Urbanism C-Terminal Hydrolase-L1 (UCH-L1) in Predic-
tion of Computed Tomography Findings in Traumatic
Brain Injury; a Meta-Analysis

Fatemeh Ramezani1, Amir Bahrami-Amiri2, Asrin Babahajian3, Kavous Shahsavari Nia4, Mahmoud
Yousefifard1

1. Physiology Research Center, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
2. Occupational Medicine Research Center, Iran University of Medical Sciences, Tehran, Iran.
3. Liver and Digestive Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran.
4. Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Received: October 2018; Accepted: October 2018; Published online: 15 December 2018

Abstract: Introduction: Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is one of the promising candidates, with an accept-
able diagnostic value for predicting head computed tomography (CT) scan findings. However, there has been a controversy between studies and still, there is no general overview on this. Therefore, the current system-
atic review and meta-analysis attempted to estimate the value of UCH-L1 in predicting intracranial lesions in traumatic brain injury (TBI). Methods: Two independent reviewers screened records from the search of four databases Medline, Embase, Scopus and Web of Science. The data were analyzed in the STATA 14.0 statistical program and the findings were reported as a standardized mean difference (SMD), summary receiver performance characteristics curve (SROC), sensitivity, specificity, and diagnostic odds ratio with 95% confidence in-
terval (95% CI). Results: Finally, the data of 13 articles were entered into the meta-analysis. The mean serum
level of UCH-L1 was significantly higher in patients with CT-positive than in TBI patients with CT negative (SMD
= 1.67, 95% CI: 1.12 to 2.23, I2 = 98.1%; p <0.0001). The area under the SROC curve for UCH-L1 in the predic-
tion of intracranial lesions after mild TBI was 0.83 (95% CI: 0.80 to 0.86). Sensitivity, specificity and diagnostic
odds ratio of serum UCH-L1 was 0.97 (95% CI: 0.92 to 0.99), 0.40 (95% CI: 0.30 to 0.51) and 19.37 (95% CI: 7.25
to 51.75), respectively. When the analysis was limited to assessing the serum level of UCH-L1 within the first 6
hours after mild TBI, its sensitivity and specificity increased to 0.99 (95% CI: 0.94 to 1.0) and 0.44 (95% CI: 0.38
to 0.052), respectively. In addition, the diagnostic odds ratio of 6-hour serum level of UCH-L1 in the prediction
of intracranial lesions was 680.87 (95% CI: 50.50 to 9197.97). Conclusion: Moderate level of evidence suggests
that serum/plasma levels of UCH-L1 have good value in prediction of head CT findings. It was also found that
evaluation of serum/plasma level of UCH-L1 within the first 6 hours following TBI would increase its predictive
value. However, there is a controversy about the best cutoffs of the UCH-L1.

Keywords: Ubiquitin C-terminal Hydrolase-L1; Traumatic Brain injuries; Diagnosis; Brain computed tomography

© Copyright (2018) Shahid Beheshti University of Medical Sciences

Cite this article as: Ramezani F, Bahrami-Amiri A, Babahajian A, Shahsavari Nia K, Yousefifard M. Ubiquitin C-Terminal Hydrolase-L1 (UCH-
L1) in Prediction of Computed Tomography Findings in Traumatic Brain Injury; a Meta-Analysis. Emergency. 2018; 6(1): e62.

1. Introduction

Traumatic brain injury (TBI) is one of the most com-
mon causes of death and disability with a global
prevalence of 8.4%. Incidence, prevalence, and years
of life lost due to TBI increased significantly from 1990 to
2016 (1). This increasing burden has led to a substantial
increase in the TBI-related emergency visits. Intracranial
lesions caused by TBI are diagnosed mainly with imaging assessments such as computed tomography (CT) scan and magnetic resonance imaging (MRI). However, for two reasons, the use of imaging techniques in emergency departments is not feasible. First, there is no access to CT scan and MRI in all emergency departments, and secondly, Imaging is not possible for all trauma patients. In addition, exposure to ionizing radiation as a result of CT scan should not ignore (2, 3). Therefore, researchers are looking for other diagnostic or screening modalities that can be used to detect the intracranial lesion.

