Heliyon 8 (2022) e12153

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Elevated C-reactive protein-to-albumin ratio with fever is a predictor of poor functional outcome in patients with mild traumatic brain injury

Eujene Jung [a], Hyun Ho Ryu [a,b,*], Cha won Ko [a], Yong Deok Lim [a]

[a] Chonnam National University Hospital, Gwangju, South Korea
[b] Chonnam National University College of Medicine

ARTICLE INFO

Keywords:
Traumatic brain injury
C-reactive protein
Albumin
Mortality

ABSTRACT

Introduction: The C-reactive protein -to-albumin ratio (CAR), a novel inflammation-based prognostic score, is useful in predicting clinical outcomes, including those in central nervous system diseases. However, no report has identified the relationship between CAR and long-term clinical outcomes in patients with mild traumatic brain injury (mTBI). We aimed to evaluate the relationship between CAR and long-term functional outcomes in patients with mTBI and analyze whether CAR is associated with the presence of fever.

Methods: This was a retrospective observational study includes 387 adult patients with mTBI who were treated at a level-1 trauma center between 2017 and 2021. The main exposure variable was an elevated CAR, and the main outcomes were degrees of disability and quality of life measured using the modified Rankin Scale (mRS). A multivariable logistic regression analysis was performed to estimate the effect size of CAR on study outcomes. An interaction analysis was performed between CAR and fever on study outcomes.

Results: Elevated CAR had no significant association with poor functional outcomes (aOR [95% CI]: 1.35 [0.39–4.69]) in patients with mTBI. In the interaction analysis, elevated CAR was not associated with increased poor functional outcomes in the absence of fever (1.08 [0.55–2.13]), but a significant increase in poor functional outcomes was observed when elevated CAR was accompanied by fever (1.32 [1.14–2.56]).

Conclusions: Elevated CAR with fever increased the risk of poor functional recovery at 6 months after hospital discharge in patients with mTBI. Our study findings suggest the need for strategies for the prevention of long-term poor functional recovery in the presence of high CAR and fever in patients with mTBI.

1. Introduction

Traumatic brain injury (TBI), a form of acquired brain injury occurs when a sudden trauma causes damage to the brain (reference). TBI is a serious public health problem, and its incidence is 823.7 per 100,000 persons per year worldwide [1]. Furthermore, in 2014, there were approximately 2.53 million TBI-related emergency department (ED) visits, approximately 288,000 hospitalizations, and 56,800 TBI-related fatalities in the US [2].

Symptoms of a TBI can be mild, moderate, or severe, depending on the extent of the damage to the brain. A patient with mild TBI (mTBI) may remain conscious or experience a loss of consciousness for few seconds or minutes. Although over 80% of patients with TBI are classified as having mTBI, the majority of whom are returning to normalcy, still a large proportion of patients with mTBI may experience functional disabilities following the injury for months or even years [3, 4]. Therefore, the early prediction of short- and long-term functional outcomes is crucial in improving the quality of life of patients with mTBI [5].

Inflammation is the bodily response to any type of injury and also an initial step in the injury recovery process [6], TBI also causes neuronal inflammation, and inflammatory activities play important roles in the recovery process following TBI [7, 8, 9]. Role of inflammatory markers, including acute-phase reactant proteins, cytokines (e.g. IL-6, IL-1, TNF-a), and their clinical significance has been studied over the past 30 years [10, 11]. Among them, C-reactive protein (CRP) is a sensitive biomarker that predicts poor clinical outcomes of TBI, but is a non-specific biomarker of systematic inflammation in response to trauma, surgery, burns, and chronic inflammatory conditions [12, 13].

Recently, the CRP-to-albumin ratio (CAR), a novel inflammation-based prognostic score, has proven useful in predicting a variety of diseases such as sepsis, cancer, and TBI in adults [14, 15, 16, 17, 18].

* Corresponding author.
E-mail address: em.ryu.hyunho@gmail.com (H.H. Ryu).

https://doi.org/10.1016/j.heliyon.2022.e12153
Received 10 July 2022; Received in revised form 7 September 2022; Accepted 29 November 2022

Although one study reported the prognostic performance of the CAR in adult patients with TBI [14], the severity of TBI was not considered, and only short-term mortality was reported. Therefore, based on the data from previous studies, we hypothesized that CAR may be a useful biomarker for predicting the long-term functional outcomes of patients with mTBI.

