



# Hospitalization and Morbidity Rates After Pediatric Traumatic Brain Injury: A Nation-Wide Population-Based Analysis

Nora Bruns<sup>1,2\*</sup>, Pietro Trocchi<sup>3</sup>, Ursula Felderhoff-Müser<sup>1,2</sup>, Christian Dohna-Schwake<sup>1</sup> and Andreas Stang<sup>3,4</sup>

<sup>1</sup> Department of Pediatrics I, Pediatric Intensive Care Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, <sup>2</sup> Center for Translational and Behavioural Neurosciences (TNBS), University Hospital Essen, University of Duisburg-Essen, Essen, Germany, <sup>3</sup> Institute for Medical Informatics, Biometry, and Epidemiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, <sup>4</sup> Department of Epidemiology, School of Public Health, Boston University, Boston, MA, United States

**Background:** Even though traumatic brain injury (TBI) is a major cause of morbidity and mortality in children around the globe, population-based and nation-wide data to assess the burden of TBI is scarce.

#### **OPEN ACCESS**

#### Edited by:

Joe Kossowsky, Harvard University, United States

#### Reviewed by:

Silvia Bressan, University of Padua, Italy Ann De Guchtenaere, Ghent University, Belgium

\*Correspondence: Nora Bruns nora.bruns@uk-essen.de

#### Specialty section:

This article was submitted to General Pediatrics and Pediatric Emergency Care, a section of the journal Frontiers in Pediatrics

Received: 26 July 2021 Accepted: 03 September 2021 Published: 30 September 2021

#### Citation:

Bruns N, Trocchi P, Felderhoff-Müser U, Dohna-Schwake C and Stang A (2021) Hospitalization and Morbidity Rates After Pediatric Traumatic Brain Injury: A Nation-Wide Population-Based Analysis. Front. Pediatr. 9:747743. doi: 10.3389/fped.2021.747743 **Methods:** Based on diagnosis related groups from nation-wide hospital data, we extracted data on all TBI-related hospitalizations in children < 18 years in Germany between 2014 and 2018. We calculated crude, age-specific and standardized incidence rates for hospitalizations, imaging, intracranial injury, neurosurgery, and mortality.

**Results:** Out of 10.2 million hospitalizations, we identified 458,844 cases with TBI as primary or secondary diagnosis, resulting in a crude incidence rate of 687/100,000 child years (CY). Age-specific rates of computed tomography were below 30/100,000 CY until the age of 10 years and increased to 162/100,000 CY until 17 years of age. Intracranial injury was diagnosed in 2.7%, neurosurgery was performed in 0.7% of patients, and 0.7% were mechanically ventilated. Mortality was 0.67/100,000 CY (0.1%).

**Conclusions:** Despite substantial hospitalization rates for pediatric TBI in Germany, the rates of imaging, the need for mechanical ventilation, neurosurgery and mortality were overall very low. Reasons for hospitalization and measures to reduce unnecessary admissions warrant further investigation.

Keywords: pediatric traumatic brain injury, epidemiology, incidence rates, mortality, morbidity, hospitalization

## **INTRODUCTION**

Traumatic brain injury frequently occurs in children and represents a relevant cause of pediatric morbidity and mortality worldwide (1, 2). Typically, a bimodal age distribution is reported with infants and adolescents as the most affected groups and male predominance across all ages (1). Incidence rates vary considerably between studies and countries, especially with respect to hospitalization and imaging practices (1). For example, in the United States of America (US), annual incidence rates of TBI have been estimated to be 799/100,000 children (3). Crude annual US hospitalization rates declined from 119/100,000 children below 18 years to  $\sim$ 73/100,000 between the 1990s and 2005 (4).

1

In European countries, annual standardized hospitalization rates after TBI vary between 81 and 643/100,000 persons (children and adults). With 584/100,000, Germany has the second highest annual hospitalization rate in Europe but with a rather low mortality of 8.3/100,000 (2). For children, populationbased data on the hospitalization rates for TBI, TBI-related morbidities, and mortality are scarce. The Collaborative Pediatric TBI Working Group recently identified epidemiologic data to assess the burden of pediatric TBI as one of the key clinical research needs in this field (5).

The aim of this study was to calculate nation-wide population-based rates of pediatric hospitalizations for TBI, imaging, treatment, and mortality in Germany. We analyzed a comprehensive data set provided by the Federal Bureau of Statistics that contains information on all hospitalizations of patients < 18 years in German hospitals between 2014 and 2018.

