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ORIGINAL ARTICLE

Posttraumatic epilepsy in critically ill children with traumatic brain injury

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Abstract

Purpose The aim of this study was to determine the clinical, laboratory, and radiological factors related with posttraumatic epilepsy (PTE).

Methods The study is a multicenter descriptive cross-sectional cohort study. Children who followed up for TBI in the pediatric intensive care unit between 2014 and 2021 were included. Demographic data and clinical and radiological parameters were recorded from electronic case forms. All patients who were in the 6-month posttraumatic period were evaluated by a neurologist for PTE.

Results Four hundred seventy-seven patients were included. The median age at the time of trauma was 66 (IQR 27–122) months, and 298 (62.5%) were male. Two hundred eighty (58.7%) patients had multiple traumas. The mortality rate was 11.7%. The mean duration of hospitalization, pediatric intensive care unit hospitalization and mechanical ventilation, Rotterdam score, PRISM III score, and GCS at admission were higher in patients with epilepsy ($p < 0.05$). The rate of epilepsy was higher in patients with severe TBI, cerebral edema on tomography and clinical findings of increased intracranial pressure, blood transfusion in the intensive care unit, multiple intracranial hemorrhages, and intubated patients ($p < 0.05$). In logistic regression analysis, the presence of intracranial hemorrhage in more than one compartment of the brain (OR 6.13, 95%CI 3.05–12.33) and the presence of seizures (OR 9.75, 95%CI 4.80–19.83) were independently significant in terms of the development of epilepsy ($p < 0.001$).

Conclusions In this multicenter cross-sectional study, intracranial hemorrhages in more than one compartment and clinical seizures during intensive care unit admission were found to be independent risk factors for PTE development in pediatric intensive care unit patients with TBI.

Keywords Children · Traumatic brain injury · Epilepsy

Abbreviation

EEG	Electroencephalography
CT	Computed tomography
GCS	Glasgow Coma Score
ICP	Intracranial pressure
ISS	Injury Severity Score
PICU	Pediatric intensive care unit
PRISM	Pediatric risk of mortality
PTE	Posttraumatic epilepsy
TBI	Traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the common causes of mortality and morbidity in the pediatric population. In addition, cognitive, social, and behavioral sequelae are well-defined long-term complications of TBI [1, 2]. TBI is one of the most common causes of acquired epilepsy in the pediatric and adult populations [3]. Posttraumatic epilepsy causes significant consequences in terms of quality of life and neuropsychological functions, especially in young patients. Even in remission, social and educational problems may be observed in adulthood. If seizures persist, the risk of early death increases in these patients compared to their peers [4, 5]. The development of epilepsy after TBI may be

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multifactorial. Age, genetic factors, development of inflammation, disruption of the blood–brain barrier, parenchymal loss, and neurological plasticity are among the many causes. However, there are reports that seizure frequency and treatment failure are more common in posttraumatic epilepsy [6–9].

In the literature, there are studies showing that the development of posttraumatic epilepsy increases with age, early seizures, the severity of head trauma, and surgical intervention in children and adult patients followed up for head trauma. Although mild head trauma has been shown to be riskier for epilepsy, the situation may be more heterogeneous in children [10, 11]. However, although early seizures are reported to be more common in young children, late seizures are more common in older children [12, 13]. In patients followed up in the pediatric intensive care unit due to TBI, many conditions that may affect the development of convulsions may be encountered. Trauma severity, hemodynamic instability, electrolyte disorders, blood glucose abnormalities, and surgical procedure transfusion need are some of them.

The primary aim of this study was to determine the clinical, laboratory, and radiological factors related with posttraumatic epilepsy (PTE).

