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CLINICAL ARTICLE

Prehospital and emergency management of pediatric traumatic brain injury: a multicenter site survey

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OBJECTIVE There is a paucity of information on pediatric traumatic brain injury (TBI) care in Asia and Latin America. In this study, the authors aimed to describe the clinical practices of emergency departments (EDs) participating in the Saline in Asia and Latin-America Neurotrauma in the Young (SALTY) study, by comparing designated trauma centers (DTCs) and nontrauma centers (NTCs) in their networks.

METHODS The authors performed a site survey study on pediatric TBI management in the EDs in 14 countries. Two European centers joined other participating sites in Asia and Latin America. Questions were formulated after a critical review of current TBI guidelines and published surveys. The authors performed a descriptive analysis and stratified centers based on DTC status.

RESULTS Of 24 responding centers (70.6%), 50.0% were DTCs, 70.8% had academic affiliations, and all centers were in urban settings. Patients were predominantly transferred to DTCs by centralized prehospital services compared to those sent to NTCs (83.3% vs 41.7%, p = 0.035). More NTCs received a majority of their patients directly from the trauma scene compared to DTCs (66.7% vs 25.0%, p = 0.041). Ten centers (41.7%) reported the use of a TBI management guideline, and 15 (62.5%) implemented CT protocols. Ten DTCs reported implementation of intervention strategies for suspected raised intracranial pressure (ICP) before conducting a CT scan, and 6 NTCs also followed this practice (83.3% vs 50.0%, p = 0.083). ED management for children with TBI was comparable between DTCs and NTCs in the following aspects: neuroimaging, airway management, ICP monitoring, fluid resuscitation, anticoagulant therapy, and serum glucose control. Hyperventilation therapy for raised ICP was used by 33.3% of sites.

CONCLUSIONS This study evaluated pediatric TBI management and infrastructure among 24 centers. Limited differences in prehospital care and ED management for pediatric patients with TBI were observed between DTCs and NTCs. Both DTCs and NTCs showed variation in the implementation of current TBI management guidelines. There is an urgent need to investigate specific barriers to guideline implementation in these regions.

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KEYWORDS pediatric; traumatic brain injury; prehospital; emergency department; guideline; Asia; Latin America

ABBREVIATIONS BTF = Brain Trauma Foundation; DTC = designated trauma center; ED = emergency department; GCS = Glasgow Coma Scale; ICP = intracranial pressure; IQR = interquartile range; LARed = Red Colaborativa Pediátrica de Latinoamerica; LICs = low-income countries; LMICs = lower-middle-income countries; NTC = nontrauma center; PACCMAN = Pediatric Acute & Critical Care Medicine Asian Network; PICU = pediatric ICU; TBI = traumatic brain injury.

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Traumatic brain injury (TBI) is a common cause of death and disability worldwide.[1] Globally, pediatric TBI is reported to occur in between 47 and 280 per 100,000 children.[2,3] In particular, children with moderate to severe TBI may have poor functional outcomes, experience neurocognitive delays, and depend on their caregivers for activities of daily living, placing a significant burden on individuals, families, and communities.[2,3]

Timely and effective acute care of children with TBI is of vital importance. In 2003 the Brain Trauma Foundation (BTF) developed an evidence-based guideline to streamline the management of pediatric TBI, and subsequently updated the guideline in 2012 and 2019.[4] The implementation of protocols was associated with a reduction in patient mortality and morbidity.[5,6] A retrospective cohort study of 236 children in 2014 reported a 1% decrease in the risk of poor functional outcomes for every 1% increase in adherence to the BTF Pediatric TBI Guidelines.[6] However, protocol implementation and compliance rates vary due to guideline applicability, providers' culture, and institutional strategies for implementation.[7]

Most of these studies were conducted in North American and European countries; few have investigated TBI management in Asian and Latin American countries, particularly in the pediatric population. Although regional epidemiology data are limited, pediatric TBI is prevalent in Latin America and Southeast Asia, with estimated TBI incidences of 909 and 948 per 100,000 people, respectively.[8] A previous Argentinian study of 117 children with severe TBI that was published in 2017 reported that adherence to best TBI practices ranged from 55.6% to 83.7% across 7 centers.[9]

There is an urgent need to understand current practices and the extent of guideline implementation in these regions. Therefore, we aimed to describe the infrastructure and practices of pediatric TBI management in emergency departments (EDs) participating in the Saline in Asia and Latin-America Neurotrauma in the Young (SALTY) study. In addition, we sought to compare practices between designated trauma centers (DTCs) and nontrauma centers (NTCs) in our network. Finally, we aimed to assess reported compliance with current pediatric TBI management guidelines among participating centers.