#### **METHODS**

Since 2004, imbursement for German hospitals is based on diagnosis related groups (DRG). By law (§21 KHEntgG), German hospitals must transmit data on all hospitalizations to the Hospital Remuneration System (InEK). After plausibility control, data are anonymized and forwarded to the Federal Bureau of Statistics. As the submission of hospitalization data is mandatory for reimbursement, hospitals have a strong incentive to supply a comprehensive data set.

For this study we analyzed 10,244,649 hospitalizations of patients < 18 years between 2014 and 2018 from all hospitals in Germany. Information on the structure of the DRG data set is supplied by the Federal Bureau of Statistics and has been described in detail elsewhere (6–8). More information is available on https://www.forschungsdatenzentrum.de/en/health/drg.

# Data Extraction and Calculation of Variables

We extracted cases with primary or secondary diagnosis of traumatic brain injury (TBI) according to the International Classification of Diseases, 10th Edition, German Modification (ICD-10-GM) (ICD-Code: S06). To assess the clinical course, we extracted information on secondary diagnoses and procedures based on ICD codes and codes for surgeries and procedures (Operations- und Prozedurenschlüssel, OPS) (**Supplementary Table 1**). New variables calculated based on ICD and OPS codes were ventilation, resuscitation, imaging, intracranial injury, combination of neurosurgery, complications (**Supplementary Table 1**).

### **Population Data and Standardization**

We extracted data of the end-of-year populations for each 1-year age group until age group 17.0–17.9 years between 2013 and 2018 from the homepage of the Federal Bureau of Statistics (https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/ Bevoelkerung/Bevoelkerungsstand/\_inhalt.html) and calculated mid-year populations for 2014 to 2018. WHO World Standard Population 2000–2025 (9), European Standard Population 
 TABLE 1 | Clinical information.