Materials and methods

The study is a multicenter descriptive cross-sectional cohort study involving five different tertiary care reference pediatric intensive care units (PICUs). All participating centers admitted pediatric patients aged between 1 month and 18 years and followed critically ill children both after trauma and surgery and for all other reasons. Pediatric patients who followed up for TBI in the pediatric intensive care unit for a total of 7 years between 2014 and 2021 were included. The data of the patients were obtained from the data collected with the case record forms sent to the centers electronically. Demographic data, Glasgow Coma Score (GCS), Injury Severity Score (ISS) [14], PRISM III score [15], trauma severity (according to GCS) [16], trauma mechanism, presence of brain edema on tomography, location of hemorrhages in the brain and presence of multiple compressions (parenchymal/epidural/subdural/subarachnoid hemorrhage), Rotterdam computed tomography (CT) score [17], and the presence of axonal damage were recorded. During follow-up, the lowest and highest serum electrolyte and glucose values, anti-edema treatment preference, the decline in GCS, presence of seizure, prophylactic antiepileptic treatment, need for transfusion, need for inotropes, surgical procedure, and vasoactive inotrope score (VIS) were recorded. After the patients/their parents were contacted by telephone and their informed consent was obtained, an experienced researcher questioned whether they had convulsions after the child was discharged from the intensive care unit, whether they received anticonvulsant treatment, and whether the treatment was discontinued. All patients who were in the 6-month posttraumatic period were evaluated by a pediatric neurologist. Patients who were on antiepileptic therapy and had epileptic activity on electroencephalography (EEG) or continued to have seizures clinically were considered to have PTE.

Exclusion criteria were as follows: being younger than 1 month or older than 18 years of age, being exitus before epilepsy evaluation, and not having access to data and follow-up information.

Statistical evaluation

IBM SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical evaluation. Frequency distributions were evaluated as number and percentage, and continuous variables (measurements) were evaluated as mean ± standard deviation. Shapiro–Wilk test was used to determine whether the data were normally distributed. In statistical evaluation, independent sample *t*-test was used to compare paired groups for normally distributed data, and Mann–Whitney *U* test was used for non-normally distributed data. Chi-square test was used to compare categorical variables. Patients with mortality were excluded in single analyses in terms of posttraumatic epilepsy development, and variables with significant association were evaluated with a multiple logistic regression models. Variables with VIF values below five were included in the model. Significance was assessed at $p < 0.05$ level.

Ethic

Data collection and retrospective analysis were conducted under the approval of Akdeniz University Clinical Research Ethics Review Board (Date: 07.07.2021 No: KAEK-528). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration.

Results

The study included 477 patients who met the inclusion criteria from 5 centers. The median age of the patients at the time of trauma was 66 (IQR 27–122) months, and 298 (62.5%) were male. The median follow-up time of the patients was 25 months (IQR 6–49). The most common cause of trauma was fall from a height (44.7%), and 280 (58.7%) patients had trauma in other organs accompanying head trauma (Tables 1

Table 1 Demographic characteristics, accompanying comorbidities, and clinical findings of the patients

