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RECRUITMENT BIAS IN MILD TRAUMATIC BRAIN INJURY RESEARCH. DESCRIPTION OF PATIENTS WITH MILD TRAUMATIC BRAIN INJURY NOT INCLUDED FOR RESEARCH IN A SINGLE CENTRE IN NORWAY.

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ABSTRACT

Study aim.

The aim of this study was to give a description of demographic and injury variables of the patients who were not included in the mild traumatic brain injury (TBI) study at St. Olav´s Hospital.

Methods.

All patients not included who; (1) had been examined with head CT because of sustained or suspected head trauma and (2) fulfilled the WHO criteria for mild TBI during the study period of the mild TBI study, were compared to the patients enrolled. Patients were referred from St. Olav's Hospital, Trondheim municipal emergency clinic and from general practitioners in Sør-Trøndelag county and Værnesregionen emergency clinic.

Results.

624 patients had a head CT and fulfilled the WHO criteria for mild TBI and 48% (n = 301) were enrolled in the mild TBI study. The remaining patients were not included, where 25% (n = 159) were missed for inclusion and 26% (n = 164) were excluded. The patients missed for inclusion tended to be younger than the patients enrolled and the injuries were more often due to violence and head CTs were more often performed during weekend nights. The patients excluded were significantly older, they were less often injured in sports accidents and if admitted, they were more often admitted to other hospital departments for treatment.

Conclusion.

The enrolment percentage in our study can be considered high and more representative than for previous mild TBI studies. However, this study demonstrates that there were some differences between patients enrolled and patients excluded or missed for inclusion. Hence, also this study suffers from a degree of recruitment bias with an unknown effect on study results. We experienced, that a low accuracy of mild TBI diagnosis set in outpatient clinics, combined with strict study criteria for inclusion and patients declining participation or being difficult to reach, made the inclusion of patients for our study demanding. We suspect these factors to contribute to recruitment bias in all mild TBI research.

INTRODUCTION

The incidence of mild TBI.

Traumatic brain injuries is known to be one of the major factors causing restriction in daily functioning in young adults.[1] In 2004, the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury calculated that the overall incidence of hospital treated mild TBI in the population to be 100-300/100 000.[2] However, many patients with mild TBI are treated at outpatients emergency clinics or do not seek medical aid at all, leaving the total incidence of mild TBI in the population unknown.[2, 3] Mild TBI can be divided into uncomplicated, sometimes named concussion, or complicated, the latter with positive findings on neuroimaging. Hence, patients with mild TBI is a very heterogeneous group, with a large variation in severity of symptoms and complications after the injury.[4, 5]

Common biases in mild TBI studies.

The outcome of mild TBI has been explored in many studies, since the morbidity is of great variety.[5-8] To investigate the true effect of mild TBI, studies have had a tradition of an extended use of exclusion criteria to avoid confounding factors. Patients with premorbid health problems are often excluded, although the risk of prolonged post-concussion symptoms is highest in this group.[6] Consequently, this has commonly lead to bias in participation. Therefore, many studies suffer from poor generalizability of the findings.[6-8] The strict criteria leads to limitations in study inclusion and the population included for follow-up does not represent the total population with mild TBI.[9] Mild TBI is considered a major public health problem that affects the broad population, but the research protocols for mild TBI investigation result in small and non-representative patient groups.[6, 9]

Extensive use of exclusion criteria are common in mild TBI studies.[6, 7, 10] In a recent study (2013), by Luoto et al., as many as 95% of 935 patients with mild TBI were excluded due to normally accepted exclusion criteria in mild TBI research.[6] However, it is also important to investigate which patients that consent to participate in these studies and which patients that are lost to follow up. McCullag et al. show that the patients with more severe injuries and an increased need for health care, tend to be more willing to participate.[7] Furthermore, Corrigan et al. show that patients lost to follow up are those from socioeconomically disadvantaged groups, who suffer from drug and/or alcohol abuse and with an injury caused by self- or other directed violence.[8] The group lost to follow up is also the group who most prevalently acquire

a TBI.[11] All these biases and confounding factors might leave the result of outcome after mild TBI inconclusive.

THE AIM OF THE STUDY

The aim of this study was to describe the patients who were not included in the large mild TBI study at St. Olav´s Hospital, to investigate if there were a difference between patients enrolled and not included in mild TBI study. All patients fulfilled the WHO criteria for mild TBI[(12)] and they were referred to a head CT because of sustained or suspected mild TBI. Additionally, patients referred to head CT from general practitioners Sør-Trøndelag county and Værnesregionen emergency clinic were described.

MATERIAL AND METHODS

Presentation of the mild TBI study.

The dataset used was retrieved from the mild TBI study at St Olav's Hospital – a prospective follow-up study of patients 16-60 years with mild traumatic brain injuries at St. Olav's Hospital and Trondheim municipal emergency clinic. The data were collected during the time period April 1st 2014-December 5th 2015. Within this period, the inclusion was only stopped for approximately 7 weeks, typically in the holiday season, resulting in a total inclusion period of 81 weeks. To establish if the patients had acquired a mild TBI, the definition by the World Health Organization (WHO) Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury was used. It defines TBI as an acute brain injury resulting from mechanical energy to the head from external physical forces. Criteria to identify the clinical diagnosis of mild TBI include 1) one or more of the following; confusion or disorientation, loss of consciousness for $\leq$ 30 minutes, post-traumatic amnesia for less than 24 hours and/or transient neurological alterations such as focal signs, seizure, and intracranial lesion not requiring surgery and 2) GCS score 13-15 after $\geq$ 30 minutes post injury. These alterations should not be due to drugs, alcohol, medications or other injuries.[12] Further inclusion and exclusion criteria used in the mild TBI study, are listed in table 1.

