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Persistence of post-concussion symptoms in patients with mild traumatic brain injury and no psychiatric history in the emergency department

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ABSTRACT

Purpose: To elucidate the predictive factors for persistent post-concussion symptoms at 1 and 3 months following minor traumatic brain injuries (mTBIs) in patients with no psychiatric history.

Methods: This was an observational study in an academic trauma centre including adult patients with a history of mTBI and no psychiatric history. Exclusion criteria were missing the follow-up phone calls, radiologic abnormalities, simultaneous injuries and refusal to participate. Outcomes were post-concussion syndrome according to the international classification of diseases (ICD)-10 (ICD-PCS) and persistence of more than one mTBI related symptoms at 1 and 3 months post-injury.

Results: From 364 enrolled patients, 16 (4.4%) developed ICD-PCS, whereas 28 (7.6%) and 8(2.1%) reported more than one symptom at one and three months, respectively. Multivariable analysis showed associations between ICD-PCS with more than one initial symptom in the emergency department (ED) and the non-motor vehicle collision (non-MVC) impact mechanism with area under curve of 0.77. The former variable was associated with the persistence of more than one post-concussion symptom at one and three months.

Conclusion: More than one symptom in the ED and the mechanism of injury not related to MVCs (sports, violence or fall injuries) may predict symptom persistence. Early treatment and follow-up strategies may be beneficial for vulnerable patients.

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Introduction

Although frequently used, post-concussion syndrome (PCS) is not a well-defined clinical entity. In general, persistence of symptoms following head trauma beyond an accepted period of time is called PCS; the symptoms are usually nonspecific and do not necessarily reflect the ongoing pathophysiology of brain injury (1). Depending on their expertise and speciality, physicians tag a wide variety of patients with head trauma with this term, from those who have persistence of one symptom for a few days to those who remain symptomatic for more than 3 months (2). The inconsistency in the definition of PCS is also found in the published literature. Many authors have used the tenth version of the international classification of diseases (ICD-10) definition, which originally included the persistence of at least three of the following eight symptoms [usually at four weeks] following head trauma: headache, dizziness, fatigue, irritability, impaired concentration, impaired memory, insomnia and stress intolerance (3). The 2007 update of the definition, however, removed the need for three symptoms and instead, referred to the persistence of any number of these symptoms as PCS (4). Trauma-related symptoms which are reported by the patients, however, may not be confined to a pre-defined list and include a wider range of symptoms (5). In spite of the presence of defined criteria, the concept of PCS as a reliably identifiable syndrome has been questioned in the recent years. As a result, many authors tend to use persistence of post-concussion symptoms for a defined period instead of rigid definitions in their studies (6,7). Likewise, the reported incidence of PCS is highly variable. Depending on the diagnostic criteria, population and timing of assessment, the incidence of persistent post-concussion symptoms following a mild traumatic brain injury (mTBI) is reported to range from 5% to more than 50% in different study populations (3,8); higher rates were reported among those who had a history of psychiatric disorders (9). Since PCS induces substantial socio-professional troubles that may last for several months (10), there are a number of studies which address the early predictors of PCS or persistence of symptoms following mTBI. Besides the demographic and non-psychiatric factors [female gender, post-traumatic loss of consciousness (LOC), post-traumatic headache or dizziness, severity of symptoms, etc.] which were shown in the literature to be associated with persistent post-concussion symptoms (11–13), pre-morbid psychiatric disorders (depression, anxiety, etc.) seem to be strongly associated with the symptom persistence (9,13–16). As a result, it is possible that, without excluding patients with positive psychiatric history, the non-psychiatric factors fail to appear in multivariable prediction models due to the presence of strong associations between symptom persistence and psychiatric predictors. This leads to the introduction of models which may not be useful for those without a positive psychiatric history. Furthermore, there is a possibility of PCS misdiagnosis in a population of patients with depressive or other psychiatric disorders (17,18). In the present study, we aim to

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evaluate the persistence of post-concussion symptoms in a population of patients with mTBI without any psychiatric history to elucidate the potential predictors which can be assessed and recorded in a routine evaluation by an emergency physician.

