations

Introduction to methodological considerations

To make the specific discussions on the methodology, the statistics, and the study limitations clearer to the reader, this separate chapter has been created. Each paper that is included in this dissertation is given its own section. The subsections recapitulate the aim, as stated in the original paper (**aim**), the data collection methods (**study methods**), and the statistical methods used to process and present the data (**study statistics**). The subsections also outline the practical difficulties (**practical difficulties**) and the theoretical limitations of the chosen methods (**theoretical study method limitations** and **statistical limitations**). A paragraph also discusses how the knowledge and the knowhow acquired during the dissertation work could be taken from theory and applied to practice in order to design scientifically better and more practically manageable studies with similar aim as that of the original study (**improved study methods**).

The discussion on improving the study methods does not include the size of the study cohort as it is not always possible to increase because of financial or practical limitations. Furthermore, it is an obvious way to make almost any study better and does not add much to the discussion.

Paper I

Aim

The main aim of Paper I was to prospectively evaluate physicians' attitudes toward CT-head scans when managing patients seeking medical attention, with head trauma as the chief complaint. Another aim was to study the adherence to the guidelines, the reasons for ordering a CT, and the impact of enhanced information regarding the usage of the guidelines.

Study method

An adapted, translated questionnaire (German to Swedish), originally used by Rohacek et al. (2012), was administered [104]. The questionnaires were distributed among emergency department physicians over two 3-month periods, with a 6-month intermission when new guidelines recommending S100B were introduced and promoted.

Study statistics

Q-Q-plots and the Shapiro-Wilks formula were employed to test the data distribution. The Mann-Whitney-U test was used to test the ordinal data with skewed distributions. The chi-square test was used to test the contingency tables. Binary multivariate analysis was performed with forward selection logistic regression, and continuous multivariate analysis was conducted with linear regression and a stepwise selection of the independent variables.

Practical difficulties

The practical difficulties encountered were as follows:

- Ensuring that one questionnaire was administered to the physician who managed each patient with head trauma.
- Having the physician complete the questionnaire.
- Having the questionnaire returned to the researchers.
- Sending friendly reminders to the physicians who had not completed the questionnaire.

Theoretical limitations in the study method

- Using a non-validated questionnaire could lead to retaining ambiguous questions or questions that are difficult to understand.
- Using a questionnaire that was developed without stakeholder involvement might lead to a reduced response rate and the retention of difficult or ambiguous questions.
- Attitudes might be difficult to capture with a quantitative study method. If anything, the quantitative answers need qualitative follow-up to be comprehensive enough to use for the development of new guidelines.

Statistical limitations

The different methods used were formally correct but using the forward selection or the stepwise inclusion instead of the enter-method inclusion might have led to statistical reliability without validity. The study's low response rate might also have yielded reliable results without validity.

Potential study improvements

- It would probably be better if the nurse in charge of the emergency department's surgical unit would also be responsible for administering the questionnaires. This way, only three people would be responsible during each 24-hour period, making it easier to remind them and follow up on how many questionnaires were administered.
- Sending friendly reminders to the physicians who had not completed the questionnaire would have been feasible if the follow-up was done once every 24 hours. On average, 5–6 patients with head injury were managed daily during this time period. It is possible that the reason why the questionnaires were not administered or not completed was simply lack of time, which means that it would have been possible to have them filled out just by ensuring that all questionnaires were administered and by doing so, kindly reminding the physicians to complete them.
- Performing follow-up every 24 hours would have allowed the researchers to be more visible, making it easier to answer the questions about the study and interact with the stakeholders and possibly making them more receptive to the questionnaire.

- Boynton et al. (2004) outlined the factors that were shown to increase the survey response rate [110]. The previous response rates were reported at the same level as that of Paper I, but a higher response rate would have made the results more applicable to the entire staff [111]. Aside from the aforementioned measures, applying the guidelines presented by Boynton et al. could also have meant offering a prize upon completion of the questionnaire.