Patients

All patients evaluated in this study had a head CT because of sustained or suspected head trauma. Throughout the inclusion period, all head CTs performed at St. Olav's Hospital due to trauma were reviewed and a CT referral log for patients with mild TBI was kept. The patients in the mild TBI study were treated at; (1) St. Olav's University Hospital, which is local hospital for 223 000 inhabitants, or (2) the outpatient emergency clinic, providing health services for residents in Trondheim, Klæbu, Midtre Gauldal, Malvik and Melhus municipality. In addition, this study also described the patients referred from the general practitioners in Sør-Trøndelag county and Værnesregionen emergency clinic, which serve 339 000 inhabitants. The screening of the log for patients referred from general practitioners was done retrospectively. Information from the head CT referral notes, medical journals and direct contact with the patients themselves, was used to evaluate if the patients met the mild TBI-criteria. Patients recognized as eligible were asked to participate in the study, while the remaining patients were sorted by the exclusion criteria (table 1). Patients who declined participation, patients who the study personnel were not able to reach or did not contact for some reason, were not included in the mild TBI study for follow up. All patients enlisted during the inclusion period were eventually divided into different subgroups, based on the inclusion and exclusion criteria.

Table 1; Inclusion and exclusion criteria for the mild TBI study.

Inclusion criteria	***Description***	***Reason for applying criteria***
Age ≥ 16 ≤ 60 years	*At the time of injury*	*Avoid co-morbid factors influencing outcome in an older population. Mild TBI is a common injury among younger patients.*
Mild TBI criteria	*WHO Collaborating Centre for Neurotrauma Task Force in mild TBI.*[12]	*Internationally used and recognized criteria*
Exclusion criteria	***Description***	***Reason for applying criteria***
GCS ≤8	*Severe TBI*	
GCS 9-12 or PTA >24h. or LOC >30 min.	*Moderate TBI*	
Too uncertain diagnosis	*Injury in association with other conditions affecting consciousness, such as syncope, seizures or intoxication.*	*WHO criteria cannot be used to recognize symptoms as an alteration due mild TBI.*[12]
Non Norwegian	*Not speaking Norwegian.*	*Norwegian study test procedures.*
Presented late (>48 hours after injury)	*No medical consult ≤48 hours after injury.*	*Investigating acute mild TBI. Acute MRI performed ≤72 hours.*
Pre-existing medical conditions	*Severe psychiatric, neurological or medical disease. Including severe ongoing chronical alcohol and/or substance abuse*	*Likely to be lost to follow up. Pre-existing cognitive impairments. Never abstaining from drugs or alcohol.*
Other major trauma	*Other severe trauma such as complex fractures, spinal injuries and internal organ injuries.*	*Injuries preventing performance of acute (2. week after injury) and 3. month follow up. Classic mild TBI symptoms could be because of major trauma impact.*

Study variables.

The different subgroups of patients were registered with a set of study variables. Firstly, the demographic variables sex and age were noted for all patients. The cause of injury was categorized as fall (from any height), violence, traffic accidents, bicycle accidents, sports accidents, hitting an object and other events. The traffic accident category comprised all motor vehicle accidents and pedestrians hit by motor vehicles. GCS score noted on hospital arrival was recorded. In cases where GCS score was not documented, GCS was estimated based on clinical information. Where the medical record stated that the patient was awake and oriented, GCS was clinically estimated to be 15. GCS score was noted as missing if the medical record did not have any information regarding this. If the patient was intoxicated or sedated, the GCS score was considered difficult to evaluate. Head CT findings was noted and categorized as normal, facial fracture, cranial fracture, intracranial finding or both intracranial findings and fractures, including both facial and cranial fractures or other non-traumatic findings. The level of medical care was listed; discharged to home, observed at the hospital $\leq$24 hours, admitted to neurosurgery department and admitted to other hospital departments. Time and weekday for all head CTs were registered.

Statistical analyses

The subgroups were compared and presented using Statistical Package for Social Science (SPSS) files. For the main presentation of the results descriptive statistics was used. Distribution of age was tested using QQ-plots and the Shapiro-Wilks test for normal distribution. For data not normally distributed, median and ranges were used. In the comparisons between groups, the Mann-Whitney U test was applied for continuous variables and Pearson chi-square test was used for categorical variables. Significance level was set to $p = 0.010$ due to multiple testing.

RESULTS

During the study period, 1094 head CTs were performed because of suspected or sustained head trauma (figure 1). 57% (n = 624) of the patients met the WHO criteria for mild TBI and out of these, 26% (n = 164) met the exclusion criteria. From the remaining 74% (n = 460), 65% (n = 301) were enrolled, while 35% (n = 159) were missed for inclusion. Among the excluded patients, the largest subgroup were the patients excluded pre-existing medical conditions (40%). Among the patie nts missed for inclusion, patients not reached 50% (n = 80) and patients who declined participation 33% (n = 53) were the largest subgroups.

