Traumatic Microbleeds in Mild Traumatic Brain Injury Are Not Associated with Delayed Return to Work or Persisting Post-Concussion Symptoms

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2021-09-01

Huovinen , A , Marinkovic , I , Isokuortti , H , Korvenoja , A , Mäki , K , Nybo , T , Raj , R & Melkas , S 2021 , ' Traumatic Microbleeds in Mild Traumatic Brain Injury Are Not Associated with Delayed Return to Work or Persisting Post-Concussion Symptoms ' , Journal of Neurotrauma , vol. 38 , no. 17 , pp. 2400-2406 . https://doi.org/10.1089/neu.2021.0055

http://hdl.handle.net/10138/347662
https://doi.org/10.1089/neu.2021.0055

acceptedVersion

Journal of Neurotrauma

DOI: 10.1089/neu.2021.0055

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Exclusivity: This study was previously submitted as a part of the lead author's master's thesis in the Faculty of Medicine, on august 14th 2020. The paper is accessible through HELDA – Digital repository of the University of Helsinki*, but has not previously been published in a peer-reviewed journal or any other media.

*Master's thesis, with a Finnish abstract, on HELDA – Digital repository of the University of Helsinki webpage: http://urn.fi/URN:NBN:fi:hulib-202010154296

In addition, the results of the study were presented as a part of a brief oral presentation on all types of traumatic intracranial lesions, by the lead author, at the International Brain Injury Association 2019 congress, in Toronto, Canada, March 13-16, 2019.* The results of the same cohort study were used in a prior publication focusing on psychiatric disorders** and a submitted manuscript on perceived injustice***

*Huovinen, A., Marinkovic, I., Isokuortti, H., Korvenoja, A., Vanni, S., and Melkas, S. (2019). Intracranial Traumatic Lesions Delay Return to Work in Mild Traumatic Injury Patients. Brain Injury, 33, 130-131.

**Marinkovic I, Isokuortti H, Huovinen A, et al. Prognosis after Mild Traumatic Brain Injury: Influence of Psychiatric Disorders. Brain Sci. 2020;10(12):916. Published 2020 Nov 27. doi:10.3390/brainsci10120916

***Submitted for Publication (to Journal of Head Trauma Rehabilitation on December 3rd, 2020): Perceived injustice after mild traumatic brain injury. Kaisa Mäki, LicA (Psych); Taina Nybo; Marja Hietanen; Antti Huovinen; Ivan Marinkovic; Harri Isokuortti; Susanna Melkas.

Key words: mild traumatic brain injury, return to work, traumatic microbleeds, post-concussion symptoms, functional recovery

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Abstract

The main objective of this prospective cohort study was to evaluate whether traumatic microbleeds (TMBs) are a significant prognostic factor of return to work (RTW), post-traumatic symptoms and overall recovery in patients with mild traumatic brain injury (MTBI). One hundred and thirteen (n=113) patients with MTBI were recruited from the Helsinki University Hospital emergency units. All patients underwent multicontrast 3T MRI imaging 3-17 days after MTBI. Patients were evaluated in the Traumatic Brain Injury Outpatient Clinic of Helsinki University Hospital one month after injury. Post-concussion symptoms were assessed with Post-Concussion Symptom Questionnaire (RPQ) and overall recovery with Glasgow Outcome Scale Extended (GOS-E). Their time to RTW was continuously measured up to one year after MTBI. Median RTW was 9 days (IQR 4 – 30) after MTBI and full RTW rate after one year was 98%. Patients with TMBs (n=22) did not have more post-concussion symptoms (median RPQ 10.0 vs. 7.0, p=0.217) or worse overall recovery (58% vs. 56% with GOS-E = 8, p=0.853) compared to patients without TMBs (n=91). There was no significant difference in time to RTW (13.5 vs. 7.0 days, p=0.063). In this study, patients with TMBs did not have delayed RTW nor more post-concussion symptoms compared to other patients with MTBI. TMBs in MTBI do not seem to be a significant prognostic factor of RTW.