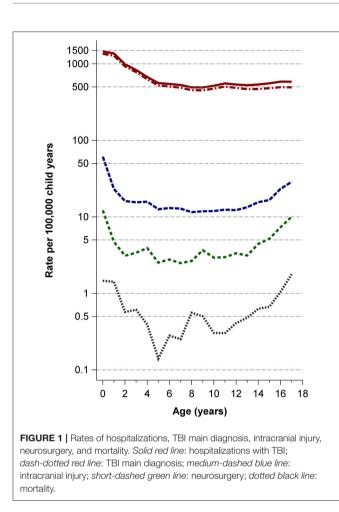
Hospitalized with diagnosis of TBI         458,844 (100)           TBI main diagnosis         418,603 (91.2)           Male         254,032 (55.4)           Female         204,812 (44.6)           Age [mean ± SD         7.1 ± 5.7           median (10th and 90th percentiles)]         6 (0-16)           Length of stay [mean ± SD         2 ± 3.9           median (10th and 90th percentiles)]         2 (1-2)           Mechanical ventilation (hours)         [mean ± SD           [mean ± SD         22 (2-352)           Died         447 (0.1)           Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,436 (0.5)           Priotural hemorrhage         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation		Overall [ <i>n</i> (%)]
TBI main diagnosis       418,603 (91.2)         Male       254,032 (55.4)         Female       204,812 (44.6)         Age [mean ± SD       7.1 ± 5.7         median (10th and 90th percentiles)]       6 (0-16)         Length of stay [mean ± SD       2 ± 3.9         median (10th and 90th percentiles)]       2 (1-2)         Mechanical ventilation       3,84 (0.7)         Mechanical ventilation (hours)       [mean ± SD         Imedian (10th and 90th percentiles)]       22 (2-352)         Died       447 (0.1)         Resuscitation       266 (0.1)         Loss of consciousness       64,692 (14.1)         Imaging (CT or MRI)       47,731 (10.4)         CT only       28,361 (6.2)         MRI only       14,864 (3.2)         CT and MRI       4,506 (1.0)         Intracranial injury       12,289 (2.7)         Subarachnoidal hemorrhage       2,154 (0.5)         Brain edema       1,250 (0.3)         Other intracranial injury       12,289 (2.7)         Subarachnoidal hemorrhage       2,154 (0.5)         Brain edema       1,250 (0.3)         Other intracranial injury       6,533 (1.4)         Neurosurgery       3,663 (0.4)         EVD	Hospitalized with diagnosis of TPI	458 844 (100)
Male         254,032 (5.4)           Female         204,812 (44.6)           Age [mean ± SD         7.1 ± 5.7           median (10th and 90th percentiles)]         6 (0-16)           Length of stay [mean ± SD         2 ± 3.9           median (10th and 90th percentiles)]         2 (1-2)           Mechanical ventilation         3,184 (0.7)           Mechanical ventilation (hours)         100.4 ± 247.2           median (10th and 90th percentiles)]         22 (2-352)           Died         447 (0.1)           Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery <t< td=""><td></td><td></td></t<>		
Female         204,812 (44.6)           Age [mean ± SD         7.1 ± 5.7           median (10th and 90th percentiles)]         6 (0-16)           Length of stay [mean ± SD         2 ± 3.9           median (10th and 90th percentiles)]         2 (1-2)           Mechanical ventilation         3,184 (0.7)           Mechanical ventilation (hours)         [mean ± SD           [mean ± SD         120.4 ± 247.2           median (10th and 90th percentiles)]         22 (2-352)           Died         447 (0.1)           Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery	0	
Age [mean $\pm$ SD7.1 $\pm$ 5.7median (10th and 90th percentiles)]6 (0-16)Length of stay [mean $\pm$ SD2 $\pm$ 3.9median (10th and 90th percentiles)]2 (1-2)Mechanical ventilation3,184 (0.7)Mechanical ventilation (hours)[mean $\pm$ SD[mean $\pm$ SD120.4 $\pm$ 247.2median (10th and 90th percentiles)]22 (2-352)Died447 (0.1)Resuscitation266 (0.1)Loss of consciousness64,692 (14.1)Imaging (CT or MRI)47,731 (10.4)CT only28,361 (6.2)MRI only14,864 (3.2)CT and MRI4,506 (1.0)Intracranial injury12,289 (2.7)Subdural hemorrhage2,154 (0.5)Brain edema1,250 (0.3)Other intracranial injury6,533 (1.4)Neurosurgery3,047 (0.7)EVD1,060 (0.2)Evacuation of hematoma1,312 (0.3)DC627 (0.1)Combinations of neurosurgery362 (0.1)DC + evacuation of hematoma139 (0.0)EVD + DC362 (0.1)DC + evacuation of hematoma146 (0.0)Visceral surgery1,062 (0.2)Seizures*3,563 (0.8)Epileptic state223 (0.0)Complication(s)1,468 (0.5)		
median (10th and 90th percentiles)]         6 (0-16)           Length of stay [mean ± SD         2 ± 3.9           median (10th and 90th percentiles)]         2 (1-2)           Mechanical ventilation         3,184 (0.7)           Mechanical ventilation (hours)         [mean ± SD           [mean ± SD         120.4 ± 247.2           median (10th and 90th percentiles)]         22 (2-352)           Died         447 (0.1)           Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         3,623 (1.4)           Visceral		, , , ,
Length of stay [mean ± SD         2 ± 3.9           median (10th and 90th percentiles)]         2 (1-2)           Mechanical ventilation         3,184 (0.7)           Mechanical ventilation (hours)         [mean ± SD           [meadian (10th and 90th percentiles)]         22 (2-352)           Died         447 (0.1)           Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         2,436 (0.5)           Subdural hemorrhage         2,436 (0.5)           Subdural hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC	0	
median (10th and 90th percentiles)]         2 (1–2)           Mechanical ventilation         3,184 (0.7)           Mechanical ventilation (hours)         120.4 ± 247.2           median (10th and 90th percentiles)]         22 (2-352)           Died         447 (0.1)           Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,154 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral		
Mechanical ventilation (hours)         120.4 ± 247.2           median (10th and 90th percentiles)]         22 (2-352)           Died         447 (0.1)           Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,154 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           DC + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0	0 , 1	
[mean $\pm$ SD120.4 $\pm$ 247.2median (10th and 90th percentiles)]22 (2-352)Died447 (0.1)Resuscitation266 (0.1)Loss of consciousness64,692 (14.1)Imaging (CT or MRI)47,731 (10.4)CT only28,361 (6.2)MRI only14,864 (3.2)CT and MRI4,506 (1.0)Intracranial injury12,289 (2.7)Subdural hemorrhage4,314 (0.9)Epidural hemorrhage2,436 (0.5)Subarachnoidal hemorrhage2,154 (0.5)Brain edema1,250 (0.3)Other intracranial injury6,533 (1.4)Neurosurgery3,047 (0.7)EVD1,060 (0.2)Evacuation of hematoma1,312 (0.3)DC627 (0.1)Combinations of neurosurgery362 (0.1)DC + evacuation of hematoma139 (0.0)EVD + DC362 (0.1)DC + evacuation of hematoma146 (0.0)Visceral surgery1,062 (0.2)Seizures*3,563 (0.8)Epileptic state223 (0.0)Complication(s)1,468 (0.5)	Mechanical ventilation	3,184 (0.7)