Our study aimed to evaluate the relationship between the CAR and long-term functional outcomes of patients with mTBI and determine whether the CAR has an interaction with fever at emergency department (ED) admission, another index reflecting systematic inflammation.

2. Methods

2.1. Study design, setting, and data sources

This was a retrospective observational study of patients with mTBI who were transported by the emergency medical services (EMS) and treated at a level-1 trauma center.

In Korea, the scoop and run system is used for all patients, including those with TBI. The EMS initiates transport after monitoring vital signs, conducting a physical examination, and providing essential treatments such as simple dressing of wounds and placing a neck brace and splint at the scene under the direct medical control of emergency physicians. If massive bleeding or hypotension occurs, fluid treatment is initiated under direct medical control; if severe trauma is suspected, the patient is transferred to a level-1 trauma center if possible. If transfer to the level-1 trauma center is not possible, the patient is transferred to the nearest level-1 or level-1 ED.

The leve-1 trauma center, where this study was conducted, was founded in 2010 and has since operated with a team of specialists in various departments including general surgery, thoracic surgery, neurosurgery, plastic surgery, radiology, anesthesiology, and emergency medicine. If a patient is suspected of having major trauma including TBI, computed tomography is performed at the earliest after arriving at the ED. Surgery is performed immediately if necessary. These protocols are followed 24 h a day throughout the year.

Prehospital EMS data, including age, sex, place of injury, and mechanism of injury were collected from the run-sheet of ambulance and dispatch records. Hospital information and clinical outcomes was extracted from the medical records of patients in ED, wards, and intensive care units.

2.2. Study population

Our study population included patients with mTBI aged $\geq$18 years who were transported to the level-1 trauma center by the EMS between January 2017 and December 2021. Only patients with mTBI were included. Patients whose CRP and albumin levels, i.e., components of the CAR, or fever were not recorded at the time of ED admission were excluded. Additionally, patients whose clinical outcomes were not investigated in the telephone survey after 6 months were excluded. mTBI was defined when a patient had a GCS score of 13–15 at the time of hospital arrival [19].

2.3. Main outcomes

The primary outcome measures were degrees of disability and quality of life assessed via a telephone survey 6 months after hospital discharge and measured using the modified Rankin Scale (mRS) [20]. mRS is commonly used scale for measuring the degree of dependence or disability in the daily activities of patients who have suffered brain injury including TBI. The mRS is scored from grade 0, indicating a lack of symptoms to grade 6, indicating dead. The secondary outcome was mortality at 6 months after hospital discharge.

2.4. Variables and measurements

The main exposure variable in our study was elevated CAR, calculated as the ratio of CRP level to the albumin level measured immediately after ED admission. The CAR values were classified into two groups, i.e., normal vs. elevated. Based on the references presented in previous studies, CAR $\leq$1.7, CRP level $\leq$1 mg/dL, and albumin level $\geq$3.5 g/dL were considered normal values [21]. Body temperature $\geq$38 °C at the time of ED admission was classified as fever.

Prehospital and hospital information were extracted from the EMS run sheet and patients' hospital electronic records, which included age, sex, comorbidities including hypertension and diabetes mellitus, mechanism of injury (traffic accident, fall down injury, other mechanism including sexual assault, stuck/hit by person or object, stab, gun shot, and so on), place of injury, fever at ED arrival (whether $\geq$38 °C), vasopressor use, types of hemorrhage, ED treatment including advanced airway and blood transfusion, and clinical outcomes.

2.5. Statistical analysis

Demographics of patients and clinical outcomes according to the CAR measured on ED arrival were compared using the chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables. Multivariable logistic regression analyses were conducted to estimate the effect sizes of CAR on clinical outcomes at 6 months after hospital discharge, adjusting for age, sex, hypertension, diabetes mellitus, mechanism and place of injury, and type of brain hemorrhage.

Crude and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Finally, an interaction analysis was performed between the calculated serum CAR and fever on study outcomes. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided significance level of 0.05 ($p < 0.05$) was used to determine statistical significance.