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Introduction

Traumatic microbleeds (TMBs), formally known and often interpreted as traumatic axonal injury,[1] remain an interesting topic in traumatic brain injury (TBI) research. Even though TMBs are often present in high-energy traumas, they appear to be quite common (up to 31%) even in minor traumas such as ground-level falls, [2-3] and have been related to mild traumatic brain injury (MTBI) in both animal and human studies.[4-6]

TMBs might be a form of traumatic vascular injury.[1] TMBs are caused by external injury, often involving shearing force, which may lead to focal axonal changes and axonal breakage.[7] The pathophysiological mechanism of TMBs is complex and remains partly unknown.

The presence of TMBs has previously been reported as a potential predictor of cognitive, behavioral, functional and emotional outcomes,[8-9] affecting recovery dynamics after MTBI and possibly correlating with long-term post-traumatic symptoms.[10]

Return to work (RTW) is widely used as an outcome parameter reflecting overall recovery after MTBI.[11-14] RTW in patients with MTBI is influenced by several factors, such as age, extracranial injuries and presence of intracranial lesions.[13] In addition, vocational and educational factors such as limited job independence, lower level of education and decision-making latitude influence RTW.[11] Some of these, such as intracranial lesions, are considered factors that merely delay RTW in patients with MTBI but are not long-term predictors of disability to work.[11]

Although MTBI can result in delayed return to work, final clinical outcome is mostly favorable,[11] eventually leading to full recovery in most cases, while a minority experiences prolonged post-concussion symptoms.[14-16]

The aim of our study was to characterize whether TMBs are a significant prognostic factor regarding RTW, persisting post-concussion symptoms and functional outcome in patients with mild traumatic brain injury.

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Methods

Patients

This cohort study included 131 patients with MTBI from the Traumatic Brain Injury Outpatient Clinic of Helsinki University Hospital. Patients were from the catchment area of the Helsinki University Hospital, with 2 million inhabitants. All patients were prospectively recruited from 2015 to 2018 and were evaluated in the TBI Outpatient Clinic by a board certified neurologist experienced in patients with TBI, one month after injury.

Exclusion criteria in this study were previously diagnosed schizophrenia, schizoaffective disorder, visual or auditory disability, presence of alcohol or drug addiction, contradictions for MRI imaging and mother tongue other than Finnish. Patients who were full or part time students were also included in this study and their return to studies was comparable and included in RTW parameters. Patients were from 18 to 68 years old. For this study, we also excluded patients who were not employed (16 patients) during the time of injury, or who underwent MRI imaging later than 17 days after injury (2 patients), to result in a total of 113 patients with MTBI (figure 1).

We used the World Health Organization (WHO) definition of MTBI.[17]

All included patients gave their written consent. This study was additionally approved by the ethics committee of Helsinki University Hospital (dnro 105/13/03/01/2014).

Initial evaluation

Initial evaluation of the patients with MTBI were performed in acute phase in the Helsinki University Hospital emergency units. Clinical status, initial GCS, presence and length of post-traumatic amnesia and loss of consciousness were documented by primary physicians in the ER. They also determined the length of initial sick leave.

At one month after injury, patients were evaluated by a board certified neurologist in the Traumatic Brain Injury Outpatient Clinic of Helsinki University Hospital, using the Neurological Outcome Scale for TBI (NOS-TBI).[18] Previous and current other illnesses and medications were thoroughly assessed using hospital records and by conducting a

structured interview with the patient. Successful return to work was verified and time to return to work was documented. If necessary due to clinical manifestation, sick leave was prolonged and additional appointments were arranged in addition to research protocol.

The presence of potential symptoms was furthermore assessed using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ),[19] and overall recovery assessed using Glasgow Outcome Scale Extended (GOS-E).[5,20] RPQ evaluates the frequency and severity of 16 post-concussion symptoms, including various physical, emotional and cognitive symptoms. GOS-E is an assessment tool for functional recovery, a scale ranging from 1 (dead) to 8 (good recovery). A score of ≥6 is considered as a favorable outcome for patients with TBI.[5]

Brain imaging

All patients underwent brain MRI imaging in 3-17 days (mean 9.6, SD 3.2) after MTBI and all MRI scans were evaluated by a board certified neuroradiologist. Lesions were assessed systematically by using Common Data Elements (CDE) for TBI neuroimaging.[21-22] A second brain MRI was performed at three-month follow-up after injury, but the data was not used in our present analyses.