Initial and a second	Mechanical ventilation (hours)	
Died         447 (0.1)           Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           DC + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	[mean $\pm$ SD	
Resuscitation         266 (0.1)           Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	median (10th and 90th percentiles)]	22 (2–352)
Loss of consciousness         64,692 (14.1)           Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           DC + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Died	447 (0.1)
Imaging (CT or MRI)         47,731 (10.4)           CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Resuscitation	266 (0.1)
CT only         28,361 (6.2)           MRI only         14,864 (3.2)           CT and MRI         4,506 (1.0)           Intracranial injury         12,289 (2.7)           Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Loss of consciousness	64,692 (14.1)
MRI only       14,864 (3.2)         CT and MRI       4,506 (1.0)         Intracranial injury       12,289 (2.7)         Subdural hemorrhage       4,314 (0.9)         Epidural hemorrhage       2,436 (0.5)         Subarachnoidal hemorrhage       2,154 (0.5)         Brain edema       1,250 (0.3)         Other intracranial injury       6,533 (1.4)         Neurosurgery       3,047 (0.7)         EVD       1,060 (0.2)         Evacuation of hematoma       1,312 (0.3)         DC       627 (0.1)         Combinations of neurosurgery       362 (0.1)         DC       362 (0.1)         DC+ evacuation of hematoma       139 (0.0)         EVD + DC       362 (0.1)         DC + evacuation of hematoma       146 (0.0)         Visceral surgery       1,062 (0.2)         Seizures*       3,563 (0.8)         Epileptic state       223 (0.0)         Complication(s)       1,468 (0.5)	Imaging (CT or MRI)	47,731 (10.4)
CT and MRI       4,506 (1.0)         Intracranial injury       12,289 (2.7)         Subdural hemorrhage       4,314 (0.9)         Epidural hemorrhage       2,436 (0.5)         Subarachnoidal hemorrhage       2,154 (0.5)         Brain edema       1,250 (0.3)         Other intracranial injury       6,533 (1.4)         Neurosurgery       3,047 (0.7)         EVD       1,060 (0.2)         Evacuation of hematoma       1,312 (0.3)         DC       627 (0.1)         COmbinations of neurosurgery       362 (0.1)         EVD + evacuation of hematoma       139 (0.0)         EVD + DC       362 (0.1)         DC + evacuation of hematoma       146 (0.0)         Visceral surgery       1,062 (0.2)         Seizures*       3,563 (0.8)         Epileptic state       223 (0.0)         Complication(s)       1,468 (0.5)	CT only	28,361 (6.2)
Intracranial injury         12,289 (2.7)           Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	MRI only	14,864 (3.2)
Subdural hemorrhage         4,314 (0.9)           Epidural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         362 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	CT and MRI	4,506 (1.0)
Epidural hemorrhage         2,436 (0.5)           Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         862 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Intracranial injury	12,289 (2.7)
Subarachnoidal hemorrhage         2,154 (0.5)           Brain edema         1,250 (0.3)           Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         802 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Subdural hemorrhage	4,314 (0.9)
Brain edema       1,250 (0.3)         Other intracranial injury       6,533 (1.4)         Neurosurgery       3,047 (0.7)         EVD       1,060 (0.2)         Evacuation of hematoma       1,312 (0.3)         DC       627 (0.1)         Combinations of neurosurgery       627 (0.1)         EVD + evacuation of hematoma       139 (0.0)         EVD + evacuation of hematoma       139 (0.0)         EVD + DC       362 (0.1)         DC + evacuation of hematoma       146 (0.0)         Visceral surgery       1,062 (0.2)         Seizures*       3,563 (0.8)         Epileptic state       223 (0.0)         Complication(s)       1,468 (0.5)	Epidural hemorrhage	2,436 (0.5)
Other intracranial injury         6,533 (1.4)           Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         627 (0.1)           Combinations of neurosurgery         139 (0.0)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Subarachnoidal hemorrhage	2,154 (0.5)
Neurosurgery         3,047 (0.7)           EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         627 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Brain edema	1,250 (0.3)
EVD         1,060 (0.2)           Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         1           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Other intracranial injury	6,533 (1.4)
Evacuation of hematoma         1,312 (0.3)           DC         627 (0.1)           Combinations of neurosurgery         627 (0.1)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Neurosurgery	3,047 (0.7)
DC         627 (0.1)           Combinations of neurosurgery         139 (0.0)           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	EVD	1,060 (0.2)
Combinations of neurosurgery           EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Evacuation of hematoma	1,312 (0.3)
EVD + evacuation of hematoma         139 (0.0)           EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	DC	627 (0.1)
EVD + DC         362 (0.1)           DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Combinations of neurosurgery	
DC + evacuation of hematoma         146 (0.0)           Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	EVD + evacuation of hematoma	139 (0.0)
Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	EVD + DC	362 (0.1)
Visceral surgery         1,062 (0.2)           Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	DC + evacuation of hematoma	146 (0.0)
Seizures*         3,563 (0.8)           Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)	Visceral surgery	
Epileptic state         223 (0.0)           Complication(s)         1,468 (0.5)		
Complication(s) 1,468 (0.5)	Epileptic state	
	Early transfer to other hospital	2,408 (0.3)