Methods

Study design and settings

This was an observational study which was performed in a single referral level 2 trauma centre in Kerman, Iran. Bahonar Academic Hospital has an annual ED census of near 100,000 patients and is the main referral trauma centre in the southeast of the country (19). Patients are triaged using a 5 level emergency severity index (ESI) system by a registered nurse. Thereafter, a resident of emergency medicine (EM) and the attending physician of EM on duty evaluate the patient. A neurosurgical consult may be requested at the discretion of the EM service.

This study was approved by the institutional review board and the committee of medical ethics of Kerman University of Medical Sciences.

Study population

Adult patients (over 16 years of age) were included in the study if they had a history of mTBI in the previous 24 hours and had no history of any psychiatric disease. The term mTBI was defined as a short-lived impairment of normal brain function following an external impact to the head with a presenting time Glasgow coma scale (GCS) of 13–15 (20). As is usual in the current medical literature (21), we used mTBI as an equivalent to the term "concussion" in this article. Exclusion criteria were missed follow-up calls, any trauma-related radiologic abnormality on brain computed tomography (which were performed at the discretion of the in-charge physicians), concurrent significant injuries or conditions which affect the neurologic assessment, patients who give unreliable information on phone interviews at the discretion of the interviewer, and patient refusal to participate.

Study variables and outcomes

Our aim was to include variables which could be evaluated in patients with mTBI during an ordinary ED examination. In the ED, many patients and their companions may not be able to respond to the questions in a quantitative manner. They, for example, may not be able to tell the duration of LOC by minutes or the exact number of their vomiting episodes. As a result, we designed our study based mostly on qualitative (e.g. two or three choice questions or yes/no questions) information to have more realistic and practical suggestions based on our results. Included variables were as follows: demographic variables [age, gender, socioeconomic status (reported by the patient as poor, moderate or good), marital status, living alone], mechanism of injury [motor vehicle collisions (MVCs), sports, violence or fall injuries], factors associated with past medical history (organic co-morbidities, history of head trauma, history of PCS) and initial symptoms and signs including GCS less than 15, LOC, post-traumatic amnesia (PTA), post-traumatic seizures, vomiting, post-traumatic headache, confusion, short-term memory impairment and immediate or delayed (more than estimated 20 minutes after the impact) development of symptoms.

Five outcomes were defined: the primary outcome, PCS, was defined according to the ICD-10 classification (ICD-PCS) at 4 weeks post-injury (see Introduction). There is not, however, a universal consensus on this definition, and both the ICD-10 and the diagnostic and statistical manual 4th edition (DSM-IV) definitions have been criticized by many authors (22,23). As a result, we added four outcomes based on the number of symptoms and their persistence: persistence of at least one symptom at 1 and 3 months, and persistence of more than one symptom at 1 and 3 months. The Rivermead post-concussion symptoms questionnaire (RPQ) (24,25) was used to collect the information from the patients at 1 and 3 months.

Study protocol

Patients who met the inclusion criteria were recruited serially from 1 January 2019 to 1 April 2019. A senior resident of emergency medicine (post-graduate year-3) collected all of the data. Firstly, she abstracted the files of the patients who were diagnosed as mTBI a few days after their admission. After recruitment, she confirmed the accuracy of the recorded data via a phone call with the patient and informed them about the study. At 1 and 3 months post-impact, she followed all of the patients by phone call interview using the RPQ. The abstraction process and the phone interviews were randomly supervised by an attending physician of emergency medicine (EM). The diagnoses of PCS were made using ICD-10 criteria (see introduction). The outcomes (see study variables and outcomes) were determined for each patient by consensus between the two aforementioned physicians.