TMBs were defined as a single or several small hemorrhagic lesion(s) in the white matter or grey-white interface, detected with SWI sequence. For this study, only the existence of TMBs was determined, the number or the location of the lesion(s) were not stratified. Apart from that, CDE guidelines for TBI neuroimaging was followed. The presence of TMBs was used as a dichotomous variable.

Other traumatic intracranial lesions include subdural hemorrhages (SDH), subarachnoid hemorrhages (SAH), epidural hemorrhages (EDH), cerebral contusions and other intracerebral hemorrhages (ICH). These were all categorized as a single variable. Their number and type were not specified in this study.

All imaging was performed with 3T Siemens Magnetom Verio (Siemens, Erlangen) scanner with a 32-channel head coil. The imaging protocol consisted of fast localizer, T1 sagittal localizer, axial FLAIR, coronal T2, 3D T2 SPACE, 3D T1 MPRAGE, 3D gradient-echo susceptibility weighted imaging (SWI) sequence, a resting state BOLD FMRI (rs-FMRI) repeated twice with single image volume with reversed phase encoding direction acquired

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after rs-FMRI time series for susceptibility induced distortion correction. Gradient echo images for field mapping and distortion correction were acquired thereafter. Also, diffusion weighted images with 30 diffusion gradient (b=1000) directions were acquired twice with reverse phase encoding directions (left-right/right-left). Four b=0 image volumes were acquired with the two opposing phase encoding directions for susceptibility induced distortion correction. In order to limit the total imaging time in the acute phase the rs-FMRI time series was shorter (190 volumes, 5 minutes) than in the follow-up session (375 volumes, 9 minutes 45 s). In the follow-up session multi-echo 3D gradient echo images were acquired as well.

Our present analysis in this study is based on conventional 3T MRI and SWI sequence results.

Return to work evaluation

Return to work was assessed retrospectively with one-day accuracy using hospital records, and patients' successful RTW was later verified by a structured telephone interview at one year after injury, by the study author.

Full RTW was determined days from injury to the first day back to full-time work, with no further significant sick leave in the follow-up period.

Patient groups

The following subgroups were a priori defined and investigated: patients with uncomplicated (n=75) vs. complicated (n=38) MTBI and patients with TMBs (n=22) vs. without TMBs (n=91). We analyzed following subgroups separately: patients with uncomplicated MTBI (n=75), patients with exclusively TMBs (n=11), patients with only other traumatic intracranial lesions (n=16) and patients with both TMBs and other traumatic intracranial lesions (n=11).

Statistical analysis

Skewed distributions were reported as medians with interquartile range (IQR) and normally distributed values in mean and standard deviation (SD). Skewed data were

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compared between groups using a non-parametric Mann-Whitney U test. With multiple groups, we used Kruskal-Wallis H test. Categorical variables were compared using a two-sided $\chi 2$ test (Pearson Chi-Square test). A Kaplan-Meier log rank analysis was performed to investigate the time differences in RTW between groups. We considered p-values <0.05 as statistically significant.

We used IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA) to perform the analyses.

Results

Clinical characteristics of the patients with MTBI are shown in table 1. The most common mechanism of injury was ground level fall (28%), followed by bicycle accident (26%) and fall from heights (20%).

Median full RTW was 9 days (IQR 4.0 – 30.0). Three months after injury, 92% of the patients had successfully returned to work, and at one year 98% of the patients had fully returned to work. For all patients, RPQ showed a median of 8.0 points (IQR 3.0 – 15.0) while in GOS-E, 56% of patients had a good (GOS-E = 8) functional recovery.

Twenty-two (19%) patients with MTBI had TMBs visible in MRI. Significant differences between MTBI patients with or without TMBs were other intracranial lesions (p=0.001), loss of consciousness (p=0.019) and previous or current illness (p=0.037), as shown in tables 1 and 2.

RTW in patients with TMBs (n=22) was slightly delayed (median 13.5 days, IQR 6.8 – 31.0) compared to RTW in those without TMBs (median 7.0 days, IQR 3.0 – 26.0), but with no statistical significance (p=0.063) (figure 2).

As seen in table 2, patients with TMBs did not suffer from post-concussion symptoms (median RPQ 10.0, IQR 5.0 – 14.0) more often than those without TMBs (median RPQ 7.0, IQR 2.0 – 15.0; p=0.217).