Patients with TBI are divided into three categories of mild, moderate and severe, based on clinical evaluations, in particular, Glasgow coma scale (GCS). Mild TBI is the most prevalent and physicians are always in trouble when patients need to go for radiography for further evaluation. Estimates have shown that about 16% of mild TBI patients have intracranial lesions (4). This means that if all mild TBI patients undergo CT scan or MRI, 84% of these imaging is unnecessary. To reduce this excessive imaging, screening tests such as serum biomarkers can be effective. Several biomarkers such as S100-B and neuron-specific enolase have been proposed to predict central nervous system injuries (5–7), but there is still a controversy between literature, and researchers are still looking for other biomarkers. Of these, ubiquitin C-terminal hydrolase-L1 (UCH-L1) is one of the promising candidates with an acceptable value in the prediction of intracranial lesions (8). However, there has been a contention between studies and there is still no general overview of this area. Therefore, the present systematic review and meta-analysis attempted to evaluate the value of UCH-L1 in the prediction of intracranial lesions in TBI patients.

2. Methods:

2.1. Search strategy

The present meta-analysis was designed to determine the value of UCH-L1 in predicting head CT findings. For this purpose, an extensive search was performed in Medline (via PubMed), Embase, Scopus, and Web of Science. The search terms were related to TBI in combination with the UCH-L1. The Medline search query is provided below. In addition, the search was done manually in the bibliography of relevant studies and review articles. Google's search engine was also searched for gray literature.

2.2. PubMed search query:

1- "Ubiquitin Thiolesterase"[mh] OR "Thiolesterase, Ubiquitin"[tiab] OR "Ubiquitin C-Terminal Hydrolase"[tiab] OR "C-Terminal Hydrolase, Ubiquitin"[tiab] OR "Hydrolase, Ubiquitin C-Terminal"[tiab] OR "Ubiquitin C-Terminal Hydrolase"[tiab] OR "Ubiquitin Carboxy-Terminal Hydrolase"[tiab] OR "Carboxy-Terminal Hydrolase, Ubiquitin"[tiab] OR "Hydrolase, Ubiquitin Carboxy-Terminal"[tiab] OR "Ubiquitin Carboxy Terminal Hydrolase"[tiab] OR "Ubiquitin C-Terminal Esterase"[tiab] OR "C-Terminal Esterase, Ubiquitin"[tiab] OR "Esterase, Ubiquitin C-Terminal"[tiab] OR "Ubiquitin C Terminal Esterase"[tiab] OR "Ubiquitin Carboxy-Terminal Esterase"[tiab] OR "Carboxy-Terminal Esterase, Ubiquitin"[tiab] OR "Esterase, Ubiquitin Carboxy-Terminal"[tiab] OR "Ubiquitin Carboxy-terminal"[tiab] OR "Ubiquitin C-Terminal Esterase"[tiab] OR "C-Terminal Esterase, Ubiquitin"[tiab] OR "Esterase, Ubiquitin C-Terminal"[tiab] OR "Ubiquitin C Terminal Esterase"[tiab] OR "Ubiquitin Carboxy-Terminal Esterase"[tiab] OR "Carboxy-Terminal Esterase, Ubiquitin"[tiab] OR "Esterase, Ubiquitin Carboxy-Terminal"[tiab] OR "Ubiquitin Carboxy-terminal"[tiab] OR "Ubiquitin Carboxy-terminal"[tiab] OR "Hydrolase Isozyme L1"[tiab] OR "Ubiquitin Carboxy-terminal Hydrolase Isozyme L1"[tiab] OR "Parkinson Disease 5 Protein"[tiab] OR "PARK5 Protein"[tiab] OR "Neuron Cytoplasmic Protein 9.5"[tiab] OR "UCH-L1 Protein"[tiab] OR "Uch-L1 Protein"[tiab] OR "Uch L1 Protein"[tiab] OR "UCH-L1"[tiab]