3. Results

3.1. Demographic findings

Of the 838 patients with TBI in the registry, patients with GCS scores <12 (n = 344) and those with an unknown history of study outcomes (n = 34) or loss to follow-up (n = 73) were excluded, and 387 patients with mTBI were included in the final analysis (Figure 1).

The demograohics of the study population according to the CAR are shown in Table 1. Among the 387 patients, 82 (21.2%) had elevated CAR, while 305 (78.8%) had normal CAR. There was no significant difference in in-hospital mortality (13.4% in elevated CAR vs. 8.9% in normal CAR, p = 0.21), poor functional outcome at 6 months (31.7% in elevated CAR vs. 31.1% in normal CAR, p = 0.91), and mortality at 6 months (23.2% in elevated CAR vs. 23.0% in normal CAR, p = 0.96) according to CAR.

The demographics of enrolled patients according to the presence of fever at ED arrival are shown in Table 2. Of the 387 patients, 60 (15.5%) had fever at ED arrival. There was a greater proportion of patients with elevated CAR among the patients with fever (26.7%) compared with those without fever (20.2%); however, this difference was not significant (p = 0.23). Therefore, there was no significant difference in the clinical outcomes after injury according to the presence of fever.

3.2. Main results

Multivariable logistic regression analysis showed that an elevated CAR had no significant association with poor functional outcomes and mortality at 6 months (aOR [95% CI]: 1.35 [0.39–4.69] for poor functional outcomes and 0.87 [0.24–3.16] for mortality).

CRP, a component of CAR, was not significantly associated with clinical outcomes, but elevated albumin was a significant risk factor for

poor functional outcomes at 6 months (4.17 [2.43–7.16]) and mortality at 6 months (3.00 [1.70–5.28]) (Table 3).

3.3. Interaction analysis

In the interaction analysis, a significant interaction was observed between the elevated CAR and fever on poor functional outcomes in mTBI patients. An elevated CAR did not increase poor functional outcomes in the absence of fever (1.08 [0.55–2.13]), but a significant increase in poor functional outcomes was observed when the elevated CAR was accompanied by fever (1.32 [1.14–2.56]) (p for interaction<0.05) (Table 4).

4. Discussion

Our retrospective cohort study to identify the association between elevated CAR and long-term functional/survival outcomes among patients with mTBI with intracranial hemorrhage identified that elevated CAR was not significantly associated with long-term clinical outcomes of mTBI, whereas elevated CAR with fever had significantly higher odds of poor functional recovery at 6 months. This research contributes to a better understanding of the relationship among CAR, fever, and long-term functional/survival outcomes after mTBI and will help in developing strategies to improve long-term functional outcomes in these patients.

CRP is an acute-phase protein produced on stimulation by various cytokines in response to infection, trauma, ischemia, and other inflammatory conditions [22]. CRP is a strong indicator of secondary brain injury, and there are studies reporting that an increased CRP is associated with mortality in patients with TBI [23, 24]. Additionally, in other types of brain injury, including hemorrhage, intracranial hemorrhage, and ischemic stroke, an increased CRP was associated with poor clinical outcomes [25, 26]. However, in our study, an elevated level of CRP in patients with mTBI was not a risk factor for long-term clinical outcomes, unlike in previous studies.

Previous studies have indicated that serum albumin levels decrease significantly after TBI [27, 28], and hypoalbuminemia contributes to poor clinical outcomes in patients with TBI [29, 30, 31]. The main possible explanation is that hypoalbuminemia leads to insufficient intravascular osmolality that induces fluid transfer from vessels to the cerebral tissue space, thereby exacerbating cerebral edema and consequently increasing intracranial pressure. In a study on prehospital fluid resuscitation in patients with TBI, the use of albumin colloid reduced the possibility of brain edema compared to the use of crystalloid fluid [32]. Another possible explanation is the association between hypoalbuminemia and systematic inflammatory response, which is associated with poor clinical outcomes in patients with TBI [33]. While there are limited reports on role of hypoalbuminemia on long-term clinical outcomes, in this study, we observed that low albumin levels alone were identified as a risk factor for increased poor functional outcomes and mortality at 6 months after hospital discharge.

Table 1. Characteristics of the study population according to the CRP Albumin ratio (CAR).