Statistical analysis

Quantitative values were reported as mean (SD) for normally distributed continuous variables or median and interquartile range (IQR) for non-normally distributed continuous variables. Qualitative values were presented as numbers and percentages. For univariable analysis, continuous data were analyzed using the student t-test if the data were normally distributed (according to the Kolmogorov-Smirnov, Shapiro and Levene's test); otherwise, the adjusted t-test was used. Categorical data were compared using Pearson $\chi 2$ test. A P value less than 0.05 was considered to be statistically significant.

All clinically relevant variables with a p value of less than 0.25 in the univariable analysis were included in the logistic regression model (using the backward conditional method) for each of the five outcomes separately (26). Receiver operating characteristics (ROC) curve was used to show the predictive capability of the final model for each outcome. SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

Results

Basic characteristics

A total of 571 patients were recruited, of whom 364 were enrolled based on the exclusion criteria (Figure 1). From 364, 220 (60%) were females. The median (IQR) age was 30 (17), with the minimum and maximum of 16 and 89, respectively. The mechanism of head impact was associated with motor vehicle collisions (MVCs), violence, sports and fall injuries in 192 (52.8%), 42 (11.5%), 40 (10.9%) and 90 (24.8%) patients, respectively. Information regarding the marital status, socioeconomic status and the other characteristics of the patients are shown in Table 1.

The presenting time GCS scores were 15 in 300 (82.4%) patients, 14 in 48 (13.2%), and 13 in 16 (4.4%). Two hundred and seventy (74%) patients showed only one initial symptom related to the head trauma in the ED, whereas 94 (26%) had more than one symptom (Table 2).

After follow-up phone calls using the RPQS, 120 (32.9%) and 50 (13.7%) patients reported at least one symptom after 1 and 3 months, respectively. Twenty eight (7.6%) and 8 (2.1%) patients reported more than one symptom at 1 and 3 months,

