The relationship between mechanism of injury and traumatic axonal injury: A prospective MRI study of patients with moderate and severe traumatic brain injury

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ABSTRACT:

Objective: To investigate the mechanism of injury and the finding of traumatic axonal injury (TAI) and TAI grades on clinical MRI in moderate and severe TBI.

Methods: A total of 390 consecutive patients, age 7-69 years, with moderate or severe TBI admitted to St.Olavs University Hospital (Trondheim, Norway) during a 9-year period were prospectively included in a database. In this study 217 of the patients with known mechanism of injury and MRI performed within 35 days post injury (median 8, IQR 4 - 17) were included. The mechanism of injury was registered as; road traffic accident (RTA), alpine, fall, violence and other. The MRI protocol consisted of; T2* weighted gradient echo (GRE), fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) sequences. TAI lesions were evaluated blinded and categorized into three grades based on location: white matter of the hemispheres (grade 1), corpus callosum (grade 2) and brain stem (grade 3).

Results: Patients injured in RTAs and any type of fall had TAI lesions in 81% and 61% of the cases respectively. There was a significant difference in TAI grades between the RTA subcategories (including the alpine category) (p=0.008): All pedestrians had TAI lesions and the highest mean TAI grade of 2.27 (95% CI 1.74–2.80), followed by the alpine accidents with TAI in 90% and mean TAI grade of 2.10 (CI 1.39 – 2.81) and patients who were inside a car with TAI in 89% and mean TAI grade of 1.97 (CI 1.72–2.21). There was also a significant difference between the TAI grades in the fall subcategories (p=0.015): Patients with falls from > own height had TAI in 76% of the cases with mean TAI grade of 1.46 (CI 1.09 – 1.83), followed by fall in stairs with TAI in 60% and mean TAI grade of 1.00 (CI 0.50–1.50). Patients with low-energy injuries such as falls from ≤ own height had TAI lesions in 37.5 % of the cases with mean TAI grade of 0.44 (CI 0.10–0.77).

Conclusion: Pedestrians had the highest percentage of TAI and TAI grade of all subcategories of injury followed by alpine accidents. Although in the fall category the highest percentage of TAI and the highest TAI grade was found among the falls from > own height, also patients with more low-energy injuries like falls from ≤ own height and fall in stairs had visible TAI lesions on clinical MRI in one to two thirds of the patients.

Key Words: traffic accidents, magnetic resonance imaging (MRI), traumatic brain injury (TBI), diffuse axonal injury, cohort study, prospective study

INTRODUCTION

Traumatic axonal injury (TAI) or diffuse axonal injury is an important type of injury that contributes to mortality and disability in patients with traumatic brain injury (TBI) (1-7). The mechanism that causes TAI is angular or rotational acceleration-deceleration forces that causes the brain tissue to be deformed and stretched (8). Hence, the normal function of the axiolemma becomes disrupted, interfering with the normal function of the axon, with the result of swelling, accumulation of amyloid beta precursor protein (B-APP) and often secondary disruption of the axon (8-10). It is well established that road traffic accidents (1, 11-13) and fall from a considerable height (13, 14) can cause TAI. There is now increasing evidence of TAI in all severities of TBI (1, 15).

The most common imaging modality in TBI patients is Computed Tomography (CT), but the sensitivity to detect TAI is much lower than for MRI (16). Therefore MRI is the imaging modality of choice in the subacute and chronic phase of TBI (17). T2*gradient echo (T2* GRE) sequences are sensitive to iron in blood breakdown products and therefore depict hemorrhagic TAI lesions, while fluid attenuated inversion recovery (FLAIR) also depict non-hemorrhagic lesions due to edema (18). Before MRI was in use, TAI was graded based on autopsy studies conducted by Adams et al. (3). Gentry et al. later described a modified grading of TAI based on location as detected on MRI (19):Grade 1 – lesion(s) in the white matter of the hemispheres, grade 2 – lesion(s) in corpus callosum and grade 3 – lesion(s) in the brain stem. It is assumed that there is a successive involvement of more central and deeper brain structures as the load of impact increases (1, 20). Hence, the TAI grades are assumed to reflect the energy of the trauma.