Overall recovery of patients with TMBs (58% of patients with GOS-E = 8) was comparable to those without TMBs (56% of patients with GOS-E = 8; p=0.853).

As illustrated in figure 3, patients with uncomplicated MTBI had a median RTW of 6 days (IQR 3.0 – 16.0) and patients with only TMBs had a median RTW of 8 days (IQR 5.0 – 15.0).

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Presence of other intracranial lesions delayed RTW significantly (p<0.001): patients with TMBs and other lesions had a median RTW of 30.0 days (IQR 12.0 – 50.0), whereas patients with only other lesions had a median RTW of 40.5 days (IQR 15.0 – 84.0).

There were no statistically significant differences between the four groups in RPQ and GOS-E (table 3).

After excluding MTBI patients with other traumatic intracranial lesions (n=27), MTBI patients with only TMBs (n=11) and patients with uncomplicated MTBI (n=75) had no significant differences in RTW (8 vs. 6 days, p=0.312), RPQ (10.0 vs 6.5, p=0.166) or GOS-E (60% vs. 59%, p=0.944).

Patients with complicated MTBI (n=38) had significantly delayed median RTW (17 days, IQR 9.5 – 50.5) compared with patients (n=75) with uncomplicated MTBI (6 days, IQR 3.0 – 16.0; p<0.001). Patients with complicated MTBI suffered significantly more frequently from post-concussion symptoms (median RPQ 12.0, IQR 5.0 – 15.0) than patients with uncomplicated MTBI (median RPQ 6.5, IQR 2.0 – 13.3; p=0.025). There was no significant difference (p=0.407) in GOS-E results, 50% vs. 59% had a good functional recovery (GOS-E = 8).

Discussion

In this study, MTBI patients with TMBs did not have delayed RTW nor more post-concussion symptoms compared to patients with uncomplicated MTBI. Thus TMBs visible in conventional MRI did not seem to impede with recovery after MTBI. Other intracranial lesions delayed RTW, although in general the patients in this cohort recovered reasonably fast.

To our knowledge, this is the first study to compare RTW in MTBI patients with and without TMBs. In a previous study by Iverson and colleagues,[23] RTW was compared between patients with complicated MTBI (n=13) and patients with uncomplicated MTBI (n=34; total n=47). In other words, MTBI patients with intracranial lesions and those without them. Patients with intracranial lesions had significantly delayed RTW (36 vs. 6

days), but they did not perform more poorly in neurocognitive testing nor report more symptoms. However, the proportion of patients with TMBs was not specified in this study.

In another study, Wäljas and colleagues studied patients with MTBI using diffusion tract imaging (DTI).[24] They found that patients with DTI abnormalities (interpreted as white matter changes) did not differ from the patients with normal DTI in terms of post-concussion symptom reporting.

Regarding RTW in general, patients in our cohort returned to work fast. Median RTW time was 9 days and RTW rate of 98.2% at one year after injury. Similar RTW results were found by Wäljas and colleagues,[13] with 97% of the patients with MTBI having returned to work in one year after injury. According to a recent meta-analysis by Bloom and colleagues,[12] RTW times of patients with MTBI varied between 13 and 93 days, and 89% of patients had returned to work in one year after injury. Some studies have found delayed RTW time due to variety of factors, for instance, intracranial lesions visible in CT scan and extracranial co-trauma.[13,23,25-26] Our finding that other intracranial lesions delay RTW is consistent with previous literature.[23]

Post-concussion syndrome (PCS) in relation to TMBs in MTBI has previously been studied in several cohorts. These include studies where abnormalities in magnetic spectroscopy[27], DWI[28] and DTI[6] were interpreted as TMBs. The authors reported that MTBI patients with PCS had lower white matter N-acetylaspartate[27] and wider structural impairment[28] than MTBI patients without PCS. In a study by D'souza and colleagues,[6] a strong correlation between DTI abnormalities and severity of post-concussion symptoms was found. These studies are, however, not in line with ours, where MTBI patients with TMBs had equal frequencies of post-concussion symptoms as MTBI patients without TMBs.