Characteristic	Total[a] (*N*: 477)	Posttraumatic epilepsy (*N*:421)		
		Yes (*N*: 58)	No (*N*: 363)	*p*
Age at TBI	66 (27–122)	73 (35.3–141.5)	82 (42–144)	0.947
Gender, *n* (%)				
Male	298 (62.5)	38 (65.5)	225 (62.0)	0.606
Female	179 (37.5)	20 (34.5)	138 (38.0)	
GCS on admission	11 (6–14)	7 (5–9)	8 (5–11)	<0.001
PRISM III	5 (2–15)	8 (5–18.5)	12 (5–27)	<0.001
ISS	14 (9–24.5)	18 (9–25)	16 (9–22)	0.065
VIS	0 (0–10)	0 (0–10)	10 (0–15)	0.529
Rotterdam CT score	2.16 (1.20)	3 (2–3)	2 (2–3)	<0.001
TBI etiology, *n* (%)				
Fall	213 (44.7)	31 (53.4)	158 (43.5)	0.153
Motor vehicle accident	90 (18.9)	6 (10.3)	74 (20.4)	
Pedestrian accident	122 (25.6)	15 (25.9)	88 (24.2)	
Motorcycle accident	19 (4)	4 (6.9)	13 (3.6)	
Other	33 (6.9)	2 (3.4)	30 (8.3)	
Intracranial pathology, *n* (%)				
Intracranial hemorrhage in more than one compartment	113 (23.7)	31 (59.6)*	52 (17.3)	<0.001
Intracranial hemorrhage	290 (60.8)	21 (40.4)	249 (82.7)*	
Subdural hemorrhage	124 (26.0)	26 (44.8)	74 (20.5)	<0.001
Subarachnoid hemorrhage	186 (39.0)	23 (39.7)	129 (35.7)	0.564
Parenchymal hemorrhage	142 (29.8)	32 (55.2)	88 (24.4)	<0.001
Epidural hemorrhage	80 (16.8)	11 (19.0)	65 (18.0)	0.860
Intraventricular hemorrhage	29 (6.1)	7 (12.1)	15 (4.2)	0.021
Multiple trauma, *n* (%)	280 (58.7)	35 (60.3)	200 (55.1)	0.455
Trauma severity according to GCS, *n* (%)				
Mild	228 (47.8)	16 (27.6)	212 (58.4)*	<0.001
Moderate	76 (15.9)	10 (17.2)	66 (18.2)	
Severe	173 (36.3)	32 (55.2)*	85 (23.4)	
Hypotension on admission, *n* (%)	109 (22.9)	13 (22.4)	52 (14.3)	0.113
Clinical findings of increased intracranial pressure, *n* (%)	180 (37.7)	35 (60.3)	98 (27.0)	<0.001
Convulsion, *n* (%)	87 (18.2)	33 (56.9)	47 (12.9)	<0.001
Diffuse axonal injury, *n* (%)	76 (15.9)	19 (44.2)	57 (24.4)	0.007
Glucose				
Minimum	96 (82–129)	89 (75–105)	91.5 (79–123)	0.056
Maximum	137 (115–90)	137.35 (124–213)	134 (121–200)	0.062
Sodium				
Minimum	136 (134–139)	136 (133.67–138)	136 (133.7–138)	0.924
Maximum	145 (141–151.4)	153(144.25–159)	145.85 (142–151.3)	<0.001
Sodium decrease in the first 7 days, *n* (%)				
< 0.5 meq/h	278 (58.4)	35 (60.3)	213 (58.8)	0.829
> 0.5 meq/h	199 (41.6)	23 (39.7)	149 (41.2)	
Magnesium	1.81 (1.53–1.81)	1.66 (1.49–1.90)	1.65 (1.40–1.90)	0.378
Calcium	8.4 (7.9–9.0)	7.92 (7.7–8.3)	8.12 (7.61–8.50)	<0.001
Duration of mechanical ventilation day, *n* (%)	4 (2–8)	7 (3.5–14)	4 (2–7)	<0.001
LOS PICU, *n* (%)	5 (3–9)	12.5 (6–20)	7 (4–12)	<0.001
LOS hospital, *n* (%)	9 (5–16)	19.5 (11.5–38.5)	15.5 (10–24)	<0.001

The continuous variables are expressed as median (interquartile range)

CT computerized tomography, *GCS* Glasgow Coma Scale, *ISS* injury severity score, *LOS* length of stay, *PRISM* pediatric risk of mortality, *TBI* traumatic brain injury, *VIS* vasoactive inotropic score

*The variable showing significance in chi-square analysis where more than two variables are compared

[a]fifty-six patients who died in the intensive care unit were excluded from statistical evaluation in terms of posttraumatic epilepsy

Table 2 Treatments and interventional procedures applied to patients

Characteristic	Total $N=477$	Posttraumatic epilepsy $N=421$		
		Yes ($N=58$)	No ($N=363$)	p
Anti-edema treatment, *n* (%)				
None	145 (30.4)	7(12.1)	133(36.6)*	0.001
Yes	332 (69.6)	51 (87.9)*	230 (63.4)	
Mannitol	13 (2.7)	1 (1.7)	11 (3.0)	0.001
%3 NaCl	221 (46.3)	26 (44.8)	164 (45.2)	
Mannitol with %3 NaCl	98 (20.5)	24 (41.4)*	55 (15.2)	
Need for erythrocyte transfusion (ED), n (%)	97 (20.3)	17(29.3)	47 (12.9)	0.001
Need for erythrocyte transfusion (PICU), n (%)	190 (39.8)	33 (56.9)	108 (29.8)	<0.001
Need for operation (PICU)	59 (12.4)	10 (17.2)	42 (11.6)	0.223
Massive transfusion (PICU)	31(6.5)	2 (3.4)	12 (3.3)	0.955
Intracranial pressure monitoring	10 (2.1)	2 (3.4)	4 (1.1)	0.162
Intubation	252 (52.8)	46 (79.3)	150 (41.3)	<0.001
Decompressive craniectomy	20 (4.2)	3 (5.2)	9 (2.5)	0.252