2- "Brain Concussion"[mh] OR "Brain Injuries"[mh] OR "Brain Injuries, Traumatic"[mh] OR "Brain Concussion"[tiab] OR "Brain Injuries"[tiab] OR "Brain Injuries, Traumatic"[tiab] OR "Brain Concussions"[tiab] OR "Concussion, Brain"[tiab] OR "Commotio Cerebri"[tiab] OR "Cerebral Concussion"[tiab] OR "Cerebral Concussions"[tiab] OR "Concussion, Cerebral"[tiab] OR "Concussion, Intermediate"[tiab] OR "Intermediate Concussion"[tiab] OR "Intermediate Concussions"[tiab] OR "Concussion, Severe"[tiab] OR "Severe Concussion"[tiab] OR "Severe Concussions"[tiab] OR "Concussion, Mild"[tiab] OR "Mild Concussion"[tiab] OR "Mild Concussions"[tiab] OR "Mild Traumatic Brain Injury"[tiab] OR "Injuries, Brain"[tiab] OR "Brain Injury"[tiab] OR "Injury, Brain"[tiab] OR "Injuries, Acute Brain"[tiab] OR "Acute Brain Injuries"[tiab] OR "Acute Brain Injury"[tiab] OR "Brain Injury, Acute"[tiab] OR "Injury, Acute Brain"[tiab] OR "Brain Injuries, Acute"[tiab] OR "Brain Lacerations"[tiab] OR "Brain Laceration"[tiab] OR "Laceration, Brain"[tiab] OR "Lacerations, Brain"[tiab] OR "Brain Injuries, Focal"[tiab] OR "Brain Injury, Focal"[tiab] OR "Focal Brain Injury"[tiab] OR "Injuries, Focal Brain"[tiab] OR "Injury, Focal Brain"[tiab] OR "Focal Brain Injuries"[tiab] OR "Brain Injury, Traumatic"[tiab] OR "Traumatic Brain Injuries"[tiab] OR "Trauma, Brain"[tiab] OR "Brain Trauma"[tiab] OR "Brain Traumas"[tiab] OR "Traumas, Brain"[tiab] OR "TBI (Traumatic Brain Injury)"[tiab] OR "Encephalopathy, Traumatic"[tiab] OR "Encephalopathies, Traumatic"[tiab] OR "Traumatic Encephalopathies"[tiab] OR "Injury, Brain, Traumatic"[tiab] OR "Traumatic Brain Injuries"[tiab] OR "TBIs (Traumatic Brain Injuries)"[tiab] OR "TBI (Traumatic Brain Injury)"[tiab] OR "Traumatic Brain Injury"[tiab] OR "TBI"[tiab]

3- #1 AND #2
2.3. Selection criteria

All of the observational studies on the predictive value of UCH-L1 in the prediction of head CT findings were included. Exclusion criteria were chronic exposure to head trauma, penetrating TBI, non-traumatic injury, lack of data, and reviews.

2.4. Data extraction and quality assessment

The method of summarizing data has been reported in our previous meta-analyses study (9-23). Two independent reviewers screened records from the database. The potentially relevant studies were assessed in detail and finally, based on the selection criteria eligible studies were identified. The reviewers recorded the type of study (cohort, case-control, cross-sectional, etc.), the age range of patients, sample size...
Table 1: Summary characteristics of studies

| Author; year; country | Type of study | Age* | CT - / CT+ | Male gender | Sampling methods | Time to sample# | Method assay | GCS |
|-----------------------|---------------|------|------------|-------------|-----------------|-----------------|--------------|-----|
| Bazarian; 2018; USA   | Cohort        | 18-98 | 1793/122  | 1107        | Convenience     | 0 to 12         | ELISA        | 9-15 |
| Diaz-Arrastia; 2014; USA | Cohort     | 37±14 | 40 / 31  | 150         | NR              | 0 to 24         | ELISA        | 14-15 |
| Dickens; 2018; Finland and UK | Cohort      | 18-91 | 95 / 114  | 152         | NR              | 0 to 12         | ELISA        | 13-15 |
| Korley; 2016; USA    | Cohort        | 26-56 | 84 / 75   | 215         | Convenience     | 0 to 24         | ELISA        | 3-15 |
| Korley; 2018; USA    | Cohort        | 24-61 | 63 / 44   | 78          | Convenience     | 0 to 24         | ELISA        | 3-15 |
| Lewis; 2017; USA     | Trial         | 18-80 | 154 / 34  | 116         | NR              | 0 to 24         | ELISA        | 13-15 |
| Mondello; 2016; USA  | Cohort        | 3.8±3.7 | 10 / 29  | 28          | NR              | 0 to 24         | ELISA        | 3-15 |
| Papa; 2012; USA      | Cohort        | 18-89 | 77 / 28   | 64          | Convenience     | 0 to 4          | ELISA        | 9-15 |
| Papa; 2016; USA      | Cohort        | 18-83 | 290 / 35  | 212         | Convenience     | 0 to 24         | ELISA        | 9-15 |
| Papa; 2017; USA      | Cohort        | 0-21  | 134 / 17  | 100         | Convenience     | 0 to 6          | ELISA        | 9-15 |
| Posti; 2016; Finland and UK | Cohort      | 45.3±19.2 | 90 / 200 | 239         | Consecutive     | 0              | ELISA        | 3-15 |
| Welch; 2016; USA     | Cohort        | 18-80 | 215 / 36  | 151         | NR              | 0 to 6          | ELISA        | 13-15 |
| Welch; 2017; USA     | Cohort        | 18-80 | 134 / 33  | 102         | NR              | 0              | ELISA        | 9-15 |

* Data are presented as mean ± standard deviation or age range. #, hours from Traumatic brain injury (TBI). CT: Computed tomography; GCS: Glasgow coma scale of patients at admission; ELISA: Enzyme-linked immunosorbent assay; NR: Not reported.