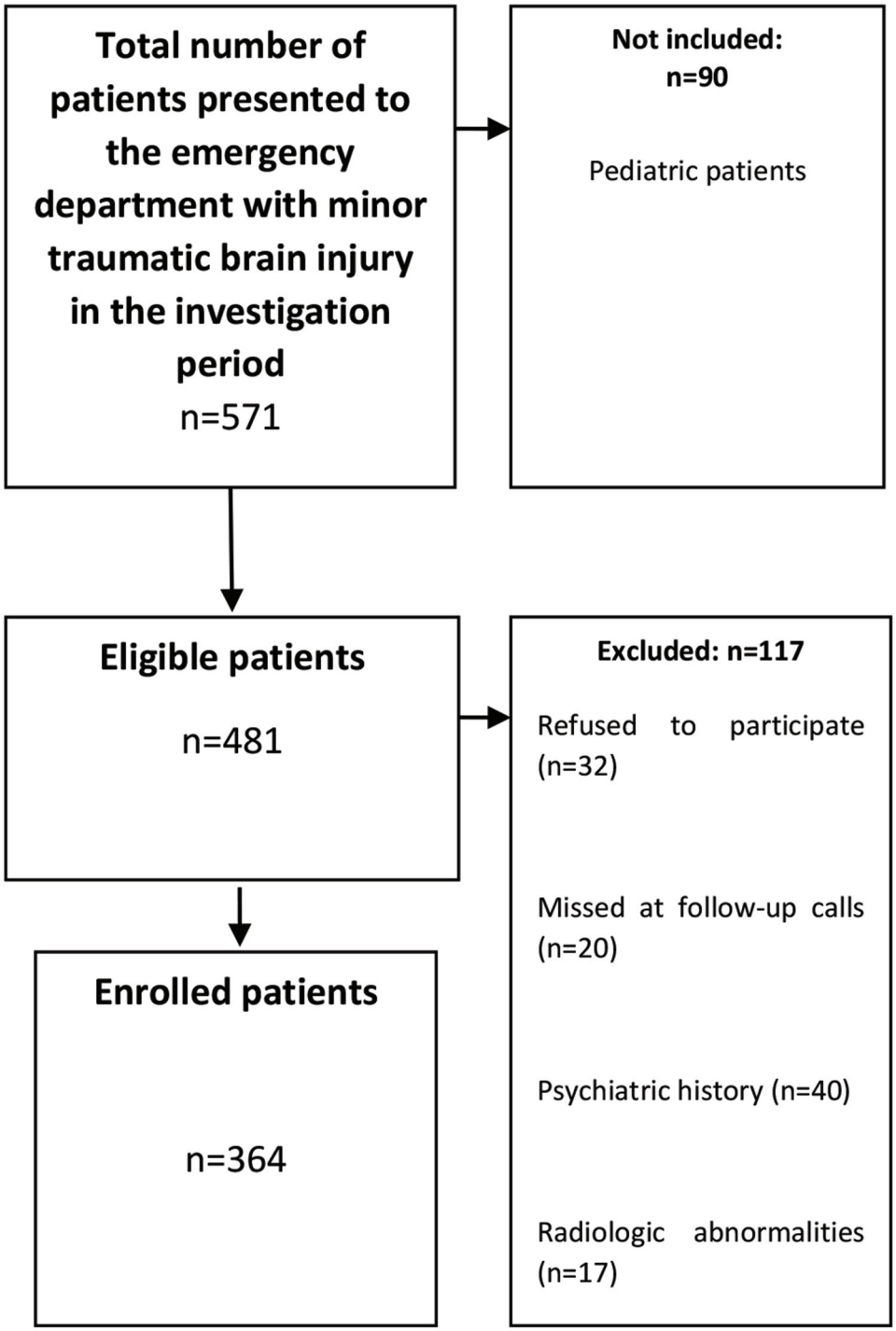

Figure 1. Flow diagram indicating patient enrollment.

Table 1. Social characteristics and history of the patients.

	Marital status		Socioeconomic status			Living alone		Co-morbidities *		Previous head trauma	
	Married	*Not married/divorced*	*Moderate or poor*	*Good*	*Undefined*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*
No. (%)	214 (58.7)	150 (41.3)	102 (28)	170 (46.7)	92 (25.3)	64 (17.5)	300 (82.5)	40 (10.9)	324 (89.1)	32 (8.7)	332 (91.3)

*co-morbidities included heart disease, lung disease and hypertension

Table 2. Initial signs and symptoms associated with head trauma.

symptom	PTA*	LOC**	Seizures	Headache	Vomiting	Post traumatic confusion	Short term memory impairment	Scalp hematoma	Scalp laceration
No. (%)	39 (10.7)	21 (5.7)	6 (1.6)	216 (59.3)	210 (57.6)	209 (57.4)	9 (2.4)	41 (11.2)	127 (34.8)

*Post traumatic amnesia
**Loss of consciousness

respectively. Using the ICD-10 criteria, the number of patients who were diagnosed as PCS (ICD-PCS) was 16 (4.4%). Headache was the most commonly reported symptom, followed by dizziness, restlessness and insomnia (Table 3).

Univariable analysis

No association between gender with the persistence of at least one symptom at 1 and 3 months, more than one symptom at 1 and 3 months and the ICD-PCS was found. The same was true for the association of marital status, socioeconomic status and living alone with the outcomes. However, the non-MVC mechanism of injury was associated with ICD-PCS and the persistence of one symptom at 3 months (Table 4).

The presenting time GCS less than 15 was associated with ICD-PCS, persistence of one symptom at three months, and persistence of more than one symptom at one month. Except for vomiting, the development of only one symptom (PTA, LOC or the other symptoms) after the head impact was not associated with any of the outcomes. However, the development of more than one symptom after the trauma was associated with ICD-PCS and the persistence of more than one symptom at 1 and 3 months (p values, 0.01, <0.01 and 0.02, respectively). No association was found between the delayed development of the symptoms with any of the outcomes (Table 5).