ED emergency department, *PICU* pediatric intensive care unit

*The variable showing significance in chi-square analysis where more than two variables are compared

and 2). Thoracic trauma was the most common comorbidity (41.5%). This was followed by orthopedic, abdominal, and spinal trauma (40.5%, 32.7%, 21.0%, respectively). The median Glasgow Coma Score was 11 (IQR 6–14), PRISM III score was 5 (IQR 2–15), Rotterdam score was 2 (IQR 1–3), and ISS was 14 (IQR 9–24) at the time of presentation to the emergency department. According to the GCS at emergency department presentation, 173 (36.3%) of the patients had severe head trauma (Tables 1 and 2). The mortality rate was 11.7%. The most common intracranial pathology was subarachnoid hemorrhage (24.9%), and 113 (23.7%) patients had intracranial hemorrhage in more than one compartment of the brain. PTE was detected in 58 (12.2%) children. Eighty-seven (18.2%) patients had clinical seizures during hospitalization, Prophylactic anticonvulsant therapy was started in 280 patients (58.7%), and PTE developed in 20.71% of these patients. The most preferred antiepileptic for prophylaxis or treatment was levetiracetam (65.7%) (Table 3). The mean duration of hospitalization, pediatric intensive care unit hospitalization and mechanical ventilation, Rotterdam score, PRISM III score, and GCS at admission were statistically significantly higher in patients with epilepsy ($p<0.05$).

Table 3 Results of multiple logistic regression analysis of variables associated with post traumatic epilepsy

	OR	95% CI		p
		Lower	Upper	
Hemorrhage at multiple sites	6.13	3.05	12.33	<0.001
Convulsion	9.75	4.80	19.83	<0.001

The rate of epilepsy was statistically significantly higher in patients with severe TBI, cerebral edema on tomography and clinical findings of increased intracranial pressure, blood transfusion in the intensive care unit, multiple intracranial hemorrhages, and intubated patients ($p<0.05$). The need for operation in the emergency department and intensive care unit did not differ in patients with epilepsy (Tables 1 and 2). In logistic regression analysis, the presence of intracranial hemorrhage in more than one compartment of the brain (OR 6.13, 95%CI 3.05–12.33) and the presence of seizures (OR 9.75, 95%CI 4.80–19.83) were independently significant in terms of the development of epilepsy ($p<0.001$) (Table 4). At least one clinical seizure was detected after discharge

Table 4 Epileptic treatment and conditions of patients

Characteristic	Posttraumatic epilepsy $N=421$		
	Yes ($N=58$)	No ($N=363$)	p
Anticonvulsant therapy			
Levetiracetam	44 (75.9)	106 (60.2)	0.177
Phenytoin	13 (22.4)	66 (37.5)	
Phenobarbital	1 (1.7)	3 (1.7)	
Oxcarbazepine	0 (0)	1 (0.6)	
EEG			
Epileptic activity	24 (41.4)	9 (9.1)	<0.001
No epileptic activity	34 (58.6)	90 (90.9)	
Convulsions after discharge	23 (39.7)	1 (0.3)	<0.001
Continuation of anticonvulsant therapy	24 (41.4)	0 (0)	<0.001

EEG electroencephalography

in 23 (39.7%) of 58 patients with PTE. Recurrent seizures were observed in 17 (19.5%) of 87 patients who had clinical seizures during intensive care hospitalization. Post-discharge clinical seizures were observed in 7 patients who did not have clinical seizures during their PICU stay, but one of these patients was not evaluated as PTE because there was no epileptic activity in EEG and the neurologist's clinical evaluation was not compatible with epilepsy. In 14 patients, PTE was diagnosed by a neurologist with clinical follow-up without a clinical seizure and epileptic activity on EEG, and antiepileptic treatment was discontinued in the follow-up of these patients. Antiepileptic treatment was discontinued in 63.8% of patients with PTE, and the mean duration of antiepileptic discontinuation was 17.62 (12.18) months. Of the patients with PTE receiving antiepileptic therapy, 4 of them were using two different antiepileptic drugs, 1 of them was using 3 different antiepileptic drugs, 1 of them was using 4 different antiepileptic drugs, and the rest were using a single antiepileptic treatment.