Methods

Study Design and Inclusion Criteria

We performed a multicenter site survey study among participating centers from two established pediatric intensive care unit (PICU) research networks: Pediatric Acute & Critical Care Medicine Asian Network (PACCMAN) and Red Colaborativa Pediátrica de Latinoamerica (LARed Network).[10,11] Two sites in Spain joined this study as parts of the LARed Network. This study was approved first in the coordinating center in Singapore (SingHealth Centralized Institutional Review Board) and subsequently in each respective center according to local ethics requirements.

Within these networks, centers with a neurosurgical service and a PICU service available for managing pediatric patients with TBI were selected and invited to participate in this study. The presence and availability of neurorehabilitation services were not mandatory for sites to be included in this study.

Survey Design

We designed survey questions surrounding institution infrastructure and ED management. We also studied international and regional guidelines (including those of the BTF) and publicly available TBI questionnaires.[5,12,13] We created both multiple-choice and open-ended questions. Where available, we requested that site protocols be attached. Feedback from key members of each network was sought before finalization. Patients or the public were not appropriate or allowed to be involved in the design, conduct, reporting, or dissemination plans of the study.

We designed 14 questions focused on aspects of hospital capacity and infrastructure (Online Appendix 1). A center was defined as a DTC if it specifically catered to children with pediatric trauma in their local region and could receive injured pediatric patients transferred from other centers.[14] The final designation of DTC status for analysis was based on local practices, and site investigators were asked to determine if their site was a DTC. Infrastructure and capacity of sites were measured by the number of inpatient pediatric beds, operating theaters, and resuscitation bays, as well as access to dedicated children's EDs and around-the-clock (i.e., 24 hours/day, 7 days/week) availability of both surgical care and CT services. Specialties involved in TBI care and their around-the-clock availability were assessed, including pediatric intensivists, anesthetists, emergency medicine physicians, pediatric physicians, pediatricians, neurologists, neurorehabilitation physicians, general surgeons, trauma surgeons, neurosurgeons, and orthopedic surgeons.

Forty-seven questions that focused on aspects of ED management were created (Online Appendix 2). Major domains included prehospital management, ED characteristics, neuroimaging at ED, airway management, intracranial pressure (ICP) monitoring, fluid resuscitation, anticoagulant therapy, and serum glucose control.

Survey Distribution and Completion

Surveys were created and distributed using Google Forms (Online Form Creator, Google Workspace, released 2008; Google LLC) and were open for submission from May 17, 2022, to June 10, 2022. We invited site principal investigators to participate, and we specified that where necessary and for data accuracy, the ED chief or the medical director from their organizations should be involved in answering questions on pediatric TBI ED management and hospital infrastructure, respectively.

Statistical Analysis

Continuous variables were described with median and interquartile range (IQR) values, depending on normality, and categorical variables were assessed using frequencies and percentages. We stratified the descriptive analysis by DTC status. Measures of association were obtained using the t-test or Wilcoxon rank-sum test (depending on normality) for continuous data and the chi-square test for dichotomous and categorical data. Statistical significance