Variables	All	CRP Albumin Ratio		p value
		Elevated	Normal	
	n(%)	n(%)	n(%)	
All	387 (100.0)	82 (100.0)	305 (100.0)	
Age				0.56
18–64	164 (42.4)	32 (39.0)	132 (43.3)	
65-	223 (57.6)	50 (61.0)	173 (56.7)	
Sex, male	265 (68.5)	57 (69.5)	208 (68.2)	0.52
Comorbidity				
Hypertension	172 (44.4)	31 (37.8)	141 (46.2)	0.81
Diabetes mellitus	112 (28.9)	19 (23.2)	93 (30.5)	0.77
Mechanism of injury				0.25
Traffic accident	140 (36.2)	24 (29.3)	116 (38.0)	
Fall down injury	172 (44.4)	38 (46.3)	134 (43.9)	
Other	75 (19.4)	20 (24.4)	55 (18.0)	
Place of injury				0.15
Home	118 (30.5)	26 (31.7)	92 (30.2)	
Street	145 (37.5)	26 (31.7)	119 (39.0)	
Other	124 (32.0)	30 (36.6)	94 (30.8)	
Fever at ED, yes	60 (15.5)	16 (19.5)	44 (14.4)	0.23
Vasopressor, yes	28 (7.2)	6 (7.3)	22 (7.2)	0.86
Types of hemorrhage				0.64
SDH	194 (50.1)	43 (52.4)	151 (49.5)	
SAH	85 (22.0)	20 (24.4)	65 (21.3)	
ICH (including hemorrhagic contusion)	49 (12.7)	7 (8.5)	42 (13.8)	
EDH	41 (10.6)	11 (13.4)	30 (9.8)	
IVH & other	18 (4.7)	1 (1.2)	17 (5.6)	
Advanced airway, yes	53 (13.7)	11 (13.4)	42 (13.8)	0.26
Blood transfusion, yes	39 (10.1)	8 (9.8)	31 (10.2)	0.93
WBC				0.74
Leukocytosis, >11000	10 (2.6)	3 (3.7)	7 (2.3)	
Leukopenia, <4000	200 (51.7)	39 (47.6)	161 (52.8)	
Clinical outcomes				
In-hospital mortality	38 (9.8)	11 (13.4)	27 (8.9)	0.21
Poor functional outcome at 6-month	121 (31.3)	26 (31.7)	95 (31.1)	0.91
Mortality at 6-month	89 (23.0)	19 (23.2)	70 (23.0)	0.96

ED, emergency department; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; EDH, epidural hemorrhage; IVH, intraventricular hemorrhage; WBC, white blood cell.

CAR, calculated from the combination of CRP and albumin, reflects the integrated effects of inflammation and nutrition. The predictive power of CAR was verified in several clinical situations including inflammatory diseases, cardiovascular diseases, cancer, and central

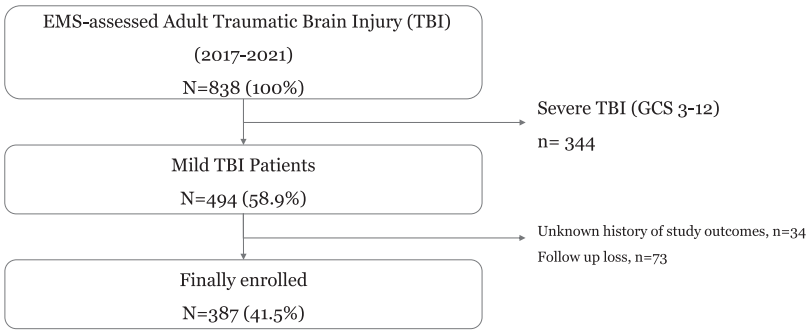

Figure 1. Study populations.

Table 2. Characteristics of the study population according to presence of fever at ED.