Discussion

Posttraumatic epilepsy is one of the well-known complications of traumatic brain injury. In this multicenter study, clinical, radiological, and laboratory parameters that are determinants of PTE development in TBI patients followed up in pediatric intensive care unit were evaluated. PTE rate was 12.2% in our cohort. Low GCS at presentation, severe head trauma, high PRISM III score, need for erythrocyte transfusion in the emergency department and intensive care unit, clinical signs of increased intracranial pressure, need for anti-edema treatment, diffuse axonal damage, presence of clinical seizures and prolonged mechanical ventilation, duration of PICU stay, and length of hospitalization were risky conditions in terms of posttraumatic epilepsy. Radiologically, subdural hemorrhage, intraventricular hemorrhage, hemorrhage in more than one compartment of the brain and high Rotterdam CT score, and laboratory findings of high sodium and low calcium were associated with PTE. When the parameters with statistically significant associations were evaluated with logistic regression model, the presence of clinical seizure and intracranial hemorrhage in more than one compartment was independently associated with the development of epilepsy.

The steps of the neurodevelopmental process in children and its change according to the age group show differences in terms of epileptogenesis compared to adults who have completed the developmental process. Therefore, the incidence and risk factors for posttraumatic epilepsy may be different. In the literature, the incidence of PTE development is reported as 15% in adults and 10% in children (CI = 5.9–15) [11, 18]. The PTE rates found in our country in this multicenter study seem to be consistent with the literature. There are conflicting interpretations in the literature in terms of children's age and PTE development. While there are studies that found being younger than 5 years of age to be an independent risk factor for the development of epilepsy, there are also studies indicating that the risk of PTE development increases with increasing age [19–21]. However, it is also thought that the incidence of posttraumatic epilepsy increases at older ages due to the higher incidence of PTE in adults compared to children [12, 21, 22]. Considering that there are many factors affecting the development of epilepsy, it may not be correct to associate it only with age. In our study, no relationship was found between age and PTE development.

Severity classification in head traumas is usually made according to GCS at the time of application, as in this study. Keret et al. reported that mild head trauma increased the development of PTE 4.5 times, similar to adults [23]. Contrary to the publications that associate moderate head trauma with the development of epilepsy in children, there are also studies in the literature that finds severe head trauma risky in terms of epilepsy development, similar to the study we presented [1, 21, 22, 24].

There is still an insufficient number of studies on markers of risk for PTE development in the intensive care units. Increased intracranial pressure (ICP), impaired cerebrovascular pressure reactivity, seizures starting in the early posttraumatic period, increased seizure burden, interictal findings on EEG, and worsening radiological findings have been shown to be risky and early markers for PTE [25]. In this study, we evaluated the factors related with epilepsy in children starting from emergency admission during pediatric intensive care unit hospitalization. It has been reported that elevated ICP and impaired cerebrovascular pressure reactivity are associated with cerebral edema that develops with increased permeability of the blood brain barrier, which increases with the severity of trauma and indicates a poor prognosis [26]. Although routine ICP measurement could not be performed in all centers included in the study, the presence of cerebral edema and the clinical findings of increased intracranial pressure have been shown to be associated with the development of epilepsy in this study. In our study, initial radiological findings were evaluated with the Rotterdam CT score, which has been shown to have prognostic value after trauma in children, and statistically significant higher scores were found in the group with PTE [27]. The scoring system includes the presence of midline shifting, the status of basal cisterns, epidural mass lesion, and intraventricular or subarachnoid hemorrhage. The presence of obliterated suprasellar cisterns alone has also been shown to be important for the development of PTE [21]. However, traumatic subarachnoid hemorrhage, contusion, presence of shunt, and subdural hemorrhages are also included among

the radiologic findings related with epilepsy in the literature [20, 21, 28]. In our single comparisons, intraventricular hemorrhage and subdural hemorrhage were found to be significant in terms of PTE development. However, although there is no previous study showing a relationship between intracranial hemorrhages in more than one compartment and epilepsy similar to our study, intracranial hemorrhage was reported as a risk factor for PTE in a recent meta-analysis without specifying the location.