Multivariable analysis

Multivariable analysis were performed separately for each of the five outcomes. Table 6 shows the included variables for each outcome and the features of the final model. Whenever the presence of more than one initial symptom, vomiting and/or headache met in one model, the latter two were excluded from the analysis since these three variables showed to be multi-collinear.

Table 3. Frequency of post-concussive symptoms at 1 and 3 months after the impact.

	Headache	Dizziness	Nausea	Insomnia	Restlessness	Blurred vision	Double vision	Memory impairment	Other***
One month* [No (%), (maximum score) **]	84 (23), (4)	48 (13.1), (3)	8 (2.2), (2)	10 (2.7), (2)	10 (2.7), (3)	4 (1.09), (2)	4 (1.1), (2)	9 (2.4), (3)	0
Three months [No (%), (maximum score)]	42 (11.5), (3)	12 (3.2), (3)	0	2 (0.5), (2)	0	0	0	3 (0.8), (3)	0

*One month after the impact
**Maximum score reported in the Rivermead post-concussion syndrome questionnaire
***Other symptoms present in the Rivermead post-concussion syndrome questionnaire, including noise intolerance, fatigability, irritability, light sensitivity, slowed thinking and concentration problems

Table 4. P values regarding the association of demographic features and the mechanism of injury with the outcomes.

	Gender	Socioeconomic status	Marital status	Living alone	Previous history of head trauma	Mechanism not related to motor vehicle collisions
At least one symptom at 1 month*	0.52	0.28	0.29	0.40	0.37	0.63
At least one symptom at 3 months	0.75	0.29	0.33	0.75	0.85	0.03
More than one symptom at 1 month	0.41	0.56	0.50	0.35	0.47	0.10
More than one symptom at 3 months	0.46	0.28	0.54	0.61	0.52	0.79
Post concussion syndrome **	0.93	0.25	0.38	0.43	0.72	0.03

*Including all of the symptoms which are mentioned in the Rivermead post-concussion syndrome questionnaire
**Defined by the international classification of diseases (ICD)-10
†Statistical significance

Table 5. P values regarding the association of initial symptoms with the development of outcomes.

Outcome	GCS<15*	PTA**	LOC***	Headache	Vomiting	Post traumatic confusion	Delayed symptoms****	More than 1 symptom
At least one symptom at 1 month*****	0.08	0.44	0.38	0.10	0.65	0.47	0.75	0.58
At least one symptom at 3 months	0.01	0.32	0.59	0.94	0.11	0.53	0.56	0.08
More than one symptom at 1 month	0.004	0.62	0.47	0.56	0.01	0.57	0.88	0.001
More than one symptom at 3 months	0.05	0.32	0.70	0.18	0.10	0.42	0.57	0.02
Post concussion syndrome ******	0.04	0.85	0.59	0.19	0.01	0.52	0.88	0.01

*Glasgow coma scale
**Post traumatic amnesia
***Loss of consciousness
**** Including all of the symptoms which are mentioned in the Rivermead post-concussion syndrome questionnaire
*****after 20 minutes from the impact
******Defined by the international classification of diseases (ICD)-10
† Statistical significance

The presence of more than one initial symptom was independently associated with the development of ICD-PCS and the persistence of more than one symptom at one and three months (ORs, 3.4, 4.1 and 8.8, respectively). Similarly, the mechanism of injury not related to MVCs increased the odds of persistent one symptom at three months, persistence of more than one symptom at one month and ICD-PCS by 2.9, 3.1 and 8.7 times, respectively.

ROC curve

ROC curves were created for each of the five models (Figure 2). The area under the curve (AUC) (95%CI) for persistence of at least one symptom at one and three months, persistence of more than one symptom at one and three months and ICD-PCS were 0.57 (0.51–64), 0.65 (0.55–0.75), 0.70 (0.58–0.89), 0.75 (0.57–0.92) and 0.77 (0.61–0.92), respectively.