Paper II

Aim

The aim of Paper II was to evaluate the characteristics of the adults presenting with the chief complaint of head trauma over a one-year period in order to identify the clinical features predicting intracranial hemorrhage. The analysis emphasized patient history, clinical findings, and epidemiological traits.

Study method

The study method involved a retrospective review of the medical records, where 37 parameters pertaining to TBI were extracted. A regulatory document guiding the parameter interpretations was established. A total of 380 days of medical records was reviewed.

Study statistics

Q-Q plots and the Shapiro-Wilks test were used to test the data distribution. Post hoc multivariate analysis was performed with simple binomial logistic regression, where significant parameters ($p < 0.4$) were inserted into a multiple binomial logistic regression model. Another regression was performed on the parameters with $p < 0.05$ in the first multiple regression. The missing data was replaced by the series median or modus. Subgroup analysis with descriptive statistics was performed to evaluate the occurrence of these parameters together with intracranial hemorrhage.

Practical difficulties

The practical difficulties encountered were as follows:

- The greatest problem with this study was the regulatory document. The parameters that the research team wanted to extract were defined in advance, but the document was not detailed enough because it was not tested sufficiently.

Theoretical limitations of the study method

The bias associated with retrospective research is the greatest limitation of the study. The subjective interpretation of the information that is in the chart and the question of what to do with the missing data both pose crucial challenges. A rigorous regulatory document can reduce the information bias by making sure that the information is construed the same way at every instance. However, this might produce a systematic error that is difficult to correct during the data processing. Even if a researcher tests the inter-interpreter reliability, giving validity to the regulatory document, this systematic error cannot be discovered in that way. It can only be avoided by rigorous scrutiny of the regulatory document.

Statistical limitations

The issue of dealing with missing values was solved by replacing them with a series median. Although not that uncommon in statistical analysis, this way of dealing with missing values introduces a systematic bias that is difficult to control.

Potential study improvements

- Test the regulatory document thoroughly to avoid misclassifying the parameters and having to redo some parts of the classification work because the researcher realizes too late that the document needs to be changed.
- In the regulatory document, decide what to do with the missing parameters in certain cases (e.g., If “loss of consciousness” is marked as “patient unsure,” this will be construed as “yes” because that is how a clinician disambiguates this question.).
- Let more than one researcher interpret at least a sample of the medical records to perform Cohen’s kappa analysis so as to establish inter-rater reliability. This validates the regulatory document as systematic.

Paper III

Aim

The primary aim of Paper III was to theoretically test a potential amendment to the SNC guidelines based on the low-risk proposal that might enable physicians to perform fewer CT scans, while maintaining the ability to identify all patients requiring neurosurgical intervention. The secondary aim was to evaluate intracranial hemorrhage incidence in patients taking thrombocyte inhibitors compared with those taking oral anticoagulants.

Study method

This study employed a retrospective review of the medical records, where 25 parameters pertaining to TBI were extracted. The regulatory document guiding the parameter interpretations was established before review began. A total of 365 days of medical records was reviewed. The guidelines for a retrospective review that were proposed by Vassar et al. (2013) were observed [108].

Study statistics

Histograms and the Shapiro-Wilks formula were used to analyze the data distribution. Descriptive statistics were applied to delineate the cohort. The guideline performance was tested with sensitivity, specificity, NPV, and PPV. The contingency tables were tested using the χ^2 test ($n > 5$). Cohen's kappa was calculated for 100 charts that were reviewed by two researchers.

Practical difficulties

Because the regulatory document was written much better than Paper II and thoroughly tested, this study had fewer practical problems.

Theoretical limitations of the study method

The bias of retrospective research was still the greatest limitation because of the missing data and the interpretations of data. However, observing the guidelines

recommended by Vassar et al. made the regulatory document and the data-gathering process more stringent [108].

The inter-interpreter bias was tested, which provided further validity to the regulatory document. However, the systematic error that the regulatory document might produce was not tested or accounted for.

Paper IV

Aim

Paper IV aimed to evaluate the correlation and the agreement between capillary S100B and venous S100B in concentrations typically found in patients at the emergency department with mild head trauma. The secondary aim was to evaluate the suggested conversion equation's ability to predict venous values of S100B.