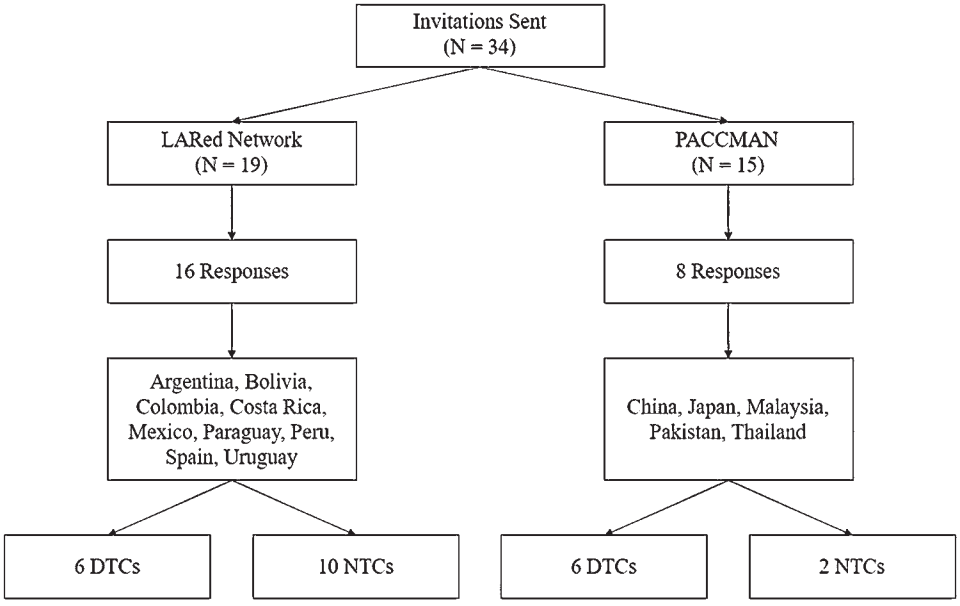

FIG. 1. Survey completion flowchart: responding rates and countries.

was taken at $p < 0.05$. Statistical analysis was performed using SPSS software (SPSS Statistics for Windows, version 26.0, released 2019; IBM Corp.).

Results

Participating Sites

Thirty-four sites fulfilled the inclusion criteria and were invited to participate in this study, among which 24 (70.6%) completed the ED management questionnaire (Fig. 1). The surveys were predominantly completed by pediatric intensivists who were the site principal investigators (19/24, 79.2%).

Description of Centers and Capabilities

Of the 24 responding sites, 8 centers were from Asia, 14 centers were from Latin America, and 2 centers were from Europe (Fig. 2). Twelve centers (50.0%) were DTCs (Table 1). DTCs reported having significantly more resuscitation bays compared to their counterparts (median 5, IQR 2–11 vs median 2, IQR 1–3; $p = 0.003$). We did not find significant differences between DTCs and NTCs

FIG. 2. Map showing participating site locations (*gray bubbles*). Numbers represent the number of sites in one location. ATLIST. https://my.atlistmaps.com/map/453b3678-bb2d-45b0-b1c2-cfc9f8a71e53. [Accessed January 10, 2023.]

TABLE 1. Characteristics of participating DTCs and NTCs

Characteristic	DTCs, n = 12	NTCs, n = 12	p Value
Academic affiliation	10 (83.3)	7 (58.3)	0.346
Urban setting; vs rural setting	12 (100)	12 (100)	NA
Children's hospital; vs nonchildren's hospital	6 (50.0)	8 (66.7)	0.408
Most common rescue vehicles			
Centralized hospital ambulance	10 (83.3)	5 (41.7)	0.035*
Private ambulance	3 (25.0)	6 (50.0)	0.206
Dedicated children's ED	12 (100)	11 (91.7)	0.307
ED observation unit	12 (100)	10 (83.3)	0.140
No. of resuscitation bays per site, median (IQR)	5 (2–11)	2 (1–3)	0.003*
No. of sites w/ 24/7 emergency op theaters	12 (100)	12 (100)	NA
No. of sites w/ 24/7 op theaters w/ staffing	10 (83.3)	12 (100)	0.140
No. of sites w/ 24/7 CT technicians/radiographers	11 (91.7)	11 (91.7)	>0.99
2019 ED attendance for all children, median (IQR)	27,318 (1444–74,339), n = 10	9587 (3453–11,525), n = 9	0.278
2019 ED attendance for children w/ TBI, median (IQR)	100 (35–3038), n = 9	140 (26–314), n = 10	0.843

NA = not applicable.
Values are expressed as number of EDs (%) or the median (IQR) among sites. Children were defined as being < 18 years old. Unless otherwise specified, there were no missing data.
* Statistically significant at $p < 0.05$.

in the type of available specialists and their around-the-clock availability.