Variables	All	Fever		p value
		fever (+)	fever (-)	
	n(%)	n(%)	n(%)	
All	387 (100.0)	60 (100.0)	327 (100.0)	
CRP albumin ration				0.23
Normal	128 (33.1)	15 (25.0)	113 (34.6)	
Elevated	130 (33.6)	20 (33.3)	110 (33.6)	
Age				0.67
18–64	164 (42.4)	27 (45.0)	137 (41.9)	
65-	223 (57.6)	33 (55.0)	190 (58.1)	
Sex, male	265 (68.5)	34 (56.7)	231 (70.6)	0.03
Comorbidity				
Hypertension	172 (44.4)	30 (50.0)	142 (43.4)	0.34
Diabetes mellitus	112 (28.9)	15 (25.0)	97 (29.7)	0.47
Mechanism of injury				0.42
Traffic accident	140 (36.2)	24 (40.0)	116 (35.5)	
Fall down injury	172 (44.4)	22 (36.7)	150 (45.9)	
Other	75 (19.4)	14 (23.3)	61 (18.7)	
Place of injury				0.09
Home	118 (30.5)	11 (18.3)	107 (32.7)	
Street	145 (37.5)	26 (43.3)	119 (36.4)	
Other	124 (32.0)	23 (38.3)	101 (30.9)	
Vasopressor, yes	28 (7.2)	5 (8.3)	23 (7.0)	0.71
Types of hemorrhage				0.74
SDH	194 (50.1)	30 (50.0)	164 (50.2)	
SAH	85 (22.0)	16 (26.7)	69 (21.1)	
ICH (including hemorrhagic contusion)	49 (12.7)	8 (13.3)	41 (12.5)	
EDH	41 (10.6)	4 (6.7)	37 (11.3)	
IVH & other	18 (4.7)	2 (3.3)	16 (4.9)	
Advanced airway, yes	53 (13.7)	10 (16.7)	43 (13.1)	0.46
Blood transfusion, yes	39 (10.1)	7 (11.7)	32 (9.8)	0.65
WBC				0.46
Leukocytosis, >11000	198 (51.2)	32 (53.3)	166 (50.8)	
Leukopenia, <4000	10 (2.6)	3 (5.0)	7 (2.1)	
Clinical outcomes				
In-hospital mortality	38 (9.8)	7 (11.7)	31 (9.5)	0.6
Poor functional outcome at 6-month	121 (31.3)	16 (26.7)	105 (32.1)	0.41
Mortality at 6-month	89 (23.0)	12 (20.0)	77 (23.5)	0.56

ED, emergency department; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; EDH, epidural hemorrhage; IVH, intraventricular hemorrhage; WBC, white blood cell.

nervous system diseases such as such as ischemic stroke and subarachnoid hemorrhage [34, 35, 36, 37, 38]. In studies of patients with TBI, an elevated CAR predicted mortality; however, the severity of TBI was not considered, and only the prediction of short-term mortality was suggested [39].

In this study, we investigated the association between elevated CAR and long-term functional outcomes in patients with mTBI, but the results were not statistically significant. However, as CRP is not a perfect biomarker for predicting inflammation, an interaction analysis was performed to determine whether there is a difference in the predictive power of CAR on clinical outcomes in the presence of fever, another predictor of inflammation. In the interaction analysis, an elevated CAR was associated with poor functional recovery at 6 months, only when accompanied by fever. As opposed to denigrating the predictive power of CRP for clinical outcomes in patients with mTBI, we are of the opinion that this result emphasizes that systematic inflammation is a risk factor for long-term poor functional outcomes.

Table 3. Multivariable logistic regression analysis on study outcomes by the CAR, components of CAR, and fever.

	Total	Outcome		Model 1	Model 2
	N	N	%	aOR (95% CI)	aOR (95% CI)
Poor functional outcome at 6 month					
Total	388	121	31.2		
CAR					
Normal (≤1.7)	306	95	31.0	1.00	1.00
Elevated	82	26	31.7	1.27 (0.37–4.40)	1.35 (0.39–4.69)
CRP					
Normal (≤1)	284	91	32.0	1.00	1.00
Elevated	104	30	28.8	0.66 (0.21–2.09)	0.65 (0.21–2.09)
Albumin					
Normal (≥3.5)	288	68	23.6	1.00	1.00
Decreased	100	53	53.0	3.89 (2.36–6.42)	4.17 (2.43–7.16)
Fever					
Fever (−)	328	105	32.0	1.00	1.00
Fever (+)	60	16	26.7	0.67 (0.35–1.31)	0.64 (0.33–1.27)
Mortality at 6 month					
Total	388	89	22.9		
CAR					
Normal (≤1.7)	306	70	22.9	1.00	1.00
Elevated	82	19	23.2	0.82 (0.23–2.92)	0.87 (0.24–3.16)
CRP					
Normal (≤1)	284	66	23.2	1.00	1.00
Elevated	104	23	22.1	1.01 (0.31–3.28)	1.12 (0.34–3.69)
Albumin					
Normal (≥3.5)	288	49	17.0	1.00	1.00
Decreased	100	40	40.0	3.23 (1.91–5.46)	3.00 (1.70–5.28)
Fever					
Fever (-)	328	77	23.5	1.00	1.00
Fever (+)	60	12	20.0	0.75 (0.37–1.55)	0.74 (0.35–1.56)