Study method

Eighteen patients with different severity levels of intracranial hemorrhage and 36 healthy people without head trauma over the past 7 days were recruited. One venous sample was drawn from the antecubital vein, and two capillary samples (one from each finger) were drawn from the lateral or the medial sides of digits II–IV. The samples from the patients with intracranial hemorrhage were taken for a maximum of four consecutive days. The samples were brought to the laboratory using a standard procedure and analyzed as part of the daily routine by the laboratory technician on duty.

Study statistics

Histograms and Shapiro-Wilks formula were used to test for normal distribution. The numeric differences between the sampling methods were treated as related samples, and Wilcoxon's signed rank test was used to evaluate the statistical significance of the differences. Spearman's correlation test (ρ) was used to evaluate the correlation between the sampling methods. The samples were compared with correlation plots and Bland-Altman plots.

Practical difficulties

The practical difficulties encountered were as follows:

- Being alerted when patients were admitted for intracranial hemorrhage.
- Acquiring samples with very high concentrations of S100B.
- Performing practical standardization of capillary sampling to produce as little preanalytical bias as possible.

Theoretical limitations of the study method

Capillary samples in general can be tainted by the sample technique, and capillary S100B in particular can be tainted by extracranial S100B, such as that from adipocytes, chondrocytes, and melanocytes, at the point of the lancet stab.

Statistical limitations

A problem with evaluating samples in a Bland-Altman plot is the researchers' assumption that the real value is somewhere in between the two methods that they want to compare, thus plotting the mean of the two methods on the x-axis. However, this becomes incorrect if one of the methods has two large margins of error. It might then be better to plot only the reliable method on the x-axis. Also, the limits of agreement have no statistically predefined limits and need to be decided by the researcher according to features of the assay and the molecule it quantifies.

Potential study improvements

- The practical problem with finding patients being admitted for intracranial hemorrhage might seem trivial but was difficult to overcome. The best way would probably be to offer some form of compensation to the persons in charge of notifying the research team. In this study, the research team relied on good will, an approach that provides little control of the input.
- The problem with acquiring patients with high levels of S100B is related to finding patients admitted for intracranial hemorrhage. Serum levels drop rapidly after the initial trauma, indicating the necessity to draw the sample from the patient as soon as possible after the trauma, which poses several practical difficulties. A possible way is to be on S100B-call all the time during the study to be able to find these patients because they are few and far between.
- The issue about the standardized sampling technique is more difficult than it seems at first glance. Prescribing a technique does not necessarily mean that all operators use it. The best way to minimize sample bias is probably to only have one operator. However, this was not feasible in this study for practical reasons.

Paper V

Aim

The aim of Paper V was to evaluate the ability of urine S100B to rule out intracranial hemorrhage in patients with head trauma.

Study method

The urine and the serum S100B of emergency department patients with head trauma were analyzed upfront in the laboratory. The precision of S100B assay in urine was determined by performing 10 assays on the same sample at 6 different levels of S100B. Temporal profile, kidney function tests, urine dilution tests, and pH were determined in patients receiving hospital care because of traumatic intracranial hemorrhage. Precision samples and temporal profile samples were taken, and kidney function tests, dilution tests, and pH tests were performed.

Study statistics

Histograms and Shapiro-Wilks formula were used to assess the normality distribution of the data. Spearman's correlation coefficient (ρ) was used to assess the correlation of the non-parametric variables. Linear regression was applied to create explanatory equations for the dispersion of the scatter plots. The ROC analysis was performed with fixed cut-offs and as an analysis of trends, where all available samples without specific cut-offs were analyzed. Serum and urine S100B samples were considered independent variables and compared with each other using the Mann-Whitney-U test.

Practical difficulties

The practical difficulties encountered were as follows:

- Having the emergency department staff remember to draw both serum and urine S100B samples from patients with intracranial hemorrhage (not just serum as was the praxis).
- Being alerted when patients were admitted for intracranial hemorrhage.
- Acquiring samples with very high concentrations of S100B.