Discussion

The incidence of PCS following mTBI in our study was lower than the broad range which has been reported in the current literature. This may be due to the exclusion of patients with psychiatric pre-morbid condition or those with radiologic abnormalities. As mentioned before, positive psychiatric history was associated with higher incidence of symptom persistence following mTBI (9,14–18,27). Moreover, symptom persistence has been evaluated and reported by incidence from one week to six months post-injury (13,14). Many authors tend to differentiate patients with PCS from those who have persistent one or two symptoms, and some others may take them as a single group. Therefore, we defined five outcomes based on the number and persistence of symptoms to cover most of the possible scenarios that a patient may present with. Regardless of the definitions, this approach may be more useful from a practical view since a single symptom at

Table 6. Variables which show independent associations with the outcomes using logistic regression analysis.

Outcome	Variables entered in the model*	Variables showing independent associations (model exit)	P value	Odds ratio (95%CI)	Standard error	Nagelkerke R square
At least one symptom at 1 month**	*GCS***<15*	GCS<15	0.06	2.18 (1.20–3.93)	0.30	0.04
	Headache	Headache	0.08	1.78 (1.11–2.86)	0.24	
At least one symptom at 3 months	*Non-MVC**** *mechanism*	Non-MVC mechanism	0.002	2.94 (1.48–5.81)	0.34	0.08
	GCS<15	GCS<15	0.01	2.63 (1.21–5.69)	0.39	
	More than 1 initial symptoms					
More than one symptom at 1 month	*Non-MVC mechanism*	Non-MVC mechanism	0.01	3.14(1.25–7.92)	0.47	0.11
	GCS<15	More than 1 initial symptoms	0.002	4.13(1.68–10.17)	0.45	
	More than 1 initial symptoms					
More than one symptom at 3 months	*GCS<15*	More than 1 initial symptoms	0.008	8.86 (1.75–44.72)	0.82	0.12
	More than 1 initial symptoms					
Post concussion syndrome *****	*Non-MVC mechanism*	Non-MVC mechanism	0.006	8.78 (1.86–41.35)	0.79	0.15
	GCS<15	More than 1 initial symptoms	0.04	3.46 (1.05–11.42)	0.60	
	More than 1 initial symptoms					

*headache, vomiting and more than initial 1 symptom showed multicollinearity. In the case of presence of the 3 variables, we entered only more than initial 1 symptom in the model.
** Including all of the symptoms which are mentioned in the Rivermead post-concussion syndrome questionnaire
***Glasgow coma scale
****Motor vehicle collision
***** Defined by the international classification of diseases (ICD)-10