Prehospital Management

Patients were predominantly transferred to DTCs by centralized prehospital services (10/12, 83.3% vs 5/12, 41.7%; p = 0.035) compared to NTCs. Although fewer children were transported via private ambulances to DTCs when compared to NTCs, this was not statistically significant (3/12, 25.0% vs 6/12, 50.0%; p = 0.206). Overall, emergency medical technicians trained in basic cardiac life support (14/24, 58.3%), nurses (13/24, 54.2%), and nonspecialists (11/24, 45.8%) were commonly reported as rescue personnel, with lesser involvement of specialists in either group (4/12 DTC, 33.3% vs 4/12 NTC, 33.3%; p > 0.99). More NTCs received their patients directly from the field, compared to DTCs (8/12, 66.7% vs 3/12, 25.0%; p = 0.041). There was no statistically significant difference in target time between the call for help and the arrival of rescue personnel between DTCs and NTCs. Eight hospitals (33.3%) reported no target time, including 5 DTCs (41.7%). Advanced prehospital procedures like chest tube placement, cardioversion, and administration of drugs were performed more commonly for patients who arrived at DTCs, but these findings were not statistically significant (p = 0.590, 0.795, and 0.827, respectively) (Fig. 3). No respondent indicated the utilization of hyperventilation in prehospital management.

ED Management

Ten DTCs reported that they would intervene for suspected raised ICP before conducting a CT scan, and 6 NTCs also follow this practice (83.3% vs 50.0%, p = 0.083). At a Glasgow Coma Scale (GCS) score of 9–12, more DTCs tended to initiate measures for raised ICP, compared to NTCs (5/12, 41.7% vs 1/10, 10.0%; p = 0.097), whereas all NTCs would initiate such measures for patients with a GCS score < 8 (Table 2). There was no statistically significant difference in the use of hyperosmolar agents for raised ICP between DTCs and NTCs. Approximately half of the participating DTCs (5/11, 45.5%) indicated using hyperventilation for managing raised ICP, whereas only 3 NTCs (3/8, 37.5%, p = 0.736) followed the same practice.

Guideline Implementation

Of the 24 participating sites, less than half of DTCs and NTCs (6/12, 50.0% vs 4/12, 33.3%; p = 0.408) reported following a guideline for pediatric TBI management at the ED. Overall, 54.2% of participating sites (7/12 DTCs, 53.8% vs 6/12 NTCs, 50.0%; p = 0.682) reported that pediatric patients with TBI were sent to the nearest hospital, regardless of DTC status. The Alert, Voice, Pain, Unresponsive (AVPU) scale was not universally adopted by DTCs and NTCs (7/12, 58.3% vs 5/12, 41.7%; p = 0.314) to assess patients at the trauma scene. Hyperventilation therapies were reported to be used among participating centers (5/11 DTCs, 45.5% vs 3/8 NTCs, 37.5%; p = 0.736).

Sixty-three percent of participating sites (15/24) implemented CT guidelines for pediatric patients with TBI in their ED. Common protocols included Pediatric Emergency Care Applied Research Network (PECARN) guidelines (8/24, 33.3%) and institute-specific guidelines (6/24, 25.0%).[15] DTCs and NTCs agreed on most indications for performing CT scans for verbal pediatric patients with TBI (Fig. 4). Neuroimaging was obtained more frequently in NTCs for preverbal children with a pediatric GCS score < 15 at 2 hours postinjury, compared to DTCs (7/12,