- Acquiring enough around-the-clock consecutive samples to establish reliable temporal profiles of in-hospital patients.

Theoretical limitations of the study method

Bladder time might affect urine S100B levels. Urine constitution, kidney function, and pH might affect urine S100B levels or at least the assay precision.

Statistical limitations

This study used standard statistical methods to evaluate the laboratory assays. Correlation coefficients are not always accurate because there might be a graphical correlation that is not detected by the correlation coefficient. Bland-Altman plots and the limits of agreement have no definitive limits. These need to be defined by the researcher, and it might be difficult to know what limits should be allowed.

Potential study improvements

- The emergency department graciously offered to include patients in the study without charge. The research team only paid for the assay cost. However, this arrangement made it difficult to demand anything more than whatever the staff could offer, and it was difficult to insist that they had to be better in remembering to take the samples. The only way to increase the study inclusion was by positive feedback, such as friendly reminders in staff meetings or placing a reminder-cake in the break room. It would probably be beneficial to pay for the sampling service to be able to make more demands and not only rely on the good nature of the staff.
- A special study phone was installed, and the researchers answered this phone at all times during the inclusion period to ensure that the patients diagnosed with intracranial hemorrhage were included in the study. This meant answering the phone and going to the hospital in the middle of the night to obtain the patient's informed consent. A better way might be to request the doctor on call in the surgical emergency department to include the eligible patients. This would probably require a longer study period because more patients would be missed, but it might also make it easier to include enough patients as it would be less strenuous to do so.

- The around-the-clock samples that were used to establish the patients' temporal profiles were also taken without cost to the research team. This is something that can be debated as argued above.
- One way of acquiring samples of S100B with very high concentrations might be to include patients with diagnoses other than head trauma, such as metastasized malignant melanoma. However, these patients are difficult to find due to their limited number and the potential bias hazard, as no research has investigated if this extracranial source of S100B is manifested differently in urine.

Chapter 6 Discussion

General aspects of guideline adherence

It is feasible that improved healthcare management of a certain group of patients can be achieved in different ways. Many of the guideline-related improvements implemented in clinics are based on local traditions and not always initiated, executed, or followed up as suggested by guideline experts [15–17, 90, 92, 94–97]. Furthermore, it can be both difficult and time consuming to implement the guidelines as recommended, and many times, follow-up is lacking so that the implementation success rate is never outlined. Even with follow-up, the guidelines are seldom followed in more than 70% of the cases [92, 96]. In the case of the guidelines for cancer treatment, a 40–99% adherence rate has been reported [112]. Perhaps the optimal guideline adherence is not 100% as a researcher might be inclined to believe. Jacke et al. showed that the survival rate among breast cancer patients increased in the group that was not managed in accordance with the guidelines [93]. This could possibly be explained by the fact that some patients do not fit into the guidelines and are better cared for with a tailored approach that takes into account the patients' unique characteristics. However, cancer care tailored by cancer experts is expected to be good, with or without guidelines. It does not necessarily mean that these results can be extrapolated and applied to TBI management. Procedures are done differently in the emergency setting, and the doctors in emergency departments are sometimes less experienced than the physicians managing advanced oncology who are working in their particular fields of expertise.

When changing the guidelines, adherence to them is likely to decline, at least for a period of time. However, not much has been written about this problem. An intervention study led by Stiel et al. (2010) (the creators of the Canadian CT Head Rule) aimed at decreasing the number of head-CT scans and increasing the guideline adherence. Instead, the intervention resulted in an increase of head-CT scans [98]. As presented in Paper I, the research team's own study showed similar results, with a guideline adherence of 60% before intervention and 40% after. Our research team conducted another survey four years later to determine if the guideline adherence would increase only by letting time pass. The response rate was approximately 80%, and the guideline adherence returned to 60%. During this time, the research

team made no particular effort to promote guideline adherence. That study could not explain why guideline adherence was regained, but it is feasible that time is of the essence. Particularly, it takes time for a set of guidelines to settle so that the stakeholders believe that it can be trusted. Furthermore, during this period, attitudes toward guidelines in general and TBI in particular could have shifted, which could also have contributed to the increased adherence.