To our knowledge, there have been no in depth study of the mechanisms of injury that causes visible TAI lesions on clinical MRI. Hence, the aim of this study is to investigate the main mechanisms of injury and the finding of TAI and TAI grades on clinical MRI performed in the early phase post injury. Road traffic accidents (RTAs) and falls will be divided in subcategories to reflect the energy of the trauma. Specifically, we will also investigate the occurrence of TAI in alpine accidents and investigate if low-energy injuries can cause visible TAI lesions on clinical MRI.

MATERIAL AND METHODS

Patients

All patients admitted to the Neurosurgical department at St.Olavs University Hospital (Trondheim, Norway) with moderate or severe head injury, according to the Head Injury Severity Scale (HISS) (21), were registered (n=489) during a 9 year period (October 2004 to October 2013). Patients under the age of 7 (n=16) and over 69 (n=82) were excluded to eliminate effects of low and high ages and comorbidity. One patient did not consent to participate in this study. This left 390 patients for further analyses and 217 patients with known mechanism of injury and MRI (*Figure 1*).

Mechanism of injury

The mechanism of injury was prospectively collected and registered as: road traffic accident (RTA), alpine, fall, violence, other mechanism or unknown mechanism. RTAs were divided into four subcategories to reflect the energy of the trauma: inside a car, on bicycle, pedestrian and motorcycle/moped/snow scooter/other motorized vehicles. Alpine is presented and analyzed in relation to RTAs because this mechanism is thought to resemble the accelerating-decelerating forces that occurs in RTAs. Another possibility would be to compare it with the falls from high heights. Fall height was divided into seven subcategories to reflect the energy of the trauma. These subcategories were; < own height, = own height, > own height but ≤ 2 meters, > 2 meters but < 5 meters, ≥ 5 meters, fall in stairs and unknown fall height. For some of the analyses we combined fall subcategories to increase the sample size: ≤ own height, also called simple falls (14), > own height, fall in stairs and unknown fall height.

Other injury variables

To present patients included in this MRI study in comparison with non-included patients from the total TBI cohort, other injury variables were registered: Intubation status, pupillary dilatation, GCS score at admission and secondary events: hypoxia (O_2 saturation below 92 %) and hypotension (systolic blood pressure <90mmHg) before or at admission. Evacuation of hematomas and in hospital mortality was also registered. K.G.M. or S.H. estimated the injury severity score (ISS) for all patients, as a measure of both intra- and extra-cranial injury.

Clinical Magnetic Resonance Imaging (MRI)

The clinical MRIs were performed at the study hospital or at one of the local hospitals in the region. At the study hospital either a 1.5 Tesla Siemens Symphony, 1.5 Tesla Siemens Avanto or a 3 Tesla Siemens Skyra (n=6) system was used. At the local hospitals also a 1.5 Tesla

Philips Gyroscan NT Intera was used. Before the study started all the involved hospitals, including the study hospital, received the MRI protocol with standardized MRI sequences and parameters for use in the early clinical MRI scanning of the patients. This protocol consisted of five different imaging sequences: 1) Sagittal turbo spin echo T2-weighted imaging, 2) Sagittal, transverse, and coronal T2-weighted fluid attenuated inversion recovery (FLAIR) imaging, 3) Transverse T2*-weighted gradient echo imaging (GRE), 4) Transverse spin echo T1-weighted imaging and 5) Diffusion weighted imaging (DWI) (1, 18).

Image analyses

The MRIs were described based on visual inspection as TAI or no TAI and further classified into grades of TAI (1, 2 and 3, the latter assumed to be the worst). This was done based on the location of lesions in T2*GRE, FLAIR and DWI. A resident in radiology (K.G.M.) and three experienced neuroradiologists (K.A.K., J.R. and M.F.) performed the image analyses. All was blinded for patient identification, clinical information and time of examination. The inter-rater reliability for lesion load for the different MRI sequences was found to be good to excellent in an earlier study: For overall TAI grading, linear Cohen's κ was 0.74 (95 % CI 0.69 – 0.80, $p < 0.001$) (18)

Analysis

Patient and injury variables are listed as numbers with percentages and median with IQR. Assumptions for normal distribution was tested by QQ-plots and the Shapiro-Wilk test. Since the continuous data did not have a normal distribution, Kruskal-Wallis and Mann-Whitney U tests were used for group comparisons. We used Chi-square test and Fishers Exact test for comparisons of proportions.