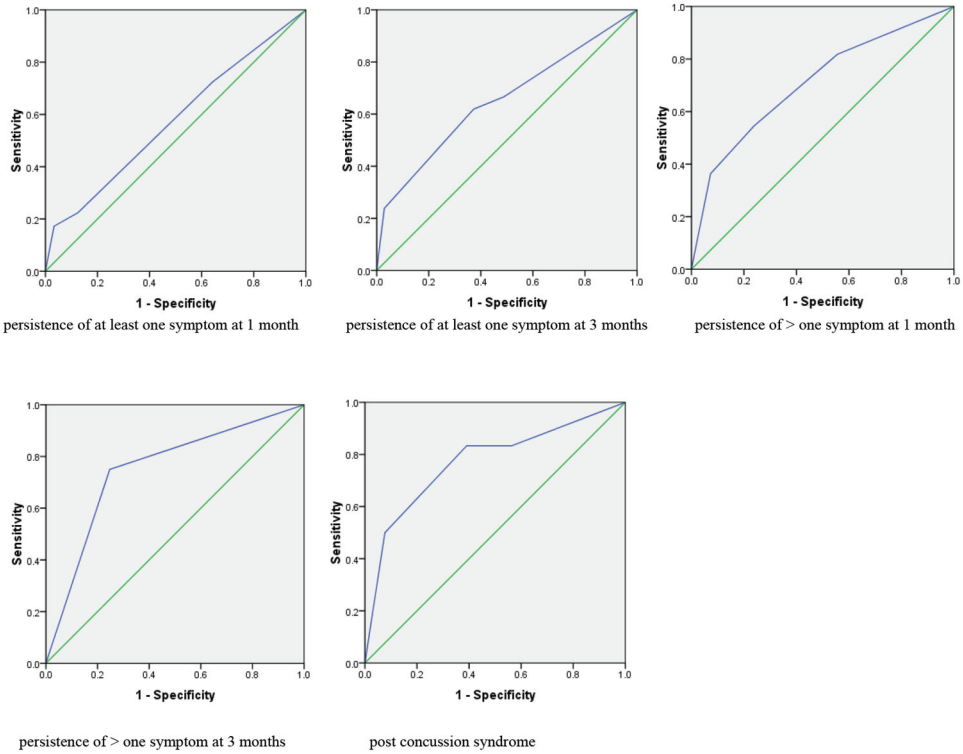

Figure 2. Receiver operating characteristics for the prediction of the outcomes by the regression models.

one month post-injury is probably in the same clinical range with symptoms which persist at 3 months.

Some authors showed that female gender was associated with the development of post-concussion symptoms (13), whereas some others did not find such an association (14). The proportion of female gender in our study population was 60%, which was not predicted at the beginning of the study. The exclusion process was the main reason for increased proportion of females in our study population since many more males were excluded due to missed follow- ups, refusal to participate and imaging abnormalities. We did not find any association between gender and persistence of post-concussion symptoms. We found some value for the initial headache and the initial lower GCS scores for prediction of at least one persistent symptom at one month post-injury. The prediction model, however, performed poorly on the ROC curve (AUC, 0.57). In the univariable analysis, headache was not significantly associated with any of the outcomes. Vomiting, though associated with the other outcomes, was not predictive of persistent one symptom at one month. There are, however, some studies who address headache as a predictor of persistence or severity of symptoms at one week to 6 months post-injury (14). In general, it may be considered rational that the absence of headache indicates a less severe injury. However, the predictive value of headache for long-standing post-concussion symptoms is not universally confirmed by the literature. Similarly, although initial GCS was not shown by the other studies to be of predictive value for PCS (28), we found associations between GCS less than 15 and at least one symptom at one month.

In the model created for the persistence of at least one symptom at 3 months, although the presence of initial GCS less than 15 increased the odds of this outcome by 2.6 fold, the mechanism of injury not related to MVCs (the mechanism involving sports, violence and fall injuries) increased the same odds by nearly 3 fold. In the study of Ganti et al. (14), the mechanism of injury involving MVCs or falls was associated with PCS at one week (and not later) post-injury. Some authors have also evaluated the increased risk of mTBI and its consequences (e.g. PCS) in domestic violent behaviours (29,30). We believe that post-concussion consequences of every mechanism of injury may at least partially be related to the amount of post-traumatic emotional stress (31,32) that may be triggered by that type of injury in each society and culture. People in different societies and nations may not be equally influenced emotionally by one mechanism of injury. In Iran or India, for example, where the rate of MVCs are much higher than Europe, a motor crash may not induce the same post-traumatic stress as a European country. MVCs were reported as the most common mechanism of mTBIs in some Iranian and non-Iranian studies (14,33,34). To our knowledge, however, comparisons between the post-traumatic stress levels of MVCs with the other mechanisms of injury have not been performed extensively. One study showed that sexual abuse causes more post-traumatic stress symptoms than MVCs or bereavement (35). Similarly, Bown et al. showed that victims of assault scored worse in self-reported post-traumatic stress than MVCs and falls; after exploratory analysis, however, the authors found that assaults and MVCs lead to worse outcomes compared to fall injuries (36). Our hypothesis on the term "emotional stress" does not include a technical definition such as acute stress disorder (ASD) or post-traumatic stress disorder (PTSD) since quantification of stress level and differentiating the diagnosis of PTSD from persistence of post-

concussion symptoms was beyond our goals in this study and also beyond the scope of the practice of an emergency physician (see Limitations).

