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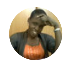

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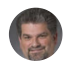

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Outcomes at Discharge of Pediatric Traumatic Brain Injury (pTBI) in Western Uganda: a Prospective Cohort Study

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Abstract:

Background: Traumatic brain injury disproportionately impacts LMICs and leads to a large number of emergency room visits and deaths, particularly within the pediatric population. The objective of this study was to describe pediatric TBI patients presenting to one regional referral hospital in Uganda and identify factors that contribute to unfavorable outcomes.

Methods: This study was a prospective, observational cohort study conducted at Mbarara Regional Referral Hospital (MRRH), located in Western Uganda. All pediatric TBI patients that presented between August 2016 to December 2020 were included in this study. Our dependent variable was the patient's outcome at discharge which was described as a binary variable (favorable vs unfavorable outcome). Favorable outcomes were defined as any patient who was either discharged from the hospital or had a Glasgow Outcome Score (GOS) greater or equal to four. Unfavorable outcomes were defined as any patient who died or had a GOS of three or less. Logistic regression was used to determine the factors significantly associated with unfavorable outcomes.

Results: A total of 560 pediatric TBI patients were included in this study with males making up 65.5% (n=367) of all patients. The main etiology of TBI cases was Road Traffic Accidents (RTA) (n=372, 66.4%) with the majority of pediatric patients being injured as pedestrians (n=271, 48.4%). Unfavorable outcomes were associated with pupillary exam findings (e.g. bilaterally abnormal pupils (OR 22.39, 2.98-168.11 CI, p-value 0.003)), incontinence (OR 19.01, 5.37-67.33 CI, p-value <0.001), need for ICU care (OR 12.17, 5.47-27.08 CI, p-value <0.001), and severe Glasgow Coma Scale (GCS) on admission (OR 11.25, 4.01-31.58 CI, p-value <0.001).

Conclusion: Demographic characteristics reflected similar trends to other studies around the world and highlighted that RTA, specifically involving pediatric patients as pedestrians, is a major driver of pTBI cases. TBI severity on presentation correlated with unfavorable outcomes reinforcing the need for rapid triage protocols and access to the necessary human and physical resources to appropriately manage pTBI.

KEYWORDS: *TBI, Global Neurosurgery, Uganda, Outcomes*

Introduction

The burden of pediatric traumatic brain injury (pTBI) is an increasing global concern. The incidence of pTBI varies between 47 and 280 per 100,000 children, and this injury has been identified as a leading cause of mortality and morbidity worldwide.[1] The Lancet Commission on Global Surgery and the World Health Organization (WHO) have reported the disproportionately high and rapidly increasing prevalence of pTBI in low- and medium-income countries (LMICs).[2,3] Furthermore, studies have shown that outcomes of pTBI vary by region even within the same country.[4] Despite this, publications reporting pTBI outcomes from LMICs, especially in sub-Saharan Africa are scarce. Our literature search has shown that prospective studies both globally and locally are in even shorter supply. We conducted a prospective study on the outcomes at hospital discharge of pTBI from a regional referral hospital in western Uganda and compared our results with other prospective published studies.

Both LCoGS and the WHO estimate that about eighty percent (80%) of the world's burden of all forms of trauma, including pTBI, occur in LMICs.[5] These organizations have used some of the available reports from LMICs to arrive at this conclusion.[6–9] While the mechanisms of injury are similar between LMICs and HICs, there are significant differences in the proportion of the patient population affected by the various mechanisms. In HICs, motor vehicle crashes (MVC) and falls from a height, specifically in patients less than 10 years, account for the majority of injuries.[10] In LMICs, MVCs are dominant and in Uganda, motorcycle transport (boda-boda) is the leading cause.[6,7] Overall, children with brain injury have lower mortality rates than adults despite the increased tendency for pediatric patients to have brain edema and increased ICP.[11,12]

Authors have reported differing mortality figures in severe pTBI, generally ranging between 10-25%.[13,14] Lichte et al. reported higher death rates in toddlers; Suominen et al. saw no difference while Hukkelhoven et al. observed higher mortality rates in older children.[5,15,16] In general, mortality was reported to be strongly associated with age, admission GCS, the length of hospital stay, the mechanism of injury, and the availability and practice of emergency and critical care services.[13,17–19] The mechanism of injury has been found to be the most important factor dictating the outcome of PTBI, though geographical variation has also been found to be significant. A multicenter study by Greene et al.[10], reported different figures respectively for mortality and disability in different states in the United States. This finding has been attributed to the differences in the quality of health services delivery and the lack of uniform use of treatment guidelines.