CAR, CRP albumin ratio; OR, odds ratio; CI, confidence interval; CRP, C-reactive protein.
Model 1 adjusted for age, sex, comorbidities (hypertension and diabetes mellitus), and fever.
Model 2 adjusted for variables in Model 1 and mechanism of injury, place of injury, and type of hemorrhage.

Table 4. Interaction analysis between the CAR and fever on study outcome.

	CAR		p for interaction
	Normal CAR	Elevated CAR	
		aOR (95% CI)	
Poor functional outcome at 6-month			<0.05
Fever (−)	ref.	1.08 (0.55–2.13)	
Fever (+)	ref.	1.32 (1.14–2.56)	
Mortality at 6-month			0.14
Fever (−)	ref.	1.07 (0.59–1.97)	
Fever (+)	ref.	1.14 (0.31–4.20)	

CAR, CRP albumin ratio; OR, odds ratio; CI, confidence interval.

Our results indicate that elevated CAR in the presence of fever is a risk factor for poor functional recovery at 6 months after hospital discharge, although CAR alone was not a risk factor for long-term clinical outcomes in patients with mTBI.

Our study has several limitations. First, our study population comprised patients with mTBI, defined as those with a GCS score of 13–15. While GCS has been most widely used triage tool to assess the severity of TBI patients, there are still potential misclassification of TBI patients, which may have affected the study outcomes. Second, we

divided the study population into two groups (normal vs. abnormal) based on the levels of CAR, CRP, and albumin, referring to previous studies. However, the reference point may not be objective. Third, 6 months after hospital discharge, the clinical outcomes including mRS and mortality were not assessed by in-person physical examinations of the patients but rather by a telephone survey; therefore, the information may be inaccurate. Finally, as the study was not a randomized controlled trial, there could have been some potential biases that were not controlled.

5. Conclusions

Elevated CAR with fever increased the risk of poor functional recovery at 6 months after hospital discharge in patients with mTBI. Our study findings suggest the need for strategies for the prevention of long-term poor functional recovery in the presence of elevated CAR and fever in patients with mTBI.

Declarations

Author contribution statement

Eujene Jung: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Hyun Ho Ryu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Cha Won Ko: Contributed reagents, materials, analysis tools or data.

Yong Deok Lim: Analyzed and interpreted the data; Wrote the paper.

Funding statement

Eujene jung was supported by Chonnam National University [BCRI-22035].

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e12153.

Acknowledgements

This study was supported by a grant (BCRI-22035) from Chonnam National University Hospital Biomedical Research Institute.

References

[1] M. Majdan, D. Plancikova, A. Brazinova, M. Rusnak, D. Nieboer, V. Feigin, et al., Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis, Lancet Publ. Heal. 1 (2) (2016) e76–e83.

[2] C.A. Taylor, J.M. Bell, M.J. Breiding, L. Xu, Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013, MMWR Surveill. Summ 66 (9) (2017) 1–16.

[3] C. Paniak, S. Reynolds, K. Phillips, G. Toller-Lobe, A. Melnyk, J. Nagy, Patient complaints within 1 month of mild traumatic brain injury: a controlled study, Arch. Clin. Neuropsychol. 17 (4) (2002) 319–334.

[4] J. Ponsford, Factors contributing to outcome following traumatic brain injury, NeuroRehabilitation 32 (4) (2013) 803–815.

[5] J. Kornbluth, A. Bhardwaj, Evaluation of coma: a critical appraisal of popular scoring systems, Neurocritical Care 14 (1) (2011) 134–143.

[6] C. Smith, M.J. Kruger, R.M. Smith, K.H. Myburgh, The inflammatory response to skeletal muscle injury: illuminating complexities, Sports Med. 38 (11) (2008) 947–969.

