TRAUMATIC BRAIN INJURY

GETTING OUR HEADS AROUND IT

DENISE JOCHEMS

Traumatic Brain Injury: Getting our heads around it
PhD thesis, Utrecht University, The Netherlands

Cover The Lexi Studio
Printed by Gildeprint, Enschede
ISBN 978-94-6419-465-4

Traumatic Brain Injury:
Getting our heads around it

Traumatisch Hersenletsel:

Een hoofdzaak
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 14 april 2022 des ochtends te 10.15 uur

door

Denise Jochems

geboren op 28 februari 1992
te Utrecht

Promotor:

Prof. dr. L.P.H. Leenen

Copromotoren:

Dr. K.J.P. van Wessem
Dr. R.M. Houwert

CONTENT

INTRODUCTION

Trauma is still a leading cause of death amongst younger people in both high income and low and middle income countries. Prevention measures and improvement of the first assessment and treatment of the trauma patient have led to a decrease in mortality in this patient group. Nonetheless, the World Health Organization (WHO) still recognises an upward trend in casualties caused by injuries and has classified it as a global health problem. Perhaps surprisingly, only 2% of deaths due to traumatic injuries is caused by war. In 2012, the three biggest causes of death due to trauma were road traffic accidents (RTAs), suicide and falls, respectively number 9, 15 and 21 on the worldwide list. It is also a major cause of life-long disability amongst people of working age and therefore has a big economic impact [1,2].Globally, RTAs alone are a major cause of death, with almost two million deaths in 2016 [3]. Furthermore, the WHO hypothesised that RTAs will be the third biggest cause of death in 2020. Nine per cent of deaths around the world are caused by injuries, 2,300 of which are children [1].

Trauma care has come a long way. Inclusive trauma systems have been implemented in many countries, with good results. In the Netherlands, this system was officially implemented in 1999 [4]. It divides all acute care hospitals in a region by the level of trauma care they can provide, distributing patients to hospitals that best meet their needs and provides care from time of accident to beyond the admission and even rehabilitation period [2,4]. The Netherlands, region "Midden Nederland", report a massive improvement in mortality rates over the last 20 years, especially due to decreased numbers of exsanguination [5]. In the Netherlands, a level 1 trauma centre has a trauma surgeon (who deals with injuries to extremities and trunk) on a resident on call 24/7 [5,6]. Whether this has significantly contributed to the drop in mortality is still not entirely clear, even though it has sped up processes in hospital significantly [7]. Other examples of successful changes in the catchment area of the UMC Utrecht are the implementation of the massive transfusion protocol and the total body CT protocol, both in 2007 [4].

The decrease in deaths due to exsanguination and multi-organ failure seemingly left traumatic brain injury (TBI) as the most common cause of death due to trauma [8]. TBI refers to all injuries of the brain caused by an external force [9]. Different types of trauma cause different injuries and therefore TBI is a very diverse disease, ranging from focal contusions, to diffuse axonal injury and extra-axial and parenchymal haematomas. Subsequently, the brain can suffer from secondary damage, due to the injury itself and the body's response to it and systemic hits because of injuries elsewhere in the body. Examples are the inflammatory process and increased release of excitatory neurotransmitters, deranged coagulation, hypotension and hypoxia [9]. Guidelines for treatment of TBI were developed, but these are based on low-level evidence and even established parts of treatment, such as the intracranial pressure meter (ICP) and decompressive craniotomy, remain under debate as no new treatment modality has been proven effective [9]. Furthermore, the use of tranexamic acid has been investigated, as early administration reduces death due to bleeding amongst patients with extracranial injuries [10]. One element of the care pathway that has shown to reduce mortality, is treatment of severe TBI patients in a neurosurgical centre [9]. Therefore, recognition of TBI by emergency medical service providers is vital as this would ensure transport to a neurosurgical centre and trigger measures to protect the brain from secondary injury, such as hypotension and hypoxia.

Some studies state that mortality has improved, but functional outcome has not and vice versa. Multiple studies investigated whether there had been progress regarding outcome after TBI at all, over the last few decades. Unfortunately, the answer to that question remains equivocal. This lack of obvious improvement may also be contributed to changing demographics amongst the TBI population, with an increasing elderly population. Although the studies that find an improvement in mortality rates state that this may be due to a less severe injury pattern in the elderly [12–18]. A study amongst children between 1999 and 2013 showed an initial decline in mortality, followed by an increase. Authors felt this might be explained by prevention legislation concerning road traffic and later increased suicide rates, although the population is most likely not comparable with ours, as 12% of mortality was explained by homicide by firearms [19].

Cause of TBI differs globally. Countries with low or middle income have less strict traffic laws and more motorised traffic and subsequently see a higher rate of injuries caused by road traffic accidents. As stated before, high income countries have an increasingly older population and falls in the elderly play a bigger role, especially as preventative measures have led to a decrease in the number of TBIs due to road traffic accidents. In addition, firearms pose a bigger problem in some countries than others. For example, in the United States of America the number of deaths due to firearms in 2014 was similar to the number of deaths due to road traffic accidents in that same year [20,21]. Opposed to this, in the Netherlands only 78 people died due to firearms in 2015 and on average 300 patients were seen every year in the accident and emergency department between 2013-2017 nationwide [22,23]. When demographic patterns of trauma Intensive Care Units of the University Medical Center Utrecht were compared with centres in Australia (John Hunter Hospital) and the United States of America (Harborview Medical Center), it was found that mortality in the Dutch unit was highest. The number of patients with severe TBI appeared to be at least partially responsible for this. The authors furthermore hypothesised that the difference in culture and therefore approach to withdrawing life-sustaining treatment could have led to discrepancies in mortality from trauma, especially TBI [8].

The aim of this thesis was to provide an insight in the extent to which moderate and severe TBI poses a problem in the Netherlands, from epidemiology to TBI as cause of death and functional outcome.

To start this assessment, it was needed to know how frequently moderate and severe TBI occurs in the Netherlands and what the causes and consequences are, therefore a epidemiology study based on data from the Dutch National Trauma Database (DNTB) was conducted in **chapters 1 and 2,** for adults and children respectively.

Following the outline of the inclusive trauma system, the journey from there continued with the pre-hospital setting. As it is crucial for these trauma patients to be treated in a level one trauma centre, the accuracy of prehospital triage was investigated in **chapter 3**.

The effect of administration of tranexamic acid to patients with polytrauma injuries and traumatic brain injury was investigated in **chapter 4.**

To confirm the hypothesis that TBI is now the main problem amongst trauma patients in the Netherlands, a study was conducted to determine the cause of death amongst deceased multiple injured patients in the UMC Utrecht in **chapter 5**.

As a first step to understand this mortality, data for all patients with moderate and severe TBI in the ICU of the UMC Utrecht was retrospectively collected, including cause of death and treatment-limiting decisions in **chapter 6.**

This thought was taken even further in **chapter 7,** as a comparison was made between patients with isolated moderate and severe TBI and patients with multiple other injuries as well.

REFERENCES

1. World Health Organization. Injuries and violence: The facts 2014. http://www.who.int/violence_injury_prevention/media/news/2015/Injury_violence_facts_2014/en/ (2014).
2. Sturm, J. A., Pape, H. C. & Dienstknecht, T. Trauma care in Germany: An inclusive system. *Clin. Orthop. Relat. Res.* **471**, 2912–2923 (2013).
3. 2016, G. H. E. Deaths by cause, age, sex, by country and by region, 2000-2016. (2018).
4. Lansink, K. W. W., Gunning, A. C., Spijkers, A. T. E. & Leenen, L. P. H. Evaluation of trauma care in a mature level i trauma center in the Netherlands: Outcomes in a Dutch mature Level i trauma center. *World J. Surg.* **37**, 2353 – 2359 (2013).
5. Hietbrink, F. *et al.* The evolution of trauma care in the Netherlands over 20 years. *Eur. J. Trauma Emerg. Surg.* **46**, 329–335 (2020).
6. Jochems, D., Leenen, L. P. H., Hietbrink, F., Houwert, R. M. & van Wessem, K. J. P. Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma. *Injury* **49**, 1661–1667 (2018).
7. Havermans, R. J. M. *et al.* Trauma care before and after optimisation in a level I trauma Centre: Life-saving changes. *Injury* **50**, 1678–1683 (2019).
8. Gunning, A. C. *et al.* Demographic Patterns and Outcomes of Patients in Level I Trauma Centers in Three International Trauma Systems. *World J. Surg.* **39**, 2677–2684 (2015).
9. Maas, A. I. R., Stocchetti, N. & Bullock, R. Moderate and severe traumatic brain injury in adults, Maas AIR et al. *Lancet N* **7**, (2008).
10. Olldashi, F. *et al.* The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* **377**, 1096–1101, 1101.e1-1101.e2 (2011).
11. Lindfors, M. *et al.* Temporal changes in outcome following intensive care unit treatment after traumatic brain injury: a 17-year experience in a large academic neurosurgical centre. *Acta Neurochir. (Wien).* 2107–2115 (2018) doi:10.1007/s00701-018-3670-1.

12. Beck, B. *et al.* Temporal trends in functional outcomes following severe traumatic brain injury: 2006-2015. *J. Neurotrauma* **1029**, neu.2017.5287 (2017).
13. Gómez, P. A., Castaño Leon, A. M., Lora, D., Cepeda, S. & Lagares, A. Final outcome trends in severe traumatic brain injury: a 25-year analysis of single center data. *Acta Neurochir. (Wien).* **160**, 2291–2302 (2018).
14. Kadar, R. *et al.* Trends in demographics and outcome of patients presenting with traumatic brain injury. *Clin. Exp. Emerg. Med.* **6**, 113–118 (2019).
15. Sawadogo, D. *et al.* Trends of clinical outcomes in patients with a Traumatic Brain Injury (TBI) in Canada between 2006 and 2012. *Injury* **51**, 76–83 (2020).
16. Lamm, A. G. *et al.* Changes in Patient Demographics and Outcomes in the Inpatient Rehabilitation Facility Traumatic Brain Injury Population from 2002 to 2016: Implications for Patient Care and Clinical Trials. *J. Neurotrauma* **36**, 2513–2520 (2019).
17. Raj, R. *et al.* Temporal Trends in Healthcare Costs and Outcome Following ICU Admission After Traumatic Brain Injury. *Crit. Care Med.* **46**, e302–e309 (2018).
18. Cheng, P., Li, R., Schwebel, D. C., Zhu, M. & Hu, G. Traumatic brain injury mortality among U.S. children and adolescents ages 0–19 years, 1999–2017. *J. Safety Res.* **72**, 93–100 (2020).
19. Roozenbeek, B., Maas, A. I. R. & Menon, D. K. Changing patterns in the epidemiology of traumatic brain injury. *Nat. Rev. Neurol.* **9**, 231–6 (2013).
20. Johnson, W. D. & Griswold, D. P. Traumatic brain injury: a global challenge. *The Lancet Neurology* 949–50 (2017) doi:10.1016/S1474-4422(17)30362-9.
21. Stam, C. Letsel door vuurwapengeweld. *VeiligheidNL* (2018).
22. Centraal bureau voor statistiek (CBS). Overledenen; doodsoorzaak (uitgebreide lijst), leeftijd, geslacht : 7233 (2021). Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/7233/table?fromstatweb.

CHAPTER 1

Incidence, causes and consequences of moderate and severe traumatic brain injury: in the Netherlands

CHAPTER 1

Title: Incidence, causes and consequences of moderate and severe traumatic brain injury: in the Netherlands.

Printed in: Scientific Reports

Cite as: Jochems D, van Rein E, Niemeyer M, van Heijl M, van Es MA, Nijboer T, et al. Incidence, causes and consequences of moderate and severe traumatic brain injury as determined by Abbreviated Injury Score in the Netherlands. Sci Rep. 2021 Oct 7;11(1):19985. doi: 10.1038/s41598-021-99484-6. PMID: 34620973; PMCID: PMC8497630.

Author list: Denise Jochems[1] (MD), Eveline van Rein[1] (PhD), Menco Niemeyer[1] (MD), Mark van Heijl[1] (PhD), Michael A. van Es[2] (PhD), Tanja Nijboer[3,4] (PhD), Luke P.H. Leenen[1] (Professor), Roderick M. Houwert[1] (PhD), Karlijn J.P. van Wessem[1] (PhD)

[1] Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

[2] Department of Neurology, University Medical Center Utrecht and de Hoogstraat Rehabilitation, Utrecht, The Netherlands

[3] Department of Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands

[4] Center of Excellence for Rehabilitation Medicine, UMC Utrecht Brain Center, University Medical Center Utrecht, and De Hoogstraat Rehabilitation, Utrecht, the Netherlands

ABSTRACT

Traumatic brain injury (TBI) is a leading cause of death and disability. Epidemiology seems to be changing. TBIs are increasingly caused by falls amongst elderly, whilst we see less polytrauma due to road traffic accidents (RTA). Data on epidemiology is essential to target prevention strategies. A nationwide retrospective cohort study was conducted. The Dutch National Trauma Database was used to identify all patients over 17 years old who were admitted to a hospital with moderate and severe TBI (AIS ≥ 3) in the Netherlands from January 2015 until December 2017. Subgroup analyses were done for the elderly and polytrauma patients. 12,295 patients were included in this study. The incidence of moderate and severe TBI was 30/100.000 person-years, 13% of whom died. Median age was 65 years and falls were the most common trauma mechanism, followed by RTAs. Amongst elderly, RTAs consisted mostly of bicycle accidents. Mortality rates were higher for elderly (18%) and polytrauma patients (24%). In this national database more elderly patients who most often sustained the injury due to a fall or an RTA were seen. Bicycle accidents were very frequent, suggesting prevention could be an important aspect in order to decrease morbidity and mortality.

INTRODUCTION

Traumatic brain injury (TBI) is a growing global health problem; it is a leading cause of death and life-long disability [1,2]. In 2012, approximately 57,000 deaths (11.2/100,000) in the European Union were estimated to be related to TBI, in 2010 almost 53,000 deaths (17.7/100,000) were attributed to TBI in the United States [2,3]. In the Netherlands, there was a significant rise in admissions for and presentations with TBI to the accident and emergency department (A&E) between 1998 and 20124. Furthermore, TBI is the main cause of death in severely injured trauma patients and contributes to at least 30% of deaths caused by trauma [5–8].

The overall incidence of TBI is increasing with changing epidemiology, where causes of injury seem to depend on the status of development of the country. In low- and middle-income countries road traffic accidents (RTA) are the main cause of TBI, as motorised traffic is more common and safety rules are lacking. However, in high-income countries, the number of elderly patients with a brain injury due to a fall is rising, whereas preventative measures have decreased the number of TBIs due to road traffic accidents [3,6,7,9,10]. Unfortunately, the precise global incidence is unknown due to a lack of data collection and comprehensive studies on the subject [8,11].

Data on epidemiology is important for healthcare policies on where to target prevention strategies. Recent literature on changing epidemiology of TBI in Western Europe4 shows that despite the increase in incidence, mortality rates remain stable. A possible explanation could be that low-energy falls are less likely to cause death than RTAs, which are more likely to cause polytrauma. Furthermore, TBI in elderly is more likely to be caused by a fall [2,4]. All grades of TBI were included in these studies. Few studies focus on moderate and severe TBI. Different definitions of severity of TBI, such as Glasgow Coma Scale scores at presentation and Intensive Care Unit (ICU) admission, make comparison difficult. Furthermore, pre-hospital intubation and intoxication can complicate these scores, which can lead to inclusion of mild TBI in analysis [12,13]. The Abbreviated Injury Score (AIS) is an established standardised score for injuries based on probability of survival with this injury, which allows for accurate classification and comparison of TBI [14].

Moderate and severe TBI are more likely to lead to mortality and poor functional outcomes than mild TBI. Therefore, data on epidemiology of true moderate and severe TBI could provide more insight into where to focus research and prevention methods in order to decrease poor outcome. Especially, when focussed on important groups: polytrauma patients and the elderly, as the hypothesis is that the first seems to contribute mainly to the increasing incidence and the latter to mortality.

The aim of this nationwide study was to describe the incidence, distribution of age, causes, and consequences of moderate and severe TBI for the whole population and in particular polytrauma patients and elderly.

METHODS

For this nationwide retrospective cohort study of patients who were admitted with moderate or severe TBI, data was collected from the Dutch Trauma Registry (DTR). The registry is an excellent representation of Dutch trauma care, as 99% of hospitals contribute to the DTR. The aim of the DTR is to uphold and monitor good standard of care for injured patients. The DTR has been used for nationwide retrospective cohort studies before, such as Peek et al. [15]. The DTR contains data of all trauma patients who were admitted to hospital through A&E, within 48 h of trauma. Patients who die prior to arrival in A&E or do not have to be admitted, are not kept in the database. This also applies to patients who are admitted, but not due to their traumatic injuries [15,16]) National demographic data were obtained, from the Dutch Population Register from the Central Bureau of Statistics to determine incidence rate of moderate and severe TBI requiring hospital admission [17].

All patients aged 17 years and older admitted to the hospital between January 2015 and December 2017 with moderate or severe TBI were identified using Abbreviated Injury Scale (AIS) codes for traumatic brain injury. The AIS is a widely accepted anatomically based scoring system to grade injuries from mild to maximal (almost certainly leading to death) on a scale from one to six and raters can use data from the patient's records to assign a score, using a supplied standardised guideline [18]. Combined AIS scores are used to determine the Injury Severity Score (ISS). AIS scores as recorded in the DTR were calculated by data managers of the participating trauma centres as per ISS 0819.

Moderate to severe TBI was classified as an AIS of the head region (AIShead) of three or higher. Two subgroups of polytrauma and elderly were analysed separately as well. Polytrauma was defined as an Injury Severity Score (ISS) of 16 or higher. Elderly patients were defined as patients aged 65 years and older. To prevent inclusion of duplicate cases, all patients who required early transfers to another hospital were excluded.The following baseline variables were obtained from the DTR: age at trauma, sex, American Society of Anesthesiologists (ASA) score, mechanism of injury, Glasgow Coma Scale (GCS), AIS scores for all body regions, Injury Severity Scores (ISS) scores and Revised Trauma Score (RTS). GCS was evaluated in the A&E department in all cases and only noted if all three

parameters (eye, motor and voice) were available. In addition, if the patient was intubated and sedated prior to GCS scoring, their GCS score was not included in analyses. The DTR does not include data on who recorded the GCS score. The Revised Trauma Score (RTS) is a widely used scoring tool to determine the initial trauma severity based on the GCS, systolic blood pressure, and respiratory rate. A lower score reflects a higher severity of injury [20].

The in-hospital treatment variables obtained were: activation of trauma team in hospital, involvement of the Mobile Medical Team (MMT), need for emergency intervention and highest level of received care. In the Netherlands, the MMT consists of a trauma surgeon or anaesthetist and a trained nurse to provide acute care at the site of the accident. The in-hospital outcome variables obtained were hospital length of stay (H-LOS), ICU length of stay (ICU-LOS), mortality, H-LOS until death and Glasgow Outcome Scale (GOS) score at the time of hospital discharge.

All variables were collected for all included patients and separately for polytrauma patients and the elderly.

Frequencies with percentages were used to describe categorical data.. The Shapiro–Wilk test and Quantile–Quantile plots confirmed whether data were normally distributed or not. Descriptive data included means with standard deviations (SD) for normally distributed continuous data and medians with interquartile ranges (IQR) for non-normally distributed continuous data. The incidence rate was calculated by dividing the total number of patients with TBI by the total Dutch population ≥ 16 years of age or > 64 for the elderly for the inclusion period. Incidence rates were presented per 100,000 person-years. For statistical analyses, SPSS statistical software (SPSS 23.0; IBM Inc., Armonk, NY, USA) was used.

The Medical Ethical Review Board of the University Medical Center Utrecht approved this study and granted a waiver of informed consent (WAG/mb/18/011,787). All methods were performed in accordance with the relevant guidelines and regulations.

RESULTS

In total, 12,650 adult patients with moderate or severe TBI were admitted to Dutch hospitals between January 2015 and December 2017 . Of all patients, 355 were excluded from analysis due to early transfer, leaving 12,295 for analysis. On 1 January 2016, 16,979,120 people lived in the Netherlands, of whom 13,766,208 (81%) were 17 or older and 3,107,842 (18%) were 65 or older.

The incidence rate of moderate or severe TBI was 30 per 100,000 person-years. Patients in our cohort had a median age of 65 years (IQR: 47–79). Patients were predominantly male (n = 7,482; 61%). Median American Society of Anesthesiologists (ASA) score was 2 (IQR: 1–2), median AIShead was 3 (IQR: 3–4) (Table 1).

Falls were the most common trauma mechanism (n = 5,579; 52%), closely followed by road traffic accidents (n = 4,328; 40%). Falls from low height accounted for 76% of all falls. RTAs included cyclists, who accounted for the, by far, largest proportion of this group (n = 2,523; 59% of all RTAs), followed by accidents with mopeds (n = 632, 15%) and motorised vehicles with more than two wheels (n = 627, 14%). Less frequent were accidents where the victim was a pedestrian (n = 355, 8%) or motorcyclist (n = 108, 2%). GCS scores were missing for a quarter of patients. GCS of 15 was noted in 5,483 (60%) patients. Median RTS in A&E was 7.8 (IQR: 6.9–7.8) (Table 1).

MMT and in-hospital trauma team were involved in, 1,856 (15%) and 4,255 (42%) of cases, respectively. Of all patients, 1,045 (10%) underwent an emergency intervention, mostly neurosurgical procedures (n = 716; 69%). Highest level of care was most often the ward (n = 6,323; 56%) (Table 2).

Median ICU-LOS was 0 days (IQR: 0–2) , and H-LOS was 5 days (IQR: 2–11),—(Table 3). Thirteen per cent of patients died. Cyclists accounted for 49% of all deaths due to an RTA. Median number of days before they died was 3 (IQR: 2–7). Patients who survived had a median GOS of 4 (IQR: 4–5) at discharge, 88% had a GOS of 4 or 5 (n = 7,290),

and 20% of GOS scores were missing. Most patients who survived were discharged to their usual place of residence (n = 6,438; 63%) (Table 3).

Polytrauma

There were 5,763 polytrauma patients, this was 47% of all moderate and severe TBI patients in our cohort. The incidence of polytrauma patients with moderate or severe TBI was 14 per 100,000 person-years. They had a median age of 64 years (IQR: 45–78), were predominantly male (n = 2092; 64%), with a median AIShead of 4 (IQR: 3–5) (Table 1).

Falls were the most common trauma mechanism (n = 2,533; 44%), closely followed by road traffic accidents (n = 2,249; 39%). Road traffic accidents (RTA) included cyclists, who accounted for a large proportion of this group (1,152 people, 51% of all RTAs), followed by motorised vehicles with more than two wheels (n = 452, 20%), mopeds (n = 322, 14%) and pedestrians (n = 205, 9%). Motorcycle accidents were less common (n = 85, 4%). Median RTS in A&E was 7.8 (5.0–7.8) (Table 1).

Both the MMT and in-hospital trauma teams were involved more often for these polytrauma patients, respectively in 1,514 (26%) and 3,161 (62%) of cases. Highest level of care was most often ICU (n = 2,705; 47%) (Table 2).

Median ICU-LOS was one day (IQR: 0–5) and H-LOS 7 days (IQR: 3–15), in ICU Fatalities were more frequent (n = 1,386; 24%). Median number of days before death was three (IQR: 2–7). Patients who survived had a median GOS of 4 (IQR: 4–5). Most patients who survived were discharged to their usual place of residence (n = 1,974; 46%) (Table 3).

Elderly

There were 6,228 elderly patients, which is 51% of our cohort. The incidence rate of elderly patients is 67 per 100,000 person-years. They had a median age of 79 years (IQR: 72–85), 52% (n = 3,264) were male with a median AIShead of 3 (IQR: 3–4). (Table 1).

Falls were the most common trauma mechanism (n = 3,543; 57%), followed by RTA (n = 1,574; 25%), consisting mostly of bicycle accidents (n = 1,155; 73%), followed by pedestrians (n = 156, 10%), mopeds (n = 149, 9%) and accidents involving motorised vehicles with more than two wheels (n = 109, 7%). Motorcycle accidents were extremely rare (n = 5, < 1%). Of all falls, most were from low height, 85%. Median RTS in A&E was 7.8 (IQR: 7.6–7.8) (Table 1).

MMT and in-hospital trauma team were involved in 568 (10%) and 1,549 (31%) of cases, respectively. Highest level of care was most often on the ward (n = 3,702; 59%) (Table 2).

Median ICU-LOS was 0 days (0–1), H-LOS was 5 (IQR: 3–11) days.. Mortality rate was 18%, (n = 1,122). Median number of days before patients died was 3 (IQR: 2–7). Patients who survived had a median GOS of 4 (IQR: 4–5). Most patients who survived were discharged to their usual place of residence (n = 2,723; 46%) (Table 3).

DISCUSSION

There were over 12,000 patients with moderate or severe traumatic brain injury in this nationwide cohort, an incidence rate of 30/100,000 person-years. Patients in our cohort had a median age of 65 years, were predominantly male and were most often discharged home. Thirteen per cent of patients died. Patients who survived most often had good outcomes, with a median GOS of 4, this was even true for the elderly and polytrauma patients. Falls occurred more often than RTAs. Bicycle accidents were a commonly found trauma mechanism, especially amongst the elderly population. Moderate and severe TBI is far more common for the elderly, than the overall study population. Mortality in elderly was 18%, which was higher than the overall mortality, but less than for polytrauma patients (24%).

Falls are currently the most common cause of TBI in the USA and Germany [14]. Ever since the introduction of preventative measures, such as the mandatory seatbelt in cars and helmets for motorcyclists, fewer TBIs have been seen due to RTAs [21]. The epidemiology is changing with a relative increase of TBI amongst older patients, especially due to falls [14,22,23]. Amongst older patients, we see relatively more women, even though the stereotypical TBI patient used to be the young male [14,23]. The increase in TBI, however, cannot be attributed to aging alone [8,23]. For example, one study showed relatively more (mental) comorbidities and pre-injury hospital admissions amongst TBI patients, when matched for age, sex and postcode suggesting these comorbidities can lead to sustainment of TBI [24].

Perhaps surprisingly, the most common cause of TBI in our polytrauma patients was also falls. RTAs were less common in the elderly, with 25%, but still account for almost 40% of TBI in polytrauma patients. More than half of RTAs consisted of bicycle accidents. Statistics show that deaths due to bicycle accidents have hardly decreased since 1996, as opposed to deaths due to car accidents [25]. In addition, almost half of our elderly patients had an ISS over 16 and almost half of polytrauma patients were elderly. This means that elderly patients do not necessarily have less severe injuries. Interestingly, a similar study in Germany found that patients who suffered a motor vehicle or

motorcycle accident were much younger compared to their cohort overall [15]. The elderly in our cohort did suffer more from bicycle accidents than the overall cohort (73% vs 59%), and more than half of deaths due to bicycle accidents in 2018 were over 70 years old, which could indicate a similar phenomenon in the Netherlands [25]. Looking at these mechanisms, there are multiple options for prevention of moderate and severe TBI. For example, the large amount of cycling injuries could (re)start the debate on mandatory helmet use. In addition, the e-bike is gaining popularity amongst the elderly in the Netherlands and injuries from e-bike accidents are more severe than for regular bicycles and less than 1% wears a helmet [26]. Helmets could prevent TBI or at least lower the chances of severe TBI and need for neurosurgical intervention for cyclists [27]. Furthermore, fall prevention in the elderly population, could also lead to a decrease in the incidence of moderate and severe TBI.

The incidence of moderate and severe TBI found in this study is high and equates to approximately 30% of the incidence of lung cancer in the Netherlands [28]. Incidence is high when compared to the aforementioned German study as well, which also used a national trauma database. However, they used a Revised Injury Severity Classification score (RISC) score to classify TBI, and only included patients who were admitted to ICU or high intensity or medium care. Only 34% (n = 3,937) of our cohort received that level of care. This equates to a lower incidence rate of moderate and severe TBI admissions needing ICU admission than in Germany. Possibly, patients in that cohort were more severely injured which could also explain the much higher mortality rate of 23.5% in Germany. However, caution should be exercised in comparing our data to the German data since the RISC score used in the German study was found to be of limited predictive value in patients with moderate to severe TBI [29].

Some patients made a full recovery, but remaining dependent on others in daily life is not uncommon [7]. Persistent disorders of consciousness, such as unresponsive wakefulness syndrome (UWS), where the patient does not demonstrate any sign of consciousness, can also occur as a result of TBI [7,30]. UWS is a rare phenomenon in the Netherlands [30]. Only 62 (0.5%) patients left hospital in this status in this cohort. Combined with the relatively short length of stay in ICU, this might lead to the

conclusion that end of life decisions are taken quite early in admission for TBI patients. However, this seems to lead to a reduction in patients with poor outcomes, as outcome amongst patients who survived TBI were good in our cohort. Median GOS was 4 overall and for both subgroups and almost 90% of patients who survived their injuries had a GOS of 4 or 5. This was lower in the German study, with 61% of patients with a GOS of 4 or 514. This phenomenon was suggested by an earlier retrospective study in the UMC Utrecht as well [7].

Overall, highest level of care was the ward for most patients, polytrauma patients being the exception. Patients cared for on the ward, however, consist of two groups: patients who did not require ICU admission or patients who are not deemed fit for ICU admission and therefore received ward-based care. Of elderly patients, 69% had the ward as their highest level of care, but their mortality rate was slightly higher than for all patients (18% vs 13%). A ward-based care policy, meaning no cardiopulmonary resuscitation, intubation or ICU admission, may have contributed to this, perhaps as a result of therapeutic nihilism [8]. Less frequent involvement of the MMT and trauma team in initial care for the elderly, might also indicate that severity of TBI in the elderly is not always recognised before admission, possibly due to a low-impact trauma mechanism such as a fall from low height. This is supported by a Dutch study that investigated diagnostic value of pre-hospital emergency medical service providers [31]. Recognition of moderate or severe TBI in mainly elderly patients before admission, could therefore be a target for improvement as well.

The large database, covering all hospitals in the Netherlands is a major strength of this study as it is definitely representative of the whole country. Furthermore, the collected data is relevant to the epidemiology of TBI and most important factors can be found in the data.

This study has some limitations as well. Firstly, we decided not to impute for missing data, as this was a study designed to describe our population and their characteristics and our numbers were large enough to achieve this. In addition, sometimes the fact that data is missing can bring forward a new conclusion, for example, GCSs were

poorly collected in this database, with only 75% available. More than half of patients had a GCS of 15, which is most likely not representative of our study population. In addition, even though alcohol and drugs intoxication can be of great impact on the nature of TBI, our database did not account for this. The same is applicable for the use of anticoagulants, as many elderly patients use these and they have a negative effect on TBI22. Therefore, we could not identify their role in our study population or recommend regulations, or stricter indication, regarding their use. In addition, the DTR uses the Glasgow Outcome Scale rather than the Glasgow Outcome Scale Extended, even though the latter is more sensitive [32]. Lastly, bicycles are an important mode of transport in the Netherlands. Therefore their contribution to moderate and severe TBI patients may well be different in other countries, as bicycles are not used as much and their position in traffic is different.

The fact that we used the AIS rather than GCS to classify TBI as moderate or severe, could potentially be seen as a limitation. The large amount of patients with a GCS of 15 included in our database, may support the theory that AIShead overscores severity of TBI, rather than poor data collection33. However, even a study who only included patients with a GCS of 3, still identified patients with mild or moderate TBI [12]. Furthermore, other studies have shown that GCS does not correlate well with the presence of TBI in elderly patients, who form a big part of our cohort34,35. As stated in our introduction, many external factors can influence GCS, such as intoxication and sedation, which make GCS less reliable [12,13]. The choice for AIS to determine severity of brain injury, rather than GCS, can make it difficult to compare our results to other studies. It seems injury is classified differently by the two parameters. The AIS can overscore injuries, when compared to the GCS [33]. A different study showed that a GCS of 3–8 predicted death better than an AIS of 5 or above in case of multiple injuries, but worse with isolated TBI [36]. This could be explained by the fact that GCS can be influenced by injuries in other regions of the body as well [36]. The AIS, however, remains one of the most common modes of classifying TBI and the gold standard of classifying traumatic injuries in general and is used commonly in retrospective data research [33]. Lastly, as the DTR does not regulate who will calculate the GCS and when in the resuscitation process this has happened, the AIShead seemed a more objective

parameter for this study. Unfortunately, even the AIS is not completely resistant to inter-interpreter variability, as coding can be a difficult process, with interrater variability, although recent research showed that reliability for AIS coding in the DTR was substantial18. It would be preferable to have a more accurate system to classify TBI than GCS or AIS and we feel more research in this area is needed to allow for standardised research.

In conclusion, a change in the epidemiology of TBI occurred in the Netherlands, even for moderate and severe TBI as defined by the AIS: a shift to more elderly patients. Most common cause of moderate or severe TBI was falls, followed closely by RTAs. Bicycle accidents were very frequent, even more so amongst the elderly, suggesting prevention could be an important aspect in order to decrease morbidity and mortality by TBI.

Table 1. Baseline variables			
	ALL n= 12,295	**POLYTRAUMA** n=5,763 (47%)	**ELDERLY** n=6,228 (51%)
Demographics			
Incidence rate *person years*	29/100,000	14/100,000	67/100,000
	Median (IQR)	**Median (IQR)**	**Median (IQR)**
Male sex	7,482 (61)	2,671 (64)	3,264 (52)
	N (%)	**N (%)**	**N (%)**
Median age	65 (47-79)	64 (45-78)	79 (72-85)
Clinical characteristics	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Median ASA	2 (1-2)	2 (1-2)	2 (2-3)
Missing	*2,093 (17)*	*963 (17)*	*997 (16)*
Median AIShead	3 (3-4)	4 (3-5)	3 (3-4)
RTS A&E	7.8 (6.9-7.8)	7.8 (5.0-7.8)	7.8 (7.6-7.8)
Missing	*4,722 (38)*	*2,137 (37)*	*2,449 (39)*
	N (%)	**N (%)**	**N (%)**
ISS>16	5,763 (47)	5,763 (100)	2,775 (45)
AIShead			
3	7,778 (63)	1,731 (30)	3,856 (62)
4	2,486 (20)	2,001 (35)	1,262 (20)
5+6	1,997 (16)	2,031 (35)	1,110 (18)
Trauma mechanism			
Fall	5,579 (52)	2,533 (44)	3,543 (57)
Low *(% of falls)*	4,245 (76)	1,662 (63)	3,013 (85)
RTA	4,328 (40)	2,249 (39)	1,574 (25)
Bicycle *(% of RTAs)*	2,523 (59)	1,152 (51)	1,155 (73)
Missing	*1547 (13)*	*603 (10)*	*866 (14)*
GCS 15	5,483 (60)	1,746 (45)	3,023 (63)
Missing	*3,067 (25)*	*1,926 (33)*	*1,360 (22)*

IQR=Interquartile range, ASA= American Society of Anaesthesiologists score, AIShead=Abbreviated Injury Scale of the head region, ISS=Injury Severity Score, RTA=Road traffic accident, GCS= Glasgow Coma Scale score, RTS= Revised Trauma Score

Table 2. Treatment variables

	ALL n= 12,295	**POLYTRAUMA** n=5,763	**ELDERLY** n=6,228
	N (%)	**N (%)**	**N (%)**
Involvement MMT	1,856 (15)	1,514 (26)	568 (10)
Missing	*526 (4)*	*155 (3)*	*304 (5)*
Trauma team activated	4,255 (42)	3,161 (62)	1,549 (31)
Missing	*2,045 (17)*	*653 (11)*	*1,194 (19)*
Emergency intervention	1,045 (10)	989 (18)	272 (5)
Craniotomy *(% of intervention)*	448 (43)	418 (42)	142 (52)
ICP *(% of intervention)*	268 (26)	248 (25)	48 (18)
Missing	*1,336 (11)*	*404 (7)*	*786 (13)*
Highest level of care			
A&E	580 (5)	262 (5)	306 (5)
Ward	6,323 (56)	1,697 (29)	3,701 (65)
Theatre	556 (5)	343 (5)	223 (4)
HC/MC	602 (5)	344 (6)	304 (5)
ICU	3,335 (29)	2,705 (47)	1,209 (21)
Missing	*899 (7)*	*412 (7)*	*482 (8)*

MMT= Mobile Medical Team, ICP=Intracranial pressure meter, A&= Accident and Emergency department, HC= High Care unit, MC= Medium Care unit, ICU= Intensive Care Unit

Table 3. Hospital outcome parameters			
	ALL n= 12,295	**POLYTRAUMA** n=5,763	**ELDERLY** n=6,228
	Median (IQR)	**Median (IQR)**	**Median (IQR)**
GOS	4 (4-5)	4 (4-5)	4 (4-5)
Missing	*394 (4)*	94 (2)	*202 (4)*
H-LOS	5 (2-11)	7 (3-15)	5 (3-11)
Missing	*257 (2)*	*95 (2)*	*130 (2)*
I-LOS	0 (0-2)	1 (1-5)	0 (0-1)
Missing	*1,517 (12)*	*491 (9)*	*893 (14)*
LOS until death	3 (2-7)	3 (2-7)	3 (2-7)
Missing	*13 (1)*	*-1*	*6 (1)*
	N (%)	**N (%)**	**N (%)**
Mortality	1,642 (13)	1,642 (28)	1,122 (18)
Discharge destination			
Usual place of residence	6,438 (63)	1,974 (46)	2,723 (56)
Rehabilitation centre	937 (9)	647 (15)	397 (8)
Nursing home	933 (9)	454 (11)	810 (17)
Care/residential home	197 (2)	89 (2)	167 (3)
Other	1,711 (17)	1,052 (25)	773 (16)
Missing	*437 (4)*	*208 (4)*	*236 (5)*

H-LOS= Length of stay in hospital, I-LOS= Length of stay in Intensive Care Unit, GOS=Glasgow Outcome Scale score

REFERENCES

1. Ghajar, J. Traumatic brain injury. *Lancet* **356**, 923–929 (2000).
2. Taylor, C. A., Bell, J. M., Breiding, M. J. & Xu, L. Traumatic Brain Injury–Related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2007 and 2013. *MMWR. Surveill. Summ.* **66**, 1–16 (2017).
3. Majdan, M. *et al.* Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *Lancet Public Heal.* **1**, e76–e83 (2016).
4. Van Den Brand, C. L. *et al.* Traumatic brain injury in the Netherlands, trends in emergency department visits, hospitalization and mortality between 1998 and 2012. *Eur. J. Emerg. Med.* **25**, 355–361 (2018).
5. Gunning, A. C. *et al.* Demographic Patterns and Outcomes of Patients in Level I Trauma Centers in Three International Trauma Systems. *World J. Surg.* **39**, 2677–2684 (2015).
6. Jochems, D., Leenen, L. P. H., Hietbrink, F., Houwert, R. M. & van Wessem, K. J. P. Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma. *Injury* **49**, 1661–1667 (2018).
7. Jochems, D. *et al.* Outcome in Patients with Isolated Moderate to Severe Traumatic Brain Injury. *Crit. Care Res. Pract.* **114**, (2018).
8. Maas, A. I. R. *et al.* Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol.* **16**, 987–1048 (2017).
9. Roozenbeek, B., Maas, A. I. R. & Menon, D. K. Changing patterns in the epidemiology of traumatic brain injury. *Nat. Rev. Neurol.* **9**, 231–6 (2013).
10. Johnson, W. D. & Griswold, D. P. Traumatic brain injury: a global challenge. *The Lancet Neurology* 949–50 (2017) doi:10.1016/S1474-4422(17)30362-9.
11. Scholten, A. C., Haagsma, J. A., Panneman, M. J. M., Van Beeck, E. F. & Polinder, S. Traumatic brain injury in the netherlands: Incidence, costs and disability-adjusted life years. *PLoS One* **9**, (2014).
12. Salottolo, K. *et al.* The epidemiology , prognosis , and trends of severe traumatic brain injury with presenting Glasgow Coma Scale of 3. *J. Crit. Care* **38**, 197–201 (2017).