In most LMICs, services are inadequate because of the limited infrastructure, low staff numbers, and in some cases due to lack of systems. Popernack ML et al. observed that TBI-associated deaths decreased in the period between 1997-2007.[1] This period coincided with major improvements in the availability and practices of emergency and critical care services in HICs. Nevertheless, pTBI studies in HICs have mixed findings regarding the utility of aggressive intervention. In a systematic review, Von-Elm et al. saw no evidence to support pre-hospital intubation, but others have noted positive results from more aggressive and earlier intervention.[1520] Jagannathan et al. reported little evidence to support aggressive treatment of intracranial hypertension, yet others have reported favorable results in patients who had decompressive craniotomy or craniectomy.[13,17,18,20] However, the use of routine prophylactic decompressive craniectomy in pTBI was discouraged.[14] The picture in LMICs and especially sub-Saharan Africa remains unclear since data on outcomes is not readily available. Services are limited and, in some areas, virtually non-existent, yet the demand for services is overwhelming.

Given the lack of published literature on pTBI, especially in LMICs, the objective of our study was to determine the outcomes of pTBI in a setting of an LMIC and compare outcomes to studies from HICs. Results of the current study will be useful in the discussion of management protocols of pTBI.

Methods

Study Area

This prospective, observational cohort study was designed to study acute pediatric traumatic brain injury at Mbarara Regional Referral Hospital (MRRH) in Mbarara, Uganda. Mbarara is located in Western Uganda and its regional referral hospital, MRRH, serves a population of over four million people. MRRH has one neurosurgeon, an emergency ward, and an ICU without provision for ventilating children less than 20 kgs.

MRRH is the teaching hospital for Mbarara University of Science and Technology and a tertiary institution that serves as a regional treatment center for the Mbarara district and surrounding districts in Western Uganda. On average, 350 neurosurgical procedures are performed annually without a dedicated pediatric or neuro anesthetist. MRRH has a CT machine on-site with patients contributing UGX 180,000 ($50 USD) for head CT scans. During the time of data collection, the hospital had one dedicated neurosurgeon (DK); he trains medical officers and Master of Medicine-General Surgery residents. These trainees participate in neurosurgery cases as assistants or leads depending on their level of training and exposure.

Study Population

All children of 18 years and below who presented to the casualty ward at MRRH with TBI were enrolled. We used the GCS score and the modified GCS for children to identify the required population, define the severity, and categorize our patients.[21] However, only those who were admitted to the hospital were considered for inclusion in this study.

Sample Size

The study was planned with an estimated minimum sample size of 400 patients. Our sample size was calculated using Stata, and a Wald test comparing one proportion (estimated mortality) to reported mortality from HIC studies, 20%, and 15% respectively. During the study period, August 2016 to December 2020, 560 pTBI patients met inclusion criteria and were included in the final analysis. All patients that presented to MRRH during the reporting time were included in the study. We did not exclude any patients from the study or analyses.

Data Collection

Data were collected at the emergency room, inpatient ward, and intensive care unit by trained research assistants with a nursing background and by physicians. Written consent was obtained from the family or guardian prior to data collection. Entry of data occurred using a structured tool and was then later double-entered into a secure Microsoft Access database. . All data were checked for completeness and skew during the data entry period and were rechecked prior to the final analysis.

Variables

Our dependent variable was the patient's outcome at discharge which was described as a binary variable (favorable vs. unfavorable outcome). Favorable outcomes were defined as any patient who either was discharged from the hospital or had a Glasgow Outcome Score (GOS) of four or five. Unfavorable outcomes were defined as any patient who died or had a GOS of three or lower. Independent variables were collected throughout the patient's admission and included sociodemographic characteristics (age, gender, education, residence type, and home district), injury characteristics (injury type, mechanism of injury, presence of associated injuries, presence of non-traumatic comorbidities, pupillary responses, neurologic examination, and timing to presentation and intervention), and management and outcome characteristics (admission and discharge GCS, management, GOS, timing, and discharge location).