TAI grades were numbered 0 to 3 and treated as a scale variable, where 0 equaled no TAI, and 1-3 equaled TAI 1-3 respectively. For each injury mechanism, the mean TAI grade was estimated with a 95 % confidence interval.

The statistical significance was set to $p < 0.05$ (two-sided). Data was analysed using IBM SPSS Statistics 21 for Windows.

Ethics

The study is approved by The Regional Committee for Medical Research Ethics. Written informed consent was given by the surviving patients or, for incapacitated individuals, their next of kin. The Norwegian Directorate of Health approved use of data from deceased individuals.

RESULTS

Patient demographics and injury related variables

Table 1 shows the characteristics of the 217 patients included in this MRI study. The included patients were significantly younger, had a higher GCS score and lower percentage with severe TBI, than the non-included patients. The non-included patients (n=167) had a higher occurrence of secondary events, such as hypoxia and hypotension and more often pupillary abnormalities at admission. They also had a higher in hospital mortality than the included patients. Concerning surgery of mass lesion there were no differences between the groups.

Mechanism of injury

There were no significant differences in the mechanisms of injury between the MRI group and the non-included patients, but there was a tendency towards more MRI performed in the alpine category (p=0.076). RTAs were the most frequent mechanism of injury (50%), followed by falls (37%) (*Table 2*). 56% of the patients in the RTA group were inside of a car. Of the eleven pedestrians eight was hit by a car, two by a trailer and one by a snow scooter. 10 patients were injured while doing alpine. 20% of the falls were from own height or less, 46% were from a higher height and 25% was fall in stairs.

Mechanism of injury and occurrence of TAI lesions on clinical MRI

Clinical MRI was performed at median 8 days (IQR 4 – 17). Of the 217 patients 72% had TAI lesions. 81% of all RTA patients (n = 88) and 89% in the subcategory inside a car had TAI (*Table 3*). Among the 11 pedestrians, all had TAI lesions, and in the alpine category 90% had TAI.

Two of the three patients who had fallen from less than their own height and 31% of the patients who had fallen from their own height had TAI. 60% of patients with fall in stairs (n = 12) had TAI lesions. Also two out of nine patients that were victims of violence had TAI.

Mechanism of injury and TAI grading on clinical MRI

In *Table 3* the different subcategories of injury mechanism are presented with TAI grades. Some subcategories are presented in *Figure 2* to better visualize the tendency of increasing or decreasing TAI grades. We chose to analyze alpine together with RTA and found that there were significant differences in TAI grades between the alpine and the four RTA subcategories ((Kruskal-Wallis analyses), p= 0.008). *Figure 3A* shows that pedestrians had the overall highest mean TAI grade of 2.27 (95% CI 1.74–2.80), followed by the alpine category; with a mean TAI grade of 2.10 (CI 1.39–2.81). Patients inside a car had a mean TAI grade of 1.97

(95% CI 1.72–2.21) and patients on other motorized vehicles had a mean TAI grade of 1.47 (95% CI 0.84–2.10). Cyclists had a mean TAI grade of 1.05 (95% CI 0.53–1.57).

We found that there were significant differences in TAI grades (Kruskal-Wallis analyses) between the four subcategories of falls: Simple falls (≤ own height), > own height, fall in stairs and unknown fall height ($p = 0.015$) (*Figure 3B*). In the > own height subcategory the mean TAI grade was 1.46 (95% CI 1.09–1.83). Patients who had fallen down the stairs had a mean TAI grade of 1.00 (95% CI 0.50–1.50) and patients with unknown fall height had a mean TAI grade of 1.00 (95% CI -.19–2.19). The mean TAI grade in the simple fall subcategory was 0.44 (95% CI 0.10-0.77).

DISCUSSION

In this MRI study of moderate and severe TBI patients we found that 72 % of the included patients had TAI lesions depicted on clinical MRI performed in the early phase post injury. Pedestrians had the highest percentage of TAI and the highest mean TAI grade of all subcategories of injury followed by patients injured in alpine accidents and those who were inside a car. Cyclists had the lowest mean TAI grade of the RTA subcategories. In the fall category the highest percentage of TAI and the highest TAI grade was found among the falls from > own height. However, also more than one third of patients with more low-energy trauma like falling from own height or even less than own height had visible TAI lesions and two thirds of the patients with fall in stairs had TAI.