In our study, functional outcome measured with GOS-E was the same for patients with and without TMBs. There is only scarce documentation on potential association between GOS-E and TMBs in MTBI. van Eijck and colleagues reported a study of 163 patients with TMBs, of which 15% (n=24) had MTBI while the rest had either moderate or severe TBI.[5] The analysis was not stratified by severity grade. The results showed that more than half of the

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patients had favorable functional outcome measured with GOS-E by the end of the follow-up (approximately 4 years). This is a high proportion keeping in mind that all severity grades were pooled together in analysis.

For this study, only the existence of TMBs was determined, not the number nor the location of the lesion(s). We know that all cases were classified as MTBI so the neuroradiological findings were minor, but otherwise the focus was not on the location of the lesion(s). A meta-analysis by Haghbayan and coauthors (2017) concluded that particularly lesions in the brainstem are associated with worse outcome.[29]

Our study has several strengths: according to our knowledge, this is the first study to directly investigate the association between TMBs and RTW. Due to our clinic's position as a specialized center for patients with TBI, we were able to get detailed information of patients' symptoms after the acute phase and follow their recovery and return to work closely. These records are so detailed that retrospective assessment of RTW is possible up-to one-day accuracy. In generally, patient records are considered reliable and detailed in Finland.[13] Even though it is a retrospective method and there are possibilities of error, we consider this method more of a strength than a limitation.

Our study has some limitations: first of all, the number of patients with TMBs was relatively low. Among 113 patients with MTBI, there were 22 patients with TMBs, and only 11 patients had exclusively TMBs. In addition, the vast majority of patients had favorable outcome, therefore statistical significance in a smaller sub-population is less likely to be achieved. Finally, our analysis is based on conventional 3T MRI with SWI sequence. The addition of DTI might have provided extra information. Conventional MRI, however, remains the golden standard in TMB research.[5,22,29-30]

Conclusions

In conclusion, our results show that TMBs visible in conventional MRI do not seem to be a predictor of poor recovery or delayed return to work after MTBI. This suggests that other factors are more relevant when a patient gets prolonged symptoms after MTBI. Instead of efforts to detect more and more microscopic structural or non-structural lesions with

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emerging methods, future research should focus on other risk factors and protective factors that play role in recovery after MTBI.

Acknowledgements

The authors thank Simo Vanni (MD, PhD) and Aarne Ylinen (MD, PhD) for their contribution for this article. Written permissions were obtained.

Authorship Contribution statement

All authors meet the criteria for authorship, defined by the International Committee of Medical Journal Editors, and have substantially contributed to this manuscript. Each author has read and approved this manuscript and agree to be accountable for all aspects of the work.

Authors' Disclosure Statement

The authors state no disclosures or conflicts of interest.

Funding statements

This study was supported by grants from Dorothea, Jarl Walter and Karl Walter Perklén's foundation, Päivikki and Sakari Sohlberg´s foundation, Maire Taponen foundation and HUS Neurocenter. This manuscript was written as part of the lead author's doctoral thesis.

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Figure legends

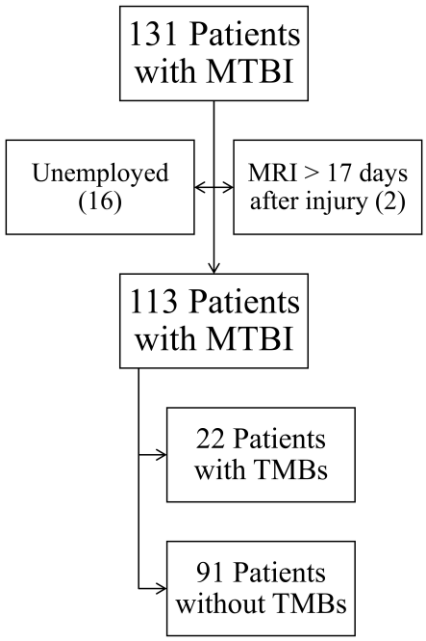

Figure 1. 131 patients met the inclusion criteria of the cohort. Those who were not employed or underwent MRI later than 17 days after injury were excluded from the study, to result in a total of 113 patients with MTBI.