13. Jonsdottir, G. M. *et al.* A population-based study on epidemiology of intensive care unit treated traumatic brain injury in Iceland. **61**, 408–417 (2017).
14. Maegele, M. *et al.* Inzidenz und Versorgung des mittelschweren bis schweren Schädel-Hirn-Traumas. *Dtsch. Arztebl. Int.* **116**, 167–173 (2019).
15. Peek, J. *et al.* Epidemiology and outcome of rib fractures: a nationwide study in the Netherlands. *Eur. J. Trauma Emerg. Surg.* (2020) doi:10.1007/s00068-020-01412-2.
16. Kuipers, E. J. & Leenen, L. P. H. Landelijke traumaregistratie 2013-2017. (2018).
17. Centraal bureau voor statistiek (CBS). Bevolking; geslacht, leeftijd en burgerlijke staat, 1 januari. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/7461bev/table?ts=1565696300750%0Ahttps://opendata.cbs.nl/statline/#/CBS/nl/dataset/7461bev/table?dl=B875 (2021).
18. Olthof, D. C., Luitse, J. S. K., De Groot, F. M. J. & Goslings, J. C. A Dutch regional trauma registry: Quality check of the registered data. *BMJ Qual. Saf.* **22**, 752–758 (2013).
19. Gennarelli TA, W. E. *Abbreviated Injury Scale 2005. Update 2008. Association for the Advancement of Automotor Medicine* (Barrington, IL, 2008).
20. Van Camp, L. A. & Deloooz, H. H. Current trauma scoring systems and their applications. *European Journal of Emergency Medicine* vol. 5 341–354 (1998).
21. Di Saverio, S. *et al.* Changes in the outcomes of severe trauma patients from 15-year experience in a Western European trauma ICU of Emilia Romagna region (1996-2010). A population cross-sectional survey study. *Langenbeck's Arch. Surg.* **399**, 109–126 (2014).
22. Schumacher, R., Müri, R. M. & Walder, B. Integrated Health Care Management of Moderate to Severe TBI in Older Patients — A Narrative Review. (2017).
23. Peeters, W., Majdan, M., Brazinova, A., Nieboer, D. & Maas, A. I. R. Changing Epidemiological Patterns in Traumatic Brain Injury: A Longitudinal Hospital-Based Study in Belgium. *Neuroepidemiology* **48**, 63–70 (2017).

24. Lystad, R. P., Cameron, C. M. & Mitchell, R. J. Excess Mortality Among Adults Hospitalized With Traumatic Brain Injury in Australia: A Population-Based Matched Cohort Study. *J. Head Trauma Rehabil.* **34**, E1–E9 (2019).

25. Centraal bureau voor statistiek (CBS). Overledenen; doden door verkeersongeval in Nederland, wijze van deelname. http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=71936ned&LA=NL (2016).

26. Poos, H. P. A. M. *et al.* [E-bikers are more often seriously injured in bicycle accidents: results from the Groningen bicycle accident database]. *Ned. Tijdschr. Geneeskd.* **161**, D1520 (2017).

27. Dodds, N. *et al.* Evaluating the impact of cycle helmet use on severe traumatic brain injury and death in a national cohort of over 11000 pedal cyclists: A retrospective study from the NHS England Trauma Audit and Research Network dataset. *BMJ Open* **9**, 1–7 (2019).

28. Nederlandse Kankerregistratie (NKR). Incidentie longkanker. 2019 https://iknl.nl/nkr-cijfers (2019).

29. Raj, R. *et al.* Validation of the revised injury severity classification score in patients with moderate-to-severe traumatic brain injury. *Injury* **46**, 86–93 (2015).

30. Erp, W. S. Van *et al.* The Vegetative State : Prevalence , Misdiagnosis , and Treatment Limitations. *JMDA* **16**, 85.e9-85.e14 (2015).

31. van Rein, E. A. J. *et al.* Diagnostic value of emergency medical services provider judgement in the identification of head injuries among trauma patients. *Eur. J. Neurol.* 1–7 (2018) doi:10.1111/ene.13804.

32. McMillan, T. *et al.* The Glasgow Outcome Scale-40 years of application and refinement. *Nat. Rev. Neurol.* **12**, 477–485 (2016).

33. Rogers, S. & Trickey, A. W. Classification of traumatic brain injury severity using retrospective data. *J. Nurs. Educ. Pract.* **7**, 23 (2017).

34. Rozenfeld, M. *et al.* The reliability of the Glasgow Coma Scale in detecting traumatic brain injury: The continuous effect of age. *Brain Inj.* **34**, 515–519 (2020).

35. Salottolo, K., Stewart Levy, A., Slone, D. S., Mains, C. W. & Bar-Or, D. The effect of age on glasgow coma scale score in patients with traumatic brain injury. *JAMA Surg.* **149**, 727–734 (2014).

36. Savitsky, B., Givon, A., Rozenfeld, M., Radomislensky, I. & Peleg, K. Traumatic brain injury: It is all about definition. *Brain Inj.* **30**, 1194–1200 (2016).

CHAPTER 2

Epidemiology of moderate and severe traumatic brain injury amongst children in the Netherlands

CHAPTER 2

Title: Epidemiology of moderate and severe traumatic brain injury amongst children in the Netherlands.

Printed in: European journal of Paediatric Neurology.

Cited by: Jochems D, van Rein E, Niemeyer M, van Heijl M, van Es MA, Nijboer T, et al. Epidemiology of paediatric moderate and severe traumatic brain injury in the Netherlands. Eur J Paediatr Neurol. 2021 Oct 9;35:123-129. doi: 10.1016/j.ejpn.2021.10.004. Epub ahead of print. PMID: 34687976.

Author list: Denise Jochems[a] (MD), Eveline van Rein[a] (MD, PhD), Menco Niemeyer[a] (MD), Mark van Heijl[a] (MD, PhD), Michael A. van Es[b] (MD, PhD), Tanja Nijboer[c, d] (PhD), Luke P.H. Leenen[a] (MD, PhD), Roderick M. Houwert[a] (MD, PhD), Karlijn J.P. van Wessem[a] (MD, PhD)

[a] Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

[b] Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands

[c] Department of Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands

[d] Center of Excellence for Rehabilitation Medicine, UMC Utrecht Brain Center, University Medical Center Utrecht, and De Hoogstraat Rehabilitation, Utrecht, the Netherlands

ABSTRACT

Introduction: Traumatic brain injury (TBI) is the main cause of death in children around the world. The last Dutch epidemiological study described the incidence over 10 years ago. Mechanism of injury seems to change with the age of the child, therefore it is important to appreciate different age groups. To be able to lower the impact of childhood TBI, an understanding of current incidence, mechanism of injury and outcome is necessary.

Materials and methods: A nationwide retrospective cohort study was conducted. The Dutch National Trauma Database was used to identify all patients 18 years and younger who were admitted to a Dutch hospital with moderate-severe TBI (Abbreviated Injury Score≥3) in the Netherlands, from January 2015 until December 2017. Subanalyses were done for different age groups.

Results: In total, 1413 patients were included, of whom 5% died. The incidence rate of moderate-severe TBI was 14/100,000 person years. Median age was 10.4 years. Largest age group was patients <5 years, incidence rate was highest in patients ≥16 years. Falls were more common than road traffic accidents (RTA), but RTAs occurred far more frequently amongst children over 10. RTAs predominantly consisted of bicycle accidents. Mortality rates increased from youngest to oldest age groups, as did the chances of a Glasgow Outcome Scale score of 3.

Conclusion: Paediatric moderate-severe TBI represents a significant problem in the Netherlands. Falls are the most common mechanism of injury amongst younger children and RTAs amongst older children. Unique for the Netherlands is the vast amount of bicycle accident related injuries.

INTRODUCTION

Traumatic brain injury (TBI) amongst children is quite common, with estimates of three million affected children globally every year and 35,000 annual hospitalisations in the United Kingdom [1,2]. A New Zealand birth cohort starting in 1977 showed that before the age of 26, 151 people (1%) had been admitted to hospital for TBI [3]. A major trauma centre in London identified 116 children with TBI proven on CT in two years [2] . In one area in the Netherlands, 130 patients were identified to have moderate or severe brain injury in 2008 and 2009 [4]. Distinct comparison of those epidemiological reports is difficult as classification of severity of TBI varies as do study design, cohort type and cohort size [1].

Defining the different degrees of TBI has proven difficult, leading to different definitions in most studies. In London, they identified clinically important TBI when the CT head showed abnormalities, in the Netherlands the Glasgow Coma Scale (GCS) was used to distinguish different grades of injury, and New Zealand used a combination of both [2-4]. When the incidence of childhood TBI in Europe was investigated, up to 90% of children had no abnormalities on the CT scan of the head [1]. In research investigating trauma to other areas than the brain, the Abbreviated Injury Score (AIS) is commonly used. Using this score, at least allows for comparison to injuries in other regions of the body. As moderate and severe TBI more often lead to mortality or disability than mild TBI, it would also be beneficial to identify them correctly, as especially the GCS can misidentify mild TBI as moderate or severe due to complicating factors such as intubation and sedation [5,6].

Moreover, TBI is the main cause of death in children around the world. Two of the peaks in the trimodal distribution described by the Centres for Disease Control and Prevention (CDC), are in children [2,7]. However, paediatric mortality rates after moderate and severe TBI are lower than for adults with rates as low as 5–16% [2,8].

Recent studies investigating epidemiology of paediatric TBI for different age groups are scarce. The last Dutch epidemiological study describes the incidence over 10 years ago[4]. In keeping with adult studies, most paediatric studies reveal falls and RTAs as the most

frequent mechanism of injury [9]. However, children are passengers rather than drivers when it comes to motor vehicles and are more often involved as a pedestrian [9]. Furthermore, in high income countries, the incidence of road traffic accidents seem to have decreased over the last decades due to preventative measures [10].

To be able to lower the impact of childhood TBI, an understanding of current incidence, mechanism of injury and outcome is necessary. This would help to identify on which areas research and prevention methods should focus. Therefore, we investigated the incidence, mechanism of injury, demographics and outcome of moderate and severe TBI requiring hospital admission amongst children of 18 years and younger, with a subanalysis of different age groups.

MATERIALS AND METHODS

A nationwide retrospective cohort study was performed using the Dutch Trauma Registry (DTR). The DTR was founded in 2007 and is maintained by the Dutch Trauma Network of Acute Care with the general purpose of monitoring trauma care with a standardised registry and to ensure high quality care for severely injured patients. The DTR covers approximately 99% of all hospitals in the Netherlands and prospectively collects data on all trauma patients who are admitted to the hospital after presenting to the Accident and Emergency department (A&E), within 48 h after trauma. Patients presented to A&E by pre-hospital Emergency Medical Services, as well as by self-admission, are included in the DTR. Patients declared dead on arrival, who are discharged home from A&E, and those admitted to the hospital for reasons other than their traumatic injury were excluded [11]. In order to determine the incidence rate of TBI requiring hospital admission, national demographic data were obtained using the Dutch Population Register from the Central Bureau of Statistics [12].

All patients aged 18 years and younger admitted to the hospital between January 2015 and December 2017 with moderate or severe TBI were identified using Abbreviated Injury Scale codes for traumatic brain injury. The AIS is a widely accepted anatomically based scoring system to grade injuries from mild to maximal (almost certainly leading to death) on a scale from one to six and coders can use data from the patient's records, including imaging and surgical reports, to assign a score, using a supplied standardised guideline [13]. Combined AIS scores are used to determine the Injury Severity Score (ISS). AIS scores as recorded in the DTR were calculated by data managers of the participating trauma centres as per ISS 08 [14]. Moderate to severe TBI was classified as an AIS of the head region (AIShead) of three or higher. Five different age groups were analysed separately: <3 years old, 3-<5 years old, 5-<10 years old, 10-<16 years old and children of 16–18 years old. The last group was analysed separately as this group is legally allowed to drive a moped and children can start driving lessons from age 16.5. To prevent inclusion of duplicate cases, all patients who required early transfers to another hospital were excluded.

The following baseline variables were obtained from the DTR: age at trauma, sex, American Society of Anesthesiologists (ASA) score, mechanism of injury, Glasgow Coma Scale Score, AIS scores for all body regions and Injury Severity Scores (ISS) scores.

The outcome variables obtained were frequency of involvement of the Mobile Medical Team (MMT), highest level of received care, hospital length of stay (H-LOS), ICU length of stay (I-LOS), mortality, and Glasgow Outcome Scale (GOS) score [15] at the time of hospital discharge. In the Netherlands, the MMT consists of a trauma surgeon or anaesthesiologist and a trained nurse to provide acute care on scene.

All variables were collected for all included patients and separately for the different age groups.

Data were analysed using descriptive statistics and presented as frequencies with percentages for categorical data, means with standard deviations (SD) for normally distributed continuous data, and medians with interquartile ranges (IQR) for non-normally distributed continuous data. The Shapiro-Wilk test and Quantile-Quantile plots were applied to detect deviations from the normal distribution. The incidence rate was calculated by dividing the total number of patients with TBI by the total Dutch population <19 years of age during the study period and for the corresponding ages for the different age groups. Incidence rates were expressed per 100,000 person-years. Statistical analyses were performed using SPSS statistical software (SPSS 23.0; IBM Inc., Armonk, NY, USA).

Results (Figure 1.a)

In total, 1413 children were included in this analysis. In January 2017, 3,424,877 children were 18 years or younger, leading to an incidence rate of moderate and severe TBI of 14/100,000 person years.

Median age was 10.4 years and median ASA score was 1 (SD: 1-1). Falls were only slightly more common than RTAs. Median AIShead was 3 (SD: 2–4). Most children had a GCS of 15 if they had an AIShead of 3 (70%), this dropped to 44% if the AIShead was 5. Median ISS was 11 (SD: 9–18.5), and roughly one third had an ISS>16 (n = 472) (Table 1).

Highest level of care was most often the ward (n = 688; 51%). ICU admission was necessary for 451 patients (34%), median length of stay was 0 days (SD: 0–2). Median LOS in hospital was 3 days (SD: 2–6) (Table 2).

Bicycle accidents and accidents involving a pedestrian were most commonly the cause of a TBI that lead to mortality (both 17 children, 23% each), followed by passengers/drivers of a motorised vehicle (11 children, 15%). Most patients who survived their injuries had a GOS score of 5 (n = 511; 57%) (Table 2). Data are graphically summarised in Fig. 1a.

Youngest age group (<3 years old) (Fig. 1b.)

The youngest age group consisted of 293 children (21%). In 2017, 520,748 children of this age lived in the Netherlands, leading to an incidence rate of moderate and severe TBI of 19/100,000 person years.

Falls were far more common than RTAs. Median AIShead was 3 (SD: 3-3), median ISS 10 (SD: 9–16) and 20% of children had an ISS over 16 (n = 57). Most children had a GCS of 15 if they had an AIShead of 3 (81%), this dropped to 15% if the AIShead was 5. (Table 1).

Highest level of care was more often the ward (n = 167; 61%). Roughly a quarter of children needed ICU admission (n = 68). Median length of stay in ICU was 0 (0–2) days, and 2 (SD: 2–4) days in hospital. Most patients who survived their injuries had a GOS score of 5 (n = 119, 63 (Table 2). Data are graphically summarised in Fig. 1b.

Children aged 3-<5 (Fig. 1c)

This was the smallest age group in this study, with 138 (9.8%) children. In 2017, 351,541 children of this age lived in the Netherlands, leading to an incidence rate of moderate and severe TBI of 13/100,000 person years.

Most common mechanism of injury was falls (n = 88; 71%). Median AIShead was 3 (SD: 3-3), median ISS 10 (SD: 9–14) and less than 20% had an ISS over 16 (n = 25). Most children had a GCS of 15 if they had an AIShead of 3 (73%), this dropped to 50% if the AIShead was 5 (Table 1).

Highest level of care was most often the ward (n = 85; 64%). Around a quarter needed ICU admission (n = 31). Median length of stay in ICU was 0 (0–1.75) days, and 2 (SD: 2–3) days in hospital. A GOS score of 5 (n = 58, 60%) was most frequent amongst patients who survived their injuries (Table 2). Data are graphically summarised in Fig. 1c.

Children aged 5-<10 (Fig. 1d)

This group consisted of 258 children (18%). In 2017, 929,180 children of this age lived in the Netherlands, leading to an incidence rate of moderate and severe TBI of 9/100,000 children.

Falls were more common than RTAs. Median AIShead was 3 (SD: 3–4), median ISS 10 (SD: 9–17) and 25% of children had an ISS higher than 16 (n = 65). Most children had a GCS of 15 if they had an AIShead of 3 (75%), this dropped to 58% if the AIShead was 5 (Table 1).

Highest level of care was most often the ward (n = 139; 56%), almost 30% was admitted to ICU (n = 72). Median length of stay in ICU was 0 (SD: 0–2) days, and 3 (SD: 2–4) days in hospital. Most patients who survived their injuries had a GOS score of 5 (n = 102; 54%) (Table 2). Data are graphically summarised in Fig. 1d.

Children aged 10-<16 (Fig. 1e)

A quarter of children were included in this age group (n = 353). In 2017, 1,185,949 children of this age lived in the Netherlands, leading to an incidence rate of moderate and severe TBI of 10/100,000 children.

RTAs were the most common trauma mechanism, falls accounted for 30% (n = 98). Median AIShead was 3 (SD: 3–4), median ISS 13 [[10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22]] and 40% of children had an ISS higher than 16 (n = 141). Most children had a GCS of 15 if they had an AIShead of 3 (65%), this dropped to 50% if the AIShead was 5 (Table 1).

Highest level of care was most often the ward (n = 155; 46%), followed by ICU (n = 123; 38%). Median length of stay in ICU was 0 (SD: 0–3) days, and 3 (SD: 2–6.25) days in hospital. GOS score of 5 was most common amongst patients who survived their injuries (n = 122, 47%) (Table 2). Data are graphically summarised in Fig. 1e.

Children aged 16 and older (Fig. 1f)

Approximately a quarter of children were included in this age group (n = 371). In 2017, 624,459 people of this age lived in the Netherlands, leading to an incidence rate of moderate and severe TBI of 20/100,000, the highest amongst age groups.

RTAs were by far the most common trauma mechanism, falls accounted for 19% (n = 65). Amongst RTAs, mopeds were most frequently mode of transport. Median AIShead was 3 (SD: 3–4), median ISS 16 (SD: 10–26) and half of the patients had an

ISS higher than 16 (n = 184). Most children had a GCS of 15 if they had an AIShead of 3 (61%), this dropped to 37% if the AIShead was 5. (Table 1).

Highest level of care was most often ICU (n = 157; 45%), followed by the ward (n = 142; 41%). Median length of stay in ICU was 1 (SD: 0–3) days, and 4 (SD:2–10) days in hospital. GOS score of 4 was most frequent amongst patients who survived their injuries (n = 135; 47%) (Table 2). Data are graphically summarised in Fig. 1f.

DISCUSSION

Moderate and severe traumatic brain injury in the paediatric population is relatively common, with 1413 cases in 2015–2017 in the Netherlands. This leads to an incidence rate of 14/100,000 person years, which approaches the incidence of childhood cancers, which had an incidence rate of 17/100,000 person years in 2017 [16]. Children with moderate or severe traumatic brain injury were predominantly male, with a median age of 10.4 years old. Approximately one-fifth of children required pre-hospital assistance from the MMT. There was a mortality rate of 5%, as 75 children died. Children mostly made a good recovery before discharge, with a GOS score of 5 for 57% of patients.

Mechanism of injury varies with age and severity of injury. Whereas babies are more likely to suffer from falls out of parent's arms and toddlers from RTAs as a pedestrian on a driveway rather than as a passenger or driver, older children are more likely to sustain injuries from their own actions, such as sport-related accidents. RTAs are in general more common in older children as well [1,17,17]. In our cohort, a fall was most commonly the mechanism of injury for children <10 years old, for children >10 years old, this was an RTA. In the USA, over 182,000 children younger than four years old visited A&E with TBI as a result of a fall, however, only five per cent had to be admitted to hospital [19]. Literature also shows that deaths from RTAs, in which the victim is a pedestrian, are less frequent than when the victim is a passenger. However, these data are over 10 years old and we expect that improved adherence to safety precaution regulations might have changed this [18]. Especially since our limited data regarding paediatric deaths due to TBI seem to indicate otherwise. Unique to the Netherlands is the amount of bicycle-related TBIs, with almost 25% of all TBIs and over 50% of road traffic accidents. Amongst RTAs, the patient most frequently used a bicycle at time of injury, this was the moped for children of 16 years and older. In contrast, in London, only 1% of moderate and severe paediatric TBI was found in cyclists who were hit by a car or fell of the bicycle, as opposed to the 39% of patients who were hit by a car as a pedestrian [2]. Another European childhood TBI study found that only 25% of RTA victims were cyclists [9].

These outcomes suggest there are several possibilities for prevention of moderate and severe TBI. For example, discussions on mandatory helmet use for cyclists and moped drivers would be warranted, considering the high proportion of cyclists in our cohort. For mopeds with a speed limit of 45 km/h, the use of a helmet is already enforced by law, this is not the case for mopeds with a speed limit of 25 km/h, e-bikes and bicycles. As incidence rates were highest in the oldest age group, investigation regarding adherence to helmet laws amongst moped drivers could be helpful. Helmet use could potentially prevent TBI or at least lower the chances of severe TBI and seems to protect against skull fractures [20-22]. In another study from Nottingham, none of the 22 children who were admitted with primarily head injuries to a paediatric ICU wore a helmet [23]. In addition, further research is necessary to investigate the cause of paediatric falls as falls are the main cause of injury in our largest age group. This could help identify additional preventative measures.

Fortunately, it seems to be characteristic for children to have a higher chance of survival and improved recovery compared to adults. Survival rates of 95% amongst moderate and severe TBI exceed those of adults massively. This vast difference seems to be multifactorial, with differences in trauma mechanism and injury pattern, the rise of TBI amongst the comorbid elderly and difficulty in determining functional outcome for children [24]. As far as recovery goes, the high amount of GOS of 5 on discharge is encouraging. However, multiple studies report an impairment which the wide definition of the GOS of 5 might overlook [25,26]. This could be especially true for children, as it is difficult to predict what their development would have been like if they had not suffered from TBI. Furthermore, assessment of true functional outcome is even difficult for adults, as questionnaires and testing environments do not reflect challenges people face in their daily lives [26].

Severity of injuries seemed to increase with age, ranging from an ISS >16 in 20% of children <3–50% in children of 16 years and older. In addition, the incidence rate was also highest amongst the oldest age group. Median AIShead, however, was most often 3 in all age groups. There is controversy as to whether younger children have a bigger chance of mortality or other long-term sequelae due to TBI. Multiple studies conclude

that the highest mortality rate is in the group of children <2 years, although we did not see this pattern in this study. Some hypothesise that this might be due to the higher contribution of non-accidental trauma in this age group, as these injuries lead to higher mortality rates [27]. Other studies show a higher mortality rate in older children, which is also true for our cohort, although not statistically significant. Hill et al. did not find any deaths in children <9 years old and van Pelt et al. noticed that older children were more likely to have severe TBI [2,4]. A study in the United States found that children between 15 and 19 years old were most at risk, although their population might not be comparable to ours, as 12% of deaths were caused by firearms [28]. As to consequences for functional outcome, it seems younger children are at higher risk, even though it was assumed for a long period that their brains would show more adaptability than those of older children [18,29].

A strength of this study is that it was nation-wide and data was retrieved from an established database. This allowed for analysis of clinically relevant factors. Furthermore, we used the AIS scores to establish whether injuries were moderate or severe, rather than mild. The fact that we used the AIS rather than GCS to classify TBI, could potentially be seen as a limitation. The large amount of patients with a GCS of 15 included in our database, may support the theory that AIShead overscores severity of TBI, rather than poor data collection [30]. Many studies use GCS scores to classify severity of TBI, but those are difficult to score on children and on a trauma population in general, as many patients receive some form of sedation and/or are intoxicated, although the latter solely applies to the older children [5].

When determining AIS scores, imaging is used, which is a more objective measurement. Unfortunately, the database did not allow for calculation of the Marshall or Rotterdam criteria, two widely accepted scores based on CT findings [31,32]. This would have allowed for more accurate comparison with other studies.

A limitation is that abusive head trauma was not classified as a separate category. There was a small number of patients classified to be the victim of assault, but we doubt that all victims were identified and classified correctly. One study even suspected 22.5% of

children with an ICP meter of being the victim of abuse [27]. Another limitation is that some parameters were not collected for every patient, resulting in missing data and that we were unable to gather data on CT scan results, such as the location of a haematoma.

In conclusion, even though paediatric moderate and severe TBI is less common than TBI in adults and has a lower mortality rate, it is still a big problem. Highest incidence rates are amongst the oldest and youngest age groups, mortality rates and chances of moderate disability seem to increase with age. Falls are the most common mechanism of injury amongst younger children and bicycle injuries amongst the older children which is unique for the Netherlands. The strongest weapon to decrease incidence is prevention.

Figure 1a-f. Left to right: Sex, Road Traffic Accident as trauma mechanism (of which bicycles), AIShead of 3, Retrieved by Mobile Medical Team, Home as discharge destination, Mortality.

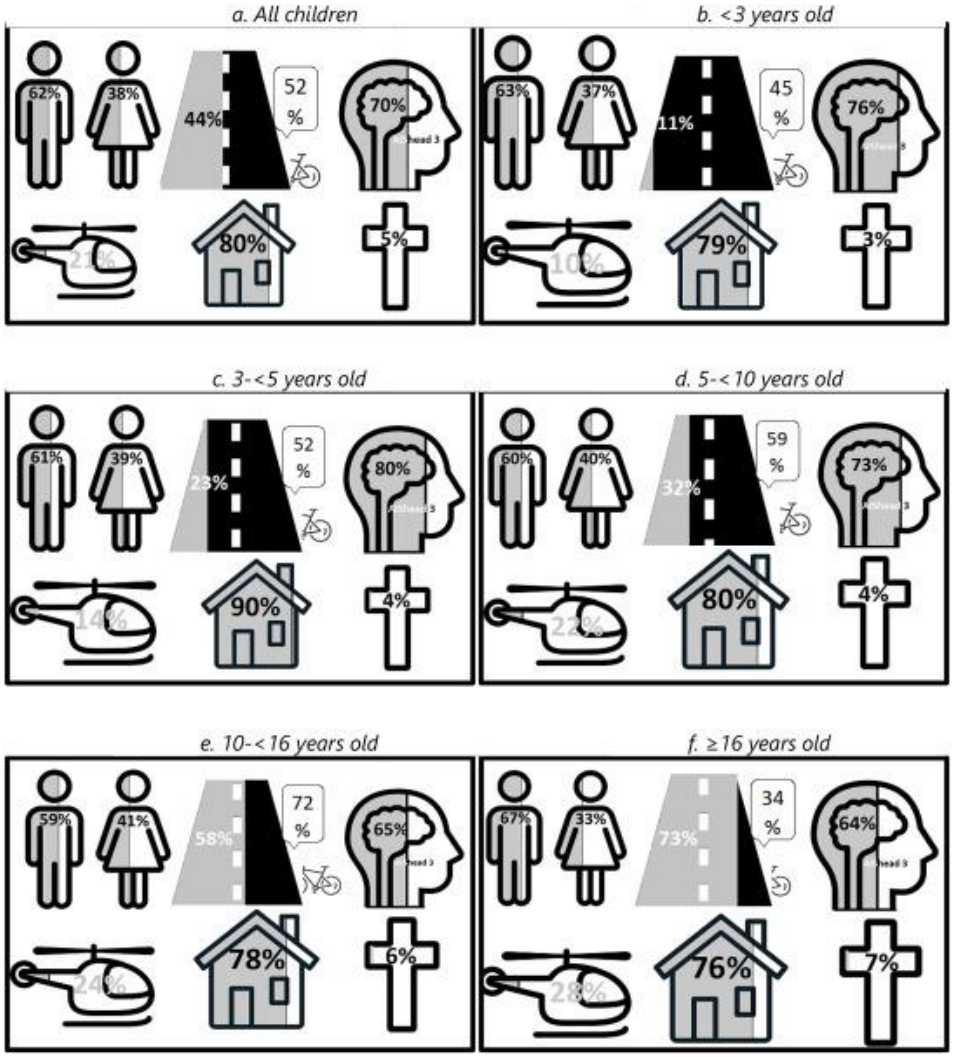


Table 1. Baseline variables

	ALL n=1,413	**<3 YEARS** n=293 (21%)	**3-<5 YEARS** n=138 (9.8%)	**5-<10 YEARS** n=258 (18%)	**10-<16 YEARS** n= 353 (25%)	**≥16 YEARS** n=371 (26%)	**p-value**
DEMOGRAPHICS							
Incidence rate *person years*	14/100,000	19/100,000	13/100,000	9/100,000	10/100,000	20/100,000	
Median (IQR)							
Age	10.4 (3.9-16.2)						
N (%)^							
Female	533 (38)	107 (37)	54 (39)	103 (40)	145 (41)	124 (33)	0.245
CLINICAL CHARACTERISTICS							
Median (IQR)*							
ASA	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	
Missing	*257 (18)*	*61 (21)*	*27 (20)*	*49 (19)*	*62 (18)*	*58 (16)*	
ISS	11 (9-18.5)	10 (9-16)	10 (9-14)	10 (9-17)	13 (10-22)	16 (10-26)	<0.001
AIShead	3 (2-4)	3 (3-3)	3 (3-3)	3 (3-4)	3 (3-4)	3 (3-4)	
N (%)^							
Mechanism							
RTA	565 (44)	29 (11)	29 (23)	73 (32)	190 (58)	244 (73)	<0.001
Bicycle	291 (52)	13 (45)	15 (52)	43 (59)	136 (72)	84 (34)	
Pedestrian	75 (13)	7 (24)	8 (28)	19 (26)	25 (13)	16 (7)	
Motor-vehicle	79 (14)	5 (17)	4 (14)	8 (11)	14 (7)	48 (20)	
Motorcycle	6 (1)	0 (0)	0 (0)	0 (0)	4 (2)	2 (1)	
Moped	104 (18)	0 (0)	1 (3)	3 (4)	8 (4)	92 (38)	
Fall	594 (47)	211 (83)	88 (71)	132 (57)	98 (30)	65 (19)	
Low height	319 (54)	103 (49)	45 (51)	70 (53)	66 (67)	30 (46)	
Missing	*142 (10)*	*39 (13)*	*14 (10)*	*28 (11)*	*26 (7)*	*35 (9)*	
AIShead							
3	998 (70)	223 (76)	110 (80)	189 (73)	228 (65)	238 (64)	0.003#
GCS 15	596 (70)	140 (81)	66 (73)	126 (75)	143 (65)	121 (61)	
4	253 (18)	45 (15)	19 (14)	42 (16)	75 (21)	72 (19)	
GCS 15	111 (51)	22 (65)	11 (50)	22 (54)	37 (54)	19 (35)	
5	172 (12)	25 (9)	9 (6)	27 (11)	50 (14)	61 (16)	
GCS 15	47 (44)	2 (15)	2 (50)	11 (58)	21 (50)	11(37)	
Missing GCS	*233 (16)*	*72 (25)*	*21 (15)*	*29 (11)*	*22 (6)*	*89 (24)*	
ISS>16	472 (33)	57 (20)	25 (18)	65 (25)	141 (40)	184 (50)	<0.001

IQR=Interquartile range, ASA= American Society of Anaesthesiologists score, RTA= Road Traffic Accident, AIShead=Abbreviated Injury Scale of the head region, ISS=Injury Severity Score

*Mann-Whitney U test, ^Chi Square test (or Fisher exact if observed value <5), # Applicable to AIShead

Table 2. Outcome variables							
	ALL n=1,413	**<3 years** n=293 (21%)	**3-<5 YEARS** n= 138 (9.8%)	**5-<10 YEARS** n= 258 (18%)	**10-<16 YEARS** n= 353 (25%)	**≥16 YEARS** n=371 (26%)	**p-value**
N (%)^							
MMT	280 (21)	29 (10)	18 (14)	54 (22)	80 (24)	99 (28)	<0.001
Missing	*57 (4)*	*10 (3)*	*7 (5)*	*13 (5)*	*14 (4)*	*13 (4)*	
Highest level of care							
ED	101 (8)	22 (8)	10 (8)	23 (9)	29 (9)	17 (5)	<0.001
Ward	688 (51)	167 (61)	85 (64)	139 (56)	155 (46)	142 (41)	
Theatre	40 (3)	3 (1)	0 (0)	6 (2)	12 (4)	19 (5)	
MC/HC	58 (4)	14 (5)	6 (2)	8 (3)	15 (5)	15 (4)	
ICU	451 (34)	68 (25)	31 (24)	72 (29)	123 (37)	157 (45)	
Missing	*75 (5)*	*19 (6)*	*6 (4)*	*10 (4)*	*19 (5)*	*21 (6)*	
Mortality	75 (5)	10 (3)	6 (4)	11 (4)	21 (6)	27 (7)	0.195
GOS							
2	6 (1)	0 (0)	0 (0)	1 (1)	2 (1)	3 (1)	<0.001
3	99 (10)	12 (6)	4 (4)	17 (9)	26 (10)	40 (14)	
4	402 (39)	57 (30)	35 (36)	68 (36)	107 (42)	135 (47)	
5	511 (57)	119 (63)	58 (60)	102 (54)	122 (47)	110 (38)	
Missing	320 (24)	95 (32)	35 (25)	59 (24)	75(23)	56 (16)	
Discharge location							
Care/residential home	3 (0)	0 (0)	0 (0)	2 (1)	0 (0)	1 (0)	<0.001
Nursing home	3 (0)	0 (0)	0 (0)	0 (0)	2 (1)	1 (0)	
Usual place of residence	1,027 (80)	227 (79)	108 (90)	188 (80)	251 (78)	253 (76)	
Rehabilitation centre	88 (7)	3 (1)	1 (1)	10 (4)	27 (8)	47 (14)	
Other	164 (13)	46 (16)	11 (9)	34 (15)	42 (13)	31 (9)	
Missing	*53 (4)*	*7 (2)*	*18 (13)*	*13 (5)*	*10 (3)*	*11 (3)*	
Median (IQR) *							
LOS ICU in days	0 (0-2)	0 (0-2)	0 (0-1.75)	0 (0-2)	0 (0-3)	1 (0-3)	<0.001
Missing	*134 (9)*	*36 (12)*	*18 (13)*	*22 (9)*	*29 (8)*	*29 (8)*	
LOS Hospital in days	3 (2-6)	2 (2-4)	2 (2-3)	3 (2-4)	3 (2-6.25)	4 (2-10)	<0.001
Missing	*55 (4)*	*18 (6)*	*7 (5)*	*13 (5)*	*7 (2)*	*10 (3)*	

MMT= Mobile Medical Team, A&E= Accident and Emergency department, MC= Medium Care unit, HC= High Care unit, ICU= Intensive Care Unit, LOS= Length of Stay, GOS= Glasgow Outcome Scale

REFERENCES

1. Dewan, M. C., Mummareddy, N., Wellons & J. C. & Bonfield, C. M. Epidemiology of Global Pediatric Traumatic Brain Injury: Qualitative Review. *World Neurosurg.* **91**, 497-509.e1 (2016).
2. Hill, C. S., McLean, A. L. & Wilson, M. H. Epidemiology of Pediatric Traumatic Brain Injury in a Dense Urban Area Served by a Helicopter Trauma Service. *Pediatr. Emerg. Care* **34**, 426–430 (2018).
3. McKinlay, A. *et al.* Prevalence of traumatic brain injury among children, adolescents and young adults: Prospective evidence from a birth cohort. *Brain Inj.* **22**, 175–181 (2008).
4. Daniëlle Van Pelt, E. *et al.* The incidence of traumatic brain injury in young people in the catchment area of the University Hospital Rotterdam, the Netherlands. *Eur. J. Paediatr. Neurol.* **15**, 519–526 (2011).
5. Salottolo, K. *et al.* The epidemiology , prognosis , and trends of severe traumatic brain injury with presenting Glasgow Coma Scale of 3. *J. Crit. Care* **38**, 197–201 (2017).
6. van Rein, E. A. J. *et al.* Diagnostic value of emergency medical services provider judgement in the identification of head injuries among trauma patients. *Eur. J. Neurol.* 1–7 (2018) doi:10.1111/ene.13804.
7. Taylor, C. A., Bell, J. M., Breiding, M. J. & Xu, L. Traumatic Brain Injury–Related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2007 and 2013. *MMWR. Surveill. Summ.* **66**, 1–16 (2017).
8. Emami, P. *et al.* Impact of Glasgow Coma Scale score and pupil parameters on mortality rate and outcome in pediatric and adult severe traumatic brain injury: a retrospective, multicenter cohort study. **126**, 760–767 (2017).
9. Riemann, L., Zweckberger, K., Unterberg, A., El Damaty, A. & Younsi, A. Injury Causes and Severity in Pediatric Traumatic Brain Injury Patients Admitted to the Ward or Intensive Care Unit: A Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study. *Front. Neurol.* **11**, (2020).
10. Roozenbeek, B., Maas, A. I. R. & Menon, D. K. Changing patterns in the

epidemiology of traumatic brain injury. *Nat. Rev. Neurol.* **9**, 231–6 (2013).