Table 2: Quality assessment of included articles based on QUADAS-2 guideline

| Author; year | Risk of bias | Applicability |
|--------------|--------------|---------------|
| Selection    | Index Test   | Reference Standard | Flow And Timing | Selection | Index Test | Reference Standard |
| Bazarian; 2018 | §             | ©             | ©                | ©         | ©            | ©                |
| Diaz-Arrastia; 2014 | ©             | ©             | ©                | ©         | ©            | ©                |
| Dickens; 2018 | ?             | ©             | ©                | ©         | ©            | ©                |
| Korley; 2016  | §             | ©             | ©                | ©         | ©            | ©                |
| Korley; 2018  | ©             | ©             | ©                | ©         | ©            | ©                |
| Lewis; 2017   | ?             | ©             | ©                | ©         | ©            | ©                |
| Mondello; 2016 | ?            | ©             | ©                | ©         | ©            | ©                |
| Papa; 2012    | §             | ©             | ©                | ©         | ©            | ©                |
| Papa; 2016    | ©             | ©             | ©                | ©         | ©            | ©                |
| Papa; 2017    | ©             | ©             | ©                | ©         | ©            | ©                |
| Posti; 2016   | ©             | ©             | ©                | ©         | ©            | ©                |
| Welch; 2016   | ?             | ©             | ©                | ©         | ©            | ©                |
| Welch; 2017   | ?             | ©             | ©                | ©         | ©            | ©                |

©: Low Risk; §: High Risk; ?: Unclear Risk

(number of CT positive and CT negative TBI patients), male gender frequency, sampling method (random, consecutive, convenience), the method of UCH-L1 assay, TBI severity and outcomes. The severity of TBI was divided into three groups, mild (GCS: 13 to 15), moderate (GCS: 9 to 12) and severe (GCS: 3 to 8). The evaluated outcomes included the mean serum level of UCH-L1 in both CT positive and CT negative groups and the number of true positive (TB), true negative (TN), false positive (FP) and false negative (FN).

In some articles, the mean serum level of UCH-L1 was reported in the graphs. In these cases, using the Plot Digitizer software (available at http://plotdigitizer.sourceforge.net/), the mean and standard deviation of the serum level of this biomarker were extracted. In addition, many articles were not reported TP, TN, FP, and FN cases. Therefore, TP, TN, FP, and FN were estimated using the reported sensitivity and specificity. Quality control of the eligible studies was evaluated using the proposed method of Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) guideline (24).

2.5. Statistical Methods

Data were analyzed in the STATA 14.2 program. Meta-analysis was performed in two sections. In the first part, the mean serum level of UCH-L1 was compared in CT positive and CT negative groups. In this section, the standardized mean difference (SMD) was calculated and finally, an overall SMD with a 95% confidence interval (95% CI) was reported. In the second section, using the TP, TN, FP, and
### Table 3: Sensitivity analysis for performance of serum level of ubiquitin C-terminal hydrolase L1 in detection of intracranial lesion (based on computed tomography findings) in mild traumatic brain injuries

| Variable          | Sensitivity   | Specificity   | Diagnostic score | Diagnostic odds ratio |
|-------------------|---------------|---------------|-------------------|-----------------------|
| **Age group**     |               |               |                   |                       |
| Children          | NA            | NA            | NA                | NA                    |
| Adult             | 0.96 (0.92 to 0.98) | 0.39 (0.29 to 0.51) | 2.82 (1.86 to 3.77) | 16.72 (6.44 to 43.39) |
| **Timing (hours after TBI)** |               |               |                   |                       |
| 0 to 6            | 0.99 (0.94 to 1.0) | 0.44 (0.38 to 0.52) | 6.52 (3.92 to 9.12) | 680.87 (50.50 to 9197.97) |
| >6                | NA            | NA            | NA                | NA                    |
| **Overall**       | 0.97 (0.92 to 0.99) | 0.40 (0.30 to 0.51) | 2.96 (1.98 to 3.95) | 19.37 (7.25 to 51.75) |

All data are presented with 95% confidence interval.

### Figure 3: Forest plot for serum level of ubiquitin C-terminal hydrolase L1 in traumatic brain injury (TBI) subjects with positive computed tomography (CT) findings compared to negative CT findings. CI: Confidence interval; SMD: Standardized mean difference.

FN data, the summary receiver operating characteristic curve (SROC), sensitivity, specificity, diagnostic score, and diagnostic odds ratio of UCH-L1 in the prediction of CT findings were reported. I² test was used to assess heterogeneity and Eager’s test was used to evaluate the publication bias. In all analyzes p < 0.05 was defined as significant level.