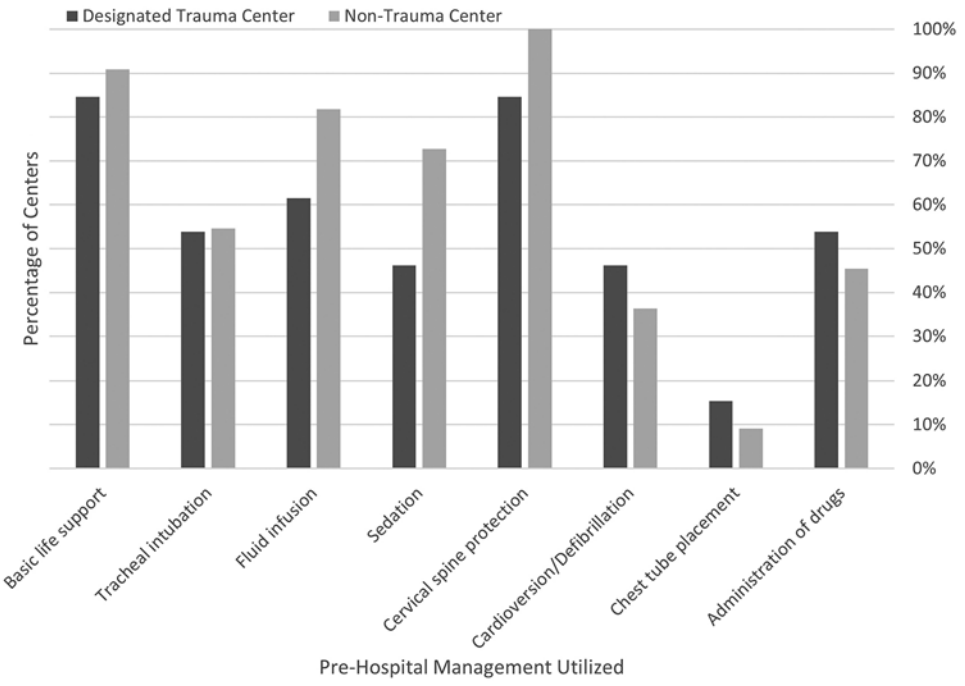

FIG. 3. Bar graph showing prehospital procedures compared between DTCs and NTCs (n = 12 each). The differences were not significant.

58.3% vs 2/12, 16.7%; p = 0.035). Among 10 centers that followed PECARN guidelines, we found that 2 centers (2/10, 20.0%) would always scan pediatric patients with TBI who had presenting GCS scores < 15, whereas the others would not.

Discussion

We performed a multicenter TBI site survey of 24 medical centers in two large pediatric networks that included countries in Asia, Europe, and Latin America. We observed variations in prehospital transportation and triaging but found limited differences between DTCs and NTCs regarding prehospital and ED management of pediatric patients with TBI. We also found similar variations from current pediatric TBI management guidelines among DTCs and NTCs.

BTF guidelines recommend that all pediatric patients in metropolitan areas should be directly transported to a pediatric DTC, if available.[12] We found that many participating NTCs in our study received patients via direct transport from the trauma scene. Our finding is in line with a study from Argentina, which reported that most patients with TBI received care at an NTC before transfer to a DTC.[16] This retrospective cohort study of 366 children also reported that 45.4% of pediatric patients with TBI were transported via private vehicles, and pointed out that the lack of centralized prehospital services in low-income countries (LICs) and lower-middle-income countries (LMICs) may contribute to patients not being triaged to DTCs.[16] Similarly, we found that among participating NTCs, more received their patients via private ambulances compared to DTCs. A prehospital system with reliable transport mechanisms, adequate medical equipment, and well-trained rescue personnel is of vital importance. There is a need for resources to be directed to strengthen prehospital trauma care globally, specifically in Asia and Latin America.[17]

A study of 324,435 pediatric TBI visits in 848 US EDs reported that NTCs were 10% less likely to perform head CT scans for children with TBI, compared to DTCs, suggesting that increased adoption of guidelines has led to a more standardized approach to CT imaging among pediatric patients with TBI.[18] Although we did not compare the prevalence of CT imaging for patients with TBI, we did find that both DTCs and NTCs had comparable indications to obtain neuroimaging. One possible explanation may be that there is an increasingly widespread uptake of imaging guidelines among both participating DTCs and NTCs. However, our data showed otherwise, and variable adherence existed even among sites with established neuroimaging guidelines, suggesting that individual physician preferences may be a major contributor to overall practices in participating centers.