11. Kuipers, E. J. & Leenen, L. P. H. Landelijke traumaregistratie 2013-2017. (2018).
12. Centraal bureau voor statistiek (CBS). Bevolking; geslacht, leeftijd en burgerlijke staat, 1 januari. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/7461bev/table?ts=1565696300750%0Ahttps://opendata.cbs.nl/statline/#/CBS/nl/dataset/7461bev/table?dl=B875 (2021).
13. Olthof, D. C., Luitse, J. S. K., De Groot, F. M. J. & Goslings, J. C. A Dutch regional trauma registry: Quality check of the registered data. *BMJ Qual. Saf.* **22**, 752–758 (2013).
14. Gennarelli TA, W. E. *Abbreviated Injury Scale 2005. Update 2008. Association for the Advancement of Automotor Medicine* (Barrington, IL, 2008).
15. McMillan, T. *et al.* The Glasgow Outcome Scale-40 years of application and refinement. *Nat. Rev. Neurol.* **12**, 477–485 (2016).
16. Nederlandse Kankerregistratie (NKR). Incidentie longkanker. 2019 https://iknl.nl/nkr-cijfers (2019).
17. De Kloet, A. J. *et al.* Youth with acquired brain injury in the Netherlands: A multi-centre study. *Brain Inj.* **27**, 843–849 (2013).
18. Keenan, H. T. & Bratton, S. L. Epidemiology and outcomes of pediatric traumatic brain injury. *Dev. Neurosci.* **28**, 256–263 (2006).
19. Haarbauer-Krupa, J. *et al.* Fall-related traumatic brain injury in children ages 0–4 years. *J Saf. Res* **70**, 127–133 (2019).
20. Dodds, N. *et al.* Evaluating the impact of cycle helmet use on severe traumatic brain injury and death in a national cohort of over 11000 pedal cyclists: A retrospective study from the NHS England Trauma Audit and Research Network dataset. *BMJ Open* **9**, 1–7 (2019).
21. Foley, J. *et al.* Cycling related major trauma in Ireland. *Injury* 21–26 (2019) doi:10.1016/j.injury.2019.11.025.
22. Forbes, A. E., Schutzer-Weissmann, J., Menassa, D. A. & Wilson, M. H. Head injury patterns in helmeted and non-helmeted cyclists admitted to a London Major Trauma Centre with serious head injury. *PLoS One* **12**, 1–9 (2017).

23. Carone, L., Ardley, R. & Davies, P. Cycling related traumatic brain injury requiring intensive care: association with non-helmet wearing in young people. *Injury* **50**, 61–64 (2019).

24. Figaji, A. A. Anatomical and physiological differences between children and adults relevant to traumatic brain injury and the implications for clinical assessment and care. *Front. Neurol.* **8**, 1–15 (2017).

25. Petranovich, C. L. *et al.* From Early Childhood to Adolescence. *J. Head Trauma Rehabil.* **80045**, 1 (2020).

26. Le Fur, C. *et al.* Executive functions and attention 7 years after severe childhood traumatic brain injury: Results of the Traumatisme Grave de l'Enfant (TGE) cohort. *Ann. Phys. Rehabil. Med.* (2019) doi:10.1016/j.rehab.2019.09.003.

27. Sarnaik, A. *et al.* Age and Mortality in Pediatric Severe Traumatic Brain Injury : Results from an International Study. **3456789**, 302–313 (2018).

28. Cheng, P., Li, R., Schwebel, D. C., Zhu, M. & Hu, G. Traumatic brain injury mortality among U.S. children and adolescents ages 0–19 years, 1999–2017. *J. Safety Res.* **72**, 93–100 (2020).

29. Keenan, H. T., Presson, A. P., Clark, A. E. & Cox, C. S. after Traumatic Brain Injury in Young Children : Are Infants More Vulnerable Than Toddlers ? **292**, 282–292 (2019).

30. Rogers, S. & Trickey, A. W. Classification of traumatic brain injury severity using retrospective data. *J. Nurs. Educ. Pract.* **7**, 23 (2017).

31. Steyerberg, E. W. *et al.* Predicting Outcome after Traumatic Brain Injury : Development and International Validation of Prognostic Scores Based on Admission Characteristics. *PLoS Med.* **5**, e165 (2008).

32. Maas, A. I. R., Hukkelhoven, C. W. P. M., Marshall, L. F. & Steyerberg, E. W. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: A comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery* **57**, 1173–1181 (2005).

CHAPTER 3

Diagnostic value of emergency medical services provider judgement in the identification of head injuries among trauma patients

CHAPTER 3

Title: Diagnostic value of emergency medical services provider judgement in the identification of head injuries among trauma patients.

Printed in: European Journal Neurology

Cite as: van Rein EAJ, Jochems D, Lokerman RD, van der Sluijs R, Houwert RM, Lichtveld RA, et al. Diagnostic value of emergency medical services provider judgement in the identification of head injuries among trauma patients. Eur J Neurol [Internet]. 2018;1–7. Available from: http://doi.wiley.com/10.1111/ene.13804

Author list: Eveline van Rein[a] (MD, PhD), Denise Jochems[a] (MD), Rogier van der Sluijs[a] (MD), Roderick M. Houwert[a,b] (MD, PhD), Rob A. Lichtveld[c] (MD, PhD), Michael A. van Es[d] (MD, PhD), Luke P.H. Leenen[a] (MD, PhD), Mark van Heijl[a,e] (MD, PhD)

[a] Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

[b] Trauma Centre Utrecht, Utrecht, The Netherlands

[c] Regional Ambulance Facilities Utrecht, Bilthoven, The Netherlands

[d] Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands

[e] Department of Surgery, Dieakonessenhuis Utrecht|Zeist|Doorn, Utrecht, The Netherlands

ABSTRACT

Introduction: Previous studies have reported that many patients with a severe head injury are not transported to a higher-level trauma centre where the necessary round-the-clock neurosurgical care is available. The aim of this study was to analyse the diagnostic value of emergency medical services (EMS) provider judgement in the identification of a head injury.

Methods: In this multicentre cohort study, all trauma patients aged 16 years and over who were transported with highest priority to a trauma centre were evaluated. The diagnostic value of EMS provider judgement was determined using an Abbreviated Injury Scale score of _1 in the head region as reference standard.

Results: A total of 980 (35.4%) of the 2766 patients who were included had a head injury. EMS provider judgement (Abbreviated Injury Scale score _1) had a sensitivity of 67.9% and a specificity of 87.7%. In the cohort, 208 (7.5%) patients had a severe head injury. Of these, 68% were transported to a level I trauma centre.

Conclusion: Identification of a head injury on-scene is challenging. EMS providers could not identify 32% of the patients with a head injury and 21% of the patients with a severe head injury. Additional education, training and a supplementary protocol with predictors of a severe head injury could help EMS providers in the identification of these patients.

INTRODUCTION

Traumatic head injury is a leading cause of death and life-long disabilities due to trauma worldwide [1,2]. It can affect the brain in multiple, complex ways, leading to long-term functional, physical, emotional, cognitive and social problems. Pre-hospital emergency care on scene and inpatient care at the hospital are crucial to patient outcomes. At the start of the chain of trauma care are the emergency medical services (EMS). The EMS providers start initial care and decide on the most appropriate hospital for the patient, i.e. a higher-level or lower-level trauma centre. Patients with a severe head injury require immediate evaluation and admission to trauma centres with access to neurosurgical care [3]. Neurosurgical care is available in different types of trauma centres, however, higher-level trauma centres are usually the only facilities that provide round-the-clock neurosurgical care [4]. These are level I and II trauma centres in the USA [5], whereas in other countries, such as the Netherlands, only level I trauma centres are capable of providing adequate care for patients with a severe head injury [6]. Treatment at higher-level trauma centres is associated with lower mortality and better outcomes in patients with a severe head injury [7,8]. Previous studies show that many patients with severe head trauma are not transported to a higher-level trauma centre [9-13]. The ability of EMS providers to accurately identify patients with a head injury is unknown. Therefore, the aim of this study was to analyse the diagnostic value of EMS provider judgement in the identification of a head injury.

MATERIALS AND METHODS

Study design and setting

In this multicentre cohort study, data from all trauma patients aged 16 years and over who were transported to a trauma centre in the Central Netherlands were prospectively collected. Patients were included from January 2015 to December 2016. In the Central Netherlands region, one level I trauma centre is fully equipped to provide the appropriate level of care 24 h per day for patients with severe head injury [6]. The region has nine level II or III trauma centres. The region covers 535 square miles and has 1.2 million residents. EMS providers use the National Protocol for Ambulance Services to identify severely injured patients (Fig. 1) [14]. Patients who were transported to hospitals outside the region were excluded. The present study protocol was judged by the Medical Ethical Committee of the University Medical Centre Utrecht as not subject to the Medical Research Involving Human Subjects Act.

Data sources

Data were collected from the ambulance services electronic records, institutional trauma registry and electronic medical records. Patient consent was not required as this was a retrospective study reviewing medical records, with no more than minimal risk to the participants and in no way affecting their treatment. Pre-hospital data from the ambulance services included: patient demographics, vital parameters, description of trauma mechanism and physical examination data on site, including whether a head injury was suspected. The Dutch National Trauma Database registered injuries for all patients admitted to a trauma centre. For patients discharged from the emergency department, data were extracted from the electronic patient documentation. The injuries were coded by trained data managers using the Abbreviated Injury Scale (AIS) 2005, update 2008. In addition, hospital data included receiving hospital, admission status and mortality.

Injury severity

The AIS is an anatomical coding system to classify injuries, including the body region, type of anatomical structure and severity of the injury. Six levels of injury severity exist: an AIS score of 1 is a minor injury (e.g. minor concussion) and an AIS score of 6 is the maximum score (an unsurvivable injury). Injuries with an AIS score ≥3 are considered to be severe injuries (e.g. skull base fracture, cerebral haematoma or basilar artery laceration) [15].

Outcomes and definitions

The diagnostic value of EMS provider judgement in the identification of a head injury was determined using the ambulance reports as index test. Any description of a head injury was considered to be a suspicion of a head injury. The reference standard was the head injury diagnosed at the trauma centre, defined as any injury with an AIS score of ≥1 in the head region. Any description of a head injury in the ambulance reports, combined with a head injury with an AIS score of ≥1 diagnosed at the hospital was considered to be a correct suspicion of a head injury. The diagnostic value in the identification of a severe head injury (AIS score ≥3) was determined in a similar fashion, i.e. any description of a head injury in the ambulance reports, combined with a head injury with an AIS score of ≥3 diagnosed at the hospital was considered to be a correct suspicion of a head injury. When no head injury was described in the ambulance reports, but a head injury with an AIS score of ≥1 was diagnosed at the hospital, it was considered to be an unsuspected head injury.

Statistical analysis

Means with SD were used to describe continuous variables. Frequencies with percentages were used for nominal and ordinal variables. To compare baseline characteristics and assess possible independence or association between patients with

and without a (severe) head injury, the Mann–Whitney *U*-test was performed for continuous variables, as these variables were not all normally distributed. The chi-squared test was used for nominal variables and Fisher's exact test was used for nominal variables that occurred in ≤5 cases. $P < 0.05$ was considered statistically significant. Frequencies and percentages were also used to describe EMS provider judgement in the identification of a head injury, stratified by AIS scores. The diagnostic value of EMS provider judgement in the identification of a head injury was assessed using sensitivity and specificity. All statistical analyses were performed using SPSS v24 (IBM Corp., Chicago, IL, USA).

RESULTS

Study population

In total, 3658 trauma patients were transported with highest priority by the ambulance services of the Central Netherlands. A total of 981 patients were excluded from this study because they were transported outside the region and/or were under the age of 16 years. Excluding these patients led to the inclusion of 2766 patients. The mean age was 49 22 years, 1605 (58.0%) were male and 1115 (40.3%) were admitted to a hospital (Table 1).

Characteristics of patients with a head injury

In this cohort, 980 (35.4%) patients had a head injury (AIS score _1 in the head region). Among these patients, 666 (68.0%) had an injury to another body region and 332 (33.9%) had an injury to multiple body regions in addition to a head injury. A severe head injury (AIS score ≥3 in the head region) was diagnosed in 208 (21.2%) patients. Of these, 177 (85.1%) had in injury to another body region and 116 (55.8%) had an injury to two or more body regions in addition to a head injury. A total of 141 (67.8%) patients with a severe head injury were transported to a level I trauma centre; patients aged 16–64 years were more often transported to a level I trauma centre (71.8%) compared with patients aged 65 years or older (62.6%).

Diagnostic value of emergency medical services provider judgement

Emergency medical services provider judgement in the identification of a head injury (AIS score ≥1) had a sensitivity of 67.9% (95% confidence interval, 64.9–70.7) and a specificity of 87.7% (95% confidence interval, 86.1–89.2). The patients with an unsuspected head injury had significant differences in vital signs, mechanisms of injury and injury types compared with patients with a suspected head injury. Among the patients with an unsuspected head injury, 72.1% had an injury to another body region

(AIS score ≥1). With higher AIS scores, a higher percentage of the head injuries were suspected (Table 2). However, 20.7% of severe head injuries were not suspected by the EMS provider. In 25.6% of these patients, EMS providers suspected an injury to the face and in 20.9% an injury to the extremities. The types of head injuries that were missed most often were as follows: cerebral haematomas, subdural bleedings and epidural bleedings, especially those without any injuries visible from the outside, such as abrasions, lacerations or contusions. In the group of patients with a head injury with an AIS score of 5, a head injury was not suspected in one patient (5.3%). In this case, cardiopulmonary resuscitation was applied and the EMS providers reported that no injuries were seen. Among the patients with an unsuspected severe head injury, 21 (48.8%) were transported to a level I trauma centre.

DISCUSSION

This is the first study to evaluate the diagnostic value of the pre-hospital identification of head injuries by EMS providers of the ground ambulance. In this study, 35% of the included trauma population suffered from a head injury. The EMS providers' prehospital assessment of head injury, as documented in the ambulance reports, had a sensitivity of 68% and a specificity of 88%. Among the patients with a head injury, 21% suffered from a severe head injury. In this group, the EMS providers suspected a head injury in 79% and 68% were transported to a level I trauma centre.

Emergency medical services provider judgement plays an essential role in the pre-hospital trauma triage process [16,17]. The EMS providers must assess the injury severity and act accordingly. The EMS providers' pre-hospital assessment had a high specificity, which might be partly explained by the low pre-test probability of a head injury. However, identifying a head injury is challenging as shown by the relatively low sensitivity. Previous studies showed that the vital signs are often not affected and may change over time. Patients suffering a head injury from low-risk mechanisms of injury might present to the EMS providers with minimal symptoms, but develop alarming symptoms hours or days later [18–22]. In this study, most patients with a head injury had a Glasgow Coma Scale (GCS) score between 12 and 15. However, presenting symptoms indicative of a head injury might not be recognized as a deviation from the patients' regular behaviour or might be attributed to intoxication [23]. Also, additional injuries to other body regions could distract attention from the head injury. Almost 40% of the patients who were not suspected of having a head injury had injuries to one of the extremities. EMS providers might have had their attention drawn to these more prominent injuries, failing to recognize or report the head injury.

Worldwide, 26–67% of patients with a severe head injury are not transported to a higher-level trauma centre [9–11,20,24]. The percentage depends greatly on the inclusion criteria, i.e. selection in trauma patients or trauma centres. For example, including only patients admitted to higher-level trauma centres leads to an underestimation of the undertriage rate, as the undertriaged patients are not included. In this study, one in three patients

was not transported to a level I trauma centre, which could be due to the currently used triage protocol. Although the triage protocol in the Netherlands includes criteria that implicate a severe head injury (e.g. GCS score <9 or anisocoria), the suspicion of a severe head injury is not a specific indication to transport a patient to a level I trauma centre. The Brain Trauma Foundation recommends transport of patients with a severe head injury to higher-level trauma centres, as this improves chances of survival [3]. Pre-hospital triage of these patients might improve with additional education, training and a supplementary or integrated protocol.

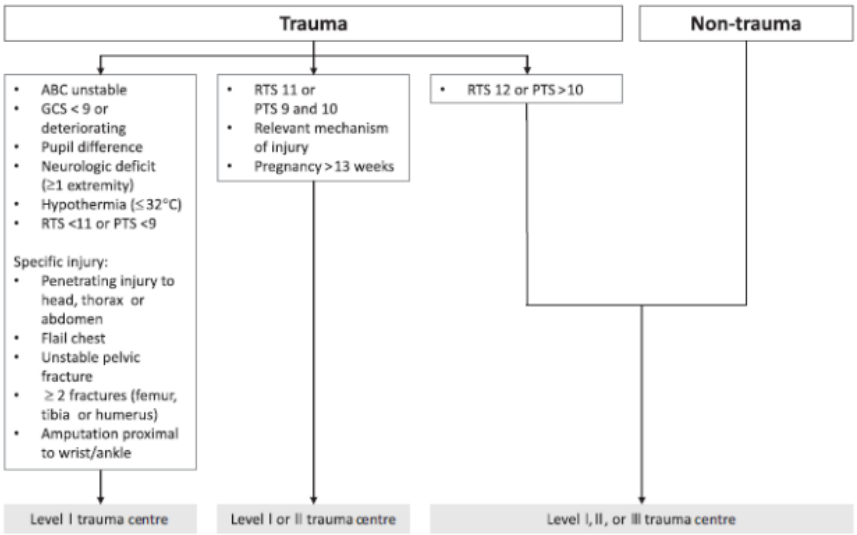
In the supplementary protocol, pre-hospital predictors could help in the identification of patients with a severe head injury. Some variables, such as age and GCS score, might be indicative of a severe head injury, as these differed significantly among patients with a severe head injury. However, more data are necessary for an in-depth analysis to develop and validate prediction models for severe head injuries as a supplementary protocol. Multiple studies show that many severely injured elderly patients are not transported to a higher-level trauma centre, especially those with a severe head injury [10–13,25]. As injuries in elderly patients are increasing in frequency, are more difficult to recognize and carry a higher mortality rate compared with those in the young, age is an important actor to consider [26–28]. Other factors that are easy to assess in the pre-hospital setting should also be considered, e.g. the AVPU (alert, voice, pain, unresponsive) and GCS score. The AVPU has been suggested as a useful measure due to its simplicity. However, it has a relatively high inter-rater reliability and it is open to question whether the four different states could be easily differentiated by EMS providers [29,30]. Unfortunately, the AVPU was not documented in the ambulance reports, so could not be evaluated in this study and its use in the pre-hospital setting has not been studied. The GCS score is considered to be a significant and reliable indicator for a severe head injury by the Brain Trauma Foundation [3]. Previous studies found that the motor component of the GCS was just as predictive as the full GCS when assessing the AIS score [31] and survival [32,33]. Therefore, the motor component of the GCS might be more suitable for incorporation in the supplementary protocol.

The study is limited by the information available in the ambulance reports. It is not mandatory for the EMS providers to report the injury severity or a suspected diagnosis. However, they have to report to what body region they suspect an injury and have the option to describe the injuries or suspected diagnosis. With this information, the diagnostic accuracy in the identification of a head injury could be determined, but the accuracy of EMS provider judgement on injury severity could not. Secondly, factors influencing EMS provider judgement, such as mechanism of injury, education and patient population, could be different for other countries. Accordingly, the diagnostic value of EMS provider judgement might vary for other countries. Lastly, outcome data were not available for this study and therefore the result of the missed head injuries could not be analysed. Future studies should be performed to gain further insight into the EMS provider judgement in the prehospital trauma triage process. A supplementary protocol in the form of a prediction model for patients at risk of a severe head injury could be developed to aid EMS providers in the identification of patients with a severe head injury.

CONCLUSIONS

The identification of a head injury on-scene is challenging. The EMS providers could not identify 32% of the patients with a head injury and 21% with a severe head injury. To improve patient outcomes, correct and timely identification of these patients is crucial. Extra education and training of EMS providers could improve the recognition of patients with a severe head injury. Additionally, a supplementary protocol with predictors of a severe head injury could help EMS providers in the identification of these patients.

Figure 1 National field triage protocol of the Netherlands.



GCS= Glasgow Coma Scale; PTS= Pediatric Trauma Score; RTS= RevisedTrauma Score

Table 1. Baseline variables				
	ALL Patients	**Head AIS score ≥1**	**Head AIS score ≥1 not suspected**	**Head AIS score ≥3**
DEMOGRAPHICS				
Age (years)	49.0 (22.0)	53.8 (22.0)*	50.2 (23.2)**	57.7 (21.4)***
Male gender	1605 (58.0)	555 (56.6)	189 (60.0)	111 (53.4)
Use of oral anticoagulants	132 (4.8)	79 (8.1)*	22 (7.0)	12 (5.8)
Alcohol use	341 (12.3)	165 (16.8)*	55 (17.5)	26 (12.5)
Drug use	22 (0.8)	7 (0.7)	2 (0.6)	1 (0.5)
VITAL SIGNS[a]				
Systolic blood pressure (mmHg)	140.5 (26.2)	142.6 (27.4)*	138.7 (25.4)**	144.7 (29.2)***
Diastolic blood pressure (mmHg)	85.3 (17.9)	85.9 (18.3)	84.5 (17.9)	88.4 (19.2)***
Puls	83.5 (21.2)	84.4 (22.5)	83.5 (20.9)	84.6 (25.0)
Respiratory rate	16.3 (4.2)	16.1 (4.2)	16.1 (4.4)	16.4 (4.7)
Oxygen saturation (%)	96.8 (3.7)	96.3 (4.0)*	96.2 (4.5)	95.4 (4.5)***
Glasgow coma scale score	14.4 (1.8)	13.7 (2.6)*	14.5 (1.5)**	11.8 (4.0)***
Eyes	3.8 (0.6)	3.7 (0.8)*	3.8 (0.5)**	3.1 (1.2)***
Motor	5.9 (0.7)	5.7 (0.9)*	5.9 (0.5)**	5.1 (1.6)***
Verbal	4.7 (0.8)	4.4 (1.1)*	4.7 (0.7)**	3.6 (1.6)***
MECHANISM OF INJURY				
Fall >2m	157 (5.7)	73 (7.4)*	25 (7.9)	20 (9.6)***
Fall ≥5m or ≥3x	133 (84.7)	67 (91.8)*	20 (80.0)	16 (80.0)***
body length	24 (15.3)	6 (8.2)	5 (20.0)**	4 (20.0)
Fall from stairs	243 (8.8)	129 (13.2)*	34 (10.8)	26 (12.5)***
1-10 steps	146 (60.1)	78 (60.5)*	18 (52.9)	21 (80.8)***
>10 steps	97 (39.9)	51 (39.5)*	16 (47.1)	5 (19.2)***
Motor vehicle accident >65km/hr	154 (5.6)	30 (3.1)*	16 (5.1)**	5 (2.4)***
Motorcycle accident >32km/hr	93 (3.4)	17 (1.7)*	10 (3.2)**	3 (1.4)
Car vs pedestrian impact >10km/hr	47 (1.7)	25 (2.6)*	6 (1.9)	8 (3.8)***
Car vs bike impact >10km/hr	156 (5.6)	87 (8.9)*	26 (8.3)	17 (8.2)
INJURY CHARACTERISTICS				
Penetrating injury to head	2 (0.1)	2 (0.2)	0 (0)	1 (0.5)
Neurological deficit (≥1 extremitiy)	41 (1.5)	9 (0.9)	4 (1.3)	1 (0.5)
Anisocoria	16 (0.6)	15 (1.5)*	0 (0)**	10 (4.8)***
Symptoms of cerebral contusion or concussion	396 (14.3)	316 (32.2)*	0 (0)**	85 (40.9)***
Agitation	105 (3.8)	59 (6.0)*	11 (3.5)**	29 (13.9)***
Suspected injury in AIS head	881 (31.9)	665 (67.9)*	0 (0)**	165 (79.3)***

CLINICAL CHARACTERISTICS				
ISS	4.7 (6.4)	7.1 (8.1)*	6.1 (7.4)**	18.7 (8.3)***
Destination				
Level I trauma centre	879 (31.8)	393 (40.1)*	128 (40.6)	141 (67.8)***
Level II/III trauma centre	1887 (68.2)	587 (59.9)	187 (59.4)	67 (32.2)
Admission to hospital	1115 (40.3)	393 (40.1)*	171 (54.3)	141 (67.8)***
In-hospital death	46 (1.7)	31 (3.2)*		23 (11.1)***

AIS= Abbreviated Injury Scale; ISS=Injury Severity Score. Systolic blood pressure missed in 5.9%, diastolic blood pressure in 6.1%, pulse in 13.5%, respiratory rate in 6.3%, oxygen saturation in 9.9% and Glasgow Coma Scale in 6.5% of patients. †The first vital signs assessed on scene by the emergency medical services provider. *Significant difference ($P < 0.05$) as compared with patients without a head injury. **Significant difference ($P < 0.05$) as compared with patients with a suspected head injury. ***Significant difference ($P < 0.05$) as compared with patients without a severe head injury. Data are given as mean (SD) and n (%).

Table 2. Number of patients with their Abbreviated Injury Scale (AIS) score

AIS score	HEAD INJURY SUSPECTED	NO HEAD INJURY SUSPECTED	TOTAL
0	219 (12.3)	1567 (87.7)	1786
1	428 (63.2)	249 (36.8)	677
2	72 (75.8)	23 (24.2)	95
3	91 (76.5)	28 (23.5)	119
4	56 (80.0)	14 (20.0)	70
5	18 (94.7)	1 (5.3)	19

Data are given as n (%) and n

REFERENCES

1. Centers for Disease Control and Prevention. Traumatic Brain Injury in the United States: Fact Sheet. *Atlanta: National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention*, (2016).

2. Maas AIR, Stocchetti N & Bullock R. Moderate and sev- ere traumatic brain injury in adults. *Lancet Neurol.* 7, 728-741 (2008).
3. Badjatia N *et al.* Guidelines for prehospital management of traumatic brain injury, 2nd edition. *Prehosp Emerg Care.* **12**, S1-S52 (2008).
4. Mans S, Reinders Folmer E, de Jongh MAC & Lansink KWW. Direct transport versus inter hospital transfer of severely injured trauma patients. *Injury.* **47**, 26-31 (2016).
5. Sasser SM *et al.* Guidelines for field triage of injured patients: recommendations of the national expert panel on field triage, 2011. *MMWR Recomm Rep.* **61**, 1-20 (2012).
6. Spijkers ATE, Meylaerts SAA & Leenen LPH. Mortality decreases by implementing a level I trauma center in a Dutch hospital. *J Trauma.* **69**, 1138-1142 (2010).
7. Patel HC, Menon DK, Tebbs S, Hawker R, Hutchinson PJ & Kirkpatrick PJ. Specialist neurocritical care and out- come from head injury. *Intensive Care Med.* **28**, 547-553 (2002).
8. Bulger E *et al.* Management of severe head injury: institutional variations in care and effect on outcome. *Crit Care Med.* **30**, 1870-1876 (2002)..
9. Faul M, Xu L, & Sasser SM. Hospitalized traumatic brain injury: low trauma center utilization and high interfacil- ity transfers among older adults. *Prehosp Emerg Care.* **20,** 594-600 (2016).
10. Flottemesch TJ *et al.* Age-related disparities in trauma center access for severe head injuries following the release of the updated Field Triage Guidelines. *Acad Emerg Med.* **24,** 447-457 (2016).

11. Scheetz LJ. Comparison of type and severity of major injuries among undertriaged and correctly triaged older patients. *J Emerg Med.* **43,** 4020-1028 (2012).
12. Voskens FJ *et al.* Analysis of the accuracy of prehospital triage in selecting severely injured trauma patients. *JAMA Surg.* **153,** 322-327 (2017).
13. Fakhry SM, Ferguson PL, Johnson EE & Wilson DA. Hospitalization in low-level trauma centres after severe traumatic brain injury: review of a population-based emergency department data base. *Brain Inj.* **31,** 1486-1493 (2017).
14. Ambulance Zorg Nederland. Landelijk Protocol Ambulancezorg (LPA). Zwolle: Stichting Landelijke Ambu- lance en Meldkamer Protocollen. (LAMP), 2007.
15. Salottolo K, Carrick M, Steward Levy A, Morgan BC, Slone DS & Bar-Or D. The epidemiology, prognosis, and trends of severe traumatic brain injury with presenting Glasgow Coma Scale of 3. *J Crit Care.* **38,** 197-201 (2017).
16. Cox S, Morrison C, Cameron P & Smith K. Advancing age and trauma: triage destination compliance and mor- tality in Victoria. Australia. *Injury*, **45,** 1312–1319 (2014).
17. Newgard CD *et al.* Out-of-hospital decision making and factors influencing the regional distribution of injured patients in a trauma sys- tem. *J Trauma.* **70,** 1345–1353 (2011).
18. Chambers J, Cohen SS, Hemminger L, Prall JA & Nichols JS. Mild traumatic brain injuries in low-risk trauma patients. *J Trauma,* **6,** 976–980 (1996).
19. Borg J *et al.* Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Trau- matic Brain Injury. *J Rehabil Med*, **43(suppl),** 61-75 (2004).
20. Fuller G, Lawrence T, Woodford M & Lecky F. The accuracy of alternative triage rules for identification of significant traumatic brain injury: a diagnostic cohort study. *Emerg Med J.* **31,** 914–919 (2014).
21. Najafi Z, Zakeri H & Mirhaghi A. The accuracy of acuity scoring tools to predict 24-h mortality in traumatic brain injury patients: a guide to triage criteria. *Int Emerg Nurs,* **36,** 27-33 (2018).

22. Bossers SM *et al.* Discrepancy between the initial assessment of injury severity and post hoc determination of injury severity in patients with apparently mild traumatic brain injury: a retrospective multicenter cohort analysis. *Eur J Trauma Emerg Surg.* **44,** 889-896 *(*2018).
23. Barton DJ, Tift FW, Cournoyer LE, Vieth JT & Hudson KB. Acute alcohol use and injury patterns in young adult prehospital patients. *Prehosp Emerg Care*. **20,** 206-2011 (2016).
24. Landelijke Traumaregistratie 2011–2015: Rapportage Nederland. Utrecht: Landelijk Netwerk Acute Zorg, (2016).
25. Chang DC, Bass RR, Cornwell EE & MacKenzie EJ. Undertriage of elderly trauma patients to state- designated trauma centers. *Arch Surg.* **143,** 776-782 (2008).
26. Maas AIR *et al.* Traumatic brain injury: integrated approaches to improve preven- tion, clinical care, and research. *Lancet Neurol*, **16,** 987-1048 (2017).
27. Hukkelhoven CW *et al.* Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. *J Neurosurg.* **99,** 666-673 (2003).
28. Mushkudiani NA *et al.* Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. *J Neurotrauma.* **24,** 259-269 (2007).
29. Wasserman EB *et al.* Identification of a neurologic scale that optimizes EMS detection of older adult traumatic brain injury patients who require transport to a trauma center. *Prehosp Emerg Care,* **19,** 202-212 (2015).
30. Gill MR, Martens K, Lynch EL, Salih A & Green SM. Interrater reliability of 3 simplified neurologic scales applied to adults presenting to the emergency depart- ment with altered levels of consciousness. *Ann Emerg Med,* **49,** 403-407 (2007).
31. Ross SE, Leipold C, Terregino C & O'Malley KF. Efficacy of the motor component of the Glasgow Coma Scale in trauma triage. *J Trauma,* **45,** 42-44 (1998).

32. Beskind DL *et al.* A comparison of the prehospital motor component of the Glasgow coma scale (mGCS) to the prehospital total GCS (tGCS) as a prehospital risk adjustment measure for trauma patients. *Prehosp Emerg Care,* **18,** 68-75 (2014).
33. Kupas DF, Melnychuk EM & Young AJ. Glasgow coma scale motor component ("patient does not follow com- mands") performs similarly to total Glasgow coma scale in predicting severe injury in trauma patients. *Ann Emerg Med,* **68,** 744-750 (2016).

CHAPTER 4

The effect of prehospital tranexamic acid on outcome in polytrauma patients with associated severe brain injury

CHAPTER 4

Title: The effect of prehospital tranexamic acid on outcome in polytrauma patients with associated severe brain injury.

Epub ahead of print: European Journal of Trauma and Emergency Surgery

Author list: Karlijn J.P. van Wessem[a] (MD, PhD), Denise Jochems[a] (MD), Falco Hietbrink (MD, PhD), Luke P.H. Leenen[a] (MD, PhD).

[a] Department of Trauma Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Introduction: Tranexamic acid (TXA) has shown to be beneficial in selected patients with hemorrhagic shock. Recently, TXA has gained interest in isolated traumatic brain injury (TBI) patients with variable results. There is limited data on TXA in polytrauma with associated TBI. This study investigated the role of TXA in severely injured patients with associated severe TBI.

Material and Methods: A 7.5-year prospective cohort study was performed to investigate the relation between prehospital TXA and mortality in consecutive trauma patients with associated severe TBI(Abbreviated Injury Scale (AIS)head>3) admitted to a Level-1 Trauma Center ICU. Indication for prehospital TXA administration was (suspicion of) hemorrhagic shock, and/or systolic blood pressure (SBP)<90mmHg. Demographics, data on physiology, resuscitation, and outcomes were prospectively collected.

Results: Two hundred thirty-four patients (67% males) with median age of 49 years and ISS 33 (98% blunt injuries) were included. Thirteen patients (6%) developed thromboembolic complications, mortality rate was 24%. Fifty-one percent of patients received prehospital TXA. TXA-patients were younger, had more deranged physiology on arrival, and received more crystalloids and blood products<24h. There was however no difference in overall outcome between TXA-patients and no-TXA patients.

Conclusions: TXA patients who were much older. Thrombo-embolic complication rate was low. Prehospital tranexamic acid has no evident effect on outcome in polytrauma patients with associated critical brain injury.