The majority (81%) of the patients injured in RTAs had TAI. In the pedestrian subcategory, all were hit by a motorized vehicle and all the eleven patients had TAI. The reason for the high TAI occurrence might be that pedestrians are not wearing any type of protective gear and that they are often hit with a relatively high speed. This will accelerate the body and often throw the patient several meters, leading to an instant deceleration when the head hits the ground. The acceleration and the injuries that occurs in the primary collision with the vehicle describes the initial or primary injury when pedestrians are hit. However, these accidents are complex and consists not only of primary injuries but also secondary (for instance getting over the vehicle) and tertiary (i.e. fall on a firm surface) injuries as well (11). An autopsy study by Davceva et al. from 2012 stated that pedestrians hit by a vehicle is a complex mechanism of injury, and that the type of head injury that occurs would depend on which of the primary, secondary and tertiary injuries that predominates, and therefore left pedestrians out of their statistical analyses (11). However, in our study the pedestrians also had the highest mean TAI grade. We have not found other MRI studies that investigate the detailed mechanism of injury in relation to TAI and TAI grades diagnosed by clinical MRI, and hence we lack studies to compare with.

In this study nine out of ten patients in the alpine category was found to have TAI, and they had a high mean TAI grade with 40 % TAI 2 and 40 % TAI 3. This is in accordance with our clinical experience considering these patients. They represent a unique clinical entity, often with minimal CT findings, but still reduced consciousness, most likely due to the extensive TAI lesions depicted with MRI. Based on their high percentage of TAI and high mean TAI grade it can be discussed whether or not these accidents are comparable to RTAs or even falls from a high height, or if they should be looked upon as an entirely own group.

Among the cyclists, we found the lowest percentage of TAI and the lowest mean TAI grade in the RTA category, although more than half, 60%, had TAI. These accidents typically involve the patient flying over the handlebars and hitting the firm surface of the ground at a relatively high speed. Davceva et al. reported that cyclists more often had acute subdural hematomas and not TAI, because of the rapid deceleration against a firm surface (11). However, autopsy studies might give different results than studies in surviving patients, and they might have different definitions of TAI and TAI grades than MRI studies. The importance of the use of helmets to prevent the development of TAI is not analyzed in this study, but a Cochrane review from 2000 found that the use of helmets reduced the risk of severe brain injury by at least 75% (22).

We also found that those with low-energy injuries such as simple falls had visible TAI lesions in 37.5% of the cases. This is in contrast to earlier autopsy studies who have concluded that this type of trauma has insufficient duration of the acceleration forces of the head to cause TAI (11, 14). Also among the three patients with fall from less than own height two patients had TAI grade 1. This injury mechanism is more commonly thought of as the reason for contusions, intracranial hematomas or skull fractures, rather than TAI. Such low-energy falls rarely cause moderate or severe TBI (only 1 % of our cohort). Hence, we conclude that such low-energy trauma mostly results in mild TBI without visible TAI lesions.

In the fall in stairs category, 60% of the patients had TAI, and three even had TAI grade 3. This indicates that fall in stairs resembles falls from high heights rather than the falls from a height of < 2 meters.

We also found that two of the nine patients that were victims of violence had TAI, grade 1 and 2, respectively. This is in contrast to former autopsy studies that stated that violence would not cause a big enough acceleration-deceleration to cause TAI (11, 14).

It is important to mention that in this study only patients with moderate and severe TBI were included. In order to suffer a moderate or severe TBI, the trauma has to involve a certain amount of energy. We have recently shown that in a cohort study of patients with mild TBI only 10% of the patients have visible TAI lesions (Skandsen et al. unpublished). Thus, the relationship between injury mechanism and TAI lesions will depend on the severity of the injury. Although some of the low-energy categories presented in the Skandsen et al study might not result in visible lesions, TAI is now considered the main type of injury also in mild TBI and can be detected by advanced MRI techniques such as diffusion tensor imaging or by blood biomarkers (23, 24). Thus, the occurrence of TAI and the mean TAI grade might have been higher in this study too if advanced MRI techniques had been used.