A Canadian retrospective study in 34 children with severe TBI reported that more than 30% of patients with increased ICP did not receive ICP-lowering interventions before admission to a DTC, and that osmotherapy and head-of-bed elevation were the only ICP management offered at NTCs.[19] We found consistent data that more DTCs would institute measures in the ED before CT confirmation of raised ICP, compared to NTCs. Specifically, NTCs initiated measures for raised ICP among patients with a GCS score < 8, whereas many DTCs would have done so in patients with a higher GCS threshold of 9–12. We postulate that resource limitation may result in specific ther-

TABLE 2. Management at the ED

Management Detail	DTCs, n = 12	NTCs, n = 12	p Value
Indications to initiate invasive ventilation			
All pts w/ GCS score <8	12 (100)	10 (83.3)	0.140
Significantly deteriorating consciousness level*	7 (58.3)	7 (58.3)	>0.99
Posttraumatic seizure	2 (16.7)	3 (25.0)	0.615
Loss of protective laryngeal reflexes	11 (91.7)	12 (100)	0.307
Irregular respiration	10 (83.3)	10 (83.3)	>0.99
ICP monitoring & management of elevated ICP			
Measures for suspected raised ICP are instituted before CT brain scan	10 (83.3)	6 (50.0)	0.083
Indications to initiate measures for raised ICP in ED			
GCS score 9–12	5 (41.7)	1 (10.0), n = 10	0.097
GCS score <8	6 (50.0)	10 (100.0), n = 10	0.009†
Asymmetrical pupillary reaction/pupil size	11 (91.7)	8 (80.0), n = 10	0.427
Cushing's response‡	10 (83.3)	8 (80.0), n = 10	0.840
Tx for raised ICP in ED			
Head tilted up at 30°§	9 (81.8), n = 11	7 (87.5), n = 8	0.737
Hyperosmolar agents	10 (90.9), n = 11	7 (87.5), n = 8	0.811
Hyperventilation	5 (45.5), n = 11	3 (37.5), n = 8	0.736
Sedation & paralysis	7 (63.6), n = 11	6 (75.0), n = 8	0.599
Management of circulation in TBI			
Fluid management strategy; permissive hypotension vs normotension	2 (16.7)	1 (8.3)	0.537
First-line resuscitation fluids			
Crystalloids	10 (83.3)	10 (83.3)	>0.99
Colloids	0 (0)	1 (8.3)	0.307
Packed red blood cells	1 (8.3)	1 (8.3)	>0.99
Glucose monitoring			
Routine monitoring of glucose performed	11 (91.7)	12 (100)	0.307
Use of prophylactic ACT for thrombotic events			
Routine for pts w/ confirmed CT abnormalities	6 (54.5), n = 11	3 (27.3), n = 11	0.193
If surgery is indicated	3 (27.3), n = 11	2 (18.2), n = 11	0.611
Not routinely used	5 (45.5), n = 11	6 (54.5), n = 11	0.670

ACT = anticoagulant therapy; pts = patients; Tx = treatment.
Values are expressed as the number of EDs (%). Unless otherwise specified, there were no missing data.
* One or more points on the motor score, even if not in a coma.
† Statistically significant at $p < 0.05$.
‡ Hypertension, bradycardia.
§ In the absence of neck injury.

apy, such as ICP monitoring, being reserved for children with a lower GCS score in NTCs, especially in LICs and LMICs.[20] In addition, physicians in DTCs may consider other clinical factors apart from GCS scores, leading them to initiate measures in patients with higher GCS scores.[19]

Prophylactic hyperventilation as a therapy for raised ICP has not been supported by clinical evidence, and is associated with complications and poor clinical outcomes.[4,14,21,22] BTF guidelines recommend against the use of hyperventilation to a partial pressure of CO_2 in arterial blood ($PaCO_2$) of < 30 mm Hg in the initial 48 hours and suggest advance evaluation for cerebral ischemia in patients receiving prolonged hyperventilation.[4] Eight of the participating centers (33.3%) reported using this technique. This is consistent with findings in 17 European trauma centers, in which prophylactic hyperventilation was used in more than half of the patients examined, and simultaneous advance monitoring of brain tissue was only observed in 9% of patients.[21] A nationwide study in the US published in 2021 reported that TBI guidelines in 22 states recommended hyperventilation and 17 states recommended a target end-tidal capnography of < 35 mm Hg.[23] These findings call for an urgent global review of current clinical practice regarding hyperventilation.