INTRODUCTION

Traumatic brain injury (TBI) has become the leading cause of death after trauma in the western world [1]. Death by TBI is often caused by acute intracranial bleeding which often continues for several hours after injury. Ongoing intracranial bleeding can lead to raised intracranial pressure, brain herniation, and death [2]. Tranexamic acid (TXA) reduces bleeding by inhibiting fibrinolysis [3]. The Clinical Randomization of an Anti-fibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial showed that early administration of TXA in adults who had either significant hemorrhage, hypotension, or who were considered to be at risk of significant hemorrhage after injury resulted in significant improvement in (hemorrhage-caused) mortality [4]. These results have led to liberal TXA administration in trauma patients with hemorrhagic shock. Since TXA might also be beneficial to TBI patients with intracranial bleeds, a sub analysis of CRASH-2 trial was performed investigating the role of TXA in isolated TBI. These data showed a non-significant reduction in hemorrhage growth, fewer focal ischemic lesions and fewer deaths [5]. The subsequent CRASH-3 trial included adults with isolated TBI who were randomized to either TXA or placebo showed a reduced head injury-related death in patients with mild to moderate TBI who received TXA within 3 h after injury [6]. This reduced mortality risk however was not demonstrated in patients with severe head injury [6]. Additionally, pooled CRASH-2 and CRASH-3 trial data showed that TXA reduced early deaths in non-moribund TBI patients regardless of TBI severity [7]. In contrast, several other studies showed no improvement in survival nor in neurologic outcome in patients with moderate to severe TBI although some studies reported a reduction in progression of intracranial hemorrhage after TXA [8-12]. A recent study showed even an increased mortality in patients with severe isolated TBI if TXA was prehospitally administered [13].

In literature, most studies on TXA focused either on patients in hemorrhagic shock or on patients with isolated TBI. In our hospital the vast majority of severely injured patients die of associated traumatic brain injury [1]. Therefore, we conducted a retrospective analysis of prospectively collected data of polytrauma patients with associated moderate to severe TBI to investigate whether prehospital TXA

administration would have an influence on mortality. We hypothesized that TXA administration was not related to mortality.

MATERIALS AND METHODS

Study setting

From November 2013, a 7.5-year prospective population-based cohort study was undertaken to investigate outcomes in severely injured patients admitted to the Intensive Care Unit (ICU) of a major (Level-1) trauma center. Details of the hospital and catchment area were previously described [14]. All consecutive polytrauma patients with associated severe TBI (AIS head >3) who were admitted to the adult ICU were included. Severe TBI was defined as being serious (AIS head 3), severe (AIS head 4), or critical (AIS head 5) [10]. Patients with associated AIS head 6 were excluded since these injuries are generally regarded as unsurvivable. Patients who had AIS head scores based on isolated C-spine injuries were excluded as well since the natural history, pathology and potential impact of these injuries are likely different from true TBI injuries.

ICU admission could be either directly from the emergency department (ED) or postoperatively from the operating room (OR) after urgent surgery. A flowchart of patient inclusion is shown in figure 1.

Data collection

All data were prospectively collected by authors KW and LL and included demographics, shock and resuscitation parameters. Crystalloid and blood products administration including Packed Red Blood Cells(PRBC), Fresh Frozen Plasma(FFP) and Platelets(PLT)) was documented in the first 24 hours after admission. Additionally, prehospital administration of tranexamic acid (TXA) was recorded. Our prehospital protocol recommends administering TXA within 3h of injury for signs of the presence of impending hemorrhagic shock, hypotension (systolic blood pressure <90mmHg), and/or clinical suspicion of major hemorrhage. Prehospital TXA dosage was 1 g bolus, 1 g infusion was repeated over 8 hours at discretion of the treating surgeon and/or

intensivist. In our hospital TXA is not routinely used in (suspicion of) isolated TBI. Denver MOF scores [15] and ARDS Berlin criteria [16] were registered daily up until 28 days or discharge from ICU. Primary outcome was the relation between prehospital TXA administration and in-hospital mortality in severely injured patients with associated severe TBI. Secondary outcome was the relation between prehospital TXA and complications such as inflammatory (ARDS, MODS), thrombo-embolic and/or infectious complications.

Ethical approval

The local ethics committee approved this prospective observational study and waived consent (reference number WAG/mb/16/026664).

Statistical analysis

All statistical analysis were performed using IBM SPSS Statistics, version 25.0 (Armonk, NY, USA). Results are presented as median and interquartile range (IQR). Kruksal-Wallis was used to test continuous variables for equality between patients who received TXA and patients who did not. Categorical data were tested with either Chi-Square or Fisher's exact test based on the number of patients (values less than 6). Variables with univariate statistical significance of less than 0.10 were included in a multivariate logistic regression analysis to identify independent risk factors for mortality and presented as odds ratios and 95% confidence intervals. Kaplan-Meier curves with log rank (Mantel-Cox) test was used to calculate 30-day survival. Statistical significance was defined as $P<0.05$.

RESULTS

Demographics

Two hundred thirty-four severely injured patients (67% male) with a median age of 49 (28-63) years who were admitted to ICU were included. Ninety-eight percent of injuries (n=231) were caused by a blunt mechanism, 63% (n=147) was prehospitally intubated, and median ISS was 33 (27-38) with most severe injuries located in the brain (Abbreviated Injury Scale (AIS) head 4 (3-4) and chest (AIS chest 3 (2-4)). Thirty-eight patients (16%) underwent an urgent laparotomy. Physiology, resuscitation and outcome data are presented in Table 1.

Fifty-one percent of patients (n=120) received prehospital TXA. Median prehospital time was 1:01 (0:57-1:09) h; Consequently, prehospital TXA was administered within an hour after injury. Patients who received prehospital TXA were younger, more often prehospitally intubated, and underwent more often an urgent laparotomy (Table 1). Further, they were more acidotic with higher PaCO2, and lower hemoglobin (Hb) in ED. They received more crystalloids and blood products <24h than patients who did not receive prehospital TXA. There was however no difference in outcome between TXA and no-TXA patients (Table 1). In patients with SBP< 90 mmHg on arrival in ED there was also no difference in outcome between TXA and no-TXA patients (supplemental Table S1).

Fifty-seven (24%) patients died; Fifty (88%) of them died of TBI, 4 (7%) died of respiratory insufficiency, 1(2%) died of cardiac origin, 1(2%) due to MODS, and 1(2%) due to sepsis. Median time to in-hospital death was 7 (3-12) days, only 2 patients died later than 30 days after admission (43 and 120 days respectively). Patients who died were older, more severely injured (mostly more severe brain injury), and had worse physiology with lower Hb on arrival in ED. Further, they received more crystalloids and blood products in the first 24 h after admission. TXA was not related to death. Patients who survived stayed longer in ICU and in hospital and developed more often infectious complications (Table 2). In multivariate analysis only age and AIS head were independent predictors for mortality (Table 3).

Sub analysis per traumatic brain injury severity

When comparing polytrauma patients per brain injury severity (AIS head 3-5), there was (besides the difference in ISS) no difference in demographics, physiology, resuscitation parameters nor in ventilator days, ICU-LOS or H-LOS between the 3 groups. Polytrauma with AIS head 3 developed most often thromboembolic complications, but died less frequently than patients with AIS head 4 or AIS head 5 (Table 4). TBI was the cause of death in all AIS head 5 patients compared to 81% in AIS head 4, and 67% in AIS head 3 (p=0.06, supplemental Table S2).

When analyzing prehospital TXA administration and mortality per AIS head classification no significant difference between TXA and mortality between AIS head groups was observed (p=0.40, Table S3).

Figure 2 shows the relation between prehospital TXA administration and 30-day mortality in polytrauma patients with associated AIS head 3 to 5. There was no difference in survival between TXA and no-TXA patients. Also, there was no difference in 30-day mortality within separate AIS head groups (Figure 2).

DISCUSSION

In this cohort of polytrauma patients with associated severe to critical TBI there was no difference in outcome between patients who received prehospital TXA and those who did not even though TXA patients had a more deranged physiology. This could potentially be interpreted as improved outcome by TXA. However, this should be concluded with caution since none of the patients died of hemorrhage, moreover, if only patients with SBP<90 mmHg in ED were analyzed, there was no difference in morbidity and mortality between patients with and without TXA. Further, patients without TXA did as well as TXA patients despite being 11 years older. This is particularly interesting since age was an independent predictor for mortality in multivariate analysis and physiologic parameters were not.

When analyzing TBI severity in the various subgroups, there was no difference in physiology between the groups, although there was an increased mortality with increasing AIS head. This was confirmed by the fact that AIS head was the largest independent predictor for mortality. There was no difference in 30-day mortality in patients with and without prehospital TXA in the whole population, nor in sub analysis with patients with associated AIS head 3 to 5.

Despite the fact that TXA patients had a more deranged physiology on arrival, there was no difference in outcome, which could be possibly explained by the fact that prehospital transport times in our region are short with prompt resuscitation making the beneficial effects of TXA smaller compared to regions with long transport times and limited resources.

The results of this study are in line with CRASH-2-Intracranial Bleeding Study (IBS), a sub analysis of CRASH-2 in which 270 patients were included who also suffered from TBI (which was defined a GCS<14 and CT head abnormalities compatible with TBI) that also showed no statistical difference in mortality [5]. The CRASH-2 study however also included mild and moderate TBI patients and is therefore not fully comparable to our study population in which only patients with AIShead >3 were included. Several

other studies on isolated TBI patients also demonstrated no clear beneficial effect of TXA [8-12], although data from subgroup analysis of the meta-analysis by Al Lawati et al. suggested that TXA might decrease hematoma expansion [9]. Data from the CRASH-3 trial that included only patients with isolated TBI demonstrated a beneficial effect of early TXA administration in mild and moderate TBI, but this effect was not seen in patients with severe TBI, which was actually the group of patients of interest in our studied population [6].

Our data are also in contrast with the results in the study by Bossers et al. that showed an increased mortality in isolated severe TBI patients who received prehospital TXA [13]. The results of this study however should be interpreted with caution there were some issues regarding confounding by indication and missing data [17].

TXA patients were more often prehospitally intubated with higher PaCO2 and lower pH. In a previous study we suggested that this relative hypoventilation could be associated with TBI resulting in more often prehospital intubation in TBI patients [18]. This was confirmed by the fact that in this current study 63% of patients were prehospitally intubated compared to 50% in a general polytrauma population [18]. Interestingly, there was no relation between prehospital intubation and severity of TBI nor mortality. This suggests that the rationale for prehospital intubation was signs of deranged physiology with associated suspicion of TBI rather than injury severity itself.

In this cohort, patients with serious TBI developed more often thromboembolic complications than severe and critical TBI patients, however there was no correlation with TXA administration. Numbers were too small to draw substantial conclusions, but it might be partly explained by higher survival rates.

To our knowledge, this is the first prospective cohort study describing the effect of TXA on polytrauma patients with combined severe to critical TBI. The indication for prehospital TXA administration in severely injured patients was suspicion of hemorrhagic shock, a rather liberal criterion, which could lead to unlimited administration of TXA. This liberal approach is confirmed by a previous study on

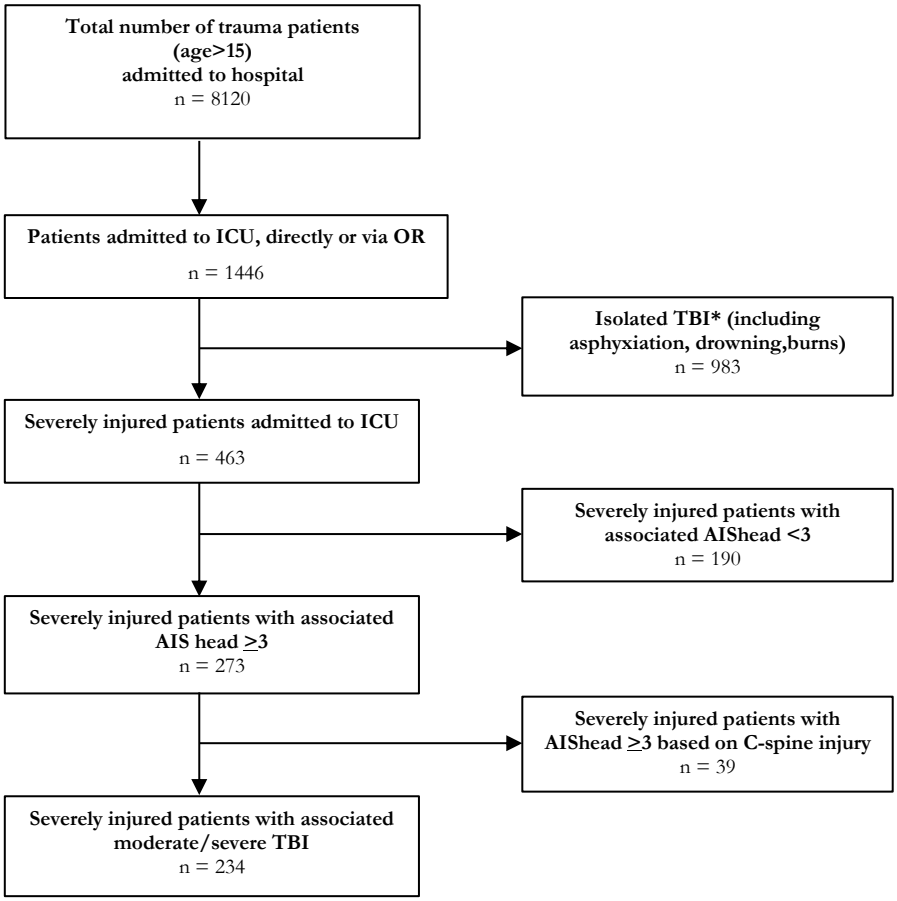
TXA in polytrauma and the fact that half of the studied patients received prehospital TXA even though only 20% was objectively in shock on arrival in ED [18]. None of the patients died of exsanguination. This could be explained by the fact that patients with both impeding exsanguination and associated severe TBI are likely to be deceased prior to arrival in ED. Based on the current data a liberal attitude regarding prehospital TXA in polytrauma patients with associated critical TBI does not demonstrate negative effects on mortality.

A few limitations need to be acknowledged: First of all, this was a retrospective analysis of a single center prospective cohort study with its accompanying limits. This includes confounding by indication and this is very difficult to account for. However, it is unlikely that another Randomized Controlled Trial (RCT) the size of CRASH-2 trial will be conducted any time soon since even with more than 20,000 patients absolute mortality reduction by TXA was low [4]. Despite its limitations a prospective cohort study can add valuable information to that obtained from an RCT and even be as informative as an RCT [19]. Further, one could argue that the number of included patients was fairly low. However, patient numbers from the current study were comparable to the number of included patients to the two other existing studies that included polytrauma with TBI [5,8]. Another limitation is the fact that the treating clinicians were also the researchers, and that no details on comorbidities and (anticoagulant) medication nor any data on prehospital and in-hospital Glasgow Coma Scale and pupillary reactivity were collected.

In this study it was decided to investigate the influence of prehospital TXA on outcome in polytrauma patients with associated severe TBI. No data on in-hospital TXA administration were shown to avoid confusion with too many data in one paper. In a previous study we have demonstrated that median time to TXA administration was an hour after injury [18]. This prompt TXA administration makes the division of prehospital versus in-hospital administration of TXA rather arbitrary and the location of TXA administration less relevant than having TXA administered early after injury. This importance of timing rather than geographical location of TXA administration has been highlighted by others as well [20].

In conclusion, in this cohort of polytrauma patients with associated serious to critical TBI TXA-patients had similar outcome compared to no-TXA patients despite having a more deranged physiology on arrival in ED, although no-TXA patients were 11 years older. There seems to be no obvious detrimental nor beneficial effect in administering prehospital TXA in polytrauma with associated TBI.

Figure 1.



* Isolated traumatic brain injury (TBI) was defined as Abbreviated Injury Score (AIS) head ≥3 and AIS ≤2 or less in other regions

Table 1. Demographics in polytrauma patients with associated severe traumatic brain injury (AIShead 3-5)

	Total population (n=234)	Prehospital TXA (n=120)	No prehospital TXA (n=114)	P-value
Age (years)	49 (28-63)	42 (23-59)	53 (33-65)	0.007*
Male gender	157 (67)	80 (67)	77 (68)	0.89
Blunt MOI	230 (98)	118 (98)	112 (98)	1
Prehospital intubation	147(63)	96 (79)	51 (45)	<0.001*
Urgent laparotomy	38 (16)	26 (22)	12 (11)	0.02*
ISS	33 (27-38)	34 (27-41)	29 (25-38)	0.06
AIS head	4 (3-4)	4 (3-4)	4 (3-5)	0.51
AIS face	1 (0-2)	0 (0-2)	1 (0-2)	0.52
AIS chest	3 (2-4)	3 (2-4)	3 (2-3)	0.35
AIS abdomen	0 (0-2)	0 (0-2)	0 (0-2)	0.37
AIS pelvis/extremities	2 (1-3)	2 (2-3)	2 (0-3)	0.13
AIS external	0 (0-1)	0 (0-1)	0 (0-1)	0.91
SBP_ED (mmHg)	123 (101-142)	120 (100-140)	127 (102-150)	0.07
SBP≤90 mmHg_ED	38 (16)	23 (19)	15 (13)	0.29
Hb_ED (mmol/L)	8.0 (7.2-8.9)	7.6 (7.0-8.4)	8.2 (7.8-9.1)	0.001*
pH_ED	7.31 (7.24-7.36)	7.29 (7.21-7.35)	7.34 (7.28-7.38)	<0.001*
PaC02_ED (mmHg)	46 (42-53)	48 (43-56)	45 (39-49)	<0.001*
BD _ED (mmol/L)	-3.0 (-6.0-0.0)	-3.0 (-7.0--1.0)	-2.0 (-5.0-0.0)	0.04*
PT_ED (sec)	14.4 (12.9-16.4)	14.6 (13.0-17.5)	14.1 (12.5-15.7)	0.06
Resuscitation parameters				
Crystalloids ≤24h (L)	7.2 (5.0-10.0)	7.9 (5.7-10.7)	6.1 (4.4-8.6)	0.001*
PRBC≤24h (U)	0 (0-4)	2 (0-4)	0 (0-4)	0.002*
FFP≤ 24h (U)	0 (0-4)	0 (0-5)	0 (0-3)	0.02*
PLT≤ 24h (U)#	0 (0-1)	0 (0-1)	0 (0-0)	0.02*
Outcome parameters				
Ventilator days	7 (3-12)	7 (3-12)	6 (2-12)	0.59
Ventilator free days	12 (1-19)	13 (1-19)	12 (3-19)	0.93
ICU LOS (days)	8 (3-14)	8 (3-15)	8 (3-14)	0.62
H-LOS (days)	20 (10-34)	20 (9-36)	20 (11-33)	0.59
MODS	36 (15)	19 (16)	17 (15)	0.86
ARDS	5 (2)	3 (3)	2 (2)	1
Infectious complications	98 (42)	49 (41)	49 (43)	0.79
Thrombo-embolic complications	13 (6)	6 (5)	7 (6)	0.78
GOS at discharge	3 (1-3)	3 (1-3)	3 (2-3)	0.4
Mortality	57 (24)	32 (27)	25 (22)	0.45

AIS= Abbreviated Injury Scale; ISS=Injury Severity Score. Systolic blood pressure missed in 5.9%, diastolic blood pressure in 6.1%, pulse in 13.5%, respiratory rate in 6.3%, oxygen saturation in 9.9% and Glasgow Coma Scale in 6.5% of patients. aThe first vital signs assessed on scene by the emergency medical services provider. *Significant difference (P < 0.05) as compared with patients without a head injury. **Significant difference (P < 0.05) as compared with patients with a suspected head injury. ***Significant difference (P < 0.05) as compared with patients without a severe head injury. Data are given as mean (SD) and n (%).

Data are expressed in median (IQR) or absolute numbers (%), *=statistically significant

1 unit of platelets contains 5 donors

MOI=Mechanism of Injury, ISS=Injury Severity Score, AIS=Abbreviated Injury Scale, ED=Emergency Department, SBP=systolic blood pressure, Hb=hemoglobin, PaC02= partial pressure of carbon dioxide in arterial blood, BD=Base Deficit, PT=prothrombin time, PRBC=packed red blood cells, FFP=fresh frozen plasma, PLT=platelets, ICU= Intensive Care Unit, LOS=length of stay, H-LOS=hospital length of stay, MODS=Multiple Organ Dysfunction Syndrome, ARDS=Adult Respiratory Distress Syndrome, GOS=Glasgow outcome score.

Table S1. Outcome of patients who arrived with SBP<90 mmHg in ED.

Outcome paramet	Patients with SBP<90 mmHg (n=38)	Prehospital TXA (n=23)	No prehospital TXA (n=15)	P-value
MODS	9 (24)	7 (30)	2 (13)	0.27
ARDS	0	0	0	
Infectious complications	18 (47)	11 (48)	7 (47)	1
Thrombo-embolic complications	1 (3)	1 (4)	0	1
Mortality	13 (34)	10 (43)	3 (20)	0.18

Data are expressed in absolute numbers (%), *=statistically significant

ED=Emergency Department SBP= systolic blood pressure, MODS=Multiple Organ Dysfunction Syndrome, ARDS=Adult Respiratory Distress Syndrome, TXA=Tranexamic Acid.

Table 2. Comparison of patients who survived and who did not.			
	Survival (n=177)	**Deceased (n=57)**	**P-value**
Age (years)	46 (28-59)	56 (32-73)	0.01*
Male gender	119 (67)	38 (67)	1
Blunt MOI	174 (98)	56 (98)	1
Prehospital intubation	106 (60)	41 (72)	0.12
ISS	29 (26-36)	38 (29-44)	<0.001*
AIS head	4 (3-4)	4 (4-5)	<0.001*
AIS face	0 (0-2)	1 (0-2)	0.57
AIS chest	3 (2-3)	3 (3-4)	0.11
AIS abdomen	0 (0-2)	0 (0-2)	0.02*
AIS pelvis/extremities	2 (1-3)	2 (2-3)	0.35
AIS external	0 (0-1)	0 (0-1)	0.04*
Urgent laparotomy	26 (15)	12 (21)	0.3
SBP_ED (mmHg)	125 (104-142)	120 (93-140)	0.19
SBP≤90 mmHg_ED	25 (14)	13 (23)	0.11
Hb_ED (mmol/L)	8.0 (7.3-9.0)	7.6 (6.5-8.4)	0.04*
pH_ED	7.33 (7.27-7.37)	7.24 (7.18-7.32)	<0.001*
PCO2_ED (mmHg)	46 (41-52)	48 (44-56)	0.02*
BD_ED (mmol/L)	-2.0 (-5.0-0.0)	-6.0 (-9.0--2.0)	<0.001*
PT_ED (sec)	14.0 (12.9-15.8)	14.9 (12.8-18.5)	0.06
Resuscitation parameters			
Prehospital TXA	88 (50)	32 (56)	0.4
Crystalloids ≤24h (L)	6.8 (4.5-9.2)	9.0 (6.1-12.2)	<0.001*
PRBC≤24h (U)	0 (0-4)	2 (0-6)	0.002*
PRBC ≥10 units ≤24h	12 (7)	6 (11)	0.25
FFP≤ 24h (U)	0 (0-4)	2 (0-5)	0.01*
PLT≤ 24h (U)#	0 (0-0)	0 (0-1)	0.03*
Outcome parameters			
Ventilator days	7 (3-12)	6 (3-10)	0.32
Ventilator free days	15 (10-20)	0 (0-1)	<0.001*
ICU LOS (days)	9 (4-15)	7 (3-13)	0.02*
H-LOS (days)	26 (16-37)	7 (3-13)	<0.001*
MODS	25 (14)	11 (19)	0.35
ARDS	4 (2)	1 (2)	1
Infectious complications	84 (47)	14 (25)	0.002*
Thrombo-embolic complications	11 (6)	2 (4)	0.74

Data are expressed in median (IQR) or absolute numbers (%), *=statistically significant
ISS=Injury Severity Score, AIS=abbreviated Injury Scale, ED=Emergency Department, SBP=systolic blood pressure, Hb=hemoglobin, PaC02= partial pressure of carbon dioxide in arterial blood, BD=Base Deficit, PT=prothrombin time, TXA=Tranexamic acid.

Table 3. Independent predictors for mortality.

Variables in the Equation	B Coefficient	P-Value	Odds Ratio	95% C.I.	
				Lower	Upper
Age	,041	,000	1,042	1,020	1,065
AIS head	1,282	,000	3,603	2,119	6,125
Hb_ED	-,016	,260	,984	,956	1,012
BD_ED	-,012	,069	,989	,976	1,001
pH_ED	-,028	,264	,972	,926	1,021
Constant	13,046	,482	463,329,772		

AIS=abbreviated injury scale, Hb=hemoglobin, BD=base deficit, ED=emergency department

Table 4. Demographics, physiology and outcome per AIS head classification				
	AIS head3 (n=82)	**AIS head 4 (n=96)**	**AIS head 5 (n=56)**	**P-value**
Age (years)	49 (29-62)	49 (31-65)	47 (24-62)	0.68
Male gender	53 (65)	65 (68)	39 (70)	0.82
Blunt MOI	80 (98)	94 (98)	56 (100)	0.52
Prehospital intubation	46 (56)	64 (67)	37 (66)	0.29
Urgent laparotomy	15 (18)	18 (19)	5 (9)	0.24
ISS	27 (22-34)	31 (29-40)	38 (35-43)	<0.001*
AIS face	1 (0-2)	1 (0-2)	0 (0-2)	0.3
AIS chest	3 (2-4)	3 (3-4)	3 (2-3)	0.56
AIS abdomen	2 (0-2)	0 (0-2)	0 (0-0)	0.05
AIS pelvis/extremities	2 (2-3)	2 (1-3)	2 (1-3)	0.45
AIS external	0 (0-1)	0 (0-1)	0 (0-1)	0.06
SBP_ED (mmHg)	120 (104-140)	124 (100-142)	129 (99-150)	0.17
SBP≤90 mmHg_ED	11 (13)	16 (17)	11 (20)	0.61
Hb_ED (mmol/L)	8.0 (7.2-9.1)	8.0 (7.3-8.7)	8.2 (7.2-9.1)	0.85
pH_ED	7.32 (7.26-7.38)	7.31 (7.24-7.36)	7.31 (7.23-7.35)	0.42
PaC02_ED (mmHg)	46 (39-54)	46 (43-52)	48 (42-53)	0.13
BD _ED (mmol/L)	-3.0 (-5.3-0.0)	-2.0 (-6.0--1.0)	-3.0 (-7.0-0.0)	0.63
PT_ED (sec)	13.7 (12.9-15.3)	14.9 (13.3-17.0)	14.4 (12.6-16.9)	0.4
Resuscitation parameters				
Prehospital TXA	46 (56)	48 (50)	26 (46)	0.51
Overall TXA	55 (67)	59 (62)	34 (61)	0.67
Crystalloids ≤24h (L)	7.0 (4.3-10.0)	6.9 (5.1-10.4)	7.7 (5.5-9.5)	0.44
PRBC≤24h (U)	0 (0-4)	0 (0-4)	0 (0-4)	0.9
PRBC ≥10 units ≤24h	7 (9)	7 (7)	4 (7)	0.95
FFP≤ 24h (U)	0 (0-4)	0 (0-4)	0 (0-4)	0.27
PLT≤ 24h (U)[#]	0 (0-0)	0 (0-1)	0 (0-1)	0.06
Outcome parameters				
Ventilator days	5 (2-10)	8 (5-14)	6 (2-10)	0.75
Ventilator free days	14 (8-21)	13 (1-20)	2 (0-13)	0.33
ICU LOS (days)	6 (3-12)	10 (5-16)	6 (3-13)	0.11
H-LOS (days)	20 (13-31)	26 (12-40)	16 (4-28)	0.06
MODS	10 (12)	21 (22)	5 (9)	0.06
ARDS	1 (1)	4 (4)	0	0.18
Infectious complications	32 (39)	48 (50)	18 (32)	0.08
Thrombo-embolic complications	9 (11)	0	4 (7)	0.005*
GOS at discharge	3 (3-4)	3 (1-3)	2 (1-3)	<0.001*
Mortality	6 (7)	26 (27)	25 (45)	<0.001*

Data are expressed in median (IQR) or absolute numbers (%), *=statistically significant

1 unit of platelets contains 5 donors

MOI=Mechanism of Injury, ISS=Injury Severity Score, AIS=Abbreviated Injury Scale, ED=Emergency Department, SBP=systolic blood pressure, Hb=hemoglobin, PaC02= partial pressure of carbon dioxide in arterial blood, BD=Base Deficit, PT=prothrombin time, TXA= tranexamic acid, PRBC=packed red blood cells, FFP=fresh frozen plasma, PLT=platelets, ICU= Intensive Care Unit, LOS=length of stay, H-LOS=hospital length of stay, MODS=Multiple Organ Dysfunction Syndrome, ARDS=Adult Respiratory Distress Syndrome, GOS=Glasgow outcome score.

Table S2. Cause of death related to AIS head				
Cause of death	**AIS head 3 (n=82)**	**AIS head 4 (n=96)**	**AIS head 5 (n=56)**	**Total deceased**
TBI	4	21	25	50
Respiratory Insufficiency	1	3	0	4
Sepsis	0	1	0	1
Cardiac	0	1	0	1
MODS	1	0	0	1
Total deceased	6	26	25	57

AIS=abbreviated injury scale, MODS=multiple organ dysfunction syndrome, TBI=traumatic brain injury

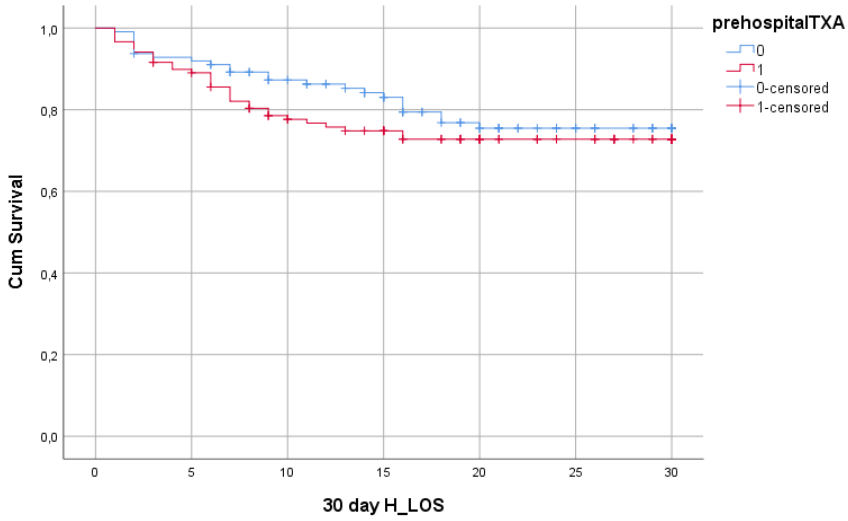
Table S3. Relation between prehospital TXA and mortality per AIS head classification				
AIS head		**Prehospital TXA**	**No prehospital TXA**	**Total nr pts**
3	survival	42	34	76
	deceased	4	2	6
total		**46**	**36**	**82**
4	survival	34	36	70
	deceased	14	12	26
total		**48**	**48**	**96**
5	survival	12	19	31
	deceased	14	11	25
total		**26**	**30**	**56**

Data are shown as absolute numbers

Figure 2.

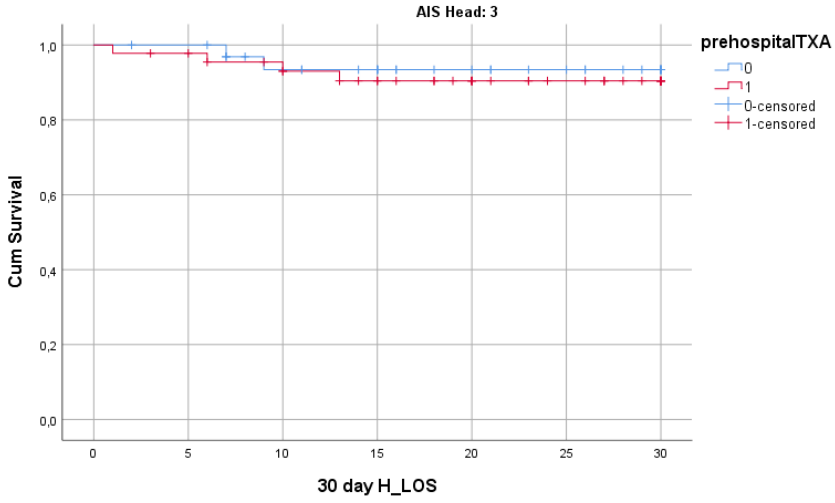
A. Total population

P=0.39



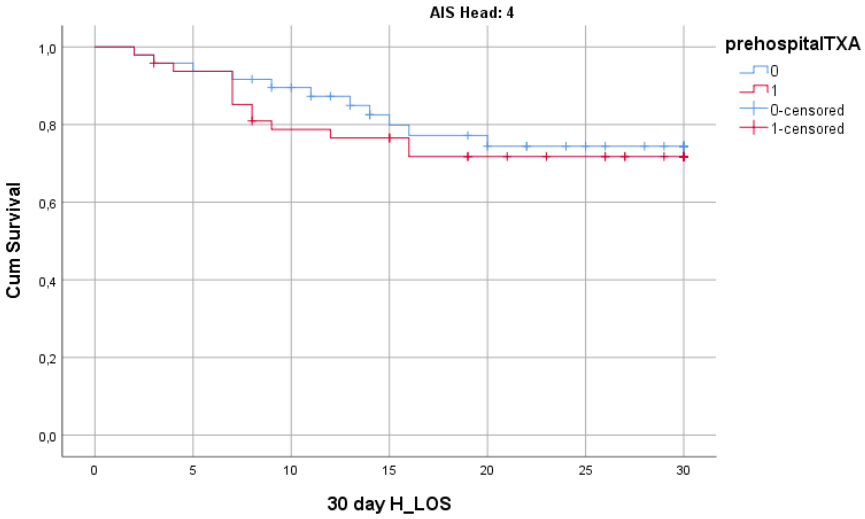
B.

P=0.65



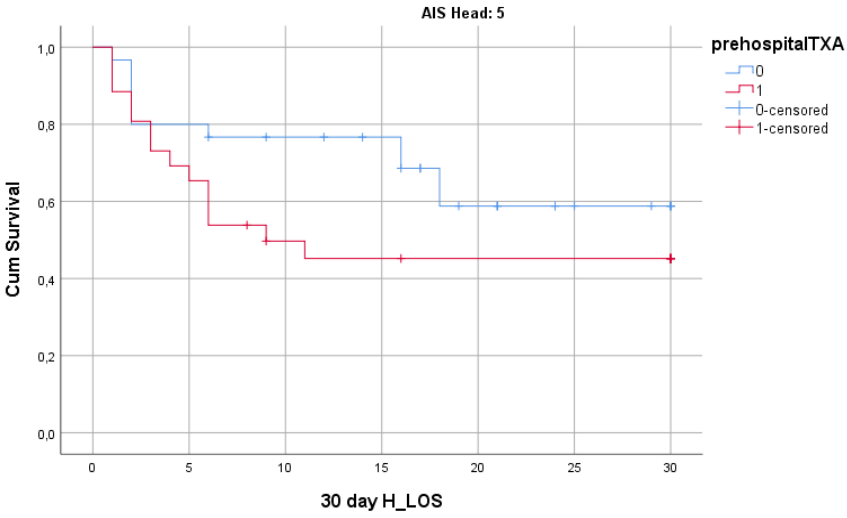
C.

P=0.64


AIS Head: 4
prehospitalTXA
0
1
0-censored
1-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
5
10
15
20
25
30
30 day H_LOS

D.

P=0.15


AIS Head: 5
prehospitalTXA
0
1
0-censored
1-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
5
10
15
20
25
30
30 day H_LOS

REFERENCES

1. Jochems D, Leenen LPH, Hietbrink F, Houwert RM & van Wessem KJP. Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma. *Injury*. **49**, 1661-1667 (2018).
2. Narayan RK, Maas AI, Servadei F, Skolnick BE, Tillinger MN & Marshall LF; Traumatic Intracerebral Hemorrhage Study Group. Progression of traumatic intracerebral hemorrhage: a prospective observational study. *J Neurotrauma,* **25,** 629-639 (2008).
3. Ramirez RJ, Spinella PC & Bochicchio GV. Tranexamic Acid Update in Trauma. *Crit Care Clin,* **33,** 85-99 (2017).
4. CRASH-2 trial collaborators *et al.* Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet.* **376,** 23-32 (2010).
5. CRASH-2 Collaborators *et al.* Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ*. **343,** d3795 (2011).
6. CRASH-3 trial collaborators *et al.* Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet*. **394,** 1713-1723 (2019).
7. CRASH-3 trial collaborators *et al.* Understanding the neuroprotective effect of tranexamic acid: an exploratory analysis of the CRASH-3 randomised trial. *Crit Care*. **24,** 560 (2020).
8. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N & Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC Emergency Medicine*. **13,** 20 (2013).