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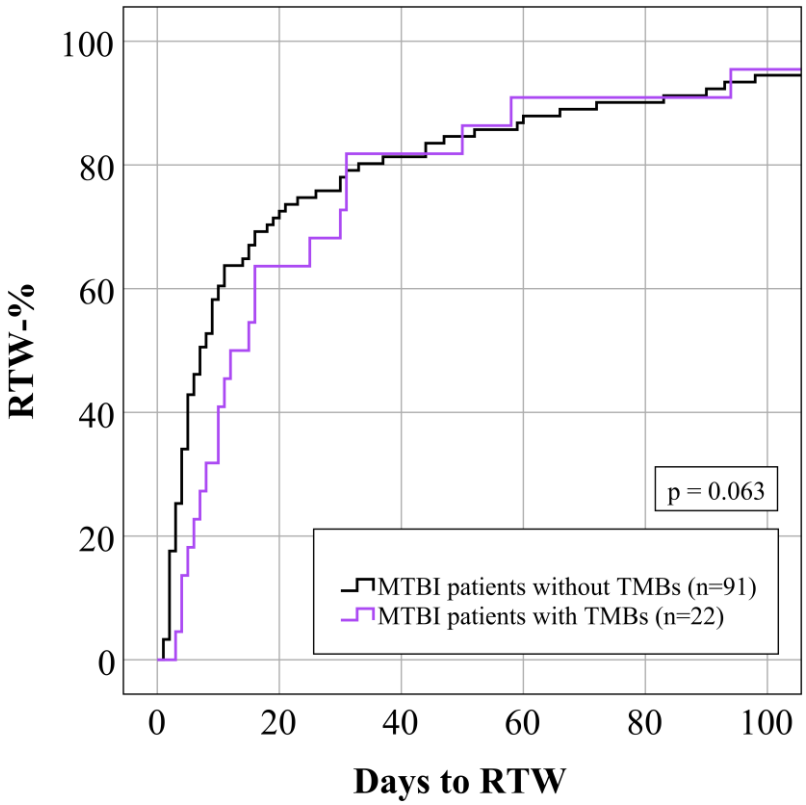

Figure 2. The effect of TMBs on RTW in patients with MTBI.

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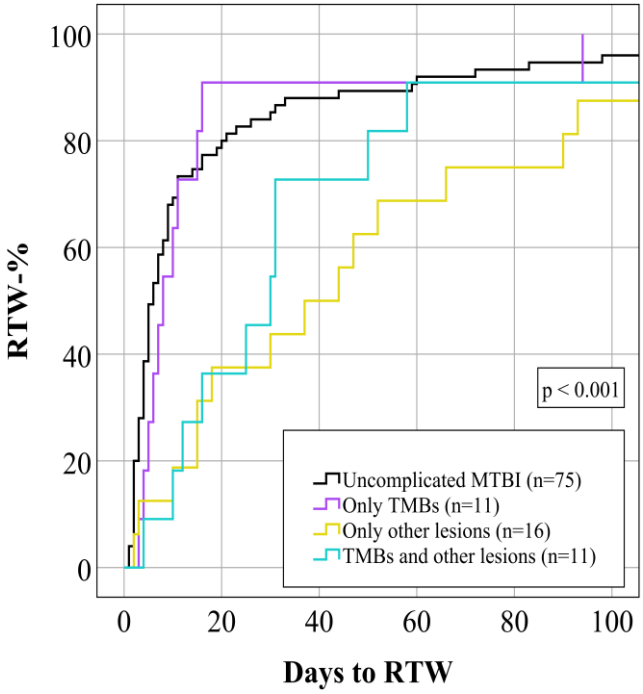

Figure 3. RTW in four MTBI subgroups: patients with uncomplicated MTBI (n=75), patients with exclusively TMBs (n=11), patients with only other traumatic intracranial lesions (n=16) and patients with both TMBs and other traumatic intracranial lesions (n=11).

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Tables

Table 1. Demographic and clinical characteristics of the patients with MTBI.