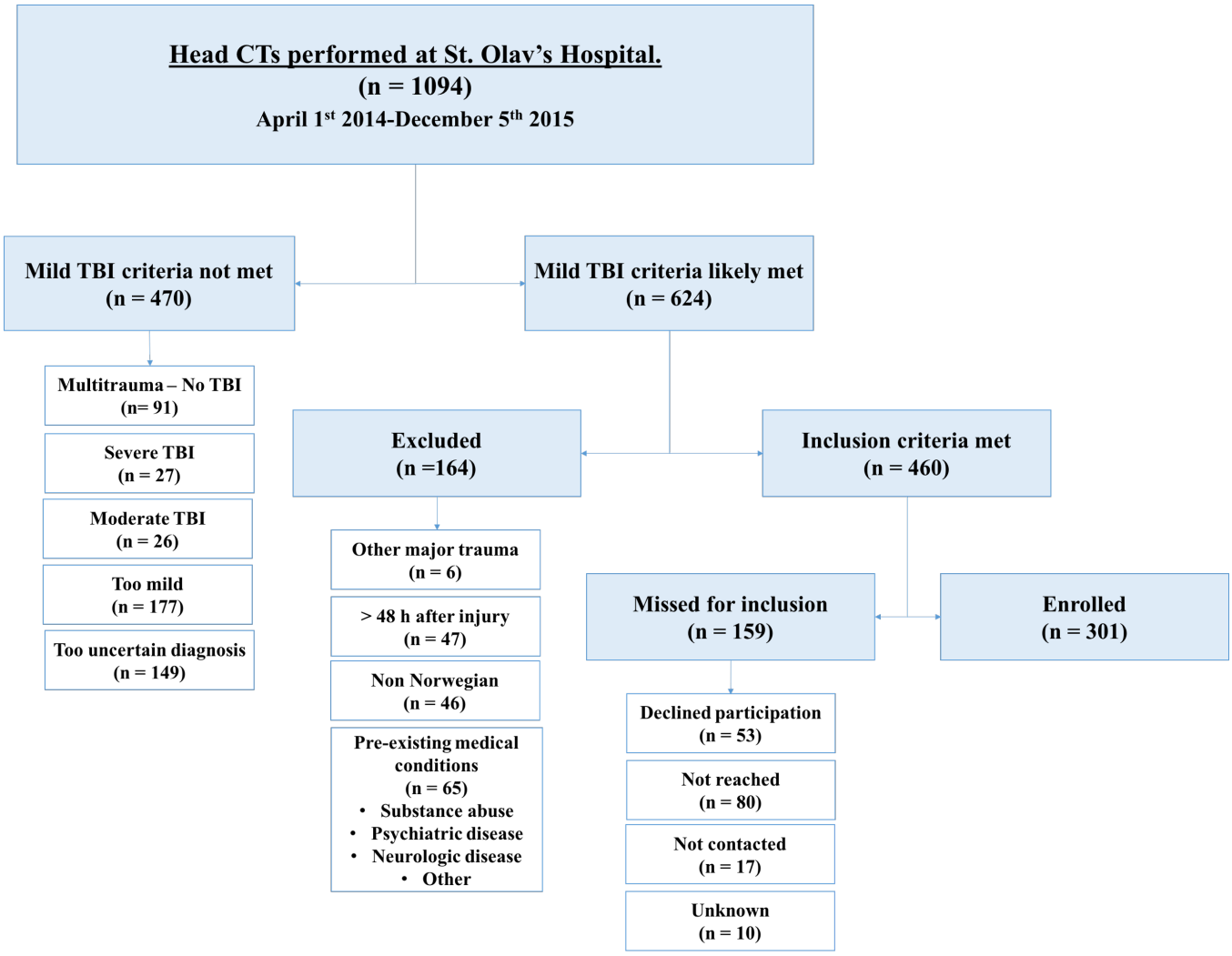

Figure 1; Head CTs performed due to head trauma at St. Olav's Hospital. Distribution of patients by mild TBI study criteria

During the study period, 101 patients with sustained head trauma were referred to a head CT by their general practitioner (figure 2). 40% (n = 40) of these were evaluated to fulfill the WHO criteria for mild TBI. The remaining patients were considered to be either too mild, to have a too uncertain diagnosis or the head CT referral note was lacking too much clinical information to diagnose a mild TBI. After applying the inclusion and exclusion criteria of the mild TBI study, 63% (n = 25) of the patients who met the WHO criteria were considered eligible for participation, while the remaining 38% (n = 15) were excluded because head CT was performed >48 hours after injury.