Persistence of more than one symptom at one and three months may be more important from the clinical view since their imposed burdens are probably higher; they are highly correlated with the definition of ICD-PCS as well. The prediction models for the persistence of more than one symptom at one and three months and ICD-PCS were almost the same. The presence of more than one initial symptom in the ED was the common predictor for all three models: the odds of the outcomes were increased by 3.5 to more than 8 fold by the presence of more than one initial symptom. Initial symptoms such as headache, dizziness and vomiting were shown by different studies to be related to the persistence of symptoms (14,37); however, no study has evaluated the presence of more than one initial symptom in the ED as a predictor. The advantage of the model using this variable instead of a single symptom (e.g. headache which was used in the first model) was its acceptable performance in the ROC analysis, with AUCs of 0.70, 0.75 and 0.77 for persistence of more than one symptom at one and three months and ICD-PCS, respectively. Moreover, our findings may be more practical to be used in the ED, where most of the patients seem to be at lower risks of PCS since they have no psychiatric history.

The literature shows that studies which used the models created by the other investigators have reported those models poorly performed in their dataset (13). This indicates the heterogeneity of the predictive factors in different populations. The majority of researchers believe that pre-morbid, injury-associated, neuropsychiatric and post-injury features of a patient-event complex will determine the persistence and the clinical burden of a traumatic event involving head trauma. The results of our study (as well as many other studies) do not aim to elucidate any cause and effect relationship. Rather, it may help us give practical recommendations for the clinicians in order to perform more accurate predictions-an inevitable part of the emergency medicine practice- for patients with mTBI and consequently, to a better discharge time guideline arrangement. According to the healthcare system or local protocols, arrangement for expert consultation and/or follow-up sessions which may lead to repeated follow-up visits or recommendations for early treatment strategies could be considered for higher risk patients. For those who may be at risk and not willing to consult/follow-up arrangement, instructions for follow-up sessions and/or phone call interviews may be considered according to the practice protocols in each facility.

Limitations

The relatively low number of outcomes was a limitation to our study: it resulted in wide confidence intervals for our odds, especially for the last three models which were more important clinically. Performing a multicenter study with a larger size of the population in the future will address this limitation. Phone calls, although frequently used in this type of studies, are better replaced by face to face interviews. However, face to face visits may lead to a larger number of missed follow-ups. As the third limitation, our follow-up calls were designed to be performed prospectively; however, the information from the ED visit was obtained from the files and confirmed by a phone call. This prevents our study to be fully prospective from the beginning. Lastly, although we had excluded patients with a psychiatric history, we did not perform any clinical evaluation for the evolving post-traumatic stress in the follow-up period (e.g. two weeks post-injury), which may not be infrequent in the non-psychiatric population. This may reveal some hidden but important associations that would help in organizing preemptive measures. Symptoms of PTSD show overlap with PCS symptoms and, in some cases, it may be difficult to differentiate between stress-related and neurotrauma-related symptoms, which may need to be managed differently (38). However, we considered the viewpoints of an emergency physician as our first priority, which would be the timely prediction of symptom persistence and proper referral to the experts. In depth differentiation of probable diagnoses and organizing the best management protocol could be considered as the next steps.

Conclusion

According to the current literature, there are a number of factors which could be used as predictors of persistent post-concussive symptoms following mTBI. We have mostly focused on the injury-related factors in a population without any positive psychiatric history. This is an area in which many studies have been done with relatively different results. Based on our models and concerning the other relevant studies, we can recommend that patients with no psychiatric history who show more than one symptom following mTBI and/or those who have experienced a non-MVC mechanism of injury may be at greater risk of post-concussion symptom persistence. These patients may gain profit if they receive expert consultations or follow-up sessions and/or be advised to seek medical help (e.g. post-trauma anxiety management) if their symptoms do not resolve within a shorter period of time.

Declaration of interests

The authors report no conflict of interest statement.

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