In our study, 41.7% of our participants reported having formal TBI protocols established in their ED. Excluding European sites, 36.4% of our participants reported implementing formal TBI protocols in the ED; this is much lower than the 53.4% reported in the US.[6,24] We found no statistically significant difference in the guideline adop-

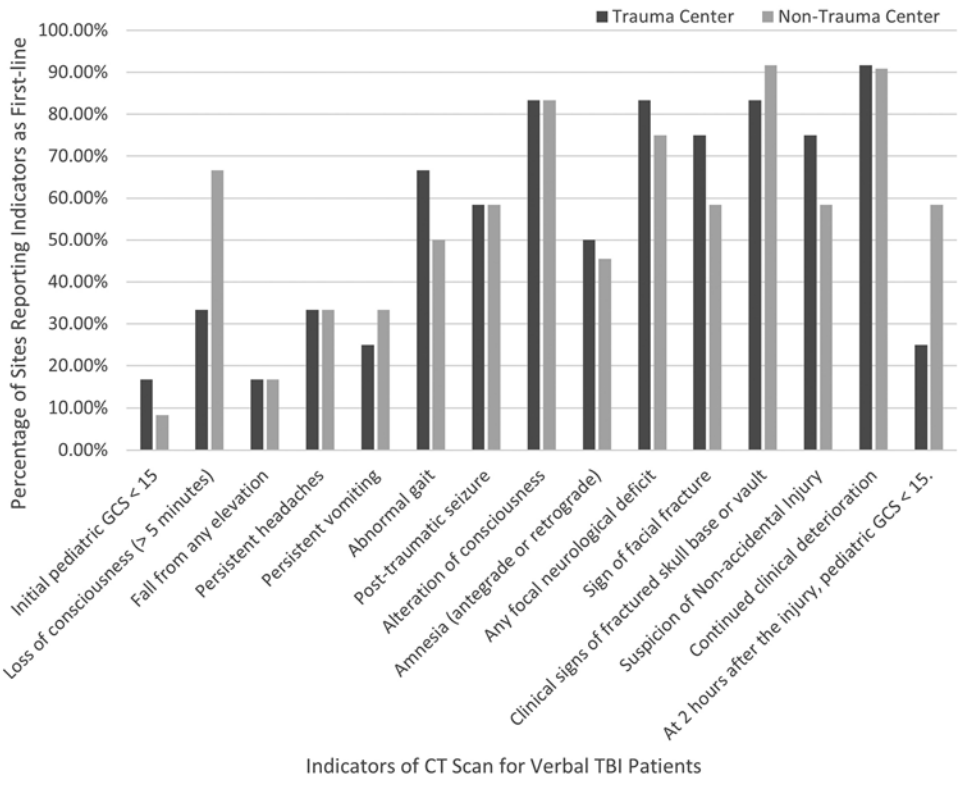

FIG. 4. Bar graph showing neuroimaging indications for verbal pediatric patients with TBI in DTC and NTC (n = 12 each) EDs.

tion rates between DTCs (40.0%) and NTCs (33.3%) in Asia and Latin America. In contrast, a retrospective US study of 413 level I and II DTCs has shown that 59.4% of level I and 36.4% of level II DTCs have implemented treatment protocols, suggesting that a trauma center designation corresponded with greater guideline adoption and adherence.[24,25] This discrepancy suggests that the uptake of TBI guidelines is still a work in progress in Asia and Latin America. Most guidelines are developed in high-income countries, and barriers to adoption and adherence exist in LICs and LMICs.[16,20] Although progress has been made in creating local guidelines based on a tiered approach,[26,27] these efforts must consider regional variations in practices and resources.[26,27]