Strengths and limitations

It is a strength that the MRI cohort is so large and that data collection was prospectively conducted. The included patients had the same injury mechanisms as the non –included patients except for the alpine category that tended to have more MRIs performed. It is also a strength of this study that the image analyses were conducted blinded for clinical information, and that inter-rater reliability has been performed (18).

A limitation of this study is that for almost all the MRIs we used a 1.5 Tesla scanner (n=211). A 3 Tesla scanner would increase the sensitivity for lesion detection (25), that could possibly show a higher occurrence of TAI, or a higher grade of TAI. However, Scheid et al.(25) concluded that T2*GRE MRI at 1.5 T seems to be sufficiently suitable for the diagnosis of probable TAI after TBI.

It is also not optimal that the time from injury to MRI is not equal for all the patients. In our study protocol we did not use susceptibility-weighted MRI imaging (SWI), which is a sequence currently used at our hospital. This sequence has been found to be more sensitive to micro hemorrhagic lesions after TBI than T2*GRE (26-28). Further studies that use SWI can possibly show an even better relationship between injury mechanism and the occurrence of TAI, and maybe show TAI as an even more commonly occurring injury.

CONCLUSION

TAI was found in 72% of the included patients, regardless of mechanism of injury. Pedestrians, alpine accidents and being inside of a car at the time of the accident are the three subcategories of injury with the highest occurrence of TAI and the highest mean TAI grades. Cyclists had the lowest mean TAI grade of the RTA subcategories. Almost one third of patients with falls from own height or less than own height also showed visible TAI lesions on clinical MRI, (and 60% of patients with fall in stairs had TAI), most of these injuries considered to be low-energy trauma. Our results shows that it is important to conduct studies in surviving patients, since autopsy studies will include other patient groups. Hence, this can increase our knowledge about TAI and biomarkers of TAI in the large patient group of surviving TBI patients.

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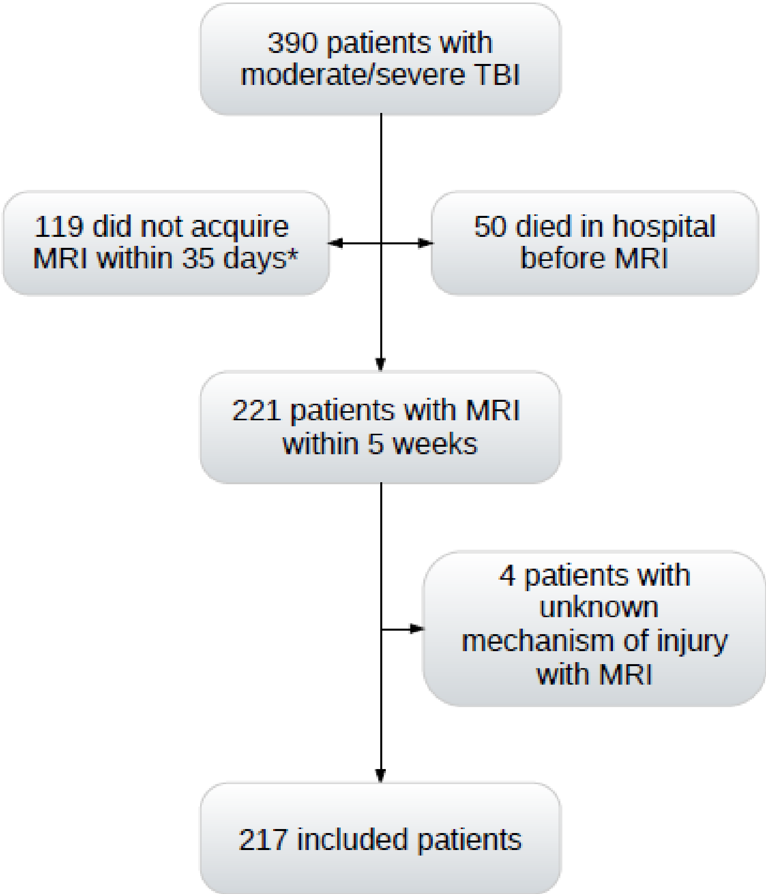
FIGURE 1: Flowchart of the TBI cohort age 7-69. 217 included patients in the MRI study.