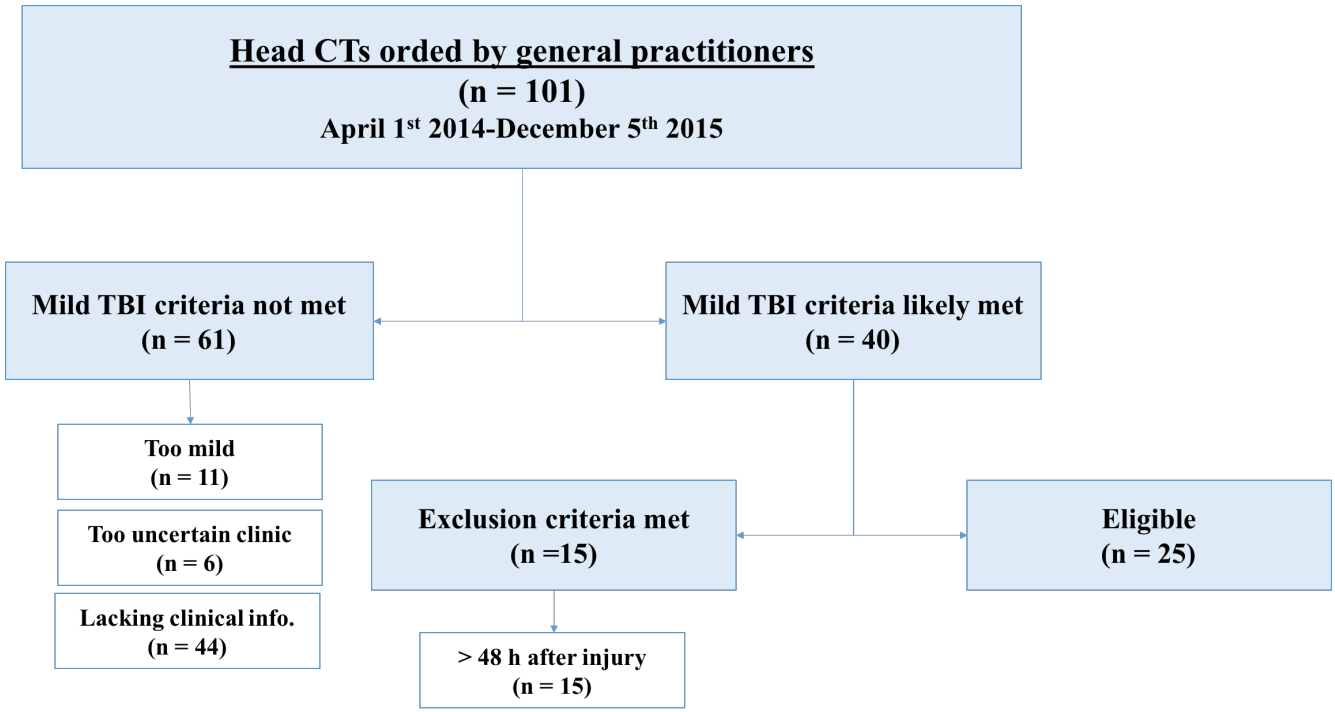

Figure 2; Distribution by mild TBI study criteria for patients referred from general practitioners.

Age and sex.

The age of the patients who met the WHO criteria for mild TBI differed significantly from a normal distribution (figure 3). In total, 44% of the patients were ≤25 years (median 28 years). The same distribution was found for the patients enrolled (median 25 years, IQR 20-43) and those missed for inclusion (median 25 years, IQR 20-38) (table 2). The patients excluded were significantly older; only 20% were ≤25 years (median 32 years, IQR: 26-47). The patients who declined participation were younger than the patients enrolled (table 3). 60% within this group were ≤25 years. Also, the Non Norwegian speakers and the patients with pre-existing medical conditions were older, with a median age of 34 and 42 years respectively (table 4).

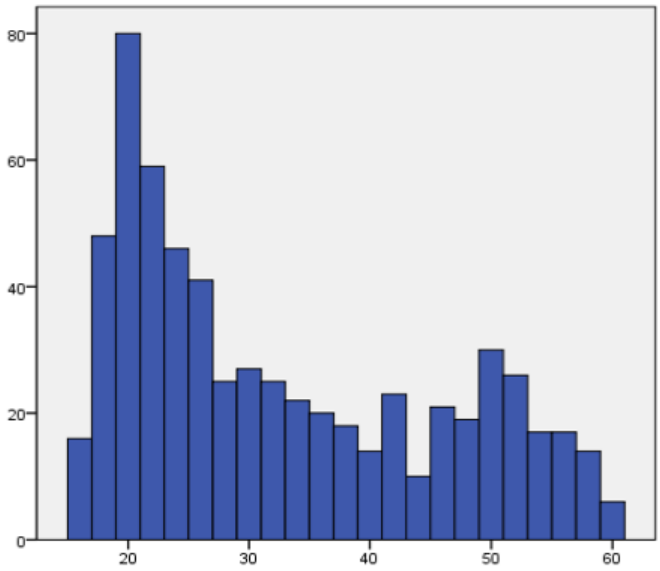

Figure 3; Histogram, age distribution for WHO criteria mild TBI met (n = 624)

The mild TBI study enrolled 65% males and 35% women (table 2). Patients declining participation differed from this distribution, with 56% females and 44% males (table 3).

Injury mechanism.

The most common injury mechanisms were falls, violence, bicycle and traffic accidents. Violence was significantly more frequent among the patients missed for inclusion (26%), compared to the patients enrolled (15%) (table 2). Among the patients excluded, only 6% were injured in sport accidents, which was significantly less frequent than for the patients enrolled (17%). Violence tended to be more frequent among the patients not reached (28%) compared to the enrolled patients (15%) (table 3).

GCS score.

The GCS scores were often missing for both the patients missed for inclusion (38%) and the patients excluded (22%) than for the patients enrolled (12%) (table 2).

The GCS scores were more often missing for the patient groups who declined participation (39%), who were not reached (35%) or not contacted (53%) (table 3).

Level of medical care.

Most of the patients were discharged to home from the ER after a head CT. The patients who were missed for inclusion were oftener discharged to home (76%), compared to the patients who were enrolled (62%) (table 2). Only 4% of the patients who declined participation had been observed <24 hours before discharged to home, which was more seldom compared to the patients enrolled (20%) (table 3). Patients who presented late were more frequently discharged to home (87%) and none were observed <24 hours (table 4).

CT findings.

CT was normal in 85% of the patients who met the mild TBI WHO criteria. Patients who were excluded tended to have a higher frequency of other, non-traumatic findings in their CT-examinations (4%), compared to the patients enrolled (<1%) (table 2). A normal CT-scan was more common among patients who were not reached for inclusion (98%) compared to the patients enrolled (85%) (table 3). The patients with pre-existing medical conditions had other findings more often (11%) than the patients enrolled (table 4).

Table 2; WHO criteria for Mild TBI met. Distribution for age, sex, injury mechanism, GCS score, level of medical care and CT findings.