### 3. Results:

#### 3.1. Study characteristics

Finally, 13 articles provided data suitable for meta-analysis (Figure 1) (8, 25-36). They were 12 cohort studies and 1 observational trial. These studies included 3977 patients with TBI. CT scan findings in 3179 (79.93%) patients were negative and in 798 (20.07%) were positive. The serum sample was obtained in five studies during the first 6 hours after the onset of TBI. In two studies, it was assessed within 12 hours and in six studies over the first 24 hours after TBI. Four studies were conducted on mild TBI, five with mild to moderate TBI and four with mild to severe TBI patients. Table 1 shows a summary of the eligible studies.

#### 3.2. Quality control and risk of bias

Quality assessment of the relevant studies according to the QUADAS-2 guidelines showed that the risk of bias in patient selection was high or unclear in 12 studies. Other items in all studies were rated as the Low risk of bias (Figure 2A and Table 2). There was no publication bias in the present study (p = 0.362) (Figure 2B).

#### 3.3. Meta-analysis

**Comparison of mean serum/plasma UCH-L1 in CT positive and CT negative patients**

The mean value of serum/plasma levels of UCH-L1 reported in each of the 13 papers were investigated (8, 25-36). The analyzes showed that the mean serum/plasma level of UCH-L1 was significantly higher in CT-positive TBI than in CT negative TBI patients (SMD = 1.67, 95% CI: 1.12 to 2.23, p <0.0001; I² = 98.1%, p < 0.0001) (Figure 3). The mean serum/plasma level of UCH-L1 within 6 hours after TBI (SMD = 1.72, 95% CI: 0.98 to 2.47, p <0.0001), during the first 12 hours after injury (SMD = 1.74, 95% CI: 0.42 to 3.07, p = 0.01) and 24 hours later (SMD = 1.55, 95% CI: 0.88 to 2.21, p <0.0001) in CT positive TBI patients were always higher than CT negative patients.

**Screening performance characteristics in the detection of an intracranial lesion in mild TBI**

Six studies, including 15 separate experiments evaluated the performance of UCH-L1 in the prediction of intracranial lesions (8, 25, 26, 29, 30, 33). The cut off used in the studies varied between 41 pg/ml and 327 pg/ml. 11 experiments were performed on mild TBI, three experiments on mild to moder-
Figure 4: Summary of receiver operating curve (SROC) of serum level of ubiquitin C-terminal hydrolase L1 in detection of intracranial lesion (based on computed tomography findings) in mild and mild to severe traumatic brain injuries (TBI). AUC: Area under the curve; Sens: Sensitivity; Spec: Specificity.

4. Discussion:

The present meta-analysis showed that after TBI, the serum/plasma UCH-L1 level increased significantly. Therefore, it could be used as a biomarker to detect intracranial lesions. The area under the SROC curve for serum/plasma UCH-L1 in the prediction of intracranial lesions after mild TBI was 0.83 (95% CI: 0.80 to 0.86) (Figure 4). The sensitivity and specificity of this serum biomarker were 0.97 (95% CI: 0.92 to 0.99) and 0.40 (95% CI: 0.30 to 0.51), respectively. The Diagnostic odds ratio of UCH-L1 in the prediction of intracranial lesions after mild TBI was 19.37 (95% CI: 7.25 to 51.75) (Figure 5). When the analysis was limited to assessing the serum/plasma UCH-L1 level within the first 6 hours after mild TBI, its sensitivity and specificity increased to 0.99 (95% CI: 0.94 to 1.0) and 0.44 (95% CI: 0.38 to 0.52), respectively. The diagnostic odds ratio of 6-hour UCH-L1 in the prediction of intracranial lesions was 680.87 (95% CI: 50.50 to 9197.97) (Table 3).