[7] V.E. Johnson, J.E. Stewart, F.D. Begbie, J.Q. Trojanowski, D.H. Smith, W. Stewart, Inflammation and white matter degeneration persist for years after a single traumatic brain injury, Brain: J. Neurol. 136 (Pt 1) (2013) 28–42.

[8] D.W. Simon, M.J. McGeachy, H. Bayır, R.S. Clark, D.J. Loane, P.M. Kochanek, The far-reaching scope of neuroinflammation after traumatic brain injury, Nat. Rev. Neurol. 13 (3) (2017) 171–191.

[9] M. Mohamadpour, K. Whitney, P.J. Bergold, The importance of therapeutic time window in the treatment of traumatic brain injury, Front. Neurosci. 13 (2019) 7.

[10] R. Krishnadas, J. Cavanagh, Depression: an inflammatory illness? J. Neurol. Neurosurg. Psychiatr. 83 (5) (2012) 495–502.

[11] S. Lanquillon, J.C. Krieg, U. Bening-Abu-Shach, H. Vedder, Cytokine production and treatment response in major depressive disorder, Neuropsychopharmacology 22 (4) (2000) 370–379.

[12] K. Matsuo, H. Aihara, T. Nakai, A. Morishita, Y. Tohma, E. Kohmura, Machine learning to predict in-hospital morbidity and mortality after traumatic brain injury, J. Neurotrauma 37 (1) (2020) 202–210.

[13] T. Naghibi, M. Mohajeri, F. Dobakhti, Inflammation and outcome in traumatic brain injury: does gender effect on survival and prognosis? J. Clin. Diagn. Res. : J. Clin. Diagn. Res. 11 (2) (2017) Pc06–pc9.

[14] R. Wang, M. He, X. Ou, X. Xie, Y. Kang, CRP Albumin ratio is positively associated with poor outcome in patients with traumatic brain injury, Clin. Neurol. Neurosurg. 195 (2020), 106051.

[15] O.T. Ranzani, F.G. Zampieri, D.N. Forte, L.C. Azevedo, M. Park, C-reactive protein/albumin ratio predicts 90-day mortality of septic patients, PLoS One 8 (3) (2013), e59321.

[16] J. Zhou, W. Wei, H. Hou, S. Ning, J. Li, B. Huang, et al., Prognostic value of C-reactive protein, glasgow prognostic score, and C-reactive protein-to-albumin ratio in colorectal cancer, Front. Cell Dev. Biol. 9 (2021), 637650.

[17] J.W. Finnie, Neuroinflammation: beneficial and detrimental effects after traumatic brain injury, Inflammopharmacology 21 (4) (2013) 309–320.

[18] M. Das, S. Mohapatra, S.S. Mohapatra, New perspectives on central and peripheral immune responses to acute traumatic brain injury, J. Neuroinflammation 9 (2012) 236.

[19] A. Capizzi, J. Woo, M. Verduzco-Gutierrez, Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management, Med. Clin. 104 (2) (2020) 213–238.

[20] T.J. Quinn, J. Dawson, M.R. Walters, K.R. Lees, Reliability of the modified Rankin Scale: a systematic review, Stroke 40 (10) (2009) 3393–3395.

[21] S. Kahraman, A.C. Dogan, G. Demirci, A.R. Demir, E. Yilmaz, H.Z. Agus, et al., The prognostic value of c-reactive protein to albumin ratio in patients with isolated degenerative aortic valve stenosis undergoing surgical aortic valve replacement, Braz. J. Cardiovasc. Surg. 35 (2019) 299–306.

[22] S.M. Nehring, B. Patel, C Reactive Protein (CRP), 2017.

[23] M.-J. Feng, W.-B. Ning, W. Wang, Z.-H. Lv, X.-B. Liu, Y. Zhu, et al., Serum S100A12 as a prognostic biomarker of severe traumatic brain injury, Clin. Chim. Acta 480 (2018) 84–91.

[24] L.-J. Cao, J. Wang, P.-P. Hao, C.-L. Sun, Y.-G. Chen, Effects of ulinastatin, a urinary trypsin inhibitor, on synaptic plasticity and spatial memory in a rat model of cerebral ischemia/reperfusion injury, Chin. J. Physiol. 54 (6) (2011) 435–442.