	Enrolled (n = 301) n (%)	Missed for inclusion (n = 159) n (%)	P-value[1]	Excluded (n = 164) n (%)	P-value[1]
Age (years)					
Median (IQR[2])	25 (20-43)	25 (20-38)	0.080	32 (26-46)	**0.000**
Gender					
Male	195 (65)	88 (55)	0.060	105 (64)	0.950
Female	106 (35)	71 (45)		59 (36)	
Injury mechanism					
Fall	104 (35)	57 (36)	0.918	67 (41)	0.241
Violence	46 (15)	41 (26)	**0.009**	30 (18)	0.479
Bicycle accident	51 (17)	17 (11)	0.097	19 (12)	0.159
Traffic accident	37 (12)	18 (11)	0.960	20 (12)	1.000
Sport accident	45 (15)	16 (10)	0.185	9 (6)	**0.004**
Hit object	11 (4)	3 (2)	0.445	11 (7)	0.210
GCS score					
15	203 (67)	81 (51)	**0.001**	107 (65)	0.706
14	54 (18)	13 (8)	0.033	15 (9)	0.016
13	5 (2)	4 (3)	0.528	0	0.234
Missing	37 (12)	60 (38)	**0.000**	36 (22)	**0.009**
Difficult to evaluate	2 (<1)	1 (<1)	1.000	6 (4)	0.046
Level of medical care					
Discharged to home	185 (62)	121 (76)	**0.002**	112 (68)	0.173
Observed <24	61 (20)	16 (10)	**0.008**	11 (7)	**0.000**
Neurosurgery	39 (13)	13 (8)	0.166	17 (10)	0.502
Admitted other	16 (5)	9 (6)	1.000	24 (15)	**0.001**
CT findings					
Normal	255 (85)	144 (91)	0.106	134 (82)	0.479
Facial fractures	19 (6)	7 (4)	0.528	611 (7)	1.000
Cranial fractures	3 (1)	0	0.513	2 (1)	1.000
Intracranial lesion	17 (6)	3 (2)	0.101	6 (4)	0.471
Intracranial lesion and fractures	5 (2)	4 (3)	0.783	4 (2)	0.818
Non-traumatic findings	2 (<1)	1 (<1)	1.000	7 (4)	0.019

[1] P-values calculated by comparing to the patients enrolled.
[2] Abbreviation IQR; interquartile range.
Note: Some of the percentages exceed 100% due to rounding.

Table 3; Subgroups within "Missed for inclusion". Distribution of age, sex, injury mechanism, GCS score, level of medical care and CT findings.

	Enrolled (n = 301) n (%)	Declined (n =53) n (%)	P-value[1]	Not reached (n = 80) n (%)	P-value[1]	Not contacted (n = 17) n (%)	P-value[1]
Age (years)							
Median (IQR)	25 (20-43)	21 (18-43)	0.023	25 (20-37)	0.202	33 (22-48)	0.337
Gender							
Male	195 (65)	23 (44)	**0.008**	48 (60)	0.509	9 (53)	0.465
Female	106 (35)	29 (56)		32 (40)		8 (47)	
Injury mechanism							
Fall	104 (35)	21 (40)	0.543	25 (31)	0.634	7 (41)	0.789
Violence	46 (15)	13 (25)	0.125	22 (28)	0.018	4 (24)	0.571
Bicycle accident	51 (17)	6 (12)	0.439	5 (6)	0.026	5 (29)	0.324
Traffic accident	37 (12)	9 (17)	0.399	7 (9)	0.543	1 (6)	0.710
Sport accident	45 (15)	2 (4)	0.051	13 (16)	0.910	0	0.173
Hit object	11 (4)	0	0.333	3 (4)	1.000	0	0.904
GCS score							
15	203 (67)	26 (50)	0.023	45 (56)	0.083	6 (35)	0.014
14	54 (18)	5 (10)	0.199	5 (6)	0.017	2 (12)	0.747
13	5 (2)	0	0.764	2 (3)	0.977	0	1.000
Missing	37 (12)	20 (39)	**0.000**	28 (35)	**0.000**	9 (53)	**0.000**
Difficult to evaluate	2 (<1)	1 (2)	0.924	0	1.000	0	1.000
Level of medical care							
Discharged to home	185 (62)	42 (81)	0.012	60 (75)	0,025	11 (65)	0.991
Observed <24	61 (20)	2 (4)	**0.008**	11 (14)	0,245	1 (6)	0.254
Neurosurgery	39 (13)	4 (8)	0.400	6 (8)	0,250	3 (18)	0.851
Admitted other	16 (5)	4 (8)	0.719	3 (4)	0,777	2 (12)	0.562
CT findings							
Normal	255 (85)	45 (87)	0.897	78 (98)	**0,004**	11 (65)	0.030
Facial fractures	19 (6)	4 (8)	0.946	1 (1)	0,128	2 (12)	0.705
Cranial fractures	3 (1)	1 (2)	1.000	0	0,853	0	1.000
Intracranial lesion	17 (6)	1 (2)	0.432	1 (1)	0,177	1 (6)	1.000
Intracranial lesion and fractures	5 (2)	1 (2)	1.000	0	0,543	3 (18)	**0.001**
Non-traumatic findings	2 (<1)	0	0.924	0	1,000	0	1.000

[1] P-values calculated by comparing to the patients enrolled.
Note: Some of the percentages exceed 100% due to rounding.

Table 4; Subgroups within "Inclusion criteria not met". Distribution of age, sex, injury mechanism, GCS score, level of medical care and CT findings.