9. Lawati KA *et al.* Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials. *Intensive Care Med.* **47,** 14-27 (2021).
10. Rowell SE *et al.* Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury. *JAMA.* **324,** 961-974 (2020). Erratum in: *JAMA.* **324,** 1683 (2020).
11. Mojallal F *et al.* The effect of intravenous tranexamic acid on preventing the progress of cerebral hemorrhage in patients with brain traumatic injuries compared to placebo: A randomized clinical trial. *Med J Islam Repub Iran*. **34,** 107 (2020).
12. Yokobori S, Yatabe T, Kondo Y & Kinoshita K; Japan Resuscitation Council (JRC) Neuroresuscitation Task Force and the Guidelines Editorial Committee. Efficacy and safety of tranexamic acid administration in traumatic brain injury patients: a systematic review and meta-analysis. *J Intensive Care.* **8,** 46 (2020).
13. BRAIN-PROTECT collaborators *et al.* Association Between Prehospital Tranexamic Acid Administration and Outcomes of Severe Traumatic Brain Injury. *JAMA Neurol.* (2020) doi: 10.1001/jamaneurol.2020.4596. Epub ahead of print.
14. Gunning AC *et al.* Demographic patterns and outcomes of patients in level-1 trauma centers in three international trauma systems. *World J Surg.* **39,** 2677-2684 (2015).
15. Sauaia A, Moore FA & Moore EE. Early predictors of postinjury multiple organ failure. *Arch Surg.* **129,** 39-45 (1994).
16. Ranieri VM *et al*; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*, **307,** 2526- 2533 (2012).
17. Volovici V & Haitsma IK. Letter: Tranexamic Acid and Severe Traumatic Brain Injury: The Futile Search for Causality? *Neurosurgery.* (2021) doi: 10.1093/neuros/nyab034. Epub ahead of print.

18. van Wessem KJP & Leenen LPH. Does Liberal Prehospital and In-Hospital Tranexamic Acid Influence Outcome in Severely Injured Patients? A Prospective Cohort Study. *World J Surg.* **45,** 2398-2407 (2021).
19. Beks RB *et al.* When observational studies are as helpful as randomized trials: Examples from orthopedic trauma. *J Trauma Acute Care Surg.* **87,** 730-732 (2019).
20. King KL & Balogh ZJ. Invited Commentary: A Decade Older Polytrauma Patients Do As Well Without As the Younger Ones with Tranexamic Acid. *World J Surg.* doi: 10.1007/s00268-021-06253-7. Epub ahead of print.

CHAPTER 5

Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma

CHAPTER 5

Title: Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma.

Published in: Injury

Cite as: Jochems D, Leenen LPH, Hietbrink F, Houwert RM, van Wessem KJP. Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma. Injury [Internet]. 2018;49(9):1661–7. Available from: https://doi.org/10.1016/j.injury.2018.05.012

Author list: Denise Jochems[a] (MD), Falco Hietbrink (MD, PhD), Luke P.H. Leenen[a] (MD, PhD), Roderick M. Houwert[a] (MD, PhD), Karlijn J.P. van Wessem[a] (MD, PhD)

[a] Department of Trauma Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Introduction: Central nervous system (CNS) related injuries and exsanguination have been the most common causes of death in trauma for decades. Despite improvements in haemorrhage control in recent years exsanguination is still a major cause of death. We conducted a prospective database study to investigate the current incidence of haemorrhage related mortality.

Materials and methods: A prospective database study of all trauma patients admitted to an urban major trauma centre between January 2007 and December 2016 was conducted. All in-hospital trauma deaths were included. Cause of death was reviewed by a panel of trauma surgeons. Patients who were dead on arrival were excluded. Trends in demographics and outcome were analysed per year. Further, 2 time periods (2007–2012 and 2013–2016) were selected representing periods before and after implementation of haemostatic resuscitation and damage control procedures in our hospital to analyse cause of death into detail.

Results: 11,553 trauma patients were admitted, 596 patients (5.2%) died. Mean age of deceased patients was 61 years and 61% were male. Mechanism of injury (MOI) was blunt in 98% of cases. Mean ISS was 28 with head injury the most predominant injury (mean AIS head 3.4). There was no statistically significant difference in sex and MOI over time. Even though deceased patients were older in 2016 compared to 2007 (67 vs. 46 years, $p < 0.001$), mortality was lower in later years ($p = 0.02$). CNS related injury was the main cause of death in the whole decade; 58% of patients died of CNS in 2007–2012 compared to 76% of patients in 2013–2016 ($p = 0.001$). In 2007–2012 9% died of exsanguination compared to 3% in 2013–2016 ($p = 0.001$).

Conclusion: In this cohort in a major trauma centre death by exsanguination has decreased to 3% of trauma deaths. The proportion of traumatic brain injury has increased over time and has become the most common cause of death in blunt trauma. Besides on-going prevention of brain injury future studies should focus on treatment strategies preventing secondary damage of the brain once the injury has occurred.

INTRODUCTION

In the 1980s a trimodal distribution of trauma deaths has been described. A first peak included immediate deaths, a second peak was caused by early in-hospital deaths and a third peak represented late in-hospital deaths [1]. Immediate and early deaths were mainly caused by exsanguination and central nervous system (CNS) related injuries whereas late deaths were mostly caused by multiple organ dysfunction syndrome (MODS). In the early 1990s, Sauaia et al. showed there was no longer a trimodal distribution of trauma deaths [2]. The observed shift from prehospital deaths towards early in–hospital deaths was attributed to improved prehospital trauma care. Others confirmed these findings [3,4].

Even though distribution of death has changed over time, cause of death has remained remarkably similar; CNS related injuries and haemorrhage have been the most common causes of death for the last 30 years [5-9]. Many efforts have been made to achieve a decrease in exsanguination. Both prevention interventions includ- ing improved car safety precautions and surgical input for early haemorrhage control (such as damage control surgery, haemo- static resuscitation, and angio- embolisation) have been developed [4-6]. Despite all those improvements death due to haemorrhage is still a major cause of death, although the last decade various reports showed a decline in haemorrhage related death [7,8]. A recent report by Oyeniji et al. showed that 25% of patients in a level-1 trauma centre still die due to haemorrhage [8].

Previous studies from our own institution also demonstrated that CNS and exsanguination were the two major causes of death a decade ago; 59.9% of patients died of CNS related injuries and a relatively low percentage of patients died of haemorrhage (12.9%) [9]. Furthermore, only 4.4% of patients died of MODS [9,10]. Both early and late deaths were predominantly caused by CNS injuries. In recent years we clinically observed a further decline in exsanguination and MODS related deaths [10]. Therefore, we conducted a prospective database study to investigate the current incidence of haemorrhage related mortality. The aim of this study was to investigate current causes of death in trauma patients. We hypothesised that the incidence of death by exsanguination was even lower than previously reported, and that CNS related injuries were the main cause of death in our population.

MATERIALS AND METHODS

Study setting

A prospective database study of all trauma patients admitted to an urban major trauma centre between January 2007 and December 2016 was performed. This major trauma centre is the only Level-1 trauma centre in the province of Utrecht and covers the central region of the Netherlands with a relatively small, but densely populated service area of 1500 square kilometres and approximately 1,3 million residents. The service area for neuro- surgery facilitates 2,1 million residents. Around 1300 trauma patients with full activation of a trauma team are annually admitted. Approximately 375 of them are multiply injured (ISS > 15) [11]. All trauma patients who died after arrival in the emergency department (ED) and prior to discharge from the hospital were included and analysed. Patients who were dead on arrival were not included in the database. In our hospital a panel of trauma surgeons evaluate all trauma deaths and determine cause of death on a weekly basis. In the Netherlands trauma deaths are reported to the coroner, and autopsies are performed at his/hers discretion. In most cases, an autopsy will not be performed. The next of kin of the deceased could also give permission for an autopsy. Annually, autopsies are performed in 5% of trauma deaths in our trauma centre [9].

Data collection

All data were prospectively collected as part of the Dutch Trauma Registry and Quality Assurance Programme. Under Dutch law informed consent is waived for quality assurance initiatives. Data of included trauma deaths included age, sex, Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), mechanism of injury (MOI), cause of death, on-scene intubation, vital signs in ED including first measured systolic blood pressure (SBP), and Glasgow Coma Score (GCS). Further, length of stay in hospital (H-LOS), in ICU (ICU-LOS), and days on the ventilator were calculated. Demographics and outcome measurements were depicted per year. Further, 2 time periods (2007–2012 and 2013–2016) were included in the analysis to further evaluate cause of death. These periods represent periods before and after implementation of haemostatic resuscitation and damage control procedures in our hospital. Haemostatic resuscitation included decreased use of crystalloids, tranexamic acid administration if bleeding was suspected

and balanced 1:1:1 packed red blood cell (PRBC): fresh frozen plasma (FFP): platelet (PLT) ratio. Damage control (orthopaedic) surgery included abbreviated surgery (with abdominal packing and temporary abdominal closure) and external fixation of long bone fractures if patient was acidotic, coagulopathic and hypothermic during surgery.

Statistical analysis

Data were analysed using IBM SPSS Statistics, version 22.0 (Armonk, NY, USA). Graphs were prepared with GraphPad Prism version 7.01 (San Diego, CA, USA). Results are presented as means (SD) or absolute numbers with percentages. Student's t–test was used to compare continuous variables and chi-squared test was used to compare categorical variables. Pearson's correlation coefficient and chi-squared for trend test were used to identify trends by calendar year. Statistical significance was defined as $P < 0.05$.

RESULTS

Demographic data

During the 10-year study period 11,553 trauma patients were admitted in our hospital. A total of 596 patients (5.2%) died. An overview per year is shown in Fig. 1A, B. Mean age of deceased patients was 61(24) years, 61% of patients were over 60 years old and 61% were male. Mechanism of injury was blunt in 98% of cases. Mean ISS was 28(13) with head injury as the most predominant injury (mean AIS head 3.4(2.0)). First measured systolic blood pressure (SBP) in ED was 131(40) mmHg and 15% of patients had a SBP < 90 mmHg on arrival in ED. First measured GCS in ED was 6.0 (4.5) with 64% of patients intubated at the scene. Patients stayed on average 7.4(12.0) days in hospital, 4.2(2.0) days in ICU, and 3.8(6.3) days on the ventilator.

Overall there was an increase in trauma admissions in the studied period ($p = 0.001$, Fig. 1A). There was no statistically significant difference in sex, MOI or SBP on arrival in ED over time. Mean age of the deceased increased over time, from 46 years in 2007 to 67 years in 2016 ($p < 0.001$, Table 1). ISS decreased over time (ISS 31 in 2007 compared to 25 in 2016, $p < 0.001$, Table 1), as did the number of patients with ISS > 15 ($p = 0.02$, Table 1). Further, there was a decrease in AIS chest and AIS extremities, and an increase in AIS external over time (Table 1).

First GCS in ED was lower in earlier years compared to later years ($p < 0.001$, Table 1), although there was no difference in AIS head in the studied period. This lower GCS in the first period was accompanied by higher on-scene intubation rates (Table 1).

Mortality decreased over the years ($p = 0.02$, Fig. 1B, Table 2). There was however no statistically significant difference in H-LOS, ICU-LOS and ventilator days over the years (Table 2).

Cause of death

The main cause of death was CNS (including high cervical spine) injury in the whole decade, although the distribution of cause of death was different over the years (Fig. 2A). Throughout the years, there was a general decrease in death by exsanguination ($p = 0.03$, Fig. 2B). Cause of death by CNS decreased from 2007 to a minimum of 52% patients in 2011 followed by a sharp increase that leveled out around 77% in the last 3 years (Fig. 2B).

When comparing both time periods 58% of patients died of brain injury in 2007–2012, compared to 76% in 2013–2016 ($p = 0.001$, Fig. 3). In 2007–2012 exsanguination was the cause of death in 9% of patients and this number decreased even further to 3% in 2013–2016 ($p = 0.001$), making this 0.13% of all admitted trauma patients in this period. A similar decline was seen in patients dying from MOF-ARDS-Sepsis: from 5% in 2007–2012 to 2% in 2013–2016 ($p = 0.001$, Fig. 3).

Time of death distribution

The time of death ranged from 0.5 h to 120 days. In 2007–2012 the first peak of in-hospital death was seen in the first two hours after arrival with exsanguination as the most common cause of death. CNS was the most common cause of death beyond these two hours (Fig. 4A). As exsanguination became rare during the 2013– 2016 period, this first peak of death, almost exclusively caused by traumatic brain injury, shifted a few hours towards 6–9 h after arrival (Fig. 4B). In both periods 30% of all deceased patients (2007– 2012 111 of 375 patients and 2013–2016 66 of 221 patients) died within the first day. Deaths beyond first 24 h in hospital were mainly caused by CNS injuries in both time periods (Fig. 5A, B). An overview of trauma deaths per hour and day categorised by cause of death is presented in Figs. 4 and 5.

DISCUSSION

In this trauma population the overall in-hospital mortality was 5.2% with lower mortality in recent years. Additionally, change in cause of death was analysed by comparison of 2 time periods representing periods before and after implementation of haemo- static resuscitation and damage control procedures in our hospital. In 2015, AIS coding was changed from AIS98 to AIS08 in the Dutch Trauma Registry. This change in coding resulted in a general decrease in ISS [14]. This decrease was also observed in this studied population.

Even though patients were older, mortality rates decreased over time. Further, cause of death changed over time; over the last decade CNS related death has increased from 58% to 76%, whereas death by exsanguination and death caused by MOF-sepsis-ARDS both have decreased from 9% to 3% and 5% to 2% respectively.

We have no clear explanation for the decrease in AIS chest over time. AIS extremities also decreased over time. This might be explained by the fact that in recent years patients with isolated extremity fractures have been more frequently distributed to level- 2 and 3 trauma centres within the region.

In this aging population with increasing CNS related deaths ISS decreased, whereas AIS head remained the same. This could possibly be explained by the fact that an elderly population will likely have more co-morbidities with increased anticoagulant usage. These patients are more vulnerable to head injury even with low energy falls. Moreover, there was a decrease in on-scene intubation in recent years even though AIS head did not change. A change in on-scene intubation criteria for prehospital emergency services has proba- bly attributed to this decrease as well. This has also likely influenced initial GCS in ED, since GCS was higher in later years even though AIS head was similar over time.

This study is the first study to describe very low rates of death by exsanguination in a level-1 trauma centre. A decrease in exsanguination rates has been reported in literature in the last decade, but most papers still report values well above 15% [5-8]. Low

exsanguination rates in this study might be explained by the fact that the studied population differed from the population in most North American studies (although we have shown in a previous study that patient demographics between the studied Dutch urban area and Harbor View Medical Center in Seattle were not very different [11]); our cohort almost exclusively consisted of blunt injuries caused by traffic accidents and falls from height in a relatively small service area with short transport times. Even though mean ISS was 28 in the deceased population only 15% of patients were hypotensive on arrival in ED. We previously described a phenomenon in which severely injured patients in smaller service areas with short transport times do not have deranged physiologic parameters on arrival in ED [10,12]. These patients are in the hospital before blood pressure, base deficit and haemoglobin will change distinctly. With implementation of aggressive haemostatic resuscitation strategies (decreased use of crystalloids and balanced 1:1:1 PRBC: FFP: PLT ratio) haemorrhagic shock could be reversed early after trauma, which might have contributed to the fact that in this cohort exsanguination rates were low. As a consequence MODS related deaths decreased as well. We have recently demonstrated that MODS related death has decreased to 3% in a polytrauma population [10].

Previous studies have shown that CNS and exsanguination are the two major causes of death in trauma [5–9]. This study demonstrated that cause of death has skewed even further to CNS related injuries. Of all deaths 76% was caused by traumatic brain injury, making it the single most common cause of death in trauma in this population. This percentage of brain/spinal cord injury- related deaths is higher than most reports on cause of death in trauma [4,7]. This could be partly explained by the fact that our level-1 trauma centre is the only referral centre for brain and spinal cord injury in the province [11]. Furthermore, once other causes of death such as exsanguination and MODS can be averted successfully, death by CNS related injuries would increase proportionally. Another explanation could be that patients with non-survivable CNS injuries who would previously die from haemorrhage are now in fact surviving the early phase, only to die later of CNS injury.

It was noted that the deceased patients of this studied population have aged 21 years in the studied decade. This is not necessarily a reflection of the whole trauma population, since only the deceased have been studied. However, it is a remarkable increase in age in 10 years. A possible explanation for this large increase could be the rise in death from CNS related injuries; advanced age is likely to be accompanied by increasing CNS related deaths. Further, there has been a gradual change in prehospital triage over time; the elderly, who are more likely to sustain more severe injuries after relatively low-impact traumas, especially when on anticoagulants, are more often transported to the level-1 trauma centre.

Death by exsanguination decreased by 6%, and CNS deaths increased by 18% when comparing both time periods. One could argue that the change in resuscitation in this blunt trauma population could have resulted in a net increase in CNS related mortality. This is however refuted by the fact that the overall mortality has not changed between both study periods. When calculating mortality rates per year, even a decrease was observed. Further, low blood pressure is also detrimental to the brain, and haemorrhagic shock needs to be addressed before saving patients from death by CNS. Damage control resuscitation (DCR) has likely not only influenced exsanguination related mortality, but also MODS/ARDS related mortality, which decreased from 5% in 2007– 2012 to 2% in 2013–2016. In order to estimate the number of patients who potentially could have died from haemorrhagic shock, but did not, and later proceeded to die from CNS, one could calculate all patients who had SBP < 90 mmHg on arrival in ED and later died from either exsanguination or CNS. The number of CNS or exsanguination related deaths in haemodynamically unstable patients were lower in 2013–2016 compared to 2007–2012; 39/ 224 (17%) patients who died of either exsanguination or CNS had SBP < 90 mmHg in 2007–2012 compared to 21/172 (12%) in 2013– 2016. 23/224 (10%) died of exsanguination and 16/224 (7%) died of CNS in 2007–2012. All 21/172 (12%) haemodynamically unstable patients in 2013–2016 died of CNS (Table S1). It was concluded that some, but not all patients who were saved from exsanguination later died of CNS related injury. There is no indication that there was a net increase in CNS related mortality by a change in resuscitation strategies.

In the first time period more patients died within 2 h after arrival in ED than in 2013–2016; In both time periods 30% of patients died within the first day after injury. Other studies, including our own previous work [9] have reported higher proportions of death within the first 24 h, with rates up to 59% [5,8,13]. This decrease in early deaths could be partly attributed to a decrease in death by exsanguination. However, in 2013–2016 where exsanguination rates were lower, the same percentage of patients died within the first 24 h. These patients mainly died due to CNS and/or high cervical spine injuries. Since patients with combined injuries no longer die as a result of exsanguination, the cause of death has shifted towards CNS injury. However, this apparently does not postpone time of death beyond the first day aftertrauma. Between 2007 and 2012 there were 25 deaths <2 h of admission (13 due to exsanguination, 5 due to CNS related injuries, and 7 due to various reasons such as burns and submersion) whereas no patient died <2 h in 2013–2016. DCR related management strategies could explain the extinction of death by exsanguination <2 h in the later period. There were, however, also several CNS related death early in the first period. A possible explanation could be that, with introduction of haemostatic resuscitation (with less crystalloids and more blood products administration), brain swelling was briefly delayed and postponed brain herniation.

One of the limitations of this study is that it was conducted in a single institution with a predominantly blunt trauma population in which the clinical treatment and research were conducted by the same clinicians. Even though the studied cohort is a unique trauma population we feel it is representative for urban areas with short hospital transport times and predominantly blunt trauma. Further, only in-hospital deaths were included in this study, therefore the number of trauma deaths in the first hour is likely underestimated. Although prehospital deaths are critical for overall mortality analysis, we focussed on in-hospital mortality to analyse in–hospital quality performance. We feel that our data are comparable to other studies that have excluded pre-hospital deaths [5,6,8,9].

In conclusion, in this study death by exsanguination has decreased to 3% of trauma deaths in a level-1 trauma centre in an inclusive trauma system. This could be considered a success of the improvements in trauma and critical care in the last decade. The proportion of traumatic brain injury has increased over time and has become the most common cause of death in blunt trauma. Besides on-going prevention of brain injury, future studies should focus on treatment strategies preventing secondary damage of the brain once the injury has occurred.

Fig. 1. Admissions related to trauma deaths and mortality percentages from 2007 to 2016 A: number of patients who survived and who died per year. B: mortality percentage per year.

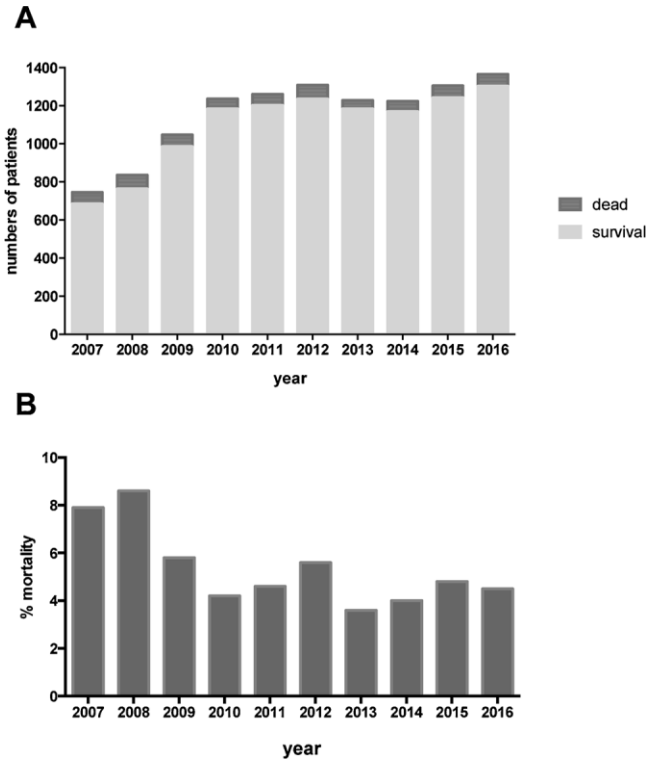


Table 1. Demographics of deaths between 2007-2016b.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	P-value
Blunt trauma	57 (97)	70 (97)	59 (97)	52 (100)	57 (98)	73 (100)	42 (96)	53 (100)	61 (98)	62 (100)	0.12
Age	46 (25)	58 (26)	56 (26)	64 (24)	63 (24)	66 (22)	62 (23)	62 (22)	67 (20)	67 (25)	<0.001*
Males	42 (71)	40 (56)	39 (64)	32 (62)	38 (66)	43 (59)	25 (57)	29 (55)	41 (66)	32 (52)	0.18
ISS	31 (13)	30 (14)	31 (13)	27 (13)	25 (11)	26 (11)	27 (12)	29 (16)	25 (12)	25 (11)	<0.001*
ISS > 15	54 (92)	66 (92)	57 (93)	44 (85)	50 (86)	62 (85)	38 (86)	47 (89)	52 (84)	48 (77)	0.02*
AIS head	3.8 (2.0)	3.3 (2.1)	3.5 (2.0)	3.3 (2.0)	3.0 (2.1)	3.0 (2.1)	3.6 (2.0)	3.6 (1.9)	3.5 (1.8)	3.5 (1.9)	1.0
AIS face	0.5 (0.9)	0.3 (0.8)	0.4 (1.0)	0.5 (0.9)	0.5 (0.9)	0.4 (0.8)	0.4 (0.8)	0.6 (1.0)	0.5 (0.9)	0.5 (0.8)	0.23
AIS chest	1.7 (1.9)	2.1 (2.0)	1.8 (2.1)	1.5 (2.0)	1.6 (2.0)	1.6 (1.9)	1.5 (1.7)	1.7 (1.9)	1.4 (1.7)	1.3 (1.5)	0.02*
AIS abdomen	0.5 (1.2)	0.5 (1.2)	0.4 (1.2)	0.6 (1.3)	0.6 (1.3)	0.4 (1.2)	0.2 (0.7)	0.5 (1.2)	0.3 (0.9)	0.7 (1.2)	0.89
AIS extremities	1.2 (1.4)	1.3 (1.5)	1.0 (1.3)	1.1 (1.4)	0.7 (1.1)	1.0 (1.3)	0.7 (1.2)	0.7 (1.1)	0.9 (1.3)	0.9 (1.2)	0.009*
AIS external	0.3 (0.8)	0.7 (1.0)	0.6 (1.0)	0.7 (0.8)	0.8 (1.1)	0.7 (1.1)	0.8 (1.1)	0.6 (1.1)	1.0 (0.8)	1.0 (0.8)	0.001*
1st SBP in ED (mmHg)	131 (34)	129 (41)	125 (41)	122 (38)	129 (39)	135 (40)	130 (39)	131 (41)	132 (43)	136 (41)	0.26
1st SBP < 90 mmHg	7(13)	18 (31)	11 (22)	8 (22)	10 (20)	8 (12)	4 (9)	8 (16)	7 (11)	9 (15)	0.03*
1st GCS in ED	4.7 (3.2)	4.6 (3.4)	5.2 (4.2)	6.8 (4.9)	6.3 (4.7)	6.4 (4.7)	6.3 (4.9)	6.1 (4.6)	7.2 (5.0)	6.7 (4.8)	<0.001*
On-scene intubation a	23 (49)	44 (94)	38 (78)	28 (76)	30 (77)	39 (53)	24 (59)	36 (69)	27 (46)	32 (52)	<0.001*

Data are presented as mean (SD) or absolute numbers (%). MOI = mechanism of injury, ISS = Injury Severity Score, AIS = abbreviated Injury Scale, SBP = systolic blood pressure, ED = emergency department, GCS = Glasgow Coma Score.

a Data were not available for all patients.

b Continuous data were analysed using Pearson's correlation coefficient and categorical data were analysed using chi-squared for trend analysis.

* Statistically significant.

Table 2. Outcome

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	p-value
H-LOS	6.1 (7.5)	7.3 (13.4)	6.7 (12.8)	6.9 (8.6)	7.2 (13.8)	7.1 (9.4)	5.7 (7.9)	8.9 (13.0)	9.2 (16.8)	8.5 (12.0)	0.13
ICU-LOS	5.2 (7.7)	3.5 (5.0)	4.4 (8.4)	3.3 (3.9)	4.0 (7.7)	3.1 (5.1)	3.1 (4.9)	6.1 (11.3)	4.7 (6.8)	4.5 (7.0)	0.56
Ventilator days	4.8 (7.2)	3.0 (4.3)	3.4 (3.9)	3.3 (3.8)	3.7 (7.4)	2.7 (4.5)	2.9 (4.1)	5.7 (11.0)	4.3 (6.5)	4.0 (6.6)	0.43
Mortality	59 (7.9)	72 (8.6)	61 (5.8)	52 (4.2)	58 (4.6)	73 (5.6)	44 (3.6)	53 (4.0)	62 (4.8)	62 (4.5)	0.02*

Data are presented as mean (SD) or absolute numbers (%). H-LOS = length of stay in hospital, ICU-LOS = length of stay in Intensive Care Unit.

a Continuous data were analysed using Pearson's correlation coefficient and categorical data were analysed using chi-squared for trend analysis.

*** Statistically significant.**

Figure 2. A. Comparison cause of death between 2007–2016. B. CNS and exsanguination related deaths through the years.

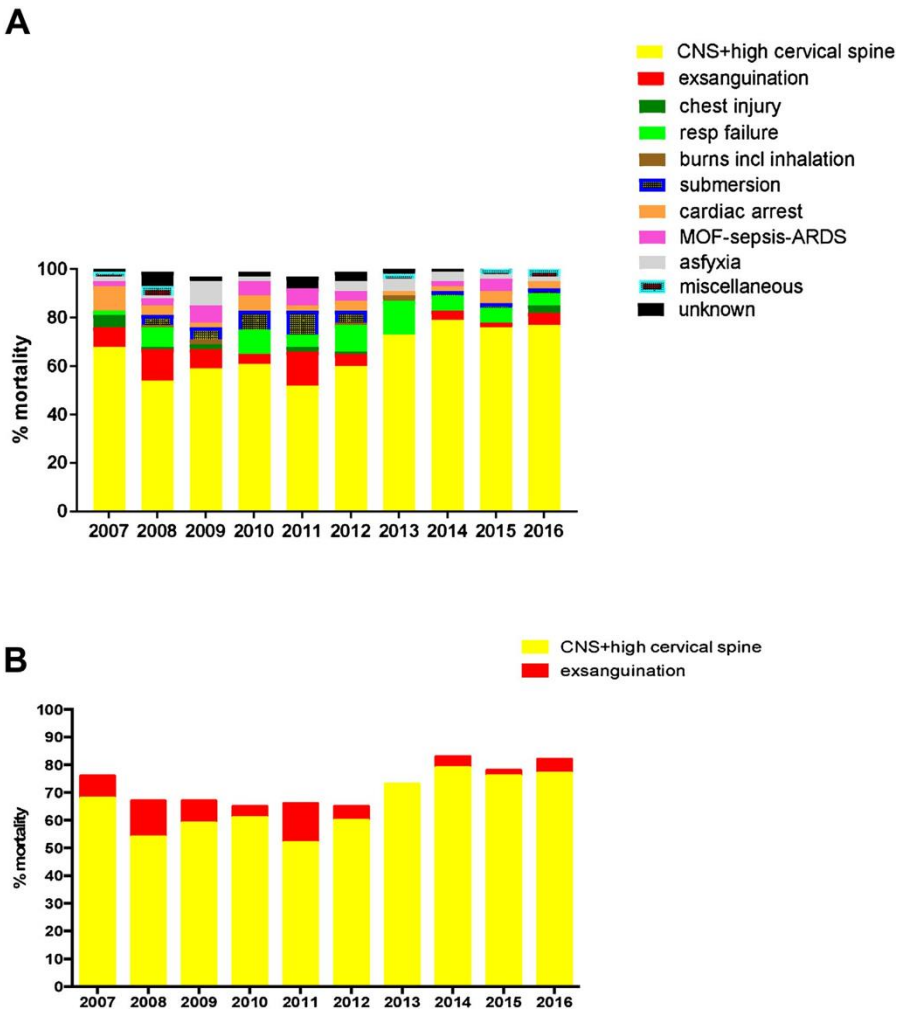


Fig. 3. Comparison cause of death between 2007–2012 (A) and 2013–2016 (B).

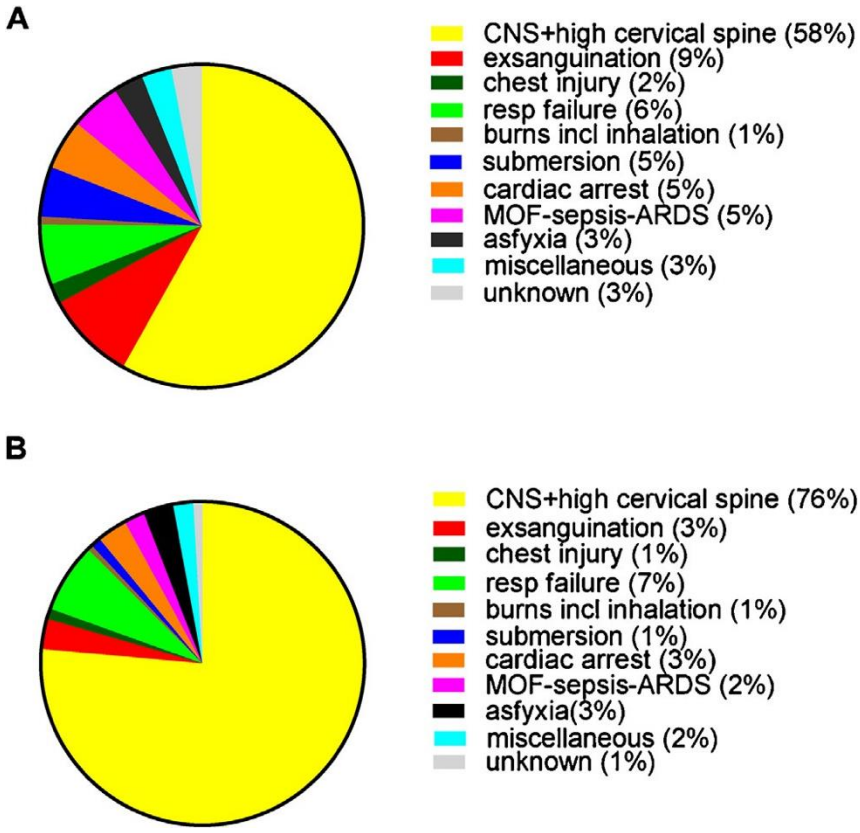


Fig. 4. Comparison cause of death between 2007–2012 (A) and 2013–2016 (B) in first 24 h after arrival in ED.

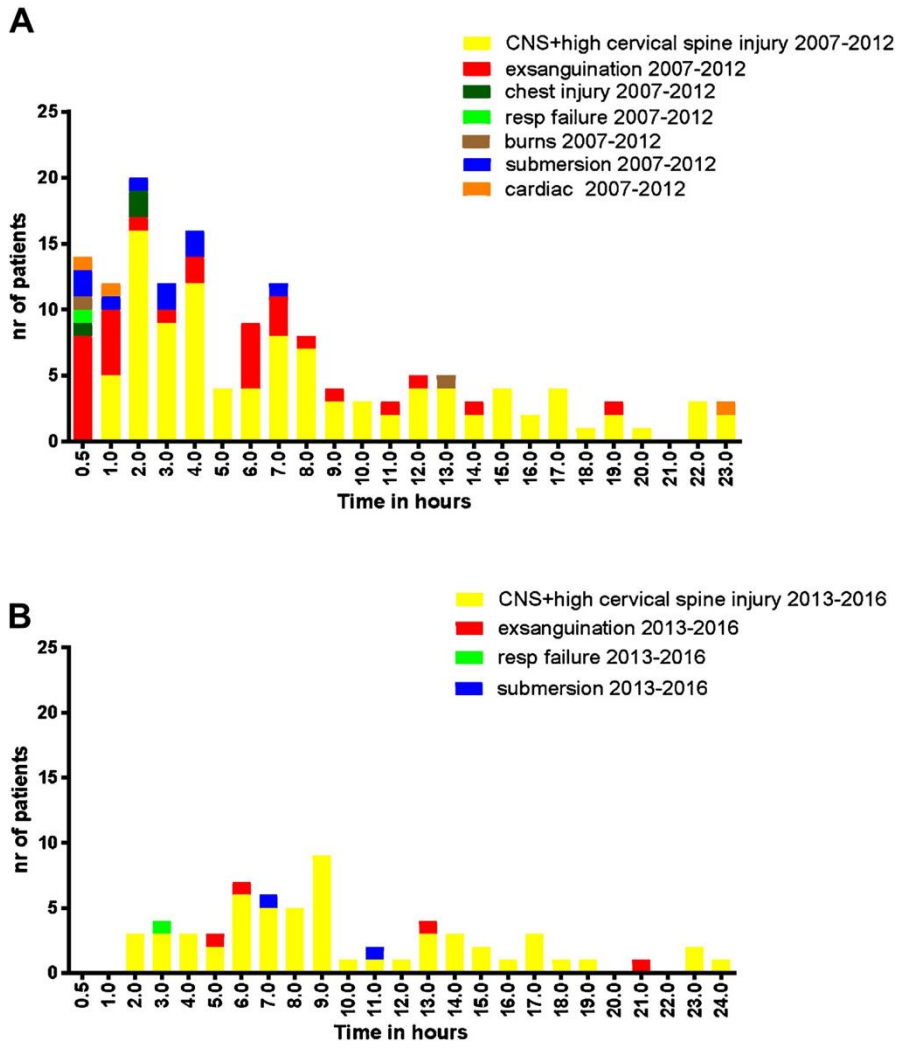
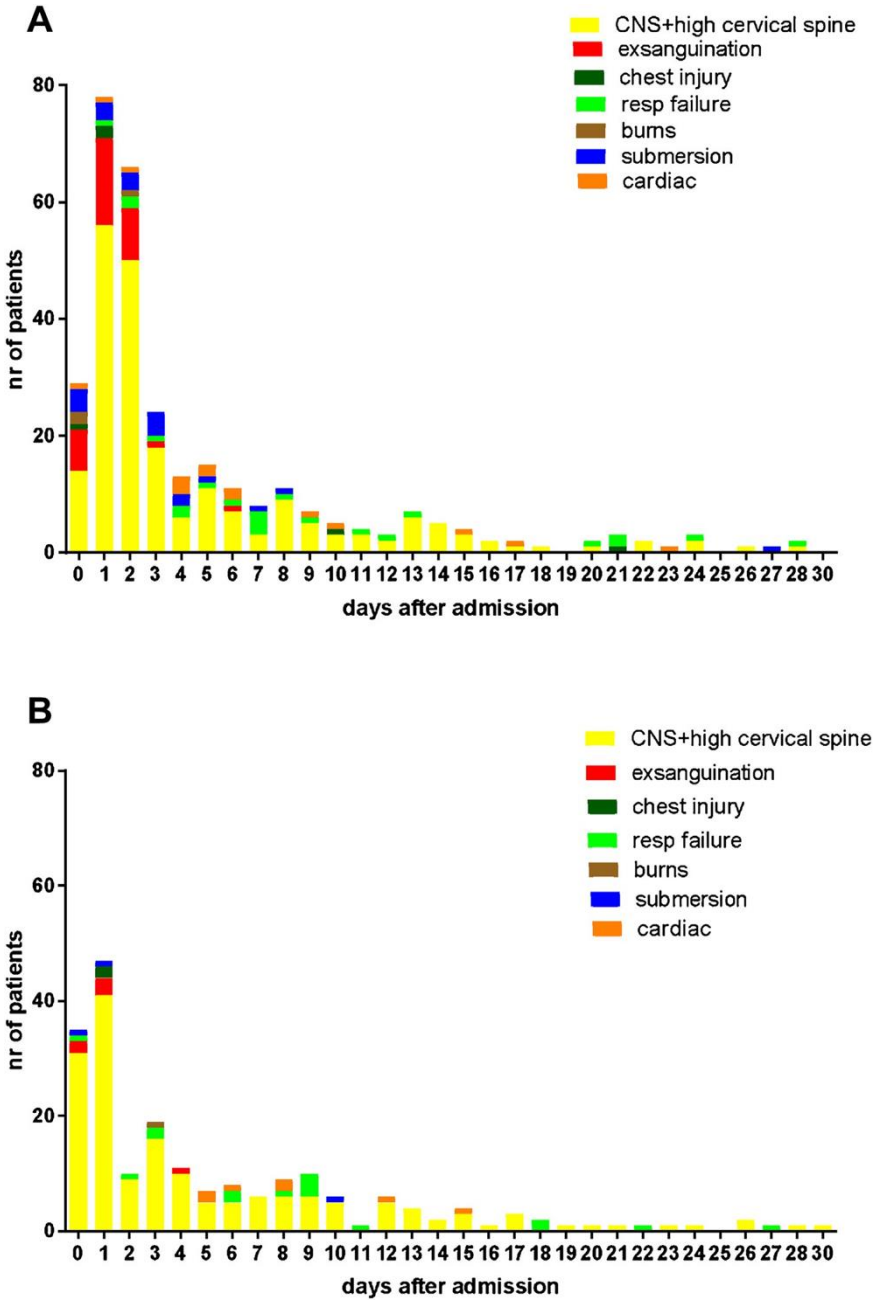


Fig. 5. Comparison cause of death between 2007–2012 (A) and 2013–2016 (B) in first 30 days after admission.