TBI, traumatic brain injury; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging; EVD, external cerebrospinal fluid drainage and/or invasive ICP monitoring; DC, decompressive craniectomy; <sup>\*</sup> including any epilepsia.

2011–2020 (10), and the U.S. Standard Population 2000 (11) were used for direct age standardization.

### **Primary and Secondary End Points**

The unit of analysis was hospital admission for/with TBI. We calculated crude and age-specific incidence rates and standardized incidence rates for TBI-associated hospitalizations, in-hospital mortality, diagnostic imaging (in the emergency department and during the hospital stay), intracranial injuries,



neurosurgery, visceral surgery, and complications in patients with TBI.

## **Missing Data**

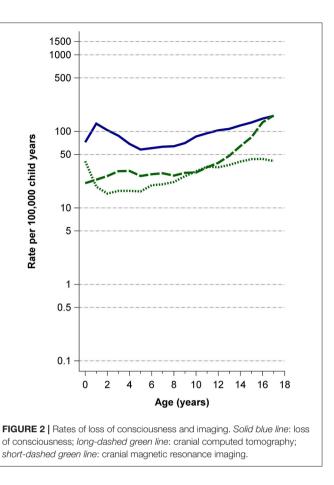
There were no missing data on age and primary diagnoses. Missing data on secondary diagnoses and procedures were impossible to detect as we could not distinguish whether the diagnosis was not present or whether the diagnosis was just not coded. We assumed that all diagnoses and procedures that are well-reimbursed were comprehensively coded and focussed on these codes for data extraction.

### Software

All calculations were carried out using SAS release 9.4 and SAS Enterprise Guide 7.1 (SAS Institute, Cary, North Carolina, USA).

# RESULTS

Out of 10,244,649 million hospitalizations < 18 years of age, we identified 458,844 cases with TBI as primary or secondary diagnosis. TBI was the primary diagnosis in 418,603 cases (91.2%, crude incidence rate 687/100,000 child years) (**Table 1**). Male patients accounted for 254,032 cases (55.4%) and predominated at all ages except at 14 and 15 years (**Supplementary Table 2**).



The median age was 6 years (10th and 90th percentiles: 0 and 16 years) and the median duration of hospital stay was 2 days (10th and 90th percentiles: 1 and 2 days). Three thousand one hundred eighty-four cases (0.7%, 5/100,000 child years) received mechanical ventilation with a median duration of 22 h (10th and 90th percentiles: 2 and 352 h).

Case numbers and incidence rates of all variables varied substantially across ages [Supplementary Table 2 and raw data file at Mendeley Data (12)]. In general, case numbers and age-specific rates were highest among infants and adolescents for hospitalization due to TBI, loss of consciousness, intracranial injury, neurosurgery, and mortality (Figures 1, 2). Hospitalization rates were highest for infants during the first year of life with 1,457/100,000 child years. Imaging by computed tomography was rarely performed up to the age of 10 years and showed a marked increase starting at age 11 (Figure 2; Supplementary Table 2). Imaging (CT/MRI) was performed in 10.4%, intracranial injury was diagnosed in 2.7%, and neurosurgery performed in 0.7% (Table 1). The age-specific incidence rates of visceral surgery increased with age but were generally very low (n = 1,062, overall rate 0.2%) (Table 1; Supplementary Table 2). Agestandardized incidence rates for all variables are presented in Table 2.