	MTBI patients without TMBs (n=91)		MTBI patients with TMBs (n=22)		All patients (n=113)		
	Mean/ n	**SD/IQR/ %**	**Mean/ n**	**SD/IQR/ %**	**Mean/ n**	**SD/IQR/ %**	**p**
Age	39.9	12.2	36.3	12.4	39.2	12.2	0.213
Sex (female)	42	46.2%	7	31.8%	49	43.4%	0.223
Years of education (median)	16.5	13.0 – 19.0	15.3	12.4 – 17.3	16.0	13.0 – 18.5	0.356
Previous or current illnesses*	43	47.3%	5	22.7%	48	42.5%	**0.037**
Type of labor							0.834
Entrepreneur	12	13.2%	4	18.2%	16	14.2%	
Management	10	11.0%	2	9.1%	12	10.6%	
Expert	31	34.1%	6	27.3%	37	32.7%	
Manual labor	17	18.7%	6	27.3%	23	20.4%	
Other	21	23.1%	4	18.2%	25	22.1%	
Students							0.410
full-time	11	12.1%	2	9.1%	13	11.5%	

part-time	6	6.6%	0	0	6	5.3%	
Mechanism of injury							0.395
Motor vehicle accident (MVA)	4	4.4%	3	13.6%	7	6.2%	
Traffic accident as a pedestrian	1	1.1%	0	0%	1	0.9%	
Sports	11	12.1%	3	13.6%	14	12.3%	
Bicycle accident	25	27.5%	4	18.2%	29	25.7%	
Ground level fall	27	29.7%	5	22.7%	32	28.3%	
Fall from heights	17	18.7%	6	27.3%	23	20.4%	
Violence	4	4.4%	0	0%	4	3.5%	
Other	1	1.1%	1	4.5%	2	1.8%	
Unknown	1	1.1%	0	0%	1	0.9%	

** Previous or current illnesses include cardiovascular diseases, diabetes and various neurological and psychiatric conditions, for instance. No single condition stood out to be significantly more frequent between groups.*

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Table 2. Comparing MTBI patients with TMBs with those without TMBs.

	MTBI patients without TMBs (n=91)			MTBI patients with TMBs (n=22)			
	Valid n	**Mean/nSD/IQR/%**		**Valid n**	**Mean/nSD/IQR/%**		**p**
Hospitalization period (days, median)	91	1.0	1.0 – 2.0	22	2.0	1.0 – 2.0	0.202
Loss of consciousness (witnessed)	91	45	49.5%	22	17	77.3%	**0.019**
LOC median time (minutes)	45	1	1 – 2	17	1	1 – 4	0.621
Post-traumatic amnesia	91	84	92.3%	22	20	90.9%	0.828
PTA median time (h:min)	84	1:00	0:20 – 4:00	20	1:20	0:10 – 2:50	0.682
GCS measured by first aid	91	50	54.9%	22	11	50%	0.676
GCS (points)	50	14.7	0.50	11	14.7	0.47	0.961
Other intracranial lesion	91	16	17.6%	22	11	50%	**0.001**
Non-head ISS*	91	1.0	0 – 2.0	22	1.5	1.0 – 6.0	0.203
Return to work, days (median)	91	7.0	3.0 – 26.0	22	13.5	6.8 – 31.0	0.063
RPQ points (median)	78	7.0	2.0 – 15.0	19	10.0	5.0 – 14.0	0.217
GOS-E = 8	81	45	55.6%	19	11	57.9 %	0.853

**Injury Severity Score (ISS) measures frequency and severity of injury from different body regions using Abbreviated Injury Scale.[25] In this case, we measured severity of extracranial injuries, such as broken limbs, vertebral fractures and wounds.*

Table 3. Comparing RTW, RPQ and GOS-E results between four MTBI subgroups.

		RTW			RPQ			GOS-E		
	N	**Valid n**	**Median (days)**	**IQR**	**Valid n**	**Median (points)**	**IQR**	**Valid n**	**GOS-E = 8**	**%**
Uncomplicated MTBI patients	75	75	6.0	3.0 – 16.0	66	6.5	2.0 – 13.3	68	40	58.8 %
MTBI patients with only TMBs	11	11	8.0	5.0 – 15.0	10	10.0	4.8 – 17.0	10	6	60.0 %
MTBI patients with TMBs and other intracranial lesions	11	11	30.0	12.0 – 50.0	9	11.0	5.5 – 13.5	9	5	55.6 %
MTBI patients with only other intracranial lesions	16	16	40.5	15.0 – 84.0	12	14.5	5.5 – 17.3	13	5	38.5 %
p			**<0.001**			0.147			0.592	

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