REFERENCES

1. Baker C.C., Oppenheimer L, Stephens B, Lewis FR & Trunkey DD. Epidemiology of traumatic deaths. *Am J Surg.* **140,** 144-150 (1980).
2. Sauaia A *et al.* Epidemiology of traumatic deaths: a reassessment. *J Trauma.* **38,** 185-193 *(*1995).
3. Pang JA, Civil I, Ng A & Adams D, Koelmeyer T. Is the trimodal pattern of death after trauma a dated concept in the 21st century? Trauma deaths in Auckland 2004. *Injury*. **39,** 102-106 (2008).
4. Evans JA, van Wessem KJP, McDougall, Lee KA, Lyons T & Balogh Z. Epidemiology of trauma deaths: comprehensive population-based assessment. *World J Surg.* **34,** 158-163 (2010).
5. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR & Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997-2008. *J Trauma.* **69,** 620-626 (2010).
6. Kahl JE, Calvo RY, Sise MJ, Sise B, Thorndike JF & Shackford SR. The changing nature of death on the trauma service. *J Trauma Acute Care Surg.* **75,** 195-201 (2013).
7. Pfeifer R, Tarkin IS, Rocos B & Pape HC. Patterns of mortality and causes of death in polytrauma patients-has anything changed? *Injury,* **40,** 907-911 (2009).
8. Oyeniyi BT, Fox EE, Scerbo M, Tomasek JS, Wade CE & Holcomb JB. Trends in 1029 trauma deaths at a level-1 trauma centre: impact of a bleeding control bundle of care. *Injury*. **48,** 5-12 (2017).
9. Lansink KWW, Gunning AC & Leenen LPH. Cause of death and time of death distribution of trauma patients in a level-1 trauma centre in the Netherlands. *Eur J Trauma Emerg Surg.* **39,** 475-483 (2013).
10. Van Wessem KJP & Leenen LPH. Reduction in mortality rates of postinjury multiple organ dysfunction syndrome: a shifting paradigm? A prospective population based cohort study. *Shock*. **49,** 33-38 (2018).
11. Gunning AC *et al.* Demographic patterns and outcomes of patients in level-1 trauma centres in three international trauma systems. *World J Surg.* **39,** 2677-2684 (2015).

12. Gunning AC & Leenen LPH. Applicability of the predictors of the historical trauma score in the present Dutch trauma population: modelling the TRISS predictors. *J Trauma Acute Care Surg.* **77,** 614-619 (2014).
13. Lefering R *et al.* Epidemiology of in-hospital trauma deaths. *Eur J Trauma Emerg Surg.* **38,** 3-9 (2012).
14. Palmer CS, Gabbe BJ & Cameron PA. Defining major trauma using the 2008 Abbreviated Injury Scale. *Injury*, **47,** 109-115 (2016).

CHAPTER 6

Outcome in patients with isolated moderate to severe traumatic brain injury

CHAPTER 6

Title: Outcome in patients with isolated moderate to severe traumatic brain injury.

Published in: Critical Care Research and Practice

Cite as: Jochems, D. *et al.* Outcome in Patients with Isolated Moderate to Severe Traumatic Brain Injury. *Crit. Care Res. Pract.* **114**, (2018).

Author list: Denise Jochems[1] (MD), Karlijn J.P. van Wessem[1] (MD, PhD), Roderick M. Houwert[1] (MD, PhD), H. Bart Brouwers[2] (MD, PhD), Jan Willem Dankbaar[3] (MD, PhD), Michael A. van Es[4] (MD, PhD), Marjolein Geurts[4] (MD PhD), Arjen JC Slooter[5] (Professor, MD, PhD) Luke P.H. Leenen[1] (Professor MD, PhD)

[1] Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

[2] Department of Neurosurgery, University Medical Center Utrecht, Utrecht, The Netherlands

[3] Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

[4] Department of Neurology, University Medical Center Utrecht and de Hoogstraat Rehabilitation, Utrecht, The Netherlands

[5] Department of Intensive Care, University Medical Center Utrecht and de Hoogstraat Rehabilitation, Utrecht, The Netherlands

ABSTRACT

Introduction: Traumatic brain injury (TBI) remains a major cause of death. Withdrawal of life-sustaining treatment (WLST) can be initiated if there is little-anticipated chance of recovery to an acceptable quality of life. The aim of this study was firstly to investigate WLST rates in patients with moderate to severe isolated TBI and secondly to assess outcome data in the survivor group.

Material and methods: A retrospective cohort study was performed. Patients aged ≥18 years with moderate or severe isolated TBI admitted to the ICU of a single academic hospital between 2011 and 2015 were included. Exclusion criteria were isolated spinal cord injury and referrals to and from other hospitals. Gathered data included demographics, mortality, cause of death, WLST, and Glasgow Outcome Scale (GOS) score after three months. Good functional outcome was defined as GOS >3.

Results: Of 367 patients, 179 patients were included after applying inclusion and exclusion criteria. 55 died during admission (33%), of whom 45 (82%) after WLST. Patients undergoing WLST were older, had worse neurological performance at presentation and more radiological abnormalities than patients without WLST. The decision to withdraw life-sustaining treatment was made on the day of admission in 40% of patients. In 33%, this decision was made while the patient was in the Emergency department. 71% of survivors had a good functional outcome after three months. No patient left hospital with an unresponsive wakefulness syndrome (UWS) or suffered from UWS after three months. One patient died within three months of discharge.

Conclusion: In-hospital mortality in isolated brain injured patients was 33%. The vast majority died after a decision to withdraw life-sustaining treatment. None of the patients were discharged with an unresponsive wakefulness syndrome.

INTRODUCTION

In 2010, over 56,000 deaths in the USA and 57,000 in the European Union were related to traumatic brain injury (TBI) [1-3]. Furthermore, TBI is the main cause of death in severely injured trauma patients, contributing to 30% of the deaths caused by trauma [1,2,4]. Interestingly, mortality rates differ greatly between level-I trauma centers across the world [4].

TBI not only causes mortality, but can also lead to severe functional impairment. Unresponsive wakefulness syn- drome (UWS) is a dreaded outcome, in which the patient does not demonstrate any sign of consciousness [5]. Withdrawal of life-sustaining treatment (withdrawal of treatment; WLST) can be initiated when treatment is considered medically futile, in cases where there is negligible chance of recovery to an acceptable quality of life [1,5,6].

The Ethicus study [7] investigated end-of-life practices in various ICUs across Europe. Differences in practices be- tween these hospitals included a higher WLST rate in Northern and Central European countries, when compared to countries in Southern Europe. Furthermore, the length of ICU stay before the first treatment limiting decision was significantly shorter in Northern Europe than in the rest of the continent. Amongst patients with acute conditions, neurological disease was the most common motive for treatment limitations [7]. Moreover, a retrospective study in a Dutch ICU found that this was true for WLST as well [8]. However, few studies have published WLST rates, especially not in combination with neurological or functional outcome data.

Therefore, the aim of this study was to investigate WLST rates in patients with moderate to severe isolated TBI and to assess outcome data of the survivors.

MATERIALS AND METHODS

A local institutional review board (IRB) waiver was formally obtained.

Study Design and Study Population.

A retrospective cohort study was conducted including all consecutive pa- tients who sustained isolated moderate or severe traumatic brain injury and were admitted to ICU of the University Medical Center Utrecht (UMCU, a level-1 trauma center) between 2011 and 2015. Isolated moderate or severe brain injury was defined as an Abbreviated Injury Score head & neck (AIShead) of more than three and no significant injury in other regions (defined as AIS of more than two). Patients under 18 years of age, patients with isolated spinal injury without TBI, and referrals to and from other hospitals were excluded. If first CT head showed only subdural and/or parenchymal hemorrhage, patients' records were checked and patients were excluded from analysis, if there was any doubt on whether the brain injury was the consequence or the cause of trauma.

Patients who passed away without WLST were only analyzed for cause of death. This decision was based on the hypothesis that this excluded group will be relatively small, and our main interest was in WLST.

Clinical Variables.

Data were collected from medical records and the local trauma database. This database in- cludes several baseline characteristics such as age, sex, ISS, and the AIS of the head region. The trauma mechanism was collected from the medical records. Collected variables in- cluded: the Glasgow Coma Scale (GCS) as assessed by the neurologist during the primary survey; pupillary light re- flexes and corneal reflexes during primary survey; the need for sedation before arrival or during the stay in the Emergency Department (ED), the concurrent use of a low molecular weight heparin (LMWH); and coumarin or a novel oral anticoagulant (NOAC). The Charlson Comorbidity Index score was calculated for every patient. This is a widely used score for comorbidity, which comprises 22 comorbidities and each is assigned a weight, according to its impact on the prognosis of the patient [9,10].

Imaging Variables.

In each patient, a noncontrast CT of the head was acquired within 30 minutes after arrival to ED. An experienced neuroradiologist, blinded to the outcome data, revaluated the CT in every patient for the presence of epidural, subdural and/or subarachnoid hemorrhage, compression of the basal cisterns, and midline shift retrospectively.

Outcome Data.

Cause of death and WLST data were collected from the medical records. For patients who re- ceived WLST, length of stay in ICU was noted. Functional outcome data, measured by the Glasgow Outcome Scale (GOS), were collected at three months (+one month) from records of outpatient clinic visits or correspondence from a neurological rehabilitation center. In case of missing data at three months, the first available GOS was used. If this was before three months' time, it was assessed with the three- month follow-up data, since further deterioration was not expected. If follow-up data were only available after the four- month mark, they were separately analyzed. The GOS allows for objective assessment of the recovery of patients with brain damage in five categories [11]. Good functional out- come was defined as GOS 3.

Statistical Analysis.

All statistical analyses were per- formed using IBM SPSS Statistics, version 21.0.0 (Armonk, NY, USA). Group differences between survivors and patients who died due to WLST were calculated using a Mann– Whitney U test in case of continuous, nonnormally dis- tributed, variables. In case of a different shape of distribu- tions in each group, mean ranks were compared for analysis of significant differences between groups, and medians were only shown. Differences in distribution of categorical or ordinal variables between groups were calculated with the chi-square test of homogeneity. Fisher's exact test instead of a chi-square test was used if the expected cell count was less than five. Statistical significance was defined as $p < 0.05$.

RESULTS

Study Population

The search in the trauma registry generated a total of 367 patients with isolated moderate or severe TBI admitted between 2011 and 2015 to the ICU. After applying our exclusion criteria, 179 patients were included in this study (Figure 1). Of these patients, 55 (33%) died during hospitalization (Table 1). The median age at time of the trauma was 57, the median AIS head was four, and the median ISS was 20. Women accounted for 37% (n=62) of the patients (Table 1).

Patients for whom WLST was initiated were signifi- cantly older and had a median AIShead of five, whereas the AIShead of the non-WLST patients was four (p 0.001). Use of coumarins, NOACs, and LMWH was more frequent in WLST patients (p 0.043). The difference in mean rank of the Charlson Comorbidity Index was not statistically significant. GCS scores in ED were higher amongst those who did not receive WLST (p=0.030). The absence of brainstem reflexes was more common in WLST-patients (both p<0.01, table 1a). Furthermore, WLST-patients were more often sedated before completion of the primary survey than non-WLST patients (p=0.005). Subdural hemorrhage, compression of the basal cisterns and midline shift on the initial CT-head were more common in the group of patients who had WLST (all p<0.05, table 1a).

Mortality, surgical intervention, complications and neurological outcome

Forty-five patients (82%) died following the decision to withdraw life-sustaining treatment. The decision to withdraw life-sustaining treatment was made on the day of admission in 18 cases (40%). In 33% (n=6) of those patients, this decision was made whilst the patient was in ED.

10 (22%) of the WLST patients and 13 (10%) of the non-WLST patients received an ICP meter (p=0.049). The amount of patients who received neurosurgical decompression during admission did not differ between the non-WLST and WLST

group (p=0.912) (table 1b.)

Median length of stay in ICU before the decision to withdraw life-sustaining treatment was made for patients who received WLST after the first day was 4 days. Of these 27 patients, 12 (44%) suffered from a systemic complication at some point during their admission. In 50% (n=6) of these patients, this complication was solely pneumonia (Table 2).

In-hospital mortality as a result of complications occurred in six patients (11%). In two patients these complications were cardiovascular: These patients died due to a cardiac arrest. Two patients died due to respiratory insufficiency and one due to a fever in combination with the TBI. One patient had a fever, complicated by respiratory insufficiency, anuria and diarrhea. This patient had several comorbidities. Four patients (7%) progressed to death by neurological criteria (Figure 1).

None of our patients were discharged to a hospice, since death was expected to follow relatively quickly after the decision to withdraw life-sustaining care.

71% (n=78) of the patients with a three-month or later follow-up scored ≥ four on the GOS at three months (Table 3c). No patient left the hospital with an unresponsive wakefulness syndrome or suffered from UWS after three months. Median GCS on the day of discharge was 15 (IQR 0). One patient died within three months of discharge. Data concerning GOS was missing in 25% of survivors (tables 3).

DISCUSSION

We have performed a single-center retrospective analysis on mortality rates, causes of death, WLST, and neurological outcome in patients who were admitted to the ICU with isolated moderate or severe TBI. The mortality rate was 33%, which is comparable to that found in other developed countries (30–40%) [1,5,12,13]. The vast majority of pa- tients died after a decision to withdraw life-sustaining treatment.

There are only four studies that have published rates of WLST in this group of patients. In-hospital mortality rates amongst patients with moderate to severe TBI varied be- tween 10.8% and 44.1%, whilst the WLST rates ranged be- tween 45.0% and 86.6% in these studies: likely due to geographical and cultural differences [1,5,14,15]. Verkade et al. [8] looked at WLST rates in a Dutch ICU. They found that WLST preceded death in 95% of patients who passed away due to irreversible catastrophic cerebral damage [8]. Our WLST rates are at the higher end of the spectrum, when compared to the aforementioned studies; however, they are in range with the earlier published Dutch data [8]. We hypothesize that this may be partly due to cultural differences such as a smaller role of religion in the decision- making [6,7]. Furthermore, we speculate that people in the Netherlands find quality of life extremely important and therefore might feel that life with UWS has no quality.

Patient wishes were always taken into account. If medical practitioners believe there is no chance of a decent outcome, they will inform the family that medical treatment would be futile. There are no cases in our database where families have doubted or opposed this statement. Unfortunately, due to the retrospective nature of our study, we are not able to trace preexistent patient documents, which might have influenced the decision.

WLST can be appropriate after severe traumatic brain injury to prevent a patient from staying alive at the cost of being left in a state of disability that might be against his or her wishes. However, WLST should not deny patients their chance of a good recovery. Numerous studies have identified several factors with a predictive relationship with

outcome after TBI. So far, no model has proven to be perfect, but two widely used prognostication models are the IMPACT score and the CRASH score [20-22]. The risk that WLSTmay lead to self-fulfilling prophecies, when the prognostic model confirms itself due to physicians basing the decision to WLST on the factors present in this model, has previously been acknowledged for patients with various types of acute brain injury [16-18].

In our study, the decision to withdraw life-sustaining treatment was made in the very acute stage of the disease. Our findings are similar to those of Turgeon et al. [5] where 45.6% of patients who died with WLSTdid so within the first three days. There is a possibility that patients might have shown clinical improvement if the decision to WLST would have been postponed. In some cases, the decision to WLST has been made when the patient was sedated. The neuro- logical state of these patients has therefore not been assessed. We believe the decision to not discontinue sedation is based on the facts that some patients are clinically not well enough to discontinue sedation or their CT head shows un- salvageable brain damage.

The Neurocritical Care Society therefore suggests delaying withdrawal of treatment and treatment limitations for at least 72 hours in cases of devastating brain injury to give the patient the chance to recover and reduce the risk of prematurely forgoing treatments that could provide clinical benefit [19]. Even though these guidelines were not written for TBI specifically, this raises the concern that the decision to withdraw treatment was made too early in some of the patients in this study.

In addition, the amount of patients who received ICP monitoring was relatively low, when compared to other studies [1,14]. Even though we have not formally in- vestigated this, we believe that, in line with hospital practice, patients who did not receive an ICP and/or neurosurgical operation were either considered to have a relatively minor injury or unsalvageable catastrophic cerebral damage.

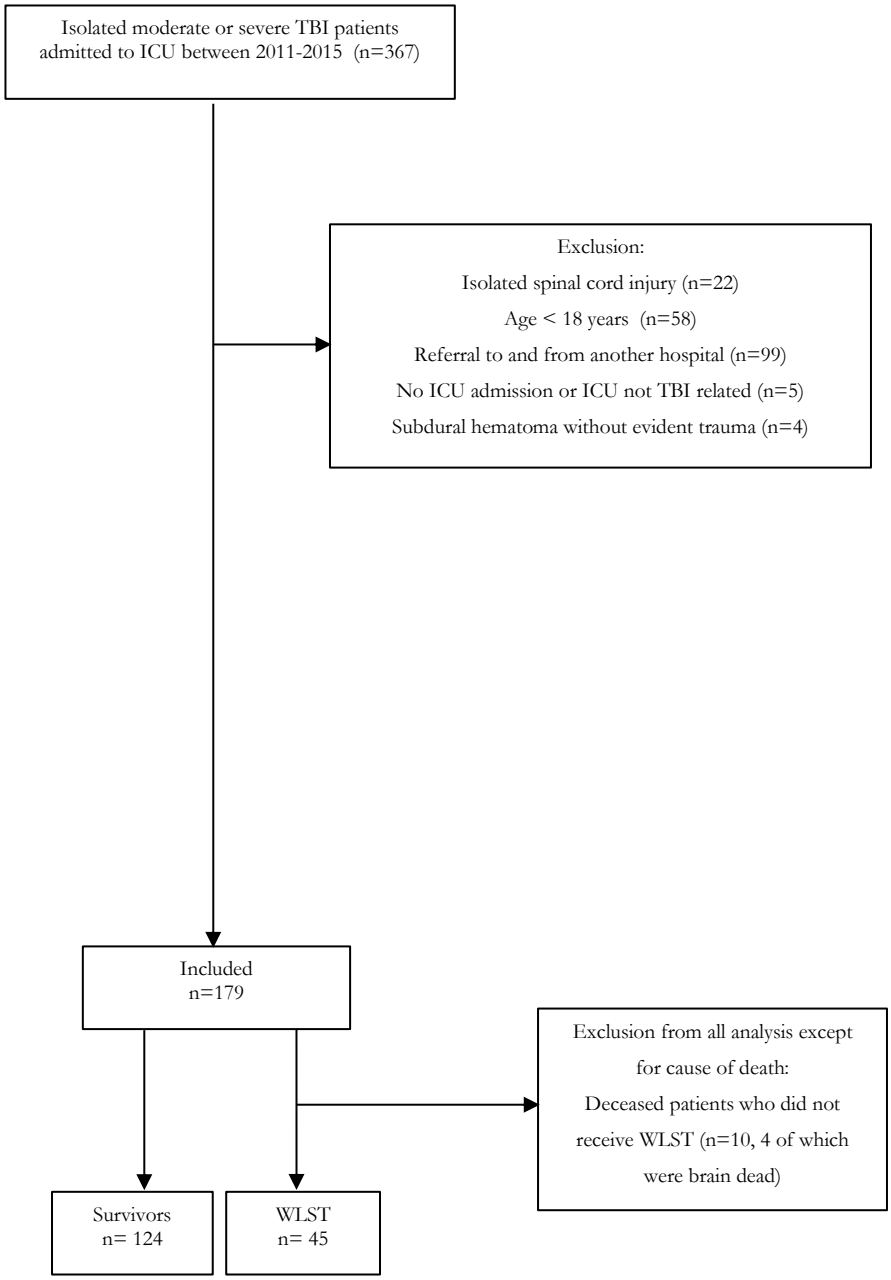
This study has several limitations. Firstly, due to the retrospective nature of this study, we encountered several missing data. One example is the agent and dosage used

sedate the patient. Therefore, we were only able to tell whether the patient was sedated before completion of the primary survey and not if and how this could have affected prognosis. The most important of missing data is that the GOS was not available for all of our patients. Furthermore, at the three-month mark, many patients were still in rehabilitation clinics, but expected to be able to return to an independent life. As such, there is a broad range of neu- rological outcomes amongst those with a GOS of three, ranging from patients requiring a tracheostomy to those who are on the verge of discharge from the rehabilitation clinic. Patients are not likely to have made their full recovery yet at three months; however, most follow-up data were available until three months. Therefore, future research including a longer follow-up period of these patients is necessary to determine the definite neurological outcome. Using the eight-point GOS scale (the extended GOS) can also specify functional outcome even more and has been recommended in the literature [23].

Unfortunately, a ret- rospective analysis makes filling out the eight-point scale too difficult; therefore, the five-point scale was considered the more appropriate option, hoping this would prevent mis- classification and limit missing data. Furthermore, a com- parison of WLST rates between several trauma centers is warranted to establish the exact influence of WLST on mortality and outcome data. In addition, as of today, there is no standard protocol regarding WLST decisions. The decision to withdraw treatment is always taken by the treating phy- sicians including trauma surgeon, neurosurgeon/neurologist, and intensivist and needs to be unanimous before treatment is withdrawn. The lack of standardized documentation of the considerations leading to this decision and therefore lack of analyzed data regarding this subject is a limitation of this study. Finally, we would like to propose a study that in- vestigates the process of, and influences on, the decision to withdraw care.

The vast majority of in-hospital deaths after moderate or severe TBI occur following a decision to withdraw life- sustaining treatments. Functional outcome of TBI survi- vors is generally good.

Figure 1. Flowchart of inclusion process.



TBI: Traumatic Brain injury; WLST: Withdrawal of life-sustaining treatment

Table 1a. Baseline characteristics and mortality.

Variable	All patients (n=169)	WLST (n=45)	Non-WLST (n=124)	P value
Mortality n= (%)*	55 (33)	100 (45)	0	
Median Age in years (IQR)	57 (32.5)	67 (22)	54 (35.25)	
Mean rank Age	n/a	114.56	74.27	<0.001
Median ISS (IQR)	20 (9)	25 (9)	20 (9)	0.01
Median AIShead (IQR)	4 (1)	5 (1)	4 (1)	
Mean rank AIShead	n/a	108.47	76.48	<0.001
Female n= (%)	62 (37)	16 (36)	46 (37)	0.854
Trauma mechanism n= (%)				0.061
Fall stairs or height	53 (32)	19 (44)	34 (28)	
Fall low height/collaps or nos	15 (24)	8 (19)	16 (13)	
Traffic accident: Two wheels	60 (36)	11 (26)	49 (41)	
Traffic accident: Car	12 (7)	1 (2)	11 (10)	
Traffic accident: Pedestrian	4 (2)	1 (2)	3 (3)	
Hit by subject	6 (4)	0 (0)	6 (5)	
Penetrating injury	3 (2)	2 (5)	1 (1)	
Hanging	2 (1)	1 (2)	1 (1)	
Missing	5(3)	2 (4)	3 (2)	
Charlson Comorbidity index (IQR)				
Median		0 (1)	0 (1)	
Mean rank		88.37	81.23	0.302
Anticoagulant Users n= (%)				
None or Platelet aggregation inhibitors		32 (82)	116 (94)	0.043
Coumarines/heparines/NOAC		7 (18)	7 (6)	
Missing		6 (13)	1 (1)	
GCS in ED (IQR)				
Median		7 (8)	8.5 (5)	
Mean rank		47.54	64.51	0.030
Sedated n= (%)		20 (44)	28 (23)	
Motor score in ED (IQR)				
Median		5 (4)	5 (1)	0.009
Missing n= (%)		20 (44)	28 (23)	
Pupil reflexes in ED n= (%)				
None or one eye		21 (50)	17 (15)	<0.001
Both eyes		21 (50)	96 (85)	
Missing		3 (7)	11 (9)	
Corneal reflexes in ED n= (%)				
None or one eye		11 (58)	4 (17)	0.009
Both eyes		8 (42)	20 (83)	
Missing		26 (58)	100 (81)	
Sedation n= (%)		20 (44)	28 (23)	0.005
Signs on first CT-scan n= (%)				
Epidural hemorrhage		17 (38)	42 (34)	0.716
Subdural hemorrhage		43 (96)	93 (75)	0.004
Subarachnoidal hemorrhage		39 (87)	91 (74)	0.097
Compression basal cisterns		34 (76)	52 (42)	<0.001
Midline shift		25 (56)	33 (27)	0.001

WLST: Withdrawal of life-sustaining treatment,

AIShead: Abbreviated Injury Score of the head region,

* 10 patients who died due to other causes than WLST are included in this analysis.

Table 1b. Neurosurgery and ICP meter.			
Neurosurgery variables	WLST n=45 (%)	Non -WLST n=124 (%)	*P* value
Received ICP meter n= (%)	10 (22)	13 (10)	0.049
Underwent neurosurgical decompression	17 (38)	48 (39)	0.912
WLST: Withdrawal of life-sustaining treatment, ICP: Intracranial p			

Table 2. ICU parameters for patients who did not receive WLST on the first day.		
ICU variables	WLST n=27	Non -WLST n=124
Median length of stay in ICU in days (IQR)	4 (5)	3 (5)
Median length of stay in hospital in days (IQR)	n/a	17.5 (21.75)
WLST following systemic complications	n= 12 (44%)	n/a
WLST: Withdrawal of life-sustaining treatment, n/a: Not applicable		

Table 3. GOS score and destination after discharge of the survivor-group.

Glasgow Outcome Scale		Patients assessed at three months n=124 (%)	Patients assessed after three months n=23 (%)	All assessed patients n=124 (%)	Discharged to	Patients n=124 (%)
	1	1 (1)	0 (0)	1 (0)	Home	50 (40)
	2	1 (0)	0 (0)	0 (0)	Rehab	69 (56)
	3	31 (31)	0 (0)	31 (28)	Home against	3 (2)
	4	52 (51)	5 (56)	57 (52)	medical advice	
	5	17 (17)	4 (44)	21 (19)	Psychiatry ward	2 (2)
Missing		23 (19)	14 (61)	14 (11)		0 (0)

The individual values are rounded to the nearest percent and may not total 100%

Score 1 is defined as death, score 2 is unresponsive wakefulness syndrome. Score 3 is defined as severe injury with permanent need for help with daily living, score 4 is moderate disability; no need for assistance in everyday life, employment is possible, but may require special equipment. When a patient scores a 5, he or she has only minor deficits in the physical, social or psychological domain[16].

REFERENCES

1. Izzy, S., Compton, R., Carandang, R., Hall, W. & Muehlschlegel, S. Self-fulfilling prophecies through withdrawal of care: Do they exist in traumatic brain injury, too? *Neurocrit. Care* **19**, 347–363 (2013).
2. Taylor CA, Bell JM, Breiding MJ & Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths – United States, 2007 and 2013. *MMWR. Surveill. Summ.* **66**, 1–16 (2017).
3. Majdan M *et al.* Years of life lost due to traumatic brain injury in Europe: A cross-sectional analysis of 16 countries. *PLoS Med.* **14,** 1–19 (2017).
4. Gunning AC *et al.* Demographic Patterns and Outcomes of Patients in Level I Trauma Centers in Three International Trauma Systems. *World J. Surg.* **39,** 2677–2684 (2015).
5. Turgeon AF *et al.* Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *CMAJ* (2011) doi:10.1503/cmaj.101786.
6. Geurts M, Macleod MR, van Thiel GJMW, van Gijn J, Kappelle LJ & van der Worp HB. End-of-life decisions in patients with severe acute brain injury. *Lancet Neurol.* **13**, 515–524 (2014).
7. Sprung CL *et al.* End-of-life practices in European intensive care units: the Ethicus study. *Jama* **290**, 790–797 (2003).
8. Verkade MA, Epker JL, Nieuwenhoff MD, Bakker J & Kompanje EJ. Withdrawal of life-sustaining treatment in a mixed intensive care unit: most common in patients with catastrophic brain injury. *Neurocrit. Care* **16**, 130–135 (2012).
9. Fraccaro P *et al.* Predicting mortality from change-over-time in the Charlson Comorbidity Index: A retrospective cohort study in a data-intensive UK health system. *Medicine (Baltimore).* **95**, e4973 (2016).
10. Yurkovich M, Avina-Zubieta JA, Thomas J, Gorenchtein M & Lacaille D. A systematic review identifies valid comorbidity indices derived from administrative health data. *J. Clin. Epidemiol.* **68**, 3–14 (2015).
11. Wilson JT, Pettigrew LE & Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use

J. Neurotrauma **15**, 573–585 (1998).

12. Marmarou A *et al.* IMPACT database of traumatic brain injury: design and description. *J. Neurotrauma* **24**, 239–250 (2007).
13. Lilley EJ, Scott JW, Weissman JS, Krasnova A, Salim A, Haider AH & Cooper Z. End-of-Life Care in Older Patients After Serious or Severe Traumatic Brain Injury in Low-Mortality Hospitals Compared With All Other Hospitals. *JAMA Surg.* **153**, 44–50 (2018).
14. Robertsen A, Førde R, Skaga NO & Helseth E. Treatment-limiting decisions in patients with severe traumatic brain injury in a Norwegian regional trauma center. *Scand. J. Trauma. Resusc. Emerg. Med.* **25**, 1–9 (2017).
15. Sise MJ, Kahl JE, Calvo RY & Shackford SR. Withdrawal of care: a 10-year perspective at a Level I trauma center. *J. Trauma Acute Care Surg.* **72**, 1186–1193 (2012).
16. Becker KJ *et* al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology* **56**, 766–772 (2001).
17. Geocadin RG, Peberdy MA & Lazar RM. Poor survival after cardiac arrest resuscitation: a self-fulfilling prophecy or biologic destiny? *Crit. Care Med.* **40**, 979–980 (2012).
18. Kirkman MA, Jenks T, Bouamra O, Edwards A, Yates D & Wilson MH. Increased mortality associated with cerebral contusions following trauma in the elderly: bad patients or bad management? *J. Neurotrauma* **30**, 1385–1390 (2013).
19. Souter MJ *et al.* Recommendations for the Critical Care Management of Devastating Brain Injury: Prognostication, Psychosocial, and Ethical Management :A Position Statement for Healthcare Professionals from the Neurocritical Care Society. *Neurocrit. Care* **23**, 4–13 (2015).
20. Roozenbeek B *et al.* Prediction of outcome after moderate and severe traumatic brain injury: external validation of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation After Significant Head injury (CRASH) prognostic models. *Crit. Care Med.* **40**, 1609–17 (2012).

21. Majdan M, Lingsma HF, Nieboer D, Mauritz W, Rusnak M & Steyerberg EW. Performance of IMPACT, CRASH and Nijmegen models in predicting six month outcome of patients with severe or moderate TBI: an external validation study. *Scand. J. Trauma. Resusc. Emerg. Med.* **22**, 1–10 (2014).
22. Steyerberhg EW *et al.* Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med.* **5**, e165 (2008).
23. Wilde EA *et al.* Recommendations for the use of common outcome measures in traumatic brain injury research. *Arch Phys Med Rehabil.* (2010) doi:10.1016/j.apmr.2010.06.033.

CHAPTER 7

Mortality in Polytrauma Patients with Moderate to Severe TBI on Par with Isolated TBI Patients: TBI as Last Frontier in Polytrauma Patients

CHAPTER 7

Title: Mortality in Polytrauma Patients with Moderate to Severe TBI on Par with Isolated TBI Patients: TBI as Last Frontier in Polytrauma Patients.

Online ahead of print: Injury

Cite as: Niemeyer MJS, Jochems D, Houwert RM, van Es MA, Leenen LPH, van Wessem KJP. Mortality in Polytrauma Patients with Moderate to Severe TBI on Par with Isolated TBI Patients: TBI as Last Frontier in Polytrauma Patients. Injury. 2022 Jan. Advance online publication. doi: https://doi.org/10.1016/j.injury.2022.01.009.

Author list: Menco JS[1] (MD), Niemeyer Denise Jochems[1] (MD), Roderick M. Houwert[1] (MD, PhD), Michael A. van Es[2] (MD, PhD), Luke P.H. Leenen[1] (Professor MD, PhD), Karlijn J.P. van Wessem[1] (MD, PhD)

[1] Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

[2] Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Background: Mortality caused by Traumatic Brain Injury (TBI) remains high, despite improvements in trauma and critical care. Polytrauma is naturally associated with high mortality and insults such as hypotension can lead to secondary injury in TBI patients. This study compared mortality rates between isolated TBI (ITBI) patients and polytrauma patients with TBI (PTBI) admitted to ICU to investigate if concomitant injuries lead to higher mortality amongst TBI patients.

Methods: A 3-year cohort study compared polytrauma patients with TBI (PTBI) with AIS head ≥3 (and AIS of other body regions ≥3) from a prospective collected database to isolated TBI (ITBI) patients from a retrospective collected database with AIS head ≥3 (AIS of other body regions ≤2), both admitted to a single level-I trauma center ICU. Patients <16 years of age, injury caused by asphyxiation, drowning, burns and ICU transfers from and to other hospitals were excluded. Patient demographics, shock and resuscitation parameters, Denver Multiple Organ Failure scores, acute respiratory distress syndrome (ARDS), and mortality data were collected and analyzed for group differences.

Results: 259 patients were included; 111 PTBI and 148 ITBI patients. The median age was 54 [33-67] years, 177 (68%) patients were male, median ISS was 26 [20-33]. Seventy-nine (31%) patients died. Patients with PTBI developed more ARDS (7% vs. 1%, p=0.041) but had similar MODS rates (18% vs. 10%, p=0.066). They also stayed longer on the ventilator (7 vs. 3 days, p=<0.001), longer in ICU (9 vs. 4 days, p=<0.001) and longer in hospital (24 vs. 11 days, p=<0.001). TBI was the most prevalent cause of death in polytrauma patients. Patients with PTBI showed no higher in-hospital mortality rate. Moreover, mortality rates were skewed towards ITBI patients (24% vs. 35%, p=0.06).

Conclusion: There was no difference in mortality rates between PTBI and ITBI patients, suggesting TBI-severity as a predominant factor for ICU mortality in an era of ever improving acute trauma care.

INTRODUCTION

Traumatic brain injury (TBI) poses a major global health challenge with the highest morbidity and mortality rates among trauma patients, estimated at 69 million patients suffering from severe TBI per annum [1]. In Europe, TBI is the primary cause for disability under the age of 40. These patients endure time-, resource- and dedication-consuming treatments, with annual costs exceeding €33 billion euros ($37 billion dollars) in Europe [2].TBI has a tremendous and long-lasting effect on these patients and their families [3].

Treatment of severely injured patients demands specialized and well-developed trauma and intensive care unit (ICU) systems. These were successfully developed over the previous decades to improve morbidity and mortality in polytrauma patients [4]. Such advancements may have contributed to the decline in mortality from exsanguination, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction syndrome (MODS), leaving central nervous system-related mortality as most prevalent cause of death in trauma [5,6].

Prevention of secondary brain injury- caused by coagulopathy, hypotension, fever and hypoxia, which initiate a sequence of ischemic and damaging biochemical processes- is key in acute TBI-management [7]. All of these insults are commonly found in polytrauma patients, therefore polytrauma could worsen brain injury.

Critical trauma care is ever-improving and TBI-related mortality rates are rising compared to other causes of death in ICU [4,8,9]. Therefore, the question arose whether mortality in our TBI population is mainly associated with the severity of polytrauma injuries or with the severity of the brain injury. The principal aim of this research was to compare outcomes in polytrauma patients with TBI (PTBI) and patients with isolated TBI (ITBI), both with moderate-to-severe TBI. The second aim was to assess TBI patient characteristics by comparing resuscitation parameters, MODS and ARDS incidences, and neurological outcomes.