In a similar meta-analysis study, Shahjouei et al. showed that the serum/plasma level of UCH-L1 has a moderate value in the prediction of intracranial lesions (39). This report was different from the findings of the present study. Shahjouei et al., included data from four studies, while in the present study, data from six studies containing 15 separate experiments were entered. On the other hand, the conclusion presented by Shahjouei et al is based on the area under the curve of UCH-L1, while our findings were presented based on TP, TN, FP, and FN. In addition, the area under the curve simultaneously represents sensitivity and specificity. In the present study, the UCH-L1 has a high sensitivity that is very suitable in the use of UCH-L1 in the management of TBI. However, it is necessary to introduce an optimum cut off for the serum/plasma level of UCH-L1. The cut offs used in the studies were between 41 pg / ml and 327 pg / ml. Therefore, in the current meta-analysis, the assessment of the best cut offs for the UCH-L1 was not possible. Therefore, further studies are recommended. The diagnostic/predictive value of biomarkers varies with time (37, 38). Since, decision making in TBI patients is performed during the first 24 hours of injury, the 24-hour serum/plasma UCH-L1 level was analyzed in the current meta-analysis. The findings indicate that the performance of UCH-L1 is higher in the first 6 hours of TBI than in the next few hours. Therefore, it seems that evaluating this biomarker as soon as possible can provide valuable information about the severity of TBI.
for a screening test, but has a low specificity that does not play a critical role in screening of patients. Therefore, it is not possible to accurately discuss about the value of a screening biomarker just by reporting the AUC. Many articles do not report TP, TN, FP, and FN and instead provide sensitivity and specificity. To overcome this problem, using standard methods and web-based applications, TP, TN, FP, and FN were obtained from sensitivity and specificity. This was one of the strengths of the present study. However, in the present study due to the high diversity among eligible studies, it was not possible to report the best cut off for serum/plasma level of UCH-L1. There was also a significant heterogeneity between studies. Unfortunately, we did not find the source of heterogeneity. Therefore, for these reasons, the evidence presented in this study was reduced to a moderate level.

5. Conclusion
A moderate level of evidence suggests that the serum/plasma level of UCH-L1 had good value in prediction of head CT findings. It was also found that evaluation of serum/plasma level of UCH-L1 within the first 6 hours after TBI would increase its predictive value. However, there is a controversy about the best cut offs of the UCH-L1 and further studies are needed.

6. Appendix
6.1. Acknowledgements
None.

6.2. Authors’ Contributions
MY and FR designed the study. MY, AB, ABA collected the data. MY and KS analyzed the data and interpreted the results. MY and FR wrote the manuscript. All authors critically revised the paper.

Authors’ ORCIDs
Fatemeh Ramezani: 0000-0001-7359-4880
Amir Bahrami-Amiri: 0000-0001-9472-4429
Asrin Babahajian: 0000-0003-0278-1560
Kavous Shahsavari Nia: 0000-0002-4049-8531
Mahmoud Yousefifard: 0000-0001-5181-4985

6.3. Funding Support
None.

6.4. Conflict of Interest
There was no conflict of interest.

References
1. Badhiwala JH, Wilson JR, Fehlings MG (2018) Global burden of traumatic brain and spinal cord injury. Lancet Neurol:[In Press].
2. Ebrahimi A, Yousefifard M, Kazemi HM, Rasouli HR, Asady H, Jafari AM, et al. (2014) Diagnostic accuracy of chest ultrasonography versus chest radiography for identification of pneumothorax: a systematic review and meta-analysis. Tanaffos 13(4):29.
3. Yousefifard M, Baikpour M, Ghelichkhani P, Asady H, Nia KS, Jafari AM, et al. (2016) Screening performance characteristic of ultrasonography and radiography in detection of pleural effusion; a meta-analysis. Emergency 4(1):1.
4. Isokuortti H, Iverson GL, Silverberg ND, Kataja A, Brander A, Ohman J, et al. (2018) Characterizing the type and location of intracranial abnormalities in mild traumatic brain injury. Journal of neurosurgery:1-10.
5. Nakhjavan-Shahraki B, Yousefifard M, Orail I, Sarveazad A, Hosseini M (2017) Meta-analysis of neuron specific enolase in predicting pediatric brain injury outcomes. EXCLI journal 16:995.
6. Yousefifard M, Sarveazad A, Babahajian A, Baikpour M, Shokranef F, Vaccaro AR, et al. (2018) Potential diagnostic and prognostic value of serum and cerebrospinal fluid biomarkers in traumatic spinal cord injury: A systematic review. Journal of neurochemistry.

7. Egea-Guerrero JJ, Rodriguez-Rodriguez A, Quintana-Diaz M, Freire-Aragon MD, Raya-Collados D, Hernandez-Garcia C, et al. (2018) Validation of S100B use in a cohort of Spanish patients with mild traumatic brain injury: a multicentre study. Brain injury 32(4):459-63.

8. Bazarian JJ, Biberthaler P, Welch RD, Lewis LM, Barzo P, Bogner-Flatz V, et al. (2018) Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. The Lancet Neurology 17(9):782-9.

9. Ahmadi S, Yousefifard M (2017) Accuracy of Pediatric Emergency Care Applied Research Network Rules in Prediction of Clinically Important Head Injuries; A Systematic Review and Meta-Analysis. International Journal of Pediatrics 5(12):6285-300.