Creating and implementing guidelines is complicated and varies with the different fields of medicine. This observation is reflected by the literature because no particular consensus has been reached on how this process should be performed to achieve the highest success rate [15–17, 89–97]. The best way could be to study this issue field by field and even at a local geographical level, instead of trying to find the universal recipe for guideline success [17, 78, 113].

Implementation of brain biomarkers for traumatic brain injury management

Having a brain biomarker as part of TBI guidelines is theoretically appealing. However, a researcher can begin to speculate that regardless of evidence, it takes some time for the clinician to trust that a single blood test can be as accurate as a head-CT scan. It has now been more than five years since the SNC guidelines were first published, and S100B has gained both acceptance and validity. A shift from one brain biomarker to another (if another one should arise with even better clinical features) or a shift toward the assay of urine S100B instead of serum S100B would probably not need as long a transition time where S100B is used because the paradigm has already shifted.

Another issue is that it might not be beneficial to diagnose all patients with intracranial hemorrhage. A biomarker-based guideline that targets patients at high risk of neurosurgical intervention would hopefully be able to recommend fewer CT scans than the current guidelines do, without compromising the safety established by these guidelines. Several studies have tried to identify the features of patients with intracranial hemorrhage who have a high risk of neurosurgical intervention, but this knowledge has not fully been incorporated in the development of new guidelines [103, 114–116].

Intracranial hemorrhages are associated with a higher incidence of postconcussion syndrome and postconcussion headache, but treatment is available [117–120]. However, when these patients are not identified by an emergency head-CT scan, identifying them in other ways is necessary so they can be provided with the appropriate treatment. A putative approach might be to give them written instructions that include information on postconcussion syndrome, on what should prompt them to contact their healthcare providers again and ensure a very easy way back into the system for neuro-rehabilitation. Some data confirms that the consequences of mild TBI are larger than expected and offering more rehabilitation might be necessary [121]. Other data supports the fact that the overall cost of TBI is much higher than just the cost of the emergency department visits [122].

Specific aspects of guidelines for traumatic brain injury

Until recently, research describing the current situation of guideline usage for TBI was mainly limited to single center studies. However, Foks et al. conducted a recent European survey of TBI management in emergency departments, which described the key points that differed among the participating countries. They studied 71 centers in 19 European countries and Israel by means of questionnaires and obtained a 96–100% response rate on their different questionnaires. The main conclusions were that different definitions of brain injury severity were used (mild TBI was defined as GCS 13–15 by 59% and GCS 14–15 by 38%) and that there were large variations in the guideline usage and the type of guidelines (49% used national guidelines, 15% used local guidelines, and 21% used no guidelines) [102].

Foks et al. pinpointed the issues associated with TBI guidelines at an international level [102]. Paper 1, along with other studies, described the problems associated with TBI guidelines at national and local levels [100, 101, 104]. It seems that the problems are similar at all levels and these studies pose more questions than they gives answers: Is there any point in having international guidelines if the definitions cannot be standardized? What are the reasons behind why not all countries have national guidelines? Why do medical centers operating in the 21st century lack formal guidelines?

A World Health Organization Collaboration Task Force put forth standardized definitions of TBI severity levels in 2005, but these have not been widely accepted [123].

The Appraisal of Guidelines for Research and Evaluation (AGREE I & II) instrument is validated and has been applied to TBI guidelines [91, 124]. It examines several important features that determine the success of the guidelines (scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence). When Tavender et al. applied AGREE I to all guidelines published in English (until 2010), they found 18 guidelines to evaluate. Their main finding was in accordance with that of Foks et al.; specifically, there is no unified definition of mild TBI [102, 124]. Furthermore, they found issues with stakeholder involvement, the updating procedures, and the applicability of the recommendations (e.g., cost implications and monitoring). They also recommended that guideline developers at the local level should adapt existing guidelines instead of designing new ones. The guideline introduced in Paper I was the algorithm of the SNC, amended with information on how to treat patients with severe head trauma and how to coordinate ambulance transfers to the neurosurgical ward. However, it did not include any local stakeholder involvement, and it is feasible that it would have had a higher adherence rate if it entailed stakeholder engagement.