#### TABLE 2 | Crude and standardized incidence rates.

		Incidence rates (/100,000 person years) and 95% confidence intervals				
	Crude	Standardized				
		WHO 2020 standard population	European standard population	U.S. standard population		
TBI hospitalizations	687.1	689.2 (687.2–691.2)	688.0 (686.0–690.0)	681.7 (679.8–683.7)		
TBI main diagnosis	626.8	629.7 (627.8-631.6)	628.4 (626.5–630.3)	622.5 (620.6-624.4)		
Male	739.4					
Female	631.7					
Mechanical ventilation	4.8	4.7 (4.5–4.8)	4.7 (4.5–4.8)	4.6 (4.5-4.8)		
Mortality	0.67	0.65 (0.59–0.71)	0.66 (0.60–0.72)	0.65 (0.59–0.71)		
Resuscitation	0.39	0.39 (0.35–0.44)	0.39 (0.35–0.44)	0.39 (0.34–0.43)		
Loss of consciousness	96.9	95.5 (94.7–96.2)	95.7 (94.9–96.4)	95.4 (94.6 - 96.1)		
Intracranial injury	18.4	18.2 (17.9–18.6)	18.2 (17.9–18.6)	18.0 (17.7–18.4)		
Subdural hemorrhage	6.5	6.4 (6.2–6.6)	6.4 (6.2–6.6)	6.3 (6.1-6.5)		
Epidural hemorrhage	3.6	3.6 (3.5–3.8)	3.6 (3.5–3.8)	3.6 (3.5–3.7)		
Subarachnoidal hemorrhage	3.2	3.1 (3.0–3.3)	3.2 (3.0–3.3)	3.1 (3.0–3.3)		
Brain edema	1.9	1.8 (1.7–1.9)	1.8 (1.7–1.9)	1.8 (1.7–1.9)		
Other intracranial injury	9.8	9.7 (9.4–9.9)	9.7 (9.4–9.9)	9.6 (9.4–9.8)		
Neurosurgery	4.6	4.5 (4.3–4.6)	4.5 (4.3–4.6)	4.4 (4.3-4.6)		
EVD	1.6	1.6 (1.5–1.6)	1.6 (1.5–1.7)	1.5 (1.5–1.6)		
Evacuation of hematoma	2.0	1.9 (1.8–2.1)	1.9 (1.8–2.1)	1.9 (1.8–2.0)		
DC	0.94	0.92 (0.85–0.99)	0.92 (0.85–0.99)	0.91 (0.84–0.99)		
Visceral surgery	1.6	1.5 (1.4–1.6)	1.5 (1.4–1.6)	1.5 (1.4–1.6)		
Imaging	71.5	69.2 (68.6–69.9)	69.7 (69.1–70.3)	69.5 (68.8–70.1)		
CT only	42.5	40.7 (40.2–41.2)	41.1 (40.6–41.6)	40.8 (40.3-41.3)		
MRI only	22.3	21.9 (21.6–22.3)	22.0 (21.6- 22.3)	22.1 (21.7-22.4)		
CT and MRI	6.7	6.6 (6.4–6.8)	6.6 (6.4–6.8)	6.6 (6.4–6.8)		
Seizures*	5.3	5.3 (5.1–5.4)	5.3 (5.1–5.4)	5.3 (5.1–5.4)		
Epileptic state	0.33	0.33 (0.29–0.38)	0.33 (0.29–0.38)	0.32 (0.28-0.37)		

TBI, traumatic brain injury; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging; EVD, external cerebrospinal fluid drainage and/or invasive ICP monitoring; DC, decompressive craniectomy; 'including any epilepsy.

# DISCUSSION

In this population-based nation-wide study on pediatric TBI, Germany has high hospitalization rates compared to international data (1, 4). Our findings with respect to age and sex distribution concur with published data: Infants had the highest incidence rates of hospitalization for TBI, and males clearly predominated at almost all ages. The rates of imaging, the need for mechanical ventilation, neurosurgery and mortality were overall very low, with highest rates in infants and adolescents. Rates of computed tomography were very low, continuously rising during adolescence.

Mortality, intracranial injuries, neurosurgery, and complications occurred in only a small fraction of patients. While the incidence rates of hospitalizations for TBI in adolescents align with the rates reported for the entire German population, mortality in the pediatric subset was very low compared to the previously published population-wide mortality (2). However, our finding is limited by the fact that it does not include pre-hospital deaths, which account for up to 88% of TBI-related deaths in children (13). The high hospitalization rates and low rates of TBI-related morbidity in our study suggest that not all admitted patients may have required a hospital stay. We assume that computed tomography was avoided at the cost of hospitalizations and patient observation to clinically rule out serious head injury. This inevitably leads to the question of how to identify patients at need for monitoring without hospitalizing healthy children or exposing them to unwarranted radiation.