	Enrolled n = 301 n (%)	Presented late n = 47 n (%)	p-value[1]	Non Norwegian n = 46 n (%)	p-value[1]	Pre-existing medical conditions n = 65 n (%)	p-value[1]
Age (years)							
Median (IQR)	25 (20-43)	29 (24-41)	0.215	34 (27-41)	0.014	42 (28-50)	**0.000**
Gender							
Male	195 (65)	24 (51)	0.099	32 (70)	0.639	45 (69)	0.589
Female	106 (35)	23 (49)		14 (30)		20 (31)	
Injury mechanism							
Fall	104 (35)	20 (42)	0.392	18 (39)	0.639	29 (45)	0.182
Violence	46 (15)	7 (15)	1.000	9 (20)	0.600	14 (22)	0.293
Bicycle accident	51 (17)	5 (11)	0.379	6 (13)	0.652	6 (9)	0.172
Traffic accident	37 (12)	3 (6)	0.380	6 (13)	1.000	7 (11)	0.954
Sport accident	45 (15)	5 (11)	0.575	2 (4)	0.084	2 (3)	0.017
Hit object	11 (4)	6 (13)	0.020	1 (2)	0.937	4 (6)	0.564
GCS score							
15	203 (67)	43 (92)	**0.001**	33 (72)	0.680	28 (63)	**0.000**
14	54 (18)	2 (4)	0.031	4 (9)	0.176	8 (12)	0.360
13	5 (2)	0	0.817	0	0.829	0	0.648
Missing	37 (12)	2 (4)	0.169	7 (16)	0.751	27 (42)	**0.000**
Difficult to evaluate	2 (<1)	0	1.000	2 (4)	0.150	2 (3)	0.299
Level of medical care							
Discharged to home	185 (62)	41 (87)	**0.001**	29 (63)	0.837	42 (65)	0.738
Observed <24	61 (20)	0	**0.001**	3 (7)	0.042	8 (12)	0.189
Neurosurgery	39 (13)	3 (6)	0.296	7 (15)	0.851	5 (8)	0.330
Admitted other	16 (5)	3 (6)	1.000	7 (15)	0.028	10 (15)	**0.009**
CT findings							
Normal	255 (85)	39 (83)	0.929	39 (85)	1.000	52 (80)	0.452
Facial fractures	19 (6)	4 (9)	0.804	4 (9)	0.774	2 (3)	0.470
Cranial fractures	3 (1)	0	1.000	2 (4)	0.266	0	0.960
Intracranial lesion	17 (6)	2 (4)	0.964	0	0.198	3 (5)	0.975
Intracranial lesion and fractures	5 (2)	2 (4)	0.536	1 (2)	1.000	1 (2)	1.000
Non-traumatic findings	2 (<1)	0	1.000	0	1.000	7 (11)	**0.000**

[1] P-values calculated by comparing to the patients enrolled.
Note: Some of the percentages exceed 100% due to rounding.

Time of CT-examination.

The patients who met the WHO criteria for mild TBI most often sought medical help during the weekends (50%). In total, 59% of the patients enrolled had a head CT during Friday-Sunday (table 5). The patients missed for inclusion, more often came to the hospital or the outpatient clinic on Saturdays (27%) than the patients enrolled. Patients who presented late, more often came on Mondays (30%) (table 7).

For the patients enrolled, 64% of the head CTs were performed between 18:00-05:30 (table 5). There was no significant difference in time for head CT between patients missed for inclusion and the patients enrolled (table 5 and 6). However, patients excluded more seldom had a head CT between 00:00-05:30 o´clock (15%) and more often between 12:00-17:30 o´clock (34%) than the patients enrolled (33% and 22% respectively) (table 5). Only 6% among the patients who presented late had a head CT between 00:00-05:30 (6%) and more often had a head CT between 12:00-17:30 (49%) (table 7).

Table 5; WHO criteria for Mild TBI met. Distribution for time of head CT.

	Enrolled (n = 301) n (%)	Missed for inclusion (n = 159) n (%)	P-value[1]	Excluded (n = 164) n (%)	P-value[1]
Weekday					
Monday	35 (12)	18 (11)	1.000	24 (15)	0.433
Tuesday	33 (11)	7 (4)	0.028	19 (12)	0.961
Wednesday	24 (8)	11 (7)	0.825	21 (13)	0.129
Thursday	32 (11)	17 (11)	1.000	17 (10)	1.000
Friday	28 (9)	9 (6)	0.196	18 (11)	0.766
Saturday	50 (17)	43 (27)	0.011	27 (17)	1.000
Sunday	99 (33)	54 (34)	0.841	38 (23)	0.043
Time					
00:00-05:30	99 (33)	63 (40)	0.159	25 (15)	**0.000**
06:00-11:30	42 (14)	14 (9)	0.145	21 (13)	0.838
12:00-17:30	66 (22)	31 (20)	0.570	56 (34)	**0.008**
18:00-23:30	94 (31)	51 (32)	0.936	62 (38)	0.183

Tabell 6; Subgroups within "Missed for inclusion". Distribution for time of head CT.

	Enrolled (n = 301) n (%)	Declined (n =53) n (%)	P-value[1]	Not reached (n = 80) n (%)	P-value[1]	Not contacted (n = 17) n (%)	P-value[1]
Weekday							
Monday	35 (12)	7 (14)	0.885	6 (8)	0.290	5 (29)	0.076
Tuesday	33 (11)	0	0.024	4 (5)	0.165	2 (12)	1.000
Wednesday	24 (8)	4 (8)	1.000	5 (6)	0.780	0	0.460
Thursday	32 (11)	8 (15)	0.446	7 (9)	0.775	2 (12)	1.000
Friday	28 (9)	2 (4)	0.273	4 (5)	0.277	3 (18)	0.513
Saturday	50 (17)	14 (27)	0.112	24 (30)	0.011	1 (6)	0.405
Sunday	99 (33)	17 (33)	1.000	30 (38)	0.485	4 (23)	0.611
Time							
00:00-05:30	99 (33)	20 (39)	0.500	33 (41)	0.186	6 (35)	1.000
06:00-11:30	42 (14)	5 (10)	0.529	3 (4)	0.020	3 (18)	0.946
12:00-17:30	66 (22)	13 (25)	0.797	16 (20)	0.777	1 (6)	0.194
18:00-23:30	94 (31)	14 (27)	0.646	28 (35)	0.612	7 (41)	0.556

[1] P-values calculated by comparing to the patients enrolled.
Note: Some of the percentages exceed 100% due to rounding.

Table 7; Subgroups within 'Inclusion criteria not met'. Distribution for time of head CT.