MATHERIALS AND METHODS

Population and study setting

All patients with moderate or severe TBI, primarily admitted to the Emergency Department (ED) of the University Medical Center Utrecht between January 2015 and December 2017, were identified. Patients <16 years of age, injury caused by asphyxiation, drowning, burns and ICU transfers from and to other hospitals were excluded.

Patient identification and data on polytrauma patients with TBI (PTBI) were derived from a prospective ICU registration in our hospital and were compared to patients with isolated TBI (ITBI) who were identified retrospectively by the Trauma Care Network of the central Netherlands and were complemented by ED and patients records. The PTBI cohort included patients admitted to ICU with an Injury Severity Score (ISS) of >15 and an Abbreviated Injury Score (AIS) head ≥ 3. The ITBI cohort included patients with an AIS head ≥ 3 and the AIS in other body regions ≤ 2.

Clinical data and resuscitation variables

The primary outcome measure was in-hospital mortality rate. Secondary outcome measures were data on MODS, ARDS, inflammatory complications, days on the ventilator, ICU length of stay (ICU-LOS), hospital length of stay (H-LOS), and functional outcome, measured through the Glasgow Outcome Scale (GOS) scores at discharge. The GOS is measured on a scale ranging from: death (1), unresponsive wakefulness syndrome (2), severe disability (3), moderate disability (4), and minor to no disability (5)[10].

MODS was defined as a Denver Multiple Organ Failure score of >3, at least 48 hours after injury.[11] Denver MOF scores were preferred over the Sequential Organ Failure Assessment (SOFA), as the Glasgow Coma Score (GCS) forms a big part of the latter, and the GCS is unreliable in sedated patients[12]. ARDS was calculated and registered according to the Berlin definition[13]. Both daily MODS scores and ARDS were assessed in ICU up to day 28 of admission.

Data on trauma patients included: patient demographics (age and sex), mechanism of injury, injury severity score (ISS), abbreviated injury score (AIS) for different body regions, pelvic fractures, and shock parameters. Arterial blood gas, temperature and coagulation status were routinely collected as per ED protocol and were repeated in ICU. Urinary output was measured during the first hour after ICU admission. Registered interventions included emergency laparotomies and neurosurgical interventions by intracranial pressure (ICP) monitoring or decompressive craniotomy. Resuscitation products were registered during the first 24 hours of admission. Mortality rates were corrected for severity of head injury and age in two separate subanalyses.

Ethical approval

Waivers of consent for PTBI and ITBI cohorts were approved by our institutional review board. (reference number: WAG/mb/16/026664 & WAG/mb/16/025499).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 25.0.0 (Armonk, NY, USA). Group differences were calculated using the Mann-Whitney U test for continuous data. Differences in distribution of dichotomous variables were calculated with Pearson's Chi square test of homogeneity. Fisher's exact test was used if expected cell count was less than five. Statistical significance was defined as $P < 0.05$. Results are displayed in N(%) or median [Q1,Q3].

RESULTS

Over the three-year study period, 259 eligible patients were admitted to ICU with 111 PTBI patients and 148 ITBI patients. Most patients were male (68%), suffered from blunt force trauma (98%), with a median age of 54 [33-67] years, a median ISS of 26 [20-33], and a median AIS head of 4 [4-5]. Further demographics and AIS scores are displayed in Table 1.

Fifty-three patients (21%) developed MODS and 11 (4%) developed ARDS during ICU stay. Seventy-eight (30%) of the patients suffered from infectious complications, of which the largest group of 34 (44%) patients suffered from a hospital-acquired-pneumonia. In total, 256 (98%) patients were intubated: Most (134 patients, 52%) were intubated in the prehospital setting and 83 patients (32%) in ED. Patients remained ventilated for a median of 4 [2-7] days. Median stay in ICU was 5 [4-11] days and subsequently 17 [11-29] days in hospital. Ultimately, 79 patients (31%) died in hospital.

Patients with ITBI vs. patients with PTBI

Patients with ITBI patients were significantly older (49 [32-62] vs. 57 years [38-70], $p=0.009$). Patients with PTBI, understandably, had higher ISS scores (33 [25-38] vs. 21 [17-26], $p<0.001$). Moreover, these patients seemed to have higher AIS head scores than ITBI (4 [4-5] vs. 4 [3-5], $p=0.004$) (Table 1). All but one of 32 pelvic fractures were in PTBI patients. On ED arrival PTBI patients also had lower systolic and diastolic blood pressures, higher leucocyte counts, and higher PaCO¬2 and PaO2 levels. Patients with PTBI had longer prothrombin times; lower base deficits. Repeated ICU measurements were comparable regarding systolic and diastolic blood pressures temperatures, hemoglobin and base deficits levels, and arterial PaO2 levels between cohorts. Both cohorts were mildly acidotic on presentation but only ITBI patients were normalized on ICU admission. Arterial PaCO2 levels were higher in patients with PTBI in ED but normalized clinically in most patients in ICU. Patients with ITBI had significant higher urine output after the first hour in the ICU (295 [120-413]ml vs. 150 [78-380]ml, $p=0.005$).

Patients with ITBI received significantly more neurosurgical interventions (43% vs. 22%, p<0.001). Patients with PTBI received significantly more units of crystalloids, packed red blood cells (PRBC), fresh frozen plasma (FFP), platelets and tranexamic acid in both the first 8 hours and 24 hours (Table 2).

Patients with PTBI suffered more from ARDS (7% vs 2%, p=0.041) and inflammatory complications (43% vs. 20%, p=<0.001) but showed comparable MODS rates (18% vs 10% p=0.066). Patients with PTBI were intubated more often in the prehospital setting compared to ITBI patients, who were mostly intubated in the ED, OR or ICU (62% vs. 44%, p= 0.004). Patients with PTBI had to be ventilated longer (7 [3-12] vs. 3 [2-9] days, p<0.001); with longer ICU (9 [4-16] vs. 4 days [3-10], p<0.001), and hospital stays (24 [9-35] vs. 11 days [4-23], p<0.001). There was no significant difference in distribution of GOS between PTBI and ITBI cohorts (3 [2-3] vs. 3 [1-4], p=0.606). However, more patients with PTBI were discharged with severe disability (GOS 3; 57% vs. 33%, p<0.001). GOS distribution is shown in figure 1.

There was no difference in mortality rates between the PTBI and ITBI patient cohorts (24% vs. 35%, p=0.061) (table 3). Fatal intracranial pressure rises accounted for 19 (37%) deaths in the ITBI cohort, whereas the remaining 32 (63%) mortalities were withdrawn from life-sustaining treatment after a very poor neurologic prognosis was acknowledged. In the PTBI cohort, most patients (n=12, 44%) died due to fatal intracranial pressures. One patient died due to severe sepsis after gastric perforation and one died after of mass ischemia due to prolonged aortic entrapment. Twelve PTBI patients (44%) were withdrawn from life-sustaining treatment; 10 had poor neurological prognosis, two patients suffered cervical spinal cord injury-related respiratory insufficiency and one patient was withdrawn after a C1-C2 complete spinal cord injury.

The median number of days before death was 7 [2-9] in PTBI and 4 [2-8] days in ITBI patients. When mortality was stratified in age (<65 and ≥65 years), comparable rates were observed in PTBI and ITBI cohorts for both age groups (<65: n=16, 19% vs. n=24, 24%, p= 0.435 and ≥65: n=11, 42% vs. n=28, 61%, p=0.129). Correction for

mortality and injury severity (AIS head) showed similar mortality rates when compared between PTBI and ITBI cohorts respectively in AIS 3 (10% vs. 9% $p>0.999$), AIS 4 (24% vs. 36% $p=0.198$) and AIS 5 (43% vs. 49% $p=0.576$).

DISCUSSION

In this population of ICU admitted TBI patients, the in-hospital mortality following moderate-to-severe TBI was 31%. In-hospital mortality was similar for both groups, although PTBI patients suffered from concomitant injuries, stayed longer on the ventilator, in ICU and in hospital.

Polytrauma-associated mortality in the western world used to be predominantly caused by exsanguination, ARDS, multi-organ failure, and sepsis [14]. Yet nearly all deaths in this study were attributed to brain injury or related unfavorable prognosis. This trend has been previously observed in studies performed in our hospital with reported TBI-related mortality up to 59,9% as shown by Lansink et al. in the first decade of the 21st century, which increased to 76% in the period from 2013 to 2016 as shown by Jochems et al. [5,8]. We suppose that the successful decline in exsanguination may be attributed to successful implementations in damage control surgery, resuscitation protocols, and polytrauma management over the last two decades [9]. Furthermore, our trauma center employs dedicated polytrauma teams, who stay involved during the entire hospital stay in addition to a 24-hour attending trauma specialist regime; both presumably to good effect when observing critical processes in acute care in our trauma center [8,9,15]. However, this successful shift in outcomes poses new challenges, as patients - who would initially have succumbed to their polytrauma injuries - must now face TBI-related morbidities with meagre treatment options.

Our results showed comparable overall distributions in GOS scores between groups but showed more PTBI patients with GOS 3 (severe disability) on discharge. It is likely that many of these patients suffered invalidating injuries to extremities before discharge, resulting in a dependency in activities of daily living. Earlier research on polytrauma patients by Jochems et al. showed significant rises in GOS scores over a one-year period after rehabilitation. However, there was a small but comparable number of patients with GOS 2 (unresponsive wakefulness syndrome) in both groups [5]. (Figure 1) These limited numbers are in line with Dutch ethical and moral believes, who commonly share the idea that interminable unresponsiveness is not worth surviving for, resulting in patients (or their next of kin) preferring withdrawal of life sustaining treatment over extensive

treatment when very poor neurological prognosis is imminent.

Treatment options for TBI are frustratingly limited. Therefore, treatment is focused on supporting cerebral oxygenation and perfusion [3,14]. Hypoxemia in PTBI patients (with or without chest injury) might have gone underrecognized in the prehospital setting and may show room for improvement, as 62% of the PTBI patients were intubated prehospitally and measured worse PaO2 and PaCO2 levels upon ED presentation. In addition, the higher PTBI prehospital intubation rate may be explained by the higher number of thorax injuries. yet, neither could have caused the mortality rate to exceed the ITBI mortality rate. Furthermore, patients with PTBI in our population presumably lost more blood prior to hospital admission and in ED, as they recorded lower blood pressures on admission and received considerably more resuscitation products in both the first 8 and following 24 hours after admission. Prolonged periods of cerebral hypoperfusion potentially aggravates secondary insults [3,16]. Inversely, severe brain injury is also known to have effect on hemostatic and inflammatory pathways as well [17]. Blood pressures remained stable on presentation and after resuscitation in both groups, which may indicate successful resuscitation among PTBI patients.

It may be disputed that PTBI patients were as injured as was previously claimed, based on the adequate hemoglobin levels and systolic blood pressures on ED presentation. (Table 2) However, previous research in our hospital by Van Wessem et al. showed comparable patient and injury characteristics, and laboratory measurements. The index hospital is an urban situated level-1 trauma center with a relatively small service perimeter with short prehospital times; preventing physiologic measurements to worsen before presentation [6]. Our polytrauma patients were undeniably severely injured with an ISS of 33 (28% of them sustained pelvic fractures, 19% underwent urgent laparotomies, 22% emergency neurosurgical interventions), were mildly acidotic and coagulopathic, and were all admitted to the ICU.

Patients with ITBI showed significantly higher injury severity to the head and received nearly twice the number of neurosurgical interventions (43% vs. 22%). Yet we observed comparable overall mortality rates and when corrected for head injury severity (AIS

head), despite concomitant injuries in PTBI patients. The AIS scoring method is a useful and validated instrument in trauma care for distinguishing injury type and severity but may not be applicable in relating AIS scores to TBI severity and outcomes. It likely that ITBI and PTBI patients suffered from dissimilar injury types while scored within the same AIS category. For example, diffuse axonal injury and an epidural hematoma could be scored within the same severity category, but treatment and outcomes differ greatly.

The ITBI population was significantly older and while mortality rates were comparable in both groups, this could have account for the skewed mortality rate towards the ITBI patients. Age is an independent predictor of TBI-mortality; associated with frailty, anticoagulant use, and higher risks of low energetic falls with blunt force brain injury [18], while younger patients typically sustain sports, work, and traffic related injuries and are more prone to polytrauma injuries [19,20]. These different types of patient characteristics, trauma mechanisms and kinetics to the brain illustrate the heterogeneity of TBI and stress the difficulties in TBI approaches [20].

This study had certain limitations. Firstly, the retrospective nature of this study resulted in missing variables mostly in ITBI patients in the ED phase, rendering many included variables in the PTBI database invalid. Secondly, mortality was not adjusted for pre-injury comorbidities and as patients in our study were relatively old, they possibly had important comorbidities, obscuring the relation between injury type and mortality. Although comparable mortality rates were observed when stratified in age, the age-adjusted and injury adjusted mortality samples may have yielded insufficient power for an adequate comparison. Thirdly, this single center observational study was performed in a level-1 trauma center servicing the central region of the Netherlands: An urban and densely populated area with short prehospital times in general. This data should therefore be handled with care, as the relation between patient characteristics (i.e. Trauma mechanism, age, and prehospital times) and outcomes may be inapplicable to trauma centers in other countries.

In conclusion, this study compared isolated TBI patients with polytraumatized TBI patients, both with moderate-to-severe brain injury, to investigate the extent to which

extracranial injuries influence mortality rates in an era of rising TBI-related mortality. No significant distinction was observed in mortality between polytrauma patients and patients with isolated TBI, suggesting that mortality is predominantly related to TBI severity regardless of extracranial injuries. This research shows potential signs for improvements in prehospital intubation and oxygenation therapy among polytraumatised TBI patients.

Table 1. Baseline variables.

Demographics and injury characteristics	Total (*n* = 259)	Polytrauma TBI (*n* = 111)	Isolated TBI (*n* = 148)	P value
		Median [Q1-Q3]		
Age	54 [33-67]	49 [32-62]	57 [38-70]	0.009*
ISS	26 [20-33]	33 [25-38]	21 [17-26]	<0.001*
AIS head	4 [4-5]			0.004*
Median		4 [3-5]	4 [4-5]	
Mean rank		116.09	140.44	
AIS face	0 [0-2]	0 [0-2]	0 [0-2]	0.128
AIS chest	0 [0-3]	3 [2-3]	0 [0-0]	
AIS abdomen	0 [0-0]	0 [0-2]	0 [0-0]	
AIS extremities/pelvis	0 [0-2]	2 [0-3]	1 [0-1]	
AIS external	1 [0-1]	0 [0-1]	1 [0-1]	
		Number (%)		
Sex (%male)	177 (68)	83 (75)	94 (64)	0.054
MOI (%blunt)	253 (98)	107 (96)	146 (99)	0.233
Prehospital intubation	134 (52)	69 (62)	65 (44)	0.004*
Pelvic fracturea	32 (12)	31 (28)	1 (1)	<0.001*
Emergency department				
		Median [Q1-Q3]		
SBP (mmHg)	130 [108-150]	120 [90-136]	140 [120-160]	<0.001*
DBP (mmHg)	79 [60-90]	73 [54-85]	80 [70-90]	0.003*
Hb (mmol/l)	8.2 [7.4-9.1]	7.9 [7.2-8.9]	8.2 [7.8-9.1]	0.001*
Leucocytes (x10^9/L)	12.3 [8.3-17.4]	14.5 [9.8-20.4]	10.7 [7.6-15.2]	<0.001*
Platelets (x10^9/L)	220 [185-275]	223 [185-278]	219 [187-268]	0.801
PT	14.7 [13.8-16.2]	15.4 [14.5-17.6]	14.1 [13.6-15.3]	<0.001*
pH	7.34 [7.29-7.39]	7.33 [7.28-7.38]	7.35 [7.29-7.40]	0.084
PaCO2 (mmHg)	46 [41-52]	48 [43-54]	45 [40-50]	0.007*
PaO2 (mmHg)	208 [122-307]	180 [101-286]	225 [136-316]	0.023*
BD (mmol/L)	2.0 [- 1-5]	3.0 [0-7]	1.0 [- 2-4]	<0.001*
Bicarbonate (mmol/L)	24 [21-26]	23 [20-25]	25 [22-27]	<0.001*
INR	1.07 [1.00-1.20]	1.10 [1.04-1.23]	1.01 [0.99-1.13]	<.001*
Intensive care unit				
		Median [Q1-Q3]		
SBP (mmHg)	122 [105-139]	119 [104-137]	125 [107-142]	0.256
DBP (mmHg)	64 [56-73]	65 [56-72]	64 [57-75]	0.647
Temperature (°C)	35.1 [34.2-35.8]	35.0 [34.2-35.7]	35.1 [34.2-35.9]	0.550
Hb (mmol/l)	7.7 [7.0-8.4]	7.6 [6.8-8.2]	7.8 [7.0-8.4	0.111
pH	7.35 [7.29-7.40]	7.33 [7.28-7.38]	7.36 [7.31-7.41]	0.007*
PaCO2 (mmHg)	42 [38-46]	43 [39-48]	41 [37-46]	0.026*
PaO2(mmHg)	142 [109-189]	140 [105-182]	147 [110-195]	0.164
BD (mmol/L)	3.4 [1-5.4]	3.5 [1.8-5.5]	3.1 [0.7-5.2]	0.065
Bicarbonate (mmol/L)	22 [21-24]	22 [21-24]	23 [21-25]	0.335
Urinary production (mL)b	220 [100-400]	150 [78-380]	295 [120-413]	0.005*

Abbreviations: MOI: Mechanism of injury. ISS: Injury Severity Score. AIS: Abbreviated Injury Scale. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PT: Prothrombin time, PaCO2: Partial pressure of arterial Carbon Dioxide, PaO2: Partial pressure of arterial Oxygen, BD: Base deficit, INR: International Normalised Ratio.
* Statistically significant (*P* <0.05).
a: One pelvic fracture in the ITBI was classified as a mild injury according to the AIS.
b: Total UP production registered in first hour after ICU admission.

Table 2. Interventions and resuscitation.

	Total ***n*** **= 259**	**Polytrauma TBI** ***n*** **= 111**	**ITBI** ***n*** **= 148**	**P value**
		Number (%)		
Urgent laparotomy	21 (8)	21 (19)	0 (0)	<0.001*
Neurosurgical intervention	87 (34)	24 (22)	63 (43)	<0.001*
PRBC (n)a				
< 8 h	62 (24)	48 (43)	14 (10)	<0.001*
< 24 h	110 (43)	51 (46)	23 (16)	<0.001*
FFP (n)a				
< 8 h	50 (19)	42 (38)	8 (5)	<0.001*
< 24 h	56 (22)	43 (39)	13 (9)	<0.001*
Platelets (n)a,b				
< 8 h	12 (5)	11 (10)	1 (1)	<0.001*
< 24 h	38 (15)	24 (22)	14 (10)	0.008*
Tranexamic acid (n)a				
< 8 h	123 (48)	69 (62)	54 (37)	<0.001*
< 24 hc	119 (46)	66 (60)	53 (36)	<0.001*
		Median [Q1-Q3]		
Crystalloids (L)d				
< 8 h	2.6 [1.0-5.0]	4.4 [2.5-6.6]	1.5 [0.5-3.2]	<0.001*
< 24 h	4 [1.8-7.3]	7.2 [4.7-10.3]	2.5 [1.0-4.3]	<0.001*

Abbreviations: PRBC: Packed red blood cells, FFP: Fresh frozen plasma,.
* Statistically significant (P <0.05).
a: Displayed as number of patients receiving transfusion with respective of total percentage of administered units within cohort (%).
b: One unit contains material from 5 donors.
c: Lower frequencies <24 h compared to <8h were caused by deceased patients between 8 and 24 h after admission.
d: Prehospital fluids were excluded.

Fig. 1.

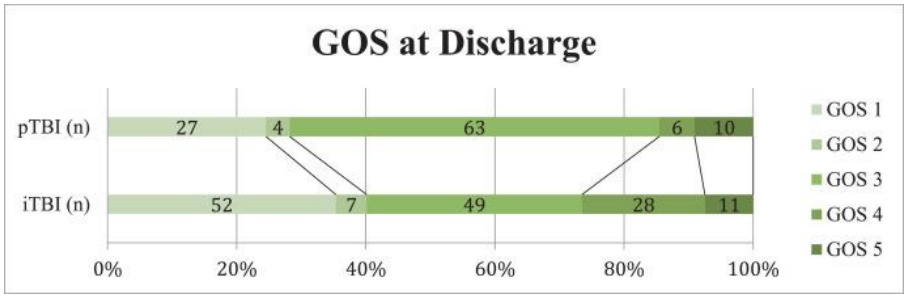

GOS at Discharge
pTBI (n)
27
4
63
6
10
iTBI (n)
52
7
49
28
11
0%
20%
40%
60%
80%
100%
GOS 1
GOS 2
GOS 3
GOS 4
GOS 5

Fig. 2.

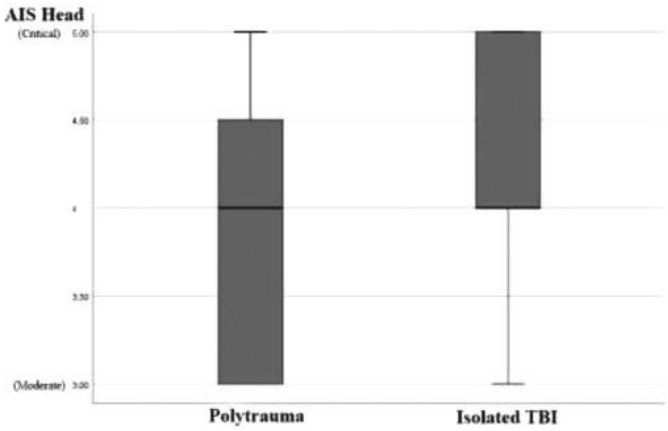
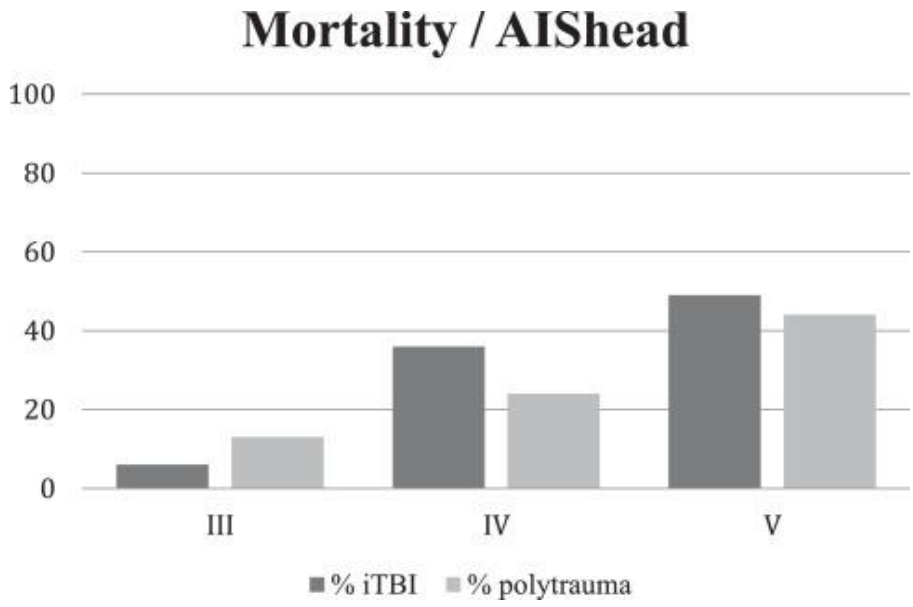

AIS Head
(Critical)
(Moderate)
Polytrauma
Isolated TBI

Table 3. ICU outcomes.

	Total ***n*** **= 259**	**Polytrauma TBI** ***n*** **= 111**	**iTBI** ***n*** **= 148**	**P value**
		Median [Q1-Q3]		
Days on ventilator	4 [2-7]	7 [3-12]	3 [2-9]	<0.001*
Days in ICU	5 [4-11]	9 [4-16]	4	<0.001*
Days in hospital	17 [11-29]	24 [9-35]	11 [4-23]	<0.001*
		Number (%)		
MODS	53 (21)	20 (18)	15 (10)	0.066
ARDS	11 (4)	8 (7)	3 (2)	0.041*
Infectious complications	78 (30)	48 (43)	30 (20)	<0.001*
In-hospital mortality	79 (31)	27 (24)	52 (35)	0.061

Qualitative variables are displayed as N(%) and quantitative variables are displayed as median [q1,q3] according to the distribution.
Abbreviations: ICU:Intensive Care Unit, MODS, Multi Organ Dysfunction syndrome, ARDS: Acute respiratory distress syndrome.
* Statistically significant ($P<0.05$).

Fig. 3.



REFERENCES

1. Dewan MC *et al.* Estimating the global incidence of traumatic brain injury. *J Neurosurg,* 1-18 (2018)
2. Olesen J, Gustavsson A, Svensson M, Wittchen HU & Jönsson B. The economic cost of brain disorders in Europe. *Eur J Neurol.* **19,** 155-162 (2012).
3. Maas AIR *et al.* Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol.* **16,** 987-1048 (2017).
4. Lansink KWW & Leenen LPH. History, development and future of trauma care for multiple injured patients in the Netherlands. *Eur J Trauma Emerg Surg.* **39,** 3-7 (2013).
5. Jochems, D. *et al.* Outcome in Patients with Isolated Moderate to Severe Traumatic Brain Injury. *Crit. Care Res. Pract.* **114,** (2018).
6. Van Wessem KJP &Leenen LPH. Reduction in Mortality Rates of Postinjury Multiple Organ Dysfunction Syndrome: A Shifting Paradigm? A Prospective Population-Based Cohort Study. *Shock.* **49,** 33-38 (2018).
7. Maas AIR, Stocchetti N & Bullock R. Moderate and severe traumatic brain injury in adults. *The Lancet. Neurology*, **7,** 728–741 (2008)
8. Lansink KWW, Gunning AC & Leenen LPH. Cause of death and time of death distribution of trauma patients in a level-1 trauma centre in the Netherlands. *Eur J Trauma Emerg Surg,* **39,** 375-383 (2013).
9. Hietbrink F *et al.* The evolution of trauma care in the Netherlands over 20 years. *Eur J Trauma Emerg Surg.* **46,** 329-335 (2020).
10. Wilson JTL, Pettigrew LEL & Teasdale GM. Structured interviews for the glasgow outcome scale and the extended glasgow outcome scale: Guidelines for their use. *J Neurotrauma.* **15,** 573-580 (1998).
11. Vogel JA *et al.* Prediction of postinjury multiple-organ failure in the emergency department. *J Trauma Acute Care Surg.* **76,** 140-145 (2014).
12. Dewar DC, White A, Attia J, Tarrant SM, King KL & Balogh ZJ. Comparison of postinjury multiple-organ failure scoring systems: Denver versus sequential organ failure assessment. *J Trauma Acute Care Surg.* **77,** 624-629 (2014).
13. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E,

14. Camporota L & Slutsky AS. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome. The Berlin Definition. *JAMA*. **307**, 2526–2533 (2012).
15. Gunning AC, *et al.* Demographic Patterns and Outcomes of Patients in Level I Trauma Centers in Three International Trauma Systems. *World J Surg.* **39,** 2677-2684 (2015).
16. van der Vliet, Q., van Maarseveen, O., Smeeing, D., Houwert, R. M., van Wessem, K., Simmermacher, R., Govaert, G., de Jong, M. B., de Bruin, I., Leenen, L., & Hietbrink, F. Severely injured patients benefit from in-house attending trauma surgeons. *Injury*. **50**, (2019)
17. Spaite DW, Hu C, Bobrow BJ, Chikani V, Sherrill D & Barnhart B, et al. Mortality and Prehospital Blood Pressure in Major Traumatic Brain Injury: The Absence of a Hypotension Threshold HHS Public Access Author manuscript. *JAMA Surg,* **152,** 360-368 (2017).
18. Qureshi AI & Qureshi MH. Acute hypertensive response in patients with intracerebral hemorrhage pathophysiology and treatment. *J Cereb Blood Flow Metab*. **38,** 1551-1563 (2018).
19. Karibe H, Hayashi T, Narisawa A, Kameyama M, Nakagawa A & Tominaga T. Clinical characteristics and outcome in elderly patients with traumatic brain injury: For establishment of management strategy. *Neurol Med Chir (Tokyo).* **57,** 418-425 (2017).
20. Peeters W *et al.* Epidemiology of traumatic brain injury in Europe. *Acta Neurochir (Wien)*. **157,** 1683-1696 (2015).
21. Liew TYS, Ng JX, Jayne CHZ, Ragupathi T, Teo CKA & Yeo TT. Changing Demographic Profiles of Patients With Traumatic Brain Injury: An Aging Concern. *Front Surg,* **6,** 1-7 (2019).

CHAPTER 8

Summary

SUMMARY

In the **Introduction**, it becomes clear that trauma is still a leading cause of death amongst younger people around the globe. In the past years, a decrease in exsanguination and multi-organ failure as cause of death after trauma was seen. This seemingly left traumatic brain injury as the most common cause of death due to trauma.

Traumatic brain injury refers to all injuries of the brain caused by an external force. This means it is a very diverse disease. In addition, secondary injury due to the brain injury itself or injuries elsewhere in the body, can also lead to damage of the brain. One example of this is low blood pressure due to blood loss.

The only treatment modality that has been proven to be effective in reducing mortaltity, is the treatment of patients with severe traumatic brain injury in a neurosurgical centre. There are other treatments based on evidence, but this evidence is usually of low quality. Furthermore, it is also unclear if the outcome of traumatic brain injury has improved at all over the last decennia.

The aim of this thesis was to provide an insight in the extent to which moderate or severe traumatic brain injury poses a problem in the Netherlands.

Chapter 1 describes the epidemiology of traumatic brain injury amongst adults in the Netherlands in the years 2015-2017. All adults who sustained moderate or severe traumatic brain injury in this time period were identified in the Dutch national trauma database, leading to a total of 12,295 patients. Thirteen per cent of these patients died. Most patients were men (61%) and on average older, median age was 65. Elderly patients and patients who suffered from injuries to other body parts than the brain, died more often as a result of their injuries (respectively 18 and 24%) than younger patients with solely brain injury. Most commonly, the injury was caused by a fall, or less often, by a road traffic accident. If elderly patients sustained a road traffic accident, they were mostly traveling by bicycle and bicycle accidents were quite common amongst our patients in

general. This suggests that prevention of bicycle accidents and falls could be an important aspect in order to decrease morbidity and mortality by TBI.

In **Chapter 2** epidemiology of traumatic brain injury amongst children was described for the same time period of 2015-2017. Again, the Dutch national trauma database was used and 1,413 patients were identified, of whom 5% died. As mechanism of injury is different for different age groups, we split the patients in groups by age: <5 years, 5-<10 years, 10-<16 years and 16-18 years old. TBI was most common for children in the oldest age groups. Percentages of children who died climbed with age. Falls were overall the most common cause of injury, but for children over 10 years old, a road traffic accident occurred more frequently than in the younger age groups. Again, there was a high percentage of bicycle injuries, which may well present a chance for prevention of these injuries.

Treatment in a neurosurgical centre is the only treatment modality that was unequivocally proven effective for patients with traumatic brain injury. To what extent traumatic brain injury is recognised by the ambulance crew in the Netherlands, was investigated in **Chapter 3.** All trauma patients older than 16 years who were transported to a trauma centre were identified. A little over a third (35.4%) of those patients had traumatic head injury. A little over two thirds of those patients were recognised as potentially having a head injury by the crew. If the ambulance crew suspected a head injury, they were right in almost 90% of cases. Patients with a severe head injury have to be transported to a neurosurgical centre. This happened for 68% of them. This means that training of ambulance crew in recognizing head injuries could help with treatment.

In **Chapter 4**, the effect of tranexamic acid on multiply injured patients with moderate or severe TBI was investigated. The patients were selected from a cohort of severely injured patients, who were admitted to the Intensive Care Unit of the UMC Utrecht. The cohort started in November 2013 and continued to include patients for 7.5 years. Tranexamic acid is administered to patients when severe bloodloss is suspected or low blood pressure is found. In this cohort, 234 patients were included and 51% of them received tranexamic acid. The patients who received this medication were severely ill,

but were also younger, the latter is associated with better outcome. There was no clear difference in outcome between patients who did or did not receive tranexamic acid.

We set out to confirm that traumatic brain injury is now the main cause of death amongst trauma patients in the Netherlands in **Chapter 5.** Data for all adult polytrauma patients who were admitted to the UMC Utrecht and died was collected for the years 2007-2016. These criteria were met by 596 patients. On average, patients were 61 years old and 61% was male. Overall, head injury was the most significant injury. Patients were significantly older in 2016 than in2007, but mortality was lower. Traumatic brain injury was the main cause of death in every year, but the percentage of deaths attributed to traumatic brain injury increased over the years, whilst this decreased for death due to major blood loss. This confirmed the hypothesis that TBI is the most important factor when it comes to mortality amongst polytrauma patients.

In order to understand mortality due to traumatic brain injury, for **Chapter 6**, data regarding treatment limiting decisions was collected for patients with moderate or severe traumatic brain injury. All patients with isolated moderate or severe traumatic brain injury admitted to the intensive care unit of the UMC Utrecht in 2011-2015 were included, leading to 179 patients. During admission, one third of those patients died, the vast majority (over 80%) of those patients died after having their life-sustaining treatment withdrawn. This decision was made on the first day of illness for 40% of these patients. Almost three quarters of the patients who survived, had a good functional outcome after three months and none of the survivors suffered from an unresponsive wakefulness syndrome (previously: vegetative state).

In **Chapter 7** the influence of other injuries on patients with traumatic brain injury was investigated. Adult patients with solely moderate or severe traumatic brain injury were compared with patients with moderate or severe injuries of the brain as well as other parts of the body. Patients from both groups were recruited from the intensive care unit of the UMC Utrecht, over the course of three years (2015-2017). There were slightly more patients included with isolated traumatic brain injury (148 patients vs 111). Patients

with injuries in other parts of the body developed complications of the lungs more often (7% vs 1%), required support from the ventilation machine for a longer period of time (7 vs 3 days) and spent longer in both the intensive care unit and hospital. Mortality rates amongst patients with multiple injuries were not higher than amongst patients with solely isolated brain injury, numbers actually leaned towards the opposite, with 24% vs 35%. This suggests the severity of the brain injury is the predominant factor for mortality amongst moderate or severely injured patients with brain injury.

CHAPTER 9

General Discussion

GENERAL DISCUSSION

One of the aims of this thesis was to emphasise the threat that TBI forms to our health. Even though this thesis has sought for clarification surrounding epidemiology and outcome, the topic of TBI still comes with many uncertainties. From uncertainty regarding incidence, definitions of grade of injury, to prognostication and decisions to limit treatment. Health care has made progress, as it is no longer only about living or dying, but also about the impact of the injury on life. Because of the nature of the injury, this might be more relevant to TBI than any other disease.

Epidemiology and the entity of TBI

In **chapters 1** and **2**, we showed that incidence of moderate and severe TBI in the Netherlands is high, with a rate of 29/100,000 person-years amongst adults and 14/100,000 amongst children [1,2]. As most high income countries, epidemiology amongst adults has shifted from young people and RTAs to the elderly and falls from a low altitude [3–5]. This shift from a younger to an older patient population is also noticeable amongst deceased trauma patients, as demonstrated in **chapter 7,** with a massive increase in mean age of 21 years [6]. In this chapter, we showed that head injury was the most predominant injury amongst all deceased patients in the UMC Utrecht over a 10-year period. In this period, the part CNS injuries played in mortality, grew even further.

When we compared polytrauma patients with moderate or severe TBI to isolated TBI patients in the UMC Utrecht **in chapter 5**, we did not find any difference in mortality. This was even the case when stratified for age and AIS of the head region. This may mean that improved care of trauma patients has left TBI as the last hurdle in trauma care. Another explanation could be that TBI in isolated TBI patients are a different entity than in polytrauma patients [6].

Comparison of incidence rates globally is incredibly difficult as the definition of severity of TBI differs in many articles. Glasgow Coma Scale (GCS) scores are often used to define a severe injury. However, the GCS can be affected by several factors, such as

sedation and intoxication, potentially misclassifying patients with mild TBI as moderate or severe [7].

Falls were the most common cause of death amongst our patients and this has been demonstrated in the United States of America and Germany as well [1,3]. The prevention of falls could therefore result in a reduction of TBI patients, especially in the elderly and younger children. The use of anticoagulants was not investigated in this thesis, but has shown to have a negative impact on severity of brain injury and is a drug commonly used by the geriatric patient [8]. Potential benefits of the shift from LMWHs and coumarines to DOACs are gathering attention [9]. This research was restricted to the Dutch population. Dutch people are known for their love of cycling and unfortunately this is reflected in the rates of people suffering from a bicycle accident, as found in **chapters 1** and **2**. More than half of RTAs leading to moderate or severe TBI amongst adults and children were due to a bicycle accident, this number was even higher amongst the elderly (73%) [1]. These numbers are extremely high compared to the rest of the world, for example, in London only 1% of children with moderate or severe TBI was a cyclist [10]. Deaths due to bicycle accidents in the Netherlands have barely decreased since 1996, unlike accidents with cars and motorcycles [11].