[25] A. Attia, M. Elmallawany, M.T. EL Far, A. EL-Fiki, M. Zater, The Value of C-Reactive Protein as a Predictor of Vasospasm and Poor Outcome in Spontaneous Subarachnoid Hemorrhage, The Medical Journal of Cairo University, 2021, pp. 889–896.

[26] P. LöPPönen, C. Qian, S. Tetri, S. Juvela, J. Huhtakangas, M.K. Bode, et al., Predictive value of C-reactive protein for the outcome after primary intracerebral hemorrhage, J. Neurosurg. 121 (6) (2014) 1374–1379.

[27] T. Montalcini, M. Moraca, Y. Ferro, S. Romeo, S. Serra, M.G. Raso, et al., Nutritional parameters predicting pressure ulcers and short-term mortality in patients with minimal conscious state as a result of traumatic and non-traumatic acquired brain injury, J. Transl. Med. 13 (2015) 305.

[28] D. Chen, L. Bao, S.Q. Lu, F. Xu, Serum albumin and prealbumin predict the poor outcome of traumatic brain injury, PLoS One 9 (3) (2014), e93167.

[29] T. Montalcini, M. Moraca, Y. Ferro, S. Romeo, S. Serra, M.G. Raso, et al., Nutritional parameters predicting pressure ulcers and short-term mortality in patients with minimal conscious state as a result of traumatic and non-traumatic acquired brain injury, J. Transl. Med. 13 (1) (2015) 1–8.

[30] D. Chen, L. Bao, S-q Lu, F. Xu, Serum albumin and prealbumin predict the poor outcome of traumatic brain injury, PLoS One 9 (3) (2014), e93167.

[31] G.A. Baltazar, A.J. Pate, B. Panigrahi, I.V.S. LaBoy, I.V.R. Prosniak, I.V.A. Mody, et al., Malnutrition as measured by albumin and prealbumin on admission is associated with poor outcomes after severe traumatic brain injury, Am. Surg. 81 (2) (2015) 61–63.

[32] M. Jungner, P.-O. Grände, G. Mattiasson, P. Bentzer, Effects on brain edema of crystalloid and albumin fluid resuscitation after brain trauma and hemorrhage in the rat, J. Am. Soc. Anesthesiologists 112 (5) (2010) 1194–1203.

[33] D.H. Esper, W.A. Harb, The cancer cachexia syndrome: a review of metabolic and clinical manifestations, Nutr. Clin. Pract. 20 (4) (2005) 369–376.

[34] Y. Zhang, G.-Q. Zhou, X. Liu, L. Chen, W.-F. Li, L.-L. Tang, et al., Exploration and validation of C-reactive protein/albumin ratio as a novel inflammation-based prognostic marker in nasopharyngeal carcinoma, J. Cancer 7 (11) (2016) 1406.

[35] X.F. Ni, J. Wu, M. Ji, Y.J. Shao, B. Xu, J.T. Jiang, et al., Effect of C-reactive protein/albumin ratio on prognosis in advanced non–small-cell lung cancer, Asia Pac. J. Clin. Oncol. 14 (6) (2018) 402–409.

[36] I. Rencuzogullari, Y. Karabağ, M. Çağdaş, S. Karakoyun, S. Seyis, M.O. Gürsoy, et al., Assessment of the relationship between preprocedural C-reactive protein/

albumin ratio and stent restenosis in patients with ST-segment elevation myocardial infarction, Rev. Port. Cardiol. 38 (4) (2019) 269–277.
[37] D. Zhang, H. Yan, Y. Wei, X. Liu, Z. Zhuang, W. Dai, et al., C-reactive protein/albumin ratio correlates with disease severity and predicts outcome in patients with aneurysmal subarachnoid hemorrhage, Front. Neurol. 10 (2019) 1186.
[38] M.B. Skrifvars, E. Moore, J. Mårtensson, M. Bailey, C. French, J. Presneill, et al., Erythropoietin in traumatic brain injury associated acute kidney injury: a randomized controlled trial, Acta Anaesthesiol. Scand. 63 (2) (2019) 200–207.
[39] R. Wang, M. He, X. Ou, X. Xie, Y. Kang, CRP Albumin ratio is positively associated with poor outcome in patients with traumatic brain injury, Clin. Neurol. Neurosurg. 195 (2020), 106051.