In the case of TBI, it is difficult to state what an adherence rate of 70% or higher would mean in terms of efficacy, effectiveness, and safety [125]. Naturally, the

cases managed in accordance with the guidelines would be safely handled (due to the high NPV of the guidelines) [65, 81]. However, it is possible that physicians sometimes use the guidelines but fail to do so at other times, depending on the characteristics of the case at hand. This can mean that cases that might appear deceptively simple at first glance are managed without the support of the guidelines and are thus dealt with erroneously. The opposite can also occur; the cases are handled without the guidelines and have better outcomes because of it. Few studies have compared guideline performance with clinician performance. An attempt was made where the major guidelines for pediatric TBI management were tested against the clinical judgment of an experienced physician. The physicians and one other guideline correctly diagnosed most of the cases with intracranial hemorrhage [126]. However, Paper 1 indicated that when no guideline was applied, more CT scans were performed than when guidelines were applied (60% versus 51%).

Because of its descriptive nature, Paper I begs the answers to several new questions. It has helped describe the nature of some of the problems associated with designing and implementing new guidelines. To make TBI guidelines even more successful, measures should be taken to answer those questions, which include the following:

- What are the rationales for not using guidelines at all? (e.g., lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, or inertia of previous practice)
- What are the rationales for adhering to guidelines prescribing CT when the doctor-estimated probability of intracranial hemorrhage is low?
- What are the rationales for not adhering to guidelines when they prescribe CT?
- Why are current guidelines sometimes applied erroneously, resulting in unnecessary CT scans?

To elucidate how TBI-specific guidelines should be designed and implemented, we firmly believe that these questions must be answered. The research team has suggested qualitative in-depth interviews and is currently collaborating with behavioral experts on this matter.

These results, in combination with the literature studies and the findings from the prospective study, described in the section “Epidemiology and clinical features of traumatic intracranial hemorrhage,” will hopefully provide sufficient material to develop or contribute to new guidelines with solid supporting evidence, applicability, and stakeholder involvement.

Epidemiology and clinical features of traumatic intracranial hemorrhage

Epidemiological studies on TBI are plentiful and can be used for post-hoc logistic regression to outline new guidelines. The Canadian CT Head Rule and the New Orleans Criteria are both based on post hoc analysis of clinical features and patient characteristics [9, 10]. The SNC guidelines are based on the review of current literature and a careful selection of what should be part of the guidelines based on the evidence through a Delphi process [12]. These two different ways of developing guidelines can both render good guidelines, and all three guidelines are validated with good results [65, 127, 128]. Paper II was designed as a retrospective review of the medical records and can at best be hypothesis generating or part of a large review, such as that of Undén et al., to lay the foundation of guidelines [65].

Paper II also differs from similar articles in that multitrauma patients were excluded based on how the patients were triaged in the emergency department and that the trauma-energy level was recorded in individual cases, not just the mechanism of the trauma and the severity of the head injury. Most studies include multitrauma patients to involve more patients with higher degrees of head injury. An extensive review of 66 studies on the TBI epidemiology in Europe, conducted by Brazinova et al., made no mention of the trauma-energy level [19]. Typically, these studies use the trauma mechanism and/or the TBI severity as common denominators.

The fact that the trauma-energy level is an important clinical feature of traumatic intracranial hemorrhage is not new but excluding patients from further clinical examination after just taking their histories is a novel possibility. As shown in Paper II, using the latter approach would have made it possible to discharge approximately half of the patients in the study. This has potential in terms of reducing radiation and cost and increasing effectiveness but still needs prospective testing within the limits of a scientific study to guarantee the safety of the study population. Most likely, this could also be promoted to increase guideline adherence (reduce the lack of agreement) with regard to the results presented in Paper I, where doctors prescribe CT scans even though they do not expect any pathologies. This matter is worth pursuing with further studies. However, considering the retrospective studies' innate weaknesses regarding information bias, these results could benefit from being tested both retrospectively and prospectively.