** Two patients with unknown mechanism of injury*

FIGURE 2: Distribution of TAI grades in percent within some of the subcategories of injury mechanism

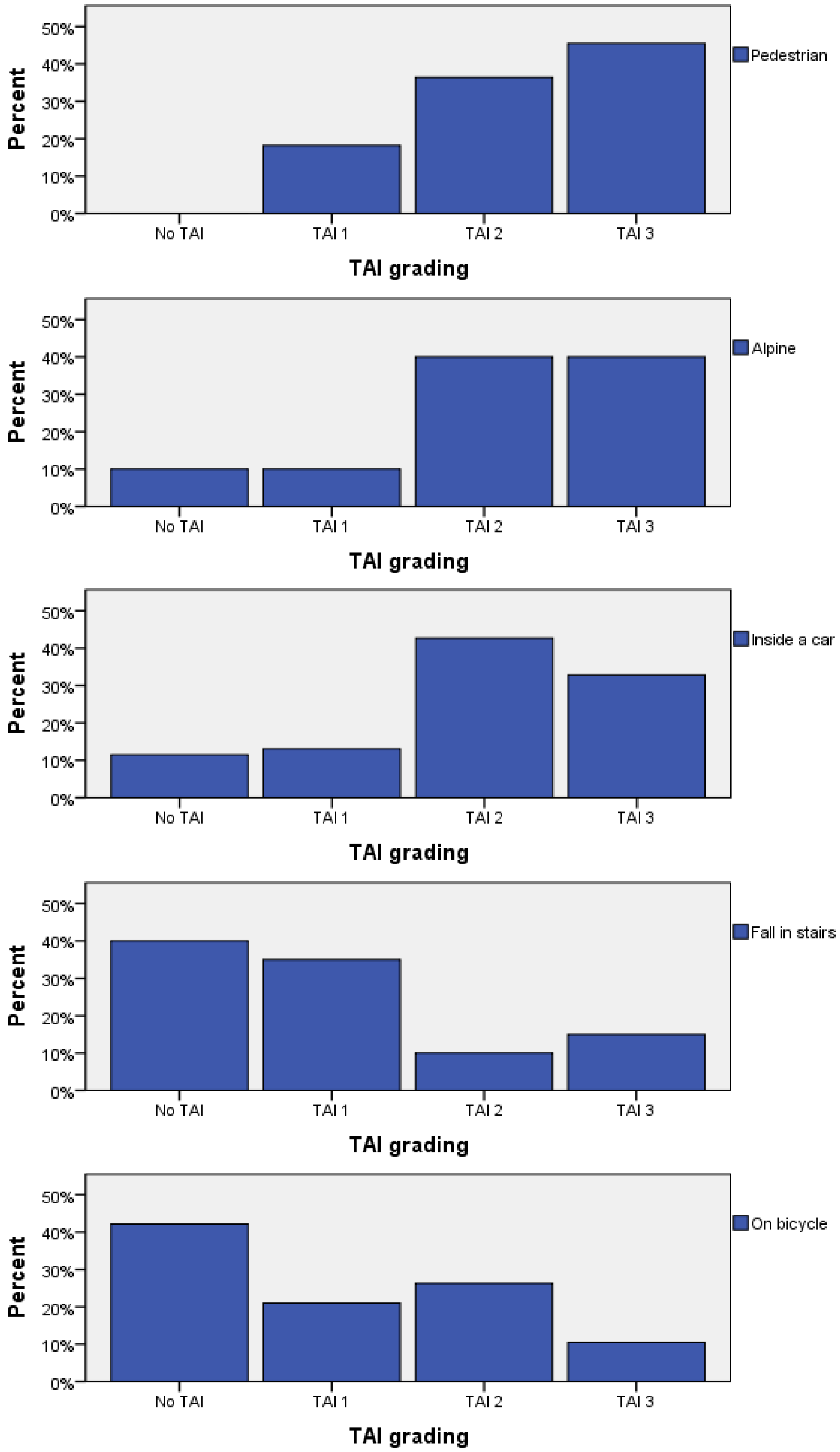
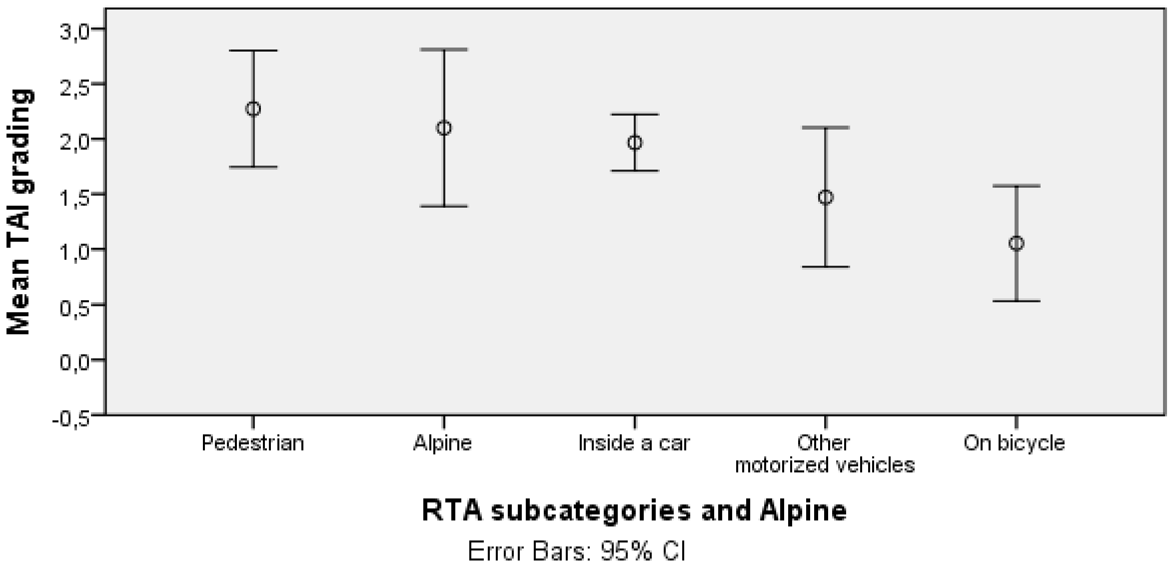