In the literature, the most commonly associated condition for PTE is the presence of early seizure. In fact, when the mechanism of epileptogenesis is examined, it has been suggested that animal models are related to neuronal disinhibition after trauma or due to the development of excitatory connections during the recovery phase after injury. In this case, there is thought to be a silent period between the initial traumatic injury and the subsequent occurrence of spontaneous seizures [29, 30]. The clinical significance of this situation is the application of empirical treatments to prevent epileptogenesis. While prophylactic antiepileptic treatment helps prevent early seizures, there is no proven treatment and duration of treatment that prevents the development of epilepsy [31]. In the present multicenter study, prophylactic antiepileptics were initiated in 280 (58.7%) patients during intensive care unit admission, and seizures during intensive care unit admission were seen in 87 (18.2%) patients. In our study, we observed that 7 patients had their first seizure in the post-discharge period. All of these patients were receiving prophylactic antiepileptic treatment. This suggests that the efficacy of prophylactic treatments in reducing the risk of late seizures needs further evaluation. We found that the presence of clinical seizure in the intensive care unit increased the probability of PTE development by 9.75 times. Mikkonen et al. reported that having a seizure during intensive care unit hospitalization increased the risk of PTE 3.41-fold [21]. Again, in a recent meta-analysis, it was reported that the presence of early seizure increased the risk of PTE 7.28-fold [18]. According to the literature and our own results, the presence of seizures in the early period is the most important condition in predicting PTE. Therefore, it should be considered in terms of follow-up and treatment in pediatric patients with head trauma.

This multicenter study has some limitations. First of these, EEG, which is an important follow-up and treatment parameter in terms of epilepsy, could not be performed in all patients. Continuous EEG monitoring was not available in all the centers included in the study. Therefore, nonconvulsive electrical seizures may not have been detected. This may lead to inaccurate detection of early posttraumatic seizure rates. Second, ICP monitoring cannot be applied in every patient with head trauma in our country. Therefore, increased intracranial pressure was evaluated clinically and radiologically. Also the relationship between the localization of intracranial bleeding and the development of epilepsy could not be evaluated. Third, the study found an association between trauma severity and PTE, but no data were collected on the prognostic effects of this condition. In the literature, long-term effects of pediatric TBI include neuropsychological effects along with epilepsy [32, 33]. This should be studied prospectively in larger series. Fourth, there is no data on the time between convulsion and trauma in patients with first convulsion after discharge. Therefore, no comment can be made on the time frame for the development of epilepsy. Fifth, nonaccidental traumas were also evaluated in studies related to PTE in children in the literature and found to be associated with the development of epilepsy [19, 24]. Our study did not include a patient from this group. We think that the frequency of intensive care unit admission may be low because these patients with milder head trauma, some of whom were neonates, were detected incidentally. However, this may have caused us to find higher rates of PTE in more severe head traumas. Studies in larger series including this group are required.

Conclusion

In this multicenter cross-sectional study, intracranial hemorrhages in more than one compartment and clinical seizures during intensive care unit admission were found to be independent risk factors for PTE development in pediatric intensive care unit patients with TBI.

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Author contribution All authors contributed to the study conception and design. Dr. Nazan Ulgen Tekerek and Dr Dursun had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Ulgen Tekerek, Dr Dursun, Dr Ekici, Dr Kinik, Dr Durak, and Dr Havan contributed to acquisition, analysis, or interpretation of data. Dr. Ulgen Tekerek contributed to statistical analysis. Dr. Ulgen Tekerek and Dr Dursun contributed to drafting of the article. All authors contributed to critical revision of the article for important intellectual content and approved the final manuscript.

Declarations

Ethics approval Data collection and retrospective analysis were conducted under the approval of Akdeniz University Clinical Research Ethics Review Board (Date: 07.07.2021 No: KAEK-528). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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