10. Ghelichkhani P, Yousefifard M, Nazemi L, Safari S, Hosseini M, Baikpour M, et al. (2016) The value of serum β2- subunit of human chorionic gonadotropin level in prediction of treatment response to methotrexate in management of ectopic pregnancy; a systematic review and meta-analysis. International Journal of Pediatrics 4(9):3503-18.

11. Hassanzadeh-Rad A, Yousefifard M, Katal S, Asady H, Fard-Esfahani A, Moghadas Jafari A, et al. (2016) The value of 18F-fluorodeoxyglucose positron emission tomography for prediction of treatment response in gastrointestinal stromal tumors: a systematic review and meta-analysis. Journal of gastroenterology and hepatology 31(5):929-35.

12. Hosseini M, Ghelichkhani P, Baikpour M, Tafakhori A, Safari S, Yanev S, et al. (2016) The efficiency of probiotics in prevention of urinary tract infection in children: A systematic review and meta-analysis. Journal of pediatric urology 13(6):581-91.

13. Hosseini M, Yousefifard M, Aziznejad H, Nasirinezhad F (2015) The Effect of Bone Marrow-Derived Mesenchymal Stem Cell Transplantation on Allodynia and Hyperalgesia in Neuropathic Animals: A Systematic Review with Meta-Analysis. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation 21(9):1537-44.

14. Hosseini M, Yousefifard M, Baikpour M, Rahimi-Movaghar V, Nasirinezhad F, Younesian S, et al. (2016) The efficacy of Schwann cell transplantation on motor function recovery after spinal cord injuries in animal models: A systematic review and meta-analysis. Journal of chemical neuroanatomy 78:102-11.

15. Izadi A, Yousefifard M, Nakhjavan-Shahraki B, Baikpour M, Mirzay Razaz J, Ataei N, et al. (2016) Value of plasma/serum neutrophil gelatinase-associated lipocalin in detection of pediatric acute kidney injury; a systematic review and meta-analysis. International Journal of Pediatrics 4(11):3815-36.

16. Izadi A, Yousefifard M, Nakhjavan-Shahraki B, Baikpour M, Mirzay Razaz J, Hosseini M (2016) Diagnostic value of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in detection of pediatric acute kidney injury; a systematic review and meta-analysis. International Journal of Pediatrics 4(11):3875-95.

17. Nakhjavan-Shahraki B, Yousefifard M, Ataei N, Baikpour M, Ataei F, Bazargani B, et al. (2017) Accuracy of cystatin C in prediction of acute kidney injury in children; serum or urine levels: which one works better? A systematic review and meta-analysis. BMC nephrology 18(1):120.

18. Nakhjavan-Shahraki B, Yousefifard M, Hajighanbari MJ, Oraii A, Safari S, Hosseini M (2017) Pediatric Emergency Care Applied Research Network (PECARN) prediction rules in identifying high risk children with mild traumatic brain injury. European journal of trauma and emergency surgery : official publication of the European Trauma Society 43(6):755-62.

19. Nakhjavan-Shahraki B, Yousefifard M, Rahimi-Movaghar V, Baikpour M, Nasirinezhad F, Safari S, et al. (2018) Transplantation of olfactory ensheathing cells on functional recovery and neuropathic pain after spinal cord injury; systematic review and meta-analysis. Scientific reports 8(1):325.

20. Safi A, Yousefifard M, Hashemi B, Baratloo A, Forouzanfar MM, Rahmati F, et al. (2016) The value of serum creatinine kinase in predicting the risk of rhabdomyolysis-induced acute kidney injury: a systematic review and meta-analysis. Clinical and experimental nephrology 20(2):153-61.

21. Yousefifard M, Rahimi-Movaghar V, Baikpour M, Ghelichkhani P, Hosseini M, Jafari A, et al. (2017) Early versus late spinal decompression surgery in treatment of traumatic spinal cord injuries; a systematic review and meta-analysis. Emergency (Tehran, Iran) 5(1):e37.

22. Yousefifard M, Rahimi-Movaghar V, Baikpour M, Ghelichkhani P, Hosseini M, Jafari A, et al. (2017) Early versus late spinal decompression surgery in treatment of traumatic spinal cord injuries: a systematic review and meta-analysis. Emergency (Tehran, Iran) 5(1):e37.

23. Yousefifard M, Rahimi-Movaghar V, Nasirinezhad F, Baikpour M, Safari S, Saadat S, et al. (2016) Neural stem/progenitor cell transplantation for spinal cord injury treatment; A systematic review and meta-analysis. Neuroscience 322:377-97.

24. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ,
Reitsma JB, et al. (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine 155(8):529-36.