FIGURE 3: Simple error bar showing mean TAI grades, with a 95% confidence interval.
A: for the RTA subcategories and alpine category. B: for the fall subcategories

A



B

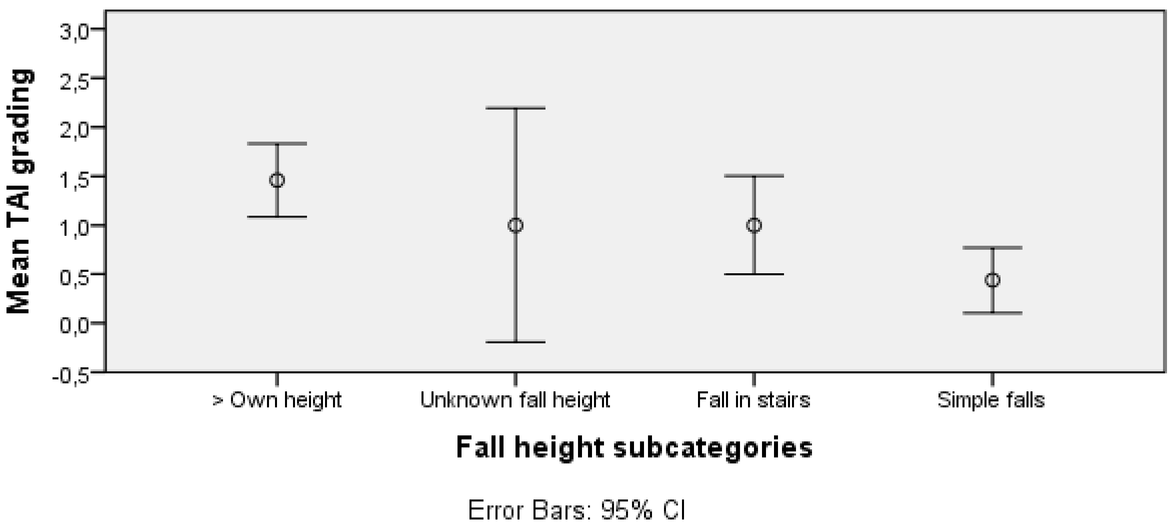


TABLE 1. Patient characteristics, injury related variables and mechanism of injury in the included and the non-included patients in the total TBI cohort