Studies have shown that DTCs provide survival and outcome advantages for patients suffering from TBI.[28,29] Some postulate that this is due to DTCs having more access to staff and physical resources, and better implementation of management protocols.[28,29] However, we observed comparable ED capacities and infrastructures between DTCs and NTCs. Multidisciplinary teams with a wide range of specialists were available for pediatric patients with TBI in both DTCs and NTCs, in contrast to findings in other studies.[22] We acknowledge that although our survey assessed the existence of resources, we did not examine the quantity or quality of these resources. A retrospective study of 443 DTCs in the US conducted in 2014 reported more surgical specialists available in higher-level DTCs.[28] Additionally, providers' expertise may also play a significant role, because providers with a higher level of expertise are associated with lower mortality and better outcomes for patients with trauma.[30] With more access to experienced providers, DTCs may provide better care for patients than do NTCs.

This study, to our knowledge, is the first to examine pediatric TBI management in the EDs of two large networks, including countries in Asia, Europe, and Latin America. We managed to obtain information on pediatric TBI care in 24 centers. However, there are several limitations. We recognize that these centers' practices may not be representative of TBI management in Asia, Latin America, and Europe, and that future studies should recruit sites in a more systematic way to enable a comprehensive understanding of TBI care. Given that all participating hospitals are in an urban setting, we were not informed of TBI practices in rural regions. Most of the site respondents were pediatric intensivists who may not have been directly responsible for ED management. Although we specified that the hospitals' medical directors or ED chiefs should be involved to assist with the relevant information, we did not mandate the designation of the respondents. We therefore recognize that site respondents may not have complete knowledge of pediatric TBI management in their hospitals. Given that DTC status and definitions vary between countries, the final assignment of DTC status was based on local site practices and was reported accordingly. The capabilities of DTCs in this study vary, which reflects true discrepancies in the standard of pediatric TBI care globally. It also highlights the urgent need to examine pediatric TBI management capabilities by comparing interventions and guideline adherence globally. Although we assessed

for basic life support including tracheal intubation, we did not report prehospital avoidance and management of hypoxia and hyperventilation, which are important prehospital components of TBI care. Although we focused on initial TBI management and therefore reported prehospital and ED interventions, we recognize that TBI care continues in the ICU. Quality and timely ICU care including ICP monitor–based interventions ultimately impact patient care and should be examined. Finally, specific management strategies for moderate versus severe TBI should be assessed individually in future studies to investigate the level of care and outcomes in each of these groups.

Future large-scale studies should investigate pediatric TBI management—especially in Asia and Latin America—and specifically prehospital care and TBI guidelines uptake. There is a great need for a prehospital system with a reliable transport mechanism and well-trained rescue personnel to ensure that injured children receive high-quality care in the initial hours postinjury. In addition, tiered and resource-specific approaches to pediatric TBI management guidelines are essential for addressing disease burden and maintaining sustainable TBI care in these regions.

Conclusions

We reported on a survey of TBI site infrastructure and practices among 24 centers in Asia, Europe, and Latin America. We found limited differences between DTCs and NTCs in both prehospital and ED management of pediatric patients with TBI. We also found a variation in the implementation of TBI management guidelines. Further research should investigate specific barriers to guideline implementation in these regions.

Acknowledgments

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Appendix

PACCMAN and LARed Network

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Conception and design: Chong, Caporal. Acquisition of data: Chong, Caporal, Dewi. Analysis and interpretation of data: Chong, Caporal. Drafting the article: Chong, Caporal. Critically revising the article: Chong, Caporal. Reviewed submitted version of manuscript: Chong, Mai, Lee, Caporal, Roa G, González-Dambrauskas, Zhu, Yock-Corrales, Abbas, Kazzaz. Approved the final version of the manuscript on behalf of all authors: Chong. Statistical analysis: Mai. Administrative/technical/material support: Dewi. Study supervision: Chong, Caporal, Abbas.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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