Several studies tried to account for this dilemma by establishing clinical rules to guide imaging practice. Among three of the most relevant rules (CHALICE, CATCH, and PECARN), PECARN performed best at ruling out clinically important TBI (14–18). In a prospective multicentre validation study, 5.1% of patients attending the emergency department after head trauma had imaging performed and 0.6% of all patients were diagnosed with clinically important TBI (19). The sensitivity for the detection of clinically important TBI was 100% with a specifity of 70%. Even more importantly, the negative predictive value was 100% (19). By ruling out clinically important TBI, the PECARN rule can help to reduce imaging rates. We assume that applying this rule could reassure physicians and parents of children classified into the very low risk group, thereby also lowering hospitalization rates and reducing the social and economic burdens of unwarranted hospitalizations.

However, an approach like the PECARN rule will be difficult to implement in Germany, because the current German DRG system drives hospitals to admit their patients for at least one or two nights to avoid cuts in reimbursement. An additional source leading to hospitalizations may be the lack of a valid German guideline on pediatric TBI and vague criteria for hospitalization after head injury in the expired guideline (20). In the future, clearly phrased criteria for hospitalization after head injury and advances in neuroimaging, like e.g., rapid sequence MRI, could help to identify patients with no need for a hospital stay.

Our study has several limitations owed to the lack of clinical information provided in the DRG data set. Due to the lack of exact information on the causes for admission and death, we likely overestimated these rates. The duration of hospital stay due to TBI may have been shorter than estimated in this study. However, the strength of this study is its comprehensiveness. We analyzed population-based data on TBI-related hospitalizations of children during the 5-year-study period, thereby completely ruling out selection bias and providing nation-wide representative data for Germany.

This study addresses one of the key clinical research needs in the field of pediatric TBI by providing nation-wide comprehensive data on hospitalizations and TBI-related morbidity in Germany. It further provides evidence that hospitalization rates for TBI in Germany were higher in children compared to other countries inside and outside of Europe, with very low rates of mechanical ventilation, intracranial injury, neurosurgery, and mortality. Our data highlight the need to clarify whether TBI-related hospitalizations are determined by actual need for treatment or by reimbursement-related reasons. It should be further explored if there is the potential for quality improvement in the German health care system to reduce a higher than needed hospitalization rate.

## REFERENCES

- Dewan MC, Mummareddy N, Wellons JC, Bonfield CM. Epidemiology of global pediatric traumatic brain injury: qualitative review. *World Neurosurg.* (2016) 91:497–509.e1. doi: 10.1016/j.wneu.2016.03.045
- Majdan M, Plancikova D, Brazinova A, Rusnak M, Nieboer D, Feigin V, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *Lancet Public Health.* (2016) 1:e76–e83. doi: 10.1016/S2468-2667(16)30017-2
- 3. Langlois JA, Rutland-Brown W, Thomas KE. The incidence of traumatic brain injury among children in the United States: differences by race. *J Head Trauma Rehabil.* (2005) 20:229–38. doi: 10.1097/00001199-200505000-00006
- Bowman SM, Bird TM, Aitken ME, Tilford JM. Trends in hospitalizations associated with pediatric traumatic brain injuries. *Pediatrics*. (2008) 122:988– 93. doi: 10.1542/peds.2007-3511
- Nacoti M, Fazzi F, Biroli F, Zangari R, Barbui T, Kochanek PM, et al. Addressing key clinical care and clinical research needs in severe pediatric traumatic brain injury: perspectives from a focused international conference. *Front Pediatr.* (2020) 8:594425. doi: 10.3389/fped.2020. 594425

# DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: the original dataset can be accessed after inquiry to the Federal Bureau of Statistics of Germany. Requests to access these datasets should be directed to https://www.forschungsdatenzentrum.de/de.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

# AUTHOR CONTRIBUTIONS

AS, CD-S, and NB: study design. AS, CD-S, NB, and PT: statistical calculations and verification. NB: drafting of the manuscript. AS, CD-S, NB, PT, and UF-M: critical review and editing of the manuscript. All authors contributed to the article and approved the submitted version.