25. Diaz-Arrastia R, Wang KK, Papa L, Sorani MD, Yue JK, Puccio AM, et al. (2014) Acute biomarkers of traumatic brain injury: relationship between plasma levels of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein. Journal of neurotrauma 31(1):19-25.

26. Dickens AM, Posti JP, Takala RSK, Ala-Seppala H, Mattila I, Coles JP, et al. (2018) Serum Metabolites Associated with Computed Tomography Findings after Traumatic Brain Injury. Journal of neurotrauma 35(22):2673-83.

27. Korley FK, Diaz-Arrastia R, Wu AH, Yue JK, Manley GT, Sair HI, et al. (2016) Circulating Brain-Derived Neurotrophic Factor Has Diagnostic and Prognostic Value in Traumatic Brain Injury. Journal of neurotrauma 33(2):215-25.

28. Korley FK, Yue JK, Wilson DH, Hrusovsky K, Diaz-Arrastia R, Ferguson AR, et al. (2018) Performance Evaluation of a Multiplex Assay for Simultaneous Detection of Four Clinically Relevant Traumatic Brain Injury Biomarkers. Journal of neurotrauma.

29. Lewis LM, Schloemann DT, Papa L, Fucetola RP, Bazarian J, Lindburg M, et al. (2017) Utility of Serum Biomarkers in the Diagnosis and Stratification of Mild Traumatic Brain Injury. Academic emergency medicine: official journal of the Society for Academic Emergency Medicine 24(6):710-20.

30. Mondello S, Kobeissy E, Vestri A, Hayes RL, Kochanek PM, Berger RP (2016) Serum Concentrations of Ubiquitin C-Terminal Hydrolase-L1 and Glial Fibrillary Acidic Protein after Pediatric Traumatic Brain Injury. Sci Rep 6:28203.

31. Papa L, Lewis LM, Silvestri S, Falk JL, Giordano P, Brophy GM, et al. (2012) Serum levels of ubiquitin C-terminal hydrolase distinguish mild traumatic brain injury from trauma controls and are elevated in mild and moderate traumatic brain injury patients with intracranial lesions and neurosurgical intervention. The journal of trauma and acute care surgery 72(5):1335-44.

32. Papa L, Brophy GM, Welch RD, Lewis LM, Braga CF, Tan CN, et al. (2016) Time Course and Diagnostic Accuracy of Glial and Neuronal Blood Biomarkers GFAP and UCH-L1 in a Large Cohort of Trauma Patients With and Without Mild Traumatic Brain Injury. JAMA neurology 73(5):551-60.

33. Papa L, Mittal MK, Ramirez J, Silvestri S, Giordano P, Braga CF, et al. (2017) Neuronal Biomarker Ubiquitin C-Terminal Hydrolase Detects Traumatic Intracranial Lesions on Computed Tomography in Children and Youth with Mild Traumatic Brain Injury. Journal of neurotrauma 34(13):2132-40.

34. Posti JP, Takala RS, Runtti H, Newcombe VF, Outtrim J, Katila AJ, et al. (2016) The Levels of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 During the First Week After a Traumatic Brain Injury: Correlations With Clinical and Imaging Findings. Neurosurgery 79(3):456-64.

35. Welch RD, Ayaz SI, Lewis LM, Unden J, Chen JY, Mika VH, et al. (2016) Ability of Serum Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase-L1, and S100B To Differentiate Normal and Abnormal Head Computed Tomography Findings in Patients with Suspected Mild or Moderate Traumatic Brain Injury. Journal of neurotrauma 33(2):203-14.

36. Welch RD, Ellis M, Lewis LM, Ayaz SI, Mika VH, Millis S, et al. (2017) Modeling the Kinetics of Serum Glial Fibrillary Acidic Protein, Ubiquitin Carboxyl-Terminal Hydrolase-L1, and S100B Concentrations in Patients with Traumatic Brain Injury. Journal of neurotrauma 34(11):1957-71.

37. Gyorgy A, Ling G, Wingo D, Walker J, Tong L, Parks S, et al. (2011) Time-dependent changes in serum biomarker levels after blast traumatic brain injury. Journal of neurotrauma 28(6):1121-6.

38. Zheng Y, Cai T, Pepe MS, Levy WC (2008) Time-dependent predictive values of prognostic biomarkers with failure time outcome. Journal of the American Statistical Association 103(481):362-8.

39. Shahjouei S, Sadeghi-Naini M, Yang Z, Kobeissy E, Rathore D, Shokraneh F, et al. (2018) The diagnostic values of UCH-L1 in traumatic brain injury: A meta-analysis. Brain Inj 32(1):1-17.