Variable	**Included patients** (n=217)	**Non-included patients** (n=167)	**p - value**
Age (median, IQR)	28.5 (19.7 – 46.6)	42.8 (23.9 – 56.4)	**<0.001**
Sex (male/female, %)	167/50 (77/23)	126/41 (75/25)	0.809
Severe TBI, HISS admission *n* (%)	98 (45)	97 (58)	**0.023**
Injury mechanism *n* (%)[1]			
Road traffic accident	108 (50)	75 (45)	0.355
Alpine	10 (5)	2 (1)	0.076
Fall	80 (37)	73 (44)	0.207
Violence	9 (4)	6 (4)	0.799
Other[2]	10 (5)	11(7)	0.498
GCS score (median, IQR)	9 (6 – 12)	7 (3 – 13)	**0.026**
Intubation *n* (%)	150 (69)	118 (71)	0.530
Hypoxia (O2 sat < 92) *n* (%)	34 (16)	45 (27)	**0.008**
Hypotension (systolic blood pressure < 90 mmHg) *n* (%)	25(12)	39 (23)	**0.002**
Pupil dilatation at admission *n* (%)			
Unilateral dilatation	19 (9)	28 (17)	**0.019**
Bilateral dilatation	6 (3)	25 (15)	**<0.001**
ISS (median, IQR)	25 (17 – 33)	25 (16 – 34)	0.626
Evacuated hematoma *n* (%)[3]	48 (22)	37 (22)	1.000
In hospital mortality *n* (%)	2 (1)	50 (30)	**<0.001**

GCS, Glasgow Coma Scale; ISS, Injury Severity Score;.

[1)] There were four patients with unknown mechanism of injury in the included group and two patients with unknown mechanism of injury in the non-included group.

[2)] including one gunshot in the included group

[3)] 5 missing in the non-included group

TABLE 2: Mechanism of injury in the 217 patients with clinical MRI

Injury mechanism	*n*	*%*
Road traffic accident:	108	50
Inside a car	61	56
On bicycle	19	18
Pedestrian	11	10
Motorcycle/Moped/Snow scooter/other motorized vehicles	17	16
Alpine:	10	5
Fall:	80	37
< own height	3	4
= own height	13	16
> own height ≤ 2 m	8	10
> 2 m < 5 m	15	19
≥ 5 m	14	18
Fall in stairs, any height	20	25
Unknown fall height	7	9
Violence:	9	4
Other:	10	5

TABLE 3: Detailed distribution of TAI in relation to mechanism of injury in the 217 patients with clinical MRI

Mechanism of injury	**No TAI** **N (%)**	**TAI 1** **N (%)**	**TAI 2** **N (%)**	**TAI 3** **N (%)**
Road traffic accident (n=108):				
Inside a car	7 (11)	8 (13)	26 (43)	20 (33)
On bicycle	8 (42)	4 (21)	5 (26)	2 (11)
Pedestrian	0	2 (18)	4 (36)	5 (45)
Motorcycle/Moped/Snow scooter/ Other motorized vehicle	5 (29)	4 (24)	3 (18)	5 (29)
Alpine (n=10):				
	1 (10)	1 (10)	4 (40)	4 (40)
Fall (n=80):				
< Own height	1 (33)	2 (67)	0	0
= Own height	9 (69)	3 (23)	1 (8)	0
> Own height ≤ 2 m	1 (13)	5 (63)	0	2 (25)
> 2 m < 5 m	4 (27)	4 (27)	3 (20)	4 (27)
≥ 5 m	4 (29)	2 (14)	5 (36)	3 (21)
Fall in stairs, any height	8 (40)	7 (35)	2 (10)	3 (15)
Unknown fall height	4 (57)	0	2 (29)	1 (14)
Violence (n=9):				
	7 (78)	1 (11)	1 (11)	0
Other (n=10):				
	2 (20)	4 (40)	3 (30)	1 (10)

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