	Enrolled (n = 301) n (%)	Presented late (n =47) n (%)	P-value[1]	Non Norwegian (n = 46) n (%)	P-value[1]	Pre-existing medical conditions (n = 65) n (%)	P-value[1]
Weekday							
Monday	35 (12)	14 (30)	**0.002**	3 (7)	0.436	7 (11)	1.000
Tuesday	33 (11)	8 (17)	0.340	1 (2)	0.109	9 (14)	0.655
Wednesday	24 (8)	5 (11)	0.741	8 (17)	0.075	7 (11)	0.625
Thursday	32 (11)	4 (9)	0.852	4 (9)	0.888	8 (12)	0.862
Friday	28 (9)	4 (9)	1.000	5 (11)	1.000	9 (14)	0.432
Saturday	50 (17)	5 (11)	0.407	11 (24)	0.315	9 (14)	0.716
Sunday	99 (33)	7 (15)	**0.022**	14 (30)	0.906	16 (25)	0.296
Time							
00:00-05:30	99 (33)	3 (6)	**0.000**	9 (20)	0.108	13 (20)	0.065
06:00-11:30	42 (14)	3 (6)	0.228	7 (15)	0.998	9 (14)	1.000
12:00-17:30	66 (22)	22 (49)	**0.001**	16 (35)	0.095	17 (26)	0.607
18:00-23:30	94 (31)	19 (40)	0.278	14 (30)	1.000	26 (40)	0.222

[1] P-values calculated by comparing to the patients enrolled.
Note: Some of the percentages exceed 100% due to rounding.

Patients referred to CT by general practitioners.

The median age for the eligible patients who were referred from their general practitioner (GP-patients) was 31 years (IQR; 21-46) (table 8). The patients who presented late, had a median age of 38 years (IQR; 24-47) and there were more females (73%) compared to the enrolled patients. The eligible GP-patients were more frequent injured by hitting an object (28%), than the patients enrolled in the mild TBI study (4%). For both the eligible GP-patients and the GP-patients who presented late, there was a higher frequency of missing GCS scores (88% and 87% respectively) than for the patients enrolled. Only 4% of the GP-patients considered eligible were admitted to hospital, all the CT scans were normal and only 12% of the head CTs were performed during the weekend. Further, both the eligible GP-patients and the GP-patients who presented late, had their head CTs more frequently during working hours (12.00-17.30, 68% and 67%, respectively) than the patients enrolled in the study.

Table 8 Patients who were referred from general practitioners because of mild TBI. Distribution of age, sex, injury mechanism, GCS score, CT findings and time of head CT.

	Enrolled (n = 301) n (%)	Eligible (n = 25) n (%)	P-value[1]	Presented late (n = 15) n (%)	P-value[1]
Age (years)					
Median (IQR)	25 (20-43)	31 (21-46)	0.225	38 (24-47)	0.093
Gender					
Male	195 (65)	11 (44)	0.064	4 (26)	**0.007**
Female	106 (35)	14 (56)		11 (73)	
Injury mechanism					
Fall	104 (35)	5 (20)	0.196	5 (33)	1.000
Violence	46 (15)	4 (16)	1.000	4 (27)	0.414
Bicycle accident	51 (17)	5 (20)	0.910	1 (7)	0.490
Traffic accident	37 (12)	1 (4)	0.380	2 (13)	1.000
Sport accident	45 (15)	2 (8)	0.513	2 (13)	1.000
Hit object	11 (4)	7 (28)	**0.000**	1 (7)	1.000
GCS score					
15	203 (67)	3 (12)	**0.000**	1 (7)	**0.000**
14	54 (18)	0	0.041	1 (7)	0.438
Missing	37 (12)	22 (88)	**0.000**	13 (87)	**0.000**
Level of medical care					
Discharged to home	185 (62)	24 (96)	**0.001**	15 (100%)	**0.006**
Admitted other	16 (5)	1 (4)	1.000	0	0.754
Weekday					
Monday	35 (12)	7 (28)	0.042	5 (33)	0.038
Tuesday	33 (11)	7 (28)	0.029	3 (20)	0.510
Wednesday	24 (8)	4 (16)	0.315	3 (20)	0.249
Thursday	32 (11)	2 (8)	0.942	2 (13)	1.000
Friday	28 (9)	2 (8)	1.000	1 (7)	1.000
Saturday	50 (17)	1 (4)	0.167	1 (7)	0.508
Sunday	99 (33)	2 (8)	0.020	0	0.018
Time					
00.00-05.30	98 (33)	4 (16)	0.136	0	0.018
06.00-11.30	42 (14)	2 (8)	0.594	4 (27)	0.323
12.00-17.30	67 (22)	17 (68)	**0.000**	10 (67)	**0.000**
18.00-23.30	94 (31)	2 (8)	0.026	1 (7)	0.083

[1] P-values calculated by comparing to the patients enrolled.
Note: Some of the percentages exceed 100% due to rounding.

DISCUSSION

This study investigated if there was a difference between patients enrolled and the patients not included in the mild TBI study at St. Olav's Hospital. We found that 48% of the 624 patients who fulfilled the WHO criteria for mild TBI were enrolled, 26% were excluded and 25% were missed for inclusion.

The patients who were missed for inclusion were more often injured by violence, at Saturdays and they were more often discharged directly home after the head CT examination. The differences were few, and rather small between the enrolled patients and those who were missed for inclusion.

When we looked at the different reasons for not being included, we found that patients who declined participation were more often females, with milder injuries caused by fall or violence. This was in contrast to the study by McCullag and Feinstein, who found that such patients were younger males, but consistent with our study, patients who declined participation had less significant head injuries.[7] The most common reason for not being included in our study however, was that study personnel did not manage to reach the patients, despite repeated attempts. These patients shared the same characteristics as the patients who declined participation in McCullag and Feinsteins study. No studies, to our knowledge, have reported findings on patients not reached for inclusion. Possibly, in other studies, these patients have been considered to decline participation.