Pre-hospital and early treatment

Pre-hospitally, it is often difficult to recognise patients with a head injury. We demonstrated in **chapter 3** that only two thirds of patients with a moderate or severe head injury were transported to a level 1 trauma centre in our region. Moreover, ambulance crew had not suspected any head injury in over 20% of patients with moderate or severe TBI and only 48.8% of these patients were transported to a level 1 trauma centre [12]. Up to now, the Dutch triage protocol does not specifically name "suspicion of severe head injury" as a criterion for transport to a level 1 trauma centre, but uses a GCS<9 and anisocoria [12]. However, many severe head injuries present with higher GCS and without anisocoria. This is especially true for elderly patients, who make up the majority of patients presenting with TBI. In our evaluation of deceased

trauma patients admitted to the UMC Utrecht in **chapter 7,** AIS of the head region did not change over the investigated 10-year period, however, GCS scores were lower in the accident and emergency department. As pre-hospital intubation rates were higher, we assume the lower GCS scores were a result of higher rates of prehospital sedation.
As stated before, pre-hospital triage is not completely accurate and therefore not all TBI patients are brought to a centre that can match their needs. Especially elderly patients seem to suffer from "undertriage", since a relatively low impact injury can cause a severe TBI. This can have a big impact, as elderly patients make up a large part of all TBI patients in the Netherlands. Therefore, improvement of the triage protocol is highly recommended.

Tranexamic acid is part of pre-hospital or early in-hospital treatment for severely injured patients. Benefit of treatment for isolated TBI was not proven and therefore not indicated, therefore a few trials have looked into the effect of tranexamic acid on TBI. Unfortunately, for TBI patients it only showed a positive effect on mortality in subgroup analyses of one randomised controlled trial; for patients with a GCS of 9-15 or pupillary reactions in both eyes when administered within three hours of injury [13] . In our observations of the use of tranexamic acid in patients with TBI, we noted that outcomes did not differ between patients who did or did not receive tranexamic acid. It could be interpreted that this means tranexamic acid has a beneficial effect, as patients who received had more deranged physiology, but these patients were also younger. Age has been proven to be associated with outcomes such as mortality on numerous occasions, whilst physiology parameters have not. A recent systemic review, which did include the CRASH 3 trial, did not show proof of effect on mortality when tranexamic acid was given [14].

Prognostication

Unfortunately, as stated before, prognostication has proven to be difficult for TBI. The CRASH and the IMPACT tools are the most widely used prediction models, even though they are not meant to replace clinical judgement. They were developed for the prediction of mortality and "unfavourable outcome". These studies have developed their models on the biggest databases in TBI prognostication research [15]. Both models use parameters measured at admission for calculation of the scores. Many studies have aimed to validate these studies, more than for any other TBI prognostication study. A total of 91 studies were published on this topic between 2006 and 2018 [15]. An even higher number have looked for new models and/or predicting parameters. The most commonly included factors were GCS, pupillary reactivity and age, all of which are included in the IMPACT and CRASH models. The CRASH and IMPACT studies conclude that age is the most powerful factor in predicting outcome [15].

A recent review on prognostication in several neurological conditions state that the standardisation of conversations regarding treatment-limiting decisions and predicted outcome could have a higher impact on outcome than any of aforementioned factors [16]. The IMPACT and CRASH models were not developed for individual prognostication and are fortunately not widely used for this purpose, although some physicians do admit that they calculate the model for guidance and validation of their own prognostication [17]. Uncertain outcomes always make for difficult decisions and this is especially true for TBI patients. When several neurosurgeons in the Netherlands and Belgium were asked whether they would choose neurosurgical management for written cases of real patients with subdural haematoma, answers varied greatly amongst centres and surgeons [18]. Another study reported significant differences regarding ICP placement between several level 1 trauma centres in the Netherlands, despite correcting for patient characteristics [19]. This might reflect both the difficulty of prognostication as well as the different views on whether an outcome is unfavourable and whether a neurosurgeon feels the chance of a favourable outcome is worth risking an unfavourable one.

Withdrawal of life-sustaining treatment

Lack of certainty regarding epidemiology, prognostication and treatment results in lack of uniformity, as reflected in the lack of universal guidelines. Over the past decades many different interventions have been suggested and investigated and so far none have proven to be effective in improving patient outcome [19,20]. Furthermore, there is no guideline on when it is appropriate to install treatment-limiting decisions or even start withdrawal of life-sustaining treatment. For stroke patients, the Neurocritical Care Society advises to wait for 72 hours to see if there is any improvement [21]. Stakeholder organisations in the United Kingdom have stated that response to treatment and resuscitation should alter initial prognostication and that decisions should possibly be delayed to somewhere between 24 and 72 hours to allow for physiological stability, although they do recognise this will only alter the outcome for the minority of patients with devastating brain injury [22]. In **chapter 6**, data shows that these decisions are often made in the first 24 hours [23].

The subject of withdrawal of life-sustaining treatment (WLST) and other treatment-limiting decisions can be sensitive. Opinions on the subject vary greatly, influenced by many factors, including culture and religion [24,25]. The rate of WLST decisions in our TBI patients was on the higher end of the spectrum when compared to other countries, as seen in **chapter 6** [23]. These decisions are not taken lightly and never by one single physician. Furthermore, it sometimes seemed on reviewing the data that an inescapable death was brought forward, rather than that the decision was made for an expected poor functional outcome, however, this cannot be proven. The uncertainty in prognostication complicates decision-making by both proxies and physicians. Treatment-limiting decisions are usually seen as less impactful, even though refraining from treatment has the same weight as withdrawing it, according to some. In addition, previous research has proven that treatment-limiting decisions in stroke patients are associated with a higher mortality rate, even if these decisions do not concern life-sustaining treatment [26]. One of the hypotheses is that a treatment-limiting decision sparks the thought that treatment, as a whole might not be appropriate, even if the decision only covers a small aspect. For example, when a patient is not deemed to be appropriate to be readmitted to ICU, this does not mean that antibiotic treatment for a pneumonia is inappropriate, but it seems

that doctors are more likely to discuss this in these situations. Furthermore, a surgical intervention seems to lower the odds of a decision to withdraw life-sustaining treatment, in addition to the decision to do a diagnostic test or medical intervention [27,28].

Autonomy is one of most important pillars and patients usually lack capacity when it comes to decision-making. Therefore, we have to rely on advance directives, patient's statements regarding quality of life to proxies and proxies' perceptions of patient wishes [24]. Again, perceptions of what a good outcome is are influenced by many factors, as culture and religion [29]. Advance directives for patients with TBI are rare, as it is an acute and usually un-anticipated injury [29]. Therefore, clinicians often have to rely on proxies when it comes to the views of the patient on what they would deem an acceptable quality of life. In addition, not only do views on what a good outcome is differ per patient, a complicating factor is that several studies have shown that people are very capable of adapting to new situations [24]. For example, one study showed that most people with locked-in syndrome report a good quality of life [30]. However, TBI often results in cognitive disabilities, rather than just physical ones. ; whereas patients with locked-in syndrome solely have, albeit severe, physical disabilities. Although, other studies have found a satisfactory quality of life in stroke patients with a poor outcome as well [26]. Moreover, we cannot base a decision to provide care on the perception that the patient will adapt to his or her disability, if we know they previously have expressed other opinions on this subject. Altogether, determining what "unacceptable badness" is for a patient, is as difficult as determining what the actual outcome would be [24,29]. The incidence and prevalence of the unresponsive wakefulness syndrome is very low in this country. This could partially be the result of the higher number of WLST.

Another difficulty is that assessing the outcome of a TBI patient is not straightforward. More and more studies report outcome, including functional outcome using the Glasgow Outcome Scale (GOS). Even though the GOS gives insight in the problems in daily life, it is a narrow scale that does not always capture patient's struggles outside of hospital. Tests to assess cognitive outcome usually take place without time restrictions or distractions. Since reality is often different, the results of these tests do not necessarily

reflect how patients cope in daily life. As gaining insight in the actual outcome and level of functioning of patients helps us understand the consequence of the injury and our treatment, it is important that we assess it as accurately as possible. In addition to this, as mentioned before, prognostication in this patient group is extremely challenging. Relating actual outcome to a patient's injury might be the first necessary step.

Recommendations for the future

In the Netherlands, people are not obligated to wear a helmet on a bicycle, or even an e-bike (apart from the speed bike) [31]. As preventative measures for road traffic accidents have shown to work in the past, e.g. seatbelts, introducing the helmet in Dutch bicycle traffic might help to reduce the number of moderate-severe TBI patients, since it seems to lower the severity of the injury and protect against fractures of the skull [32,33]. This might be especially helpful for e-bicyclists, as the e-bike is often utilised by the elderly population [31]. This principle may also apply to teenage moped-users, as the moped was involved in more accidents in children of 16 years and older than the bicycle (LTR). The helmet is mandatory for mopeds that can reach a speed of 45 km per hour, but it is not for the slower mopeds that reach 25 km per hour. Considering the impact of the bicycle, e-bike and moped accidents on the incidence of TBI in the Netherlands, I believe a mandatory helmet could have a positive impact on prevention of TBI. Therefore I fully support and celebrate the decision of the Dutch Government to make helmet use mandatory for slower mopeds from January 2023 [34].

Adjusting and revalidating prognostication tools in our current patient population might be impossible, as decisions regarding treatment often rely at least partially on factors that feature in the models. If so, these possibly life or death decisions would prove the prediction model to be true, therefore fulfilling our own prophecy [22,35]. This problem could mean that prospective research regarding prediction models is no longer an option, as it would be unethical to no longer make treatment-limiting decisions. Some countries, however, are far less likely to offer withdrawal of life-sustaining treatment. Data from these areas may well still be suitable for research regarding prediction of outcome.

Several researchers are working on a more accurate assessment tool, which incorporates real-life situations in their assessment. Currently, our research group is working on a Virtual Reality test. Eye movements, time and walking patterns, amongst other parameters, are noted and analysed. Patients need to have a certain level of understanding to be assessed this way and these patients are far less likely to receive any treatment-limiting decision from this point. Therefore, these assessments could be used to see if we can predict the extent of the recovery we expect them to make. As this kind of test provides an enormous amount of data, artificial intelligence can be used to create hypotheses, rather than solely testing the researcher's idea.

I hypothesise that the Dutch value autonomy as part of quality of life highly and that religion plays a smaller role in the decision-making, which could be an explanation for the relatively high rates of withdrawal of life-sustaining treatment. I feel that the variability of the WLST rates and prevalence of patients with unresponsive wakefulness syndrome cannot be an indicator of quality of care in any country. The lack of accurate prognostication and impact of lower functional outcomes on lives, mean the decision-making is highly dependent on someone's outlook, or rather the family's perception of this outlook, on life. Without evidence to base protocols on, honest communication with family and next of kin is the next-best thing we have to ensure these decision are made in the best interest of the patients. The fact that we cannot base decisions on hard facts, does not mean that the process cannot be improved. In order to improve quality of care, insight in decision-making, and the grounds for these decisions, in patients with TBI surrounding treatment limitations is vital, however difficult. A good place to start would be to look into early decision, those within 24 hours, as this is not in line with the 72-hour window that has been recommended for stroke patients. Insight in the reasons for these decisions, could show whether a delay in these decisions would at all be possible. I think that our decision-making is in line with Dutch culture and certainly do not wish to fix a system that is not broken. I do, however, want to investigate if there is any room for improvement.

CONCLUSION

Moderate and severe traumatic brain injury are a common cause of death and disability in the Netherlands and pose a threat, much bigger than exsanguination and multi-organ failure, for our isolated TBI and multiple injured trauma patients. Many of these injuries are caused by falls, especially in the elderly community and amongst infants. Unfortunately, the nationwide love for cycling seems to come with its dangers, as many TBI patients suffered their injury after a bicycle accident. Research of prevention measures is recommended, as no treatment modality has proven to be effective yet and prevention may be the answer in decreasing the mortality and disability caused by TBI. Investigating possibilities for mandatory helmet use for cyclists, e-cyclists and all moped users is highly recommended. Improvement of the prehospital triage protocol is necessary to ensure transport of patients with moderate and severe TBI straight from scene of the injury to a level 1 trauma centre. Investigating options to determine functional outcome should help to determine the actual effect of treatment. Research regarding prognostication, however, is complicated by treatment-limiting decisions leading to self-fulfilling prophecies and an inability to assess functional outcome correctly.

REFERENCES

1. Jochems, D. *et al.* Incidence, causes and consequences of moderate and severe traumatic brain injury as determined by Abbreviated Injury Score in the Netherlands. *Sci. Rep.* **11**, 1–8 (2021).
2. Jochems, D. *et al.* Epidemiology of paediatric moderate and severe traumatic brain injury in the Netherlands. *Eur. J. Paediatr. Neurol.* **35**, 123–129 (2021).
3. Maegele, M. *et al.* Inzidenz und Versorgung des mittelschweren bis schweren Schädel-Hirn-Traumas. *Dtsch. Arztebl. Int.* **116**, 167–173 (2019).
4. Schumacher, R., Müri, R. M. & Walder, B. Integrated Health Care Management of Moderate to Severe TBI in Older Patients — A Narrative Review. (2017).
5. Peeters, W., Majdan, M., Brazinova, A., Nieboer, D. & Maas, A. I. R. Changing Epidemiological Patterns in Traumatic Brain Injury: A Longitudinal Hospital-Based Study in Belgium. *Neuroepidemiology* **48**, 63–70 (2017).
6. Jochems, D., Leenen, L. P. H., Hietbrink, F., Houwert, R. M. & van Wessem, K. J. P. Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma. *Injury* **49**, 1661–1667 (2018).
7. Salottolo, K. *et al.* The epidemiology , prognosis , and trends of severe traumatic brain injury with presenting Glasgow Coma Scale of 3. *J. Crit. Care* **38**, 197–201 (2017).
8. Gardner, R. C., Dams-O'Connor, K., Morrissey, M. R. & Manley, G. Geriatric Traumatic Brain Injury: Epidemiology, Outcomes, Knowledge Gaps, and Future Directions. *J. Neurotrauma* (2017) doi:10.1089/neu.2017.5371.
9. Shin, S. S. *et al.* Comparison of Traumatic Intracranial Hemorrhage Expansion and Outcomes Among Patients on Direct Oral Anticoagulants Versus Vitamin k Antagonists. *Neurocrit. Care* **32**, 407–418 (2020).
10. Hill, C. S., McLean, A. L. & Wilson, M. H. Epidemiology of Pediatric Traumatic Brain Injury in a Dense Urban Area Served by a Helicopter Trauma Service. *Pediatr. Emerg. Care* **34**, 426–430 (2018).
11. Centraal bureau voor statistiek (CBS). Overledenen; doden door verkeersongeval in Nederland, wijze van deelname. 1–2 (2016).

12. van Rein, E. A. J. *et al.* Diagnostic value of emergency medical services provider judgement in the identification of head injuries among trauma patients. *Eur. J. Neurol.* 1–7 (2018) doi:10.1111/ene.13804.
13. Roberts, I. *et al.* Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): A randomised, placebo-controlled trial. *Lancet* **394**, 1713–1723 (2019).
14. Lawati, K. Al *et al.* Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials. *Intensive Care Med.* **47**, 14–27 (2021).
15. Models, P. *et al.* Prognosis in Moderate and Severe Traumatic Brain Injury : A Systematic Review of Contemporary Models and Validation. 1–37 (2019) doi:10.1089/neu.2019.6401.
16. Wartenberg, K. E. *et al.* Gap Analysis Regarding Prognostication in Neurocritical Care: A Joint Statement from the German Neurocritical Care Society and the Neurocritical Care Society. *Neurocrit. Care* **31**, 231–244 (2019).
17. Moskowitz, J. *et al.* Should We Use the IMPACT-Model for the Outcome Prognostication of TBI Patients? A Qualitative Study Assessing Physicians' Perceptions. *MDM Policy Pract.* **3**, 238146831875798 (2018).
18. van Essen, T. A., de Ruiter, G. C. W., Kho, K. H. & Peul, W. C. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *J. Neurotrauma* **34**, 881–889 (2017).
19. Cnossen, M. C. *et al.* Causes and Consequences of Treatment Variation in Moderate and Severe Traumatic Brain Injury: A Multicenter Study. *Crit. Care Med.* **45**, 660–669 (2017).
20. Maas, A. I. R., Stocchetti, N. & Bullock, R. Moderate and severe traumatic brain injury in adults, Maas AIR et al. *Lancet N* **7**, (2008).
21. Souter, M. J. *et al.* Recommendations for the Critical Care Management of Devastating Brain Injury: Prognostication, Psychosocial, and Ethical Management: A Position Statement for Healthcare Professionals from the Neurocritical Care Society. *Neurocrit. Care* **23**, 4–13 (2015).

22. Harvey, D. *et al.* Management of perceived devastating brain injury after hospital admission: a consensus statement from stakeholder professional organizations. *Br. J. Anaesth.* **120**, 138–145 (2018).
23. Jochems, D. *et al.* Outcome in Patients with Isolated Moderate to Severe Traumatic Brain Injury. *Crit. Care Res. Pract.* **114**, (2018).
24. Geurts, M. *et al.* End-of-life decisions in patients with severe acute brain injury. *Lancet Neurol.* **13**, 515–524 (2014).
25. Sprung, C. L., Cohen, S. L., Sjokvist, P., Lippert, A. & Phelan, D. End-of-Life Practices in European. *Jama* **290**, 790–797 (2003).
26. Geurts, M. *et al.* Treatment restrictions in patients with severe stroke are associated with an increased risk of death. *Eur. Stroke J.* **2**, 244–249 (2017).
27. Gerges, P. R. A. *et al.* Intensity of care and withdrawal of life-sustaining therapies in severe traumatic brain injury patients: a post-hoc analysis of a multicentre retrospective cohort study. *Can. J. Anesth.* **65**, 996–1003 (2018).
28. Côte, N. *et al.* Factors associated with the withdrawal of life-sustaining therapies in patients with severe traumatic brain injury: A multicenter cohort study. *Neurocrit. Care* **18**, 154–160 (2013).
29. Honeybul, S., Gillet, G. & Ho, K. Futility in Neurosurgery: A Patient-Centered Approach. *Neurosurgery* **73**, 917–922 (2013).
30. Bruno, M. A. *et al.* A survey on self-Assessed well-being in a cohort of chronic locked-in syndrome patients: Happy majority, miserable minority. *BMJ Open* **1**, 1–9 (2011).
31. Poos, H. P. A. M. *et al.* [E-bikers are more often seriously injured in bicycle accidents: results from the Groningen bicycle accident database]. *Ned. Tijdschr. Geneesk.* **161**, D1520 (2017).
32. Dodds, N. *et al.* Evaluating the impact of cycle helmet use on severe traumatic brain injury and death in a national cohort of over 11000 pedal cyclists: A retrospective study from the NHS England Trauma Audit and Research Network dataset. *BMJ Open* **9**, 1–7 (2019).
33. Foley, J. *et al.* Cycling related major trauma in Ireland. *Injury* 21–26 (2019) doi:10.1016/j.injury.2019.11.025.

34. Rijksoverheid. Moet ik een helm dragen op mijn snorfiets? https://www.rijksoverheid.nl/onderwerpen/verkeersveiligheid/vraag-en-antwoord/helmplicht-snorfietsers (2021).

35. Izzy, S., Compton, R., Carandang, R., Hall, W. & Muehlschlegel, S. Self-fulfilling prophecies through withdrawal of care: Do they exist in traumatic brain injury, too? *Neurocrit. Care* **19**, 347–363 (2013).

Appendices

Dutch Summary (Nederlandse Samenvatting), List of publications, Acknowledgements (Dankwoord), and Biography

NEDERLANDSE SAMENVATTING

In de **Introductie** wordt uitgelegd dat trauma nog steeds een grote rol speelt in het overlijden van jonge mensen over de hele wereld. In de afgelopen jaren werd een daling in verbloeding en multi-orgaanfalen als doodsoorzaak na trauma gezien. Hierdoor lijkt het erop dat traumatisch hersenletsel nu het meest vaak overlijden veroorzaakt na een ongeluk.

Traumatisch hersenletsel wordt beschreven als een verwonding van het brein veroorzaakt door een kracht van buitenaf. Het is dus een erg breed ziektebeeld, waarbij er ook secundaire schade aan het brein kan optreden door het letsel zelf of letsel elders in het lichaam. Hierbij kun je denken aan bijvoorbeeld een lage bloeddruk door bloedverlies.

De enige interventie die bewezen effectief is, is dat de behandeling plaatsvindt in een neurochirurgisch centrum. Sommige andere behandelingen zijn wel gefundeerd op bewijs, maar van een laag niveau. Daarbij is het ook onduidelijk of de uitkomst van traumatisch hersenletsel wel is verbeterd in de afgelopen decennia.

Het doel van deze thesis was om inzicht te verkrijgen in de grootte van het probleem dat traumatisch hersenletsel vormt in Nederland. Om deze vraag te kunnen beantwoorden, is de thesis opgesplitst in de volgende hoofdstukken:

Hoofdstuk 1 beschrijft de epidemiologie van traumatisch hersenletsel onder volwassenen in Nederlands tussen 2015 en 2017. Alle volwassenen die in deze periode getroffen werden door matig of ernstig traumatisch hersenletsel in de Landelijke Trauma Registratie werden geïncludeerd. Dit waren 12.295 patiënten. Dertien procent van deze patiënten overleed. Mannen waren in de meerderheid (61%) en patiënten waren gemiddeld wat ouder, met een mediaan van 65 jaar. Geriatrische patiënten en patiënten met meerdere verwondingen buiten het hoofd, overleden vaker als gevolg van hun verwondingen (respectievelijk 18 en 24%) dan de gehele populatie. Het hersenletsel werd meestal door een val veroorzaakt, maar een ongeluk op de weg kwam ook vaak voor. Ouderen die gewond raakten door een ongeluk op de weg, waren meestal op de fiets. Fietsongelukken waren voor de algehele populatie vaak de oorzaak van het ongeval. Dit suggereert dat de preventie van fietsongelukken en vallen een belangrijke rol kan spelen in het verminderen van ziekte en overlijden als het gevolg van traumatisch hersenletsel.

De epidemiologie van traumatisch hersenletsel onder kinderen in dezelfde tijdsperiode wordt beschreven in **Hoofdstuk 2.** Ook hiervoor werd de Landelijke Trauma Registratie gebruikt, nu werden er 1.413 kinderen geïncludeerd. Vijf procent van deze kinderen overleed. Aangezien de oorzaak van het traumatisch hersenletsel per leeftijdsgroep lijkt te verschillen volgens de literatuur, zijn de kinderen in verschillende leeftijdsgroepen opgesplitst: <5 jaar, 5-<10 jaar, 10-<16 jaar en 16-18 jaar. Traumatisch hersenletsel kwam het vaakst voor bij de oudste leeftijdsgroep. Ook het deel van de kinderen dat overleed als gevolg van het letsel nam toe met de leeftijd. Bij kinderen kwam de val weer als meest voorkomende oorzaak van traumatisch hersenletsel naar boven, opnieuw gevolgd door een ongeluk op de weg. Bij de kinderen ouder dan 10 jaar was een ongeluk op de weg veel meer frequent de oorzaak van het ongeval dan bij de jongere kinderen. De bijdrage van het fietsongeval was wederom opvallend, waardoor het voorkomen van fietsongelukken of het dragen van helmen het aantal kinderen met traumatisch hersenletsel zou kunnen verminderen.

De enige interventie die bewezen effectief is in de behandeling van traumatisch hersenletsel, is de plaats waar de behandeling plaatsvindt: Een neurochirurgisch

centrum. In **Hoofdstuk 3** werd onderzocht hoe goed de ambulancemedewerkers in Nederland hoofdletsel herkennen, aangezien dit invloed heeft op de bestemming van de patiënt. Alle traumapatiënten ouder dan 16 jaar die werden vervoerd naar een traumacentrum werden geïdentificeerd. Iets meer dan een derde van deze patiënten had een traumatisch hoofdletsel. Een hoofdletsel werd vermoed bij ruim twee-derde van deze patiënten. Als de ambulancemedewerkers dachten dat een patiënt een verwonding van het hoofd had, klopte dit in bijna 90% van de gevallen. Helaas werd niet iedere patiënt met ernstig hersenletsel naar een neurochirurgisch centrum vervoerd, dit gebeurde bij 68%. Dit betekent dat het trainen van ambulancemedewerkers in het herkennen van hoofdletsels zou kunnen bijdragen aan de behandeling van deze patiënten.

In **Hoofdstuk 4** werd er gekeken naar de invloed van het medicijn tranexaminezuur op polytrauma patiënten met matig of ernstig hersenletsel. De patiënten werden geselecteerd uit een cohort van ernstige gewonde patiënten die werden opgenomen op de intensive care van het UMC Utrecht. Het cohort startte in november 2013 en inclusie duurde 7.5 jaar. Tranexaminezuur wordt toegediend als wordt vermoed dat de patiënt ernstig bloedverlies of een lage bloeddruk heeft. Er werden 234 patiënten geïncludeerd, waarvan 51% tranexaminezuur had ontvangen. De patiënten die het medicijn hadden gekregen, waren er vaak ernstiger aan toe, maar ze waren ook jonger, het laatste is normaal geassocieerd met een betere uitkomst. Er werd geen duidelijk verschil in uitkomst gezien tussen deze patiënten en andere traumapatiënten in het onderzoek.

In **Hoofdstuk 5** wilden we bevestigen dat traumatisch hersenletsel is nu de grootste oorzaak van overlijden onder traumapatiënten. We verzamelden data over alle volwassen polytrauma patiënten die waren opgenomen en overleden in het UMC Utrecht tussen 2007-2016. Er konden 596 patiënten worden geïncludeerd in het onderzoek. Gemiddeld, patiënten waren 61 jaar oud en 61% was van het mannelijk geslacht. Traumatisch hersenletsel was de meest ernstige verwonding. Patiënten waren significant ouder in 2016 dan in 2007, maar de mortaliteit was lager. Traumatisch hersenletsel was de grootste oorzaak van overlijden in ieder jaar, maar het percentage

van overlijdens door traumatisch hersenletsel steeg over de jaren, terwijl het aandeel van verbloeding afnam. Dit bevestigde dat traumatisch hersenletsel is de meest belangrijke factor in mortaliteit onder polytrauma patiënten.

Om de hoge overlijdenscijfers ten gevolge van traumatisch hersenletsel te kunnen begrijpen, werd in **Hoofdstuk 6** data met betrekking tot het stoppen van de behandeling bij patiënten met matig of ernstig traumatisch hersenletsel op de intensive care verzameld. De patiënten die hiervoor werden behandeld in het UMC Utrecht tussen 2011 en 2015 werden in dit onderzoek meegenomen. Uiteindelijk konden 179 patiënten worden geïncludeerd. Ruim een derde van de patiënten overleed tijdens de opname in het ziekenhuis. Van deze patiënten overleed de overgrote meerderheid (ruim 80%) nadat werd besloten de behandeling te staken. Deze beslissing werd voor 40% van de patiënten op de eerste dag van opname genomen. Bijna driekwart van de overlevenden had een goede functionele uitkomst na drie maanden en geen van de patiënten bevond zich in een vegetatieve status (nu: unresponsive wakefulness syndrome).

De invloed van verwondingen van andere lichaamsdelen dan het hoofd op patiënten met traumatisch hersenletsel werd bestudeerd in **Hoofdstuk 7**. Volwassen patiënten met matig of ernstig geïsoleerd traumatisch hersenletsel werden vergeleken met volwassen patiënten met naast matig of ernstig traumatisch hersenletsel ook matig en ernstige verwondingen in andere delen van het lichaam. Voor dit onderzoek werden patiënten gebruikt die opgenomen waren geweest op de intensive care van het UMC Utrecht in 2015-2017. In deze tijdsperiode waren er iets meer patiënten met geïsoleerd hersenletsel dan meervoudig gewonde patiënten (148 vs 111). Patiënten met verwondingen in andere delen van het lichaam hadden vaker last van complicaties met betrekking tot de longen (7 vs 1%), hadden langer ondersteuning van een beademingsapparaat nodig (7 vs 3 dagen) en waren langer opgenomen op zowel de intensive care als in het ziekenhuis. Patiënten die meervoudig gewond waren, overleden niet vaker dan patiënten met alleen traumatisch hersenletsel. De cijfers lijken zelfs op het tegenovergestelde te wijzen (24 vs 35%). Dit alles suggereert dat de ernst van het hersenletsel de grootste rol speelt in het overlijden van patiënten met matig of ernstig traumatisch hersenletsel.

LIST OF PUBLICATIONS

1. Jochems D, van Rein E, Niemeyer M, van Heijl M, van Es MA, Nijboer T, et al. Incidence, causes and consequences of moderate and severe traumatic brain injury as determined by Abbreviated Injury Score in the Netherlands. Sci Rep. 2021 Oct 7;11(1):19985. doi: 10.1038/s41598-021-99484-6. PMID: 34620973; PMCID: PMC8497630.
2. Jochems D, van Rein E, Niemeyer M, van Heijl M, van Es MA, Nijboer T, et al. Epidemiology of paediatric moderate and severe traumatic brain injury in the Netherlands. Eur J Paediatr Neurol. 2021 Oct 9;35:123-129. doi: 10.1016/j.ejpn.2021.10.004. Epub ahead of print. PMID: 34687976.
3. van Rein EAJ, Jochems D, Lokerman RD, van der Sluijs R, Houwert RM, Lichtveld RA, et al. Diagnostic value of emergency medical services provider judgement in the identification of head injuries among trauma patients. Eur J Neurol [Internet]. 2018;1–7. Available from: http://doi.wiley.com/10.1111/ene.13804
4. van Wessem KJP, Jochems D, Leenen LPH. The effect of prehospital tranexamic acid on outcome in polytrauma patients with associated severe brain injury. *Eur J Trauma Emerg Surg.* (2021) doi: 10.1007/s00068-021-01827-5. Online ahead of print.
5. Jochems D, Leenen LPH, Hietbrink F, Houwert RM, van Wessem KJP. Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma. Injury [Internet]. 2018;49(9):1661–7. Available from: https://doi.org/10.1016/j.injury.2018.05.012
6. Jochems, D. *et al.* Outcome in Patients with Isolated Moderate to Severe Traumatic Brain Injury. *Crit. Care Res. Pract.* **114**, (2018).
7. Niemeyer MJS, Jochems D, Houwert RM, van Es MA, Leenen LPH, van Wessem KJP. Mortality in polytrauma patients with moderate to severe TBI on par with isolated TBI patients: TBI as last frontier in polytrauma patients. *Injury.* (2018) doi: https://doi.org/10.1016/j.injury.2022.01.009

QUOTES

1. Just keep swimming, just keep swimming, just keep swimming… - Dory, Finding Nemo
2. I did a thing! – Jeremy Clarkson, Clarkson's farm
3. Behalve als ze dood gaan, dan is het eerder klaar. – Denise Jochems *over follow-up*
4. I am sick of sitting around here, trying to write this book. – Dancing in the dark, Bruce Springsteen
5. Gonna do my very best and it ain't no lie, if you put me to the test, if you let me try. – Take a chance, ABBA
6. I don't know what got in to me. I'm going to be the REAL me from now on. *Which is Batman?* Which is Batman. – Heart and *Brain,* The Awkward Yeti

DANKWOORD

Geachte Professor Leenen, ruim 5 jaar geleden vroeg ik u om een project voor een wetenschapsstage, zonder onderzoekservaring of aanbevelingen. U gaf mij een kans en nu zijn we hier. Ik zal u nooit genoeg kunnen bedanken voor dit vertrouwen en alle steun die daarop gevolgd is.

Beste Karlijn en Marijn, jullie hebben je ongetwijfeld wel eens afgevraagd of het ooit wel zo ver zou komen. Ik had niet kunnen hopen op zoveel steun, goede feedback en hulp als ik van jullie heb gekregen. Als ik later een half zo goede chirurg, supervisor en onderzoeker word, is mijn levensdoel behaald. Enorm bedankt voor de afgelopen jaren, zonder jullie was dit niet eens bijna gelukt!

Beste Menco, je werkt te hard. Zoals ik zo vaak heb gezegd, maar nu in mijn dankwoord zodat je wel moet luisteren: Ga eens op de bank zitten. Gebruik deze jaren om nieuwe hobby's te ontwikkelen zodat je biografie interessanter is dan die van mij. Zonder gekheid: Ontzettend bedankt. Zonder jouw slimheid, humor en eindeloze inzet had ik dit niet kunnen doen! Ik kijk uit naar de uitnodiging voor de verdediging van jouw proefschrift.

Beste co-auteurs; Eveline, Marjolein, Michael, Bart, Jan Willem, Mark, Professor Slooter, Rogier, Robin: Dank voor al jullie wijsheid, brainstormen en harde werk!

Lieve Tyche en Tessa, lieve paranimfen, ik kan jullie nooit genoeg bedanken. Ik hoop dat deze gelegenheid om een nieuwe jurk te kopen een beetje laat zien hoe ontzettend dankbaar ik ben voor jullie vriendschap, kookkunsten en grenzeloze liefde. Bedankt, dat we maar nog decennia lang bij elkaars mijlpalen vooraan staan.

Lieve vriendinnen, lieve Marieke, Emma, Lieselotte, Rimke, May, Stefanie, Mayte, Ludwike, Marloes, Suze en Simone. Door jullie is Utrecht nog meer als thuis gaan voelen dan het al deed. Als ik aan mijn stadsie denk, denk ik aan jullie. Bedankt voor alle gesprekken, steun op moeilijke dagen, vertrouwen en de koffietjes. Bedankt voor een

geweldige tijd als student en yup;). Mijn liefde breidt zich uit naar alle komende generaties. Dat de kleine kruimels maar jarenlang "ik heb een tante in Engeland en die komt, hiep hoi" mogen zingen.

Lieve papa en mama, het klinkt misschien cliché, maar het is toch echt zo: Zonder jullie was ik hier nooit gekomen. Niet alleen letterlijk (qua biologie en transport), maar ook figuurlijk. Jullie geloofden in mij nog voor ik geboren werd en hebben het nooit opgegeven. Bedankt, deze is voor jullie.

Lieve Moreno, als echt klein broertje kwam het beetje druk van de familie van jou. Ik hoop dat ik jouw bijnaam voor mij als "golden child" zo een beetje eer aan heb gedaan. Nu is het jouw beurt. Doe alles waarvan ik weet dat je het kan en word "platinum child". Ik zal vooraan staan om je aan te moedigen (als de Corona het toelaat, uiteraard).

Dear Ying, Emiko, Holly, Mehereen, Dimitrios and Megha. Moving countries, specialty application, MRCS exams, COVID redeployment and PhD writing would have been impossible without you. Thank you for keeping me sane in the NHS and for listening to my rants. It means the world to me!

Dear Matt. I promised you a special shout-out for the great work of art that is the title of my thesis. So here it is. Thank you for all your help, political insight and for laughing at my jokes. Truly appreciated.

Dear Karim, a simple "thank you" is not quite enough, but I guess it is all I can give you at this point. So, here we go: Thank you for all your reading, your laughs, encouragements and your love. And of course, thank you for letting me nap on the couch on our only days off together.

BIOGRAPHY

Denise Jochems was born on 28th of February 1992 in the Wilhelmina Kinderziekenhuis in Utrecht, the Netherlands.

She spent her first 10 years in Utrecht, before moving to Houten. Denise attended secondary school at the Oosterlicht College in Nieuwegein, from which she graduated Cum Laude.

Denise chose to attend University close to home at Utrecht University for both her Bachelor and Master of Science degree. For the former, she received a Cum Laude mark. She has had a passion for Surgery for as long as she can remember and dedicated her final year to the specialty. This is when she commenced her research for the Trauma Surgery department.

After graduation, she combined research with jobs in the Accident and Emergency Department of the UMC Utrecht and as a Clinical Teacher for the third year medical students during their surgical rotation. She applied successfully to the stand-alone second year of the United Kingdom Foundation Programme and migrated to the United Kingdom in August 2019. In 2020, she secured a training spot on the Improving Surgical Training programme for General Surgery in Birmingham, where she has worked for the Thoracic Surgery, Urology and General Surgery Departments. Sometimes, childhood dreams do come true.

Before lockdown restrictions, Denise enjoyed travelling, shopping, watching movies at the cinema and discovering new places to eat. She was worried that these hobbies made her seem a bit dull, but she did not feel like searching for a new one whilst juggling a full-time job, thesis-writing and COVID pandemic. And then Disney+ came along and she just gave up on the idea altogether. Currently, she misses Dutch cheese, cycling

to work with only moderate risk of injury, digital patient records and widely available ultrasounds and CT scans, but of course, mostly her family, friends and colleagues. All of which are only slightly compensated by scones and pies, her newly-purchased Mini Cooper, her handsome cat named Winston Purrchill, lovely colleagues and new friends and almost-nearby living boyfriend.