In 2018, our research team launched a prospective study of these features, which would evaluate the safety and the efficacy of a set of guidelines that would recommend discharge in triage based on patient history (including trauma-energy level, age, current medication, and previous and current diseases).

Potential amendment of present guidelines

When trying to amend the current SNC guidelines with the low-risk proposal, 44.8% of the patients were recommended for a head-CT scan, 13% lower than the SNC guidelines' theoretical recommendation. The cost of a CT scan varies between US\$200 and US\$2,000 [129]. Even at the lowest cost, a 13% reduction would yield yearly savings of US\$ 22,400 (112 x 200) in Helsingborg alone. This reduction of head-CT scans in Sweden, with its approximately 10,000,000 people, would be around US\$750,000. Other benefits include decreased exposure to radiation and faster processing time in emergency departments.

However, this cost reduction will most likely increase the number of undetected intracranial hemorrhages. Given the low number of patients who actually need neurological intervention, it is possible that doctors do not have to detect all intracranial hemorrhages in the emergency department. Before a guideline that is specifically designed not to detect all intracranial hemorrhages is put forth, it should be rigorously tested within the tenets of a prospective clinical trial because its potential to generate fewer head-CT scans might also lead to missing an intracranial hemorrhage requiring neurological intervention.

The cohorts presented in Paper II and Paper III were similar in size, incidence of intracranial hemorrhage, age, and gender distribution and should be comparable, but several intracranial hemorrhages were found in the low-risk proposal cohort in Paper III and none in Paper II. This variation can represent actual variations in the entire population, and it is possible that intracranial hemorrhages occur even in the low-risk proposal cohort with low-energy trauma, such as falling on the ground.

However, when reviewing the specific trauma mechanisms of patients with low-energy intracranial hemorrhage (Paper III), all of the patients had a slightly different trauma mechanism than just falling on the ground. They all fell head-first without breaking the fall with other body parts, and all but one patient were intoxicated. It is plausible that this is not a low-energy trauma mechanism after all [130].

It is difficult to review this trauma mechanism retrospectively because the details pertaining to the fall are important; if doctors want to rule out intracranial hemorrhage based on the patient history, the history needs to be reliable. In this case, it should be reliable enough to evaluate if the patient fell head first or broke the fall in some manner. This level of detail can only be obtained from a prospective study.

Another way to improve guideline performance would be to use another brain biomarker or a combination of biomarkers. S100B has never been approved by the United States Food and Drug Administration, which is the main reason why it has never spread across North America. A combination of biomarkers has recently been introduced after being approved by the Food and Drug Administration. It employs a combination of glial fibrillary acidic protein and ubiquitin C-terminal hydrolase L1 and has shown similar NPV and sensitivity to those of S100B [45].

S100B in venous, capillary, and urine samples

A reliable method of S100B assay in capillary blood and/or urine would alleviate the process of blood sampling and open the possibilities to analyze S100B in children. Our research team had hopes that that capillary sampling would be able to replace venous sampling and that urine would be applicable for a longer time than 6 hours after trauma.

Using the capillary sampling method and the method of assay described in Paper IV, the research team concluded that capillary samples had very poor correlation and agreement with venous samples. The correlation and the agreement between capillary samples was better, but there was still too much variation for a blood test used as a binary test to rule out intracranial hemorrhage, at least at the current clinical cut-off used for serum protein S100B. Furthermore, the prediction equation described by Åstrand et al. predicted too many patients as below the cut-off when the actual venous value was above the cut-off for this to be a valid way of using capillary S100B to rule out intracranial hemorrhage [62].

However, with a smaller sampling volume, it might be possible to acquire a sample that would better represent the true concentration of S100B in serum and achieve a good correlation between capillary samples. The companies DiaSorin® and FujiRebio® both offer an analysis of S100B with a sample volume of 100 μL .