The patients who were excluded differed from the patients who were enrolled by being older, they were seldom injured in sports accidents and if admitted, they were more often admitted to other hospital departments for treatment. In addition, the patients with pre-existing medical conditions more often had non-traumatic findings on their CT scans. This is in accordance with the recent study on patients excluded from a mild TBI study by Isokuortti et al., who ended up with excluding 96% of the patients who were screened.[10] However, since they started out with patients in all ages and e.g. classified also patients younger than 18 and older than 60 as excluded, it is not straight forward to compare their finding to ours. Some studies only report the percentage of excluded patients but do not provide any clinical description of them, which make it difficult to say if our findings are representative regarding these patients.[6, 7] Nevertheless, since only 26% of the patients with mild TBI were excluded in our

study, the potential bias that can be ascribed to these patients, is probably less than in many previous studies.

The patients referred from their general practitioner had a higher median age than the patients enrolled and a larger proportion in this group were females. Further, the GCS scores were mostly missing, they were seldom admitted to hospital and they had their head CTs performed during working hours, all with normal findings. The patients referred from their general practitioner constituted a small group in this study and we found no other studies to compare the findings regarding this group to. However, our findings suggest that most people consider mild TBI as an acute injury to be treated in the emergency room or outpatient clinics, and that the patients who choose to see their general practitioners for medical care, tend to be less severe cases of mild TBI. Hence, since most TBI studies enroll their patients from the emergency rooms, this may be one of the reasons that patients enrolled in studies of mild TBI tend to be skewed towards more severe injuries.[7]

A striking finding in our study were the missing GCS scores for the patients not included. The GCS scores for patients enrolled were not missing to the same extent, because the mild TBI study personnel obtained much information by face to face or telephonic contact with the patients. This information was obtained retrospectively from medical records and CT referrals for the patients not included. We found that the diagnostic symptoms of mild TBI were often not described (loss of consciousness, post traumatic amnesia or confusion and GCS score) which is in accordance with a previous studies.[13, 14] Thus, it was challenging to evaluate how severe these injuries were. However, since CT scans were mainly normal and few of the patients were referred to hospital treatment, we believe that most of these injuries were of a mild degree.

A study by Powell et al has investigated the discrepancy in diagnostic accuracy of mild TBI between study personnel and ER physicians.[14] They found that only 50% of the patients, where study personnel recognized clinical symptoms of mild TBI, had the corresponding diagnosis documented in their medical record after a visit in the ER-department. All though this was not scientifically investigated in the present study, this tendency was clearly present, both in the medical notes written by the ER physicians and, particularly, the general practitioners. Apparently, study personnel do not experience the time pressure in a busy ER clinic or the general practitioner's office, and they only have to focus on diagnosing mild TBI.

Thus, they ask the important questions to easily map out the clinical symptoms characterizing mild TBI. Further, Strand et al. investigated the compliance of Scandinavian guidelines for CT and admission recommendations for mild (and moderate) TBI, and that they were followed in only 31% of the cases.[13] Mild TBI is considered a common injury in the population, with an yearly incidence of hospital treated cases of 300/100 000. If including patient self-reports on mild TBI, the incidence is estimated to be above 600/100,000.[2] Therefore, a focus on more accurate clinical diagnosis set for mild TBI, would be the first step in correct use of diagnostic resources.

Among the patients missed for inclusion, many were injured by fall or violence on a weekend night. Although influence by alcohol and other substances was not registered in this study, one might assume that many of these patients were intoxicated based on their time and mechanism of their injury. Similarly, this could also apply for some of the patients with pre-existing conditions, especially those suffering from substance abuse. These factors and the lacking information on diagnostic symptoms in might to some extent give false positive and false negative mild TBI diagnosis in the ER-department, the municipal ER clinic and in mild TBI study context. Mild TBI symptoms are not specific for mild TBI only, and therefore, the WHO Collaborating Centre for Neurotrauma states that the manifestations of mild TBI should not be due to factors such as intoxication by alcohol or other substances.[12] Therefore, these factors are common reasons for exclusion in mild TBI studies.[6, 10, 14]

Strengths and limitations

Study personnel in the mild TBI study were present all day throughout the week and on call during weekends. In addition to screening lists of performed head CTs, they personally contacted neurosurgeons on call and the municipal emergency clinic to find eligible patients for study participation. This presence of study personnel was one of the major strengths of the mild TBI study, and a crucial contributing factor to the high participation rate. However, a limitation associated to this may have been, that many persons were involved in the patient inclusion and study procedures might have been conducted differently. Further, the source of information regarding injury variables was a limitation in this study. While study personnel were in direct contact with the enrolled patients shortly after their head injury, the information regarding the patients not included was soley based on medical records and referrals.

CONCLUSION

In our study, the most common reasons why patients were not included were; (1) the study personnel were not able to reach eligible patients, (2) the patients were excluded because of pre-existing medical conditions and (3) the patients declined participation. We also found that few patients with mild TBI seek their general practitioners for medical care in the acute setting. Some of these findings were already presented by other studies from other countries, suggesting that some traits regarding these patients are persistent across geographical distances. Although the enrolment percentage in our study can be considered to be high and representative compared to other mild TBI studies, this study also found some significant differences between patients who were missed for inclusion and those who were enrolled. Hence, also this study suffers from a degree of recruitment bias and the effect of this bias is unknown. The heterogeneity of patients who sustain head trauma and the lack of specific symptoms of mild TBI, may reduce the precision of mild TBI diagnosis. The low accuracy of mild TBI diagnosis set in the outpatient clinics, can lead to both false positive and false negative diagnoses. We experienced that these factors made the inclusion of patients demanding, and we suspect them to contribute to recruitment bias in all mild TBI research. It remains a challenge to reduce bias in mild TBI studies.

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