# FUNDING

NB received an internal research grant from the Medical Faculty of the University of Duisburg-Essen (IFORES) and a grant from the Stiftung Universitätsmedizin Essen that enabled the conduction of this work.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped. 2021.747743/full#supplementary-material

- Stang A, Katalinic A, Dieckmann K-P, Pritzkuleit R, Stabenow R, Network of German Cancer Registries (GEKID). A novel approach to estimate the German-wide incidence of testicular cancer. *Cancer Epidemiol.* (2010) 34:13– 9. doi: 10.1016/j.canep.2009.11.007
- Stang A, Stausberg J. Inpatient management of patients with skin cancer in Germany: an analysis of the nationwide DRGstatistic 2005-2006. Br J Dermatol. (2009) 161 (Suppl. 3):99– 106. doi: 10.1111/j.1365-2133.2009.09457.x
- Walendy V, Strauss C, Rachinger J, Stang A. Treatment of aneurysmal subarachnoid haemorrhage in Germany: a nationwide analysis of the years 2005-2009. *Neuroepidemiology*. (2014) 42:90–7. doi: 10.1159/000355843
- Ahmad OB, Boshi-Pinto C, Lopez AD. Age-Standardization of Rates. A New WHO Standard—GPE Discussion Paper Series: n. 31. Geneva: World Health Organization (2001).
- 10. Eurostat. Revision of the European Standard Population. Luxembourg: Eurostat (2013).
- Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. *Natl Vital Stat Rep.* (1998) 47:1– 16–20.

- Bruns N, Trocchi P, Felderhoff-Müser U, Dohna-Schwake C, Stang A. Dataset

   Hospitalisations and morbidities after paediatric traumatic brain injury in Germany. *Mendeley Data*. (2021). doi: 10.17632/bdkbc7w8nk.1
- Kuppermann N, Holmes JF, Dayan PS, Hoyle JD, Atabaki SM, Holubkov R, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. *Lancet.* (2009) 374:1160–70. doi: 10.1016/S0140-6736(09)61558-0
- Olsen M, Vik A, Lund Nilsen TI, Uleberg O, Moen KG, Fredriksli O, et al. Incidence and mortality of moderate and severe traumatic brain injury in children: a ten year population-based cohort study in Norway. *Eur J Paediatr Neurol.* (2019) 23:500–6. doi: 10.1016/j.ejpn.2019.01.009
- Dunning J, Daly JP, Lomas J-P, Lecky F, Batchelor J, Mackway-Jones K, et al. Derivation of the children's head injury algorithm for the prediction of important clinical events decision rule for head injury in children. Arch Dis Childhood. (2006) 91:885–91. doi: 10.1136/adc.2005. 083980
- Osmond MH, Klassen TP, Wells GA, Correll R, Jarvis A, Joubert G, et al. CATCH: a clinical decision rule for the use of computed tomography in children with minor head injury. *CMAJ.* (2010) 182:341–8. doi: 10.1503/cmaj.091421
- Babl FE, Borland ML, Phillips N, Kochar A, Dalton S, McCaskill M, et al. Accuracy of PECARN, CATCH, and CHALICE head injury decision rules in children: a prospective cohort study. *Lancet.* (2017) 389:2393– 402. doi: 10.1016/S0140-6736(17)30555-X
- Easter JS, Bakes K, Dhaliwal J, Miller M, Caruso E, Haukoos JS. Comparison of PECARN, CATCH, and CHALICE rules for children with minor head injury: a prospective cohort study. *Ann Emerg Med.* (2014) 64:145–52–152.e1– 5. doi: 10.1016/j.annemergmed.2014.01.030

- Lorton F, Poullaouec C, Legallais E, Simon-Pimmel J, Chêne MA, Leroy H, et al. Validation of the PECARN clinical decision rule for children with minor head trauma: a French multicenter prospective study. *Scand J Trauma Resusc Emerg Med.* (2016) 24:98–8. doi: 10.1186/s13049-016-0287-3
- Jorch G, Kieslich M, Firsching R, Skalej M, Alzen G, Schreiber M, et al. Leitlinie "Das Schädel-Hirn-Trauma im Kindesalter." Available at: https://www.awmf.org/uploads/tx\_szleitlinien/024-018l\_S2k\_Schaedel-Hirn-Trauma\_im\_Kindesalter-2011-abgelaufen.pdf (accessed June 18, 2021).

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Bruns, Trocchi, Felderhoff-Müser, Dohna-Schwake and Stang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.