For instance, the assay for hemoglobin from HemoCue® only requires 10 μL of capillary blood. It is difficult to know exactly how small the sample volume should be. The lancet stab might injure adipocytes and melanocytes, causing extra-capillary S100B to contaminate the sample. It is theoretically possible that the optimal sample volume is not as low as 10 μL because the drop-to-drop variation might be too large [131]. Further studies are needed to determine the optimal sample volume and given that no commercially available methods offer sample volumes lower than 100 μL , these studies are experimental, time consuming, and expensive. Our research team will not pursue the issue at this point.

The urine protein S100B assay shows good precision. The slightly higher CV that is observed in urine samples simply reflect the normal variation for any method of analysis where the best precision is sought at the clinically relevant levels. The difference in CV is not negligible, but the precision of the analysis at the urine levels relevant to this study (around 0.07 $\mu\text{g/l}$) makes the assay feasible.

There is neither good correlation nor good agreement between the serum protein S100B samples and the urine protein S100B samples; thus, they are not interchangeable. Neither the S-S100B nor the U-S100B performance is outstanding even though the serum samples perform slightly better than the urine samples. The performance of the arithmetic difference between the serum samples and the urine samples seems better than both serum and urine samples. The study was not designed to examine the reasons for this difference, but it is possible that by

subtracting the urine value of S100B, a researcher can correct some of the false positive values that are associated with using S100B to exclude intracranial hemorrhage. This could be studied further in a more specific subgroup, such as that suggested for the clinical use of serum protein S100B by Undén et al. [12].

The analysis of the temporal pattern in urine S100B did not yield any particular time pattern, other than the findings that both urine and serum levels were low after 6 hours, and urine had almost no variation at all after 6 hours. Furthermore, aside from urine pH, the other chemical compounds and chemical properties of urine and renal function did not affect urine S100B levels. However, urine pH had a strong correlation with urine S100B concentrations within the first 6 hours after trauma and should be studied further in an in-vitro setting.

Summary and main conclusions

- The guidelines for TBI management are difficult to develop, implement, adhere to, and sometimes to understand. Increased education and information alone do not necessarily increase guideline adherence.
- The Scandinavian epidemiology of TBI is shifting toward older people taking different medications than in the past, affecting hemostasis. The trauma mechanism has also changed from motor vehicle accidents to falls. An algorithm based partially on trauma energy, instead of or together with the trauma mechanism and the severity of the brain injury, could be a way to simplify TBI management.
- Capillary-sampled blood for the serum protein S100B assay had poor concordance with venous serum protein S100B assay and lacked sufficient precision around the cut-off value of 0.1 µg/l to be used at this cut-off for ruling out intracranial hemorrhage. This might be related to the large sample volume of 400 µl that was used. Unless the sample volume is decreased, further testing of capillary sampling for S100B cannot be recommended.
- Urine protein S100B had poor concordance with venous serum protein S100B but showed similar performance in ruling out intracranial hemorrhage. However, the arithmetic difference between serum S100B and urine S100B might have better performance than both samples individually and could be one way of improving the current guidelines.

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Chapter 7 References

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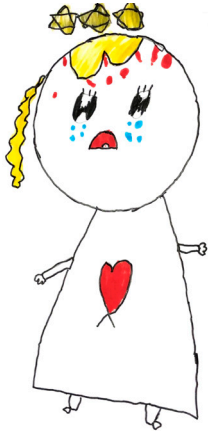
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Klara, 6 years, and Kalle, 4 years were asked to illustrate what their dad has been working on in the basement for all these years. Kalle helped by cheering on.

The author Tomas Vedin is a specialist in general surgery working at Helsingborg General Hospital with colorectal surgery, emergency surgery and trauma surgery. Upon completing medical school at Umeå University in 2007, he moved to Värmland for 21 months of internship. After the internship, he started his surgical residency in Karlstad in 2009. After a brief work holiday at an internal medicine emergency department in 2010/2011, he continued his surgical residency in Helsingborg and completed it in 2015. During the entire time, he has been interested in clinical teaching and academic mentoring. He has received "Best clinical teacher"-awards by medical student, interns and residents. He hopes to continue teaching and strives to pursue both a clinical career and an academic career.