Data Analysis

Data were imported, cleaned, and analyzed using Stata 17 (College Station, TX: StataCorp LLC). Descriptive statistics were performed for all continuous and categorical variables. Continuous variables were described using means and standard deviations while frequency and percentages were used for categorical variables. After checking for normality and other parameters, parametric tests were chosen for analysis to assess associations between variables and outcomes. Pearson's chi-square and two-tailed t-tests were used to assess associations. Binary logistic regression was used to assess the association between dependent and independent variables. The odds of an unfavorable outcome were represented using the odds ratio output from the multivariate logistic regression model. Odds ratios are presented with 95% confidence intervals (CI) and p-values (<0.05 denoted statistically significant results).

Ethical Statement

Ethical approval was obtained from the Mbarara University of Science and Technology Research Ethics Committee and Duke University Health System Institutional Review Board.

Results

Sociodemographic Characteristics

Of the patients that presented to the MRRH emergency room during the study period, 560 met our inclusion criteria and were included in the final analysis (Table 1). Males predominated our cohort making up 65.5% (n=367) of the total sample. Most of the patients were between the ages of 1 month to 5 years old (n=203, 36.3%) with a total cohort mean age of 8.2 (*SD*=5.3). Reflective of the age breakdown of our cohort, 73.4% of the patients had only completed up to primary school. An overwhelming majority of our patients were from rural households (n=491, 87.7%) with Isingiro, Mbarara, and Ntungamo being the top three most common districts of the 36 home districts in our study sample.

	N
Total Sample	560
	Mean (SD)
Age (years)	8.2 (5.3)
Age (years)	**N (%)**
0-5	203 (36.3)
6-10	146 (26.1)
11-15	96 (17.1)
16-18	115 (20.5)
Gender	**N (%)**
Female	193 (34.5)
Male	367 (65.5)
Education	**N (%)**
None	115 (20.7)
Kindergarten/Nursery	128 (22.9)
Primary	167 (29.8)
Secondary and Beyond	46 (8.2)
Unknown	104 (18.6)
Residence Type	**N (%)**
Rural	491 (87.7)
Urban	40 (7.1)
Unknown	29 (5.2)

*SD=Standard deviation

Table 1. Sociodemographic characteristics

Pattern and Mechanism of Traumatic Brain Injury

The main driver of pTBI cases was Road Traffic Accidents (RTA) (n=372, 66.4%) caused by pediatric patients being injured while interacting as a pedestrian on the road (n=271, 48.4%) (Table 2). Motorized vehicles, primarily motorcycles, contributed to the other forms of RTA and most patients were not following safety guidelines (i.e. helmet or seatbelt usage). It took an average of 4.3 hours (*SD*=26.2 hours) for a patient to arrive at MRRH post-injury. Only a small fraction of patients presented to MRRH with associated injuries (n=51, 9.1%) or non-traumatic comorbidity (n=4, 0.7%). On examination the majority of patients had bilaterally equal pupils (n=438, 78.2%), bilaterally normal pupil sizes (n=421, 75.2%), and a normal motor exam (n=341, 60.9%). Other signs of neurological damage and injury severity were found in a minority of patients: seizures (n=94, 16.8%), incontinence (n=11, 2.0%), need for nasal cannula oxygen (n=96, 17.1%), intubation or tracheostomy (n=6, 1.1%), need for ICU care (n=39, 7.0%), and infection (n=29, 5.2%).

Glasgow Coma Score, Management, and Outcomes

Upon admission to MRRH most patients' TBI severity was categorized as mild (GCS 13-15) (n=240, 42.9%) with less than a fifth being categorized in the worst severity categories: severe TBI (GCS 6-8) (n=88, 15.7%) and critical TBI (GCS 3-5) (n=14, 2.50%) (Table 3). Only 87 patients (15.5%) were managed operatively with the rest being managed conservatively. At discharge, there was a greater number of patients with GCS categorized as mild TBI than at admission (n=447, 92.4%).

Injury Type	N (%)
Road Traffic Accident	372 (66.4)
Assault	77 (13.8)
Fall	62 (11.1)
Other	21 (3.8)
Unknown	28 (5.0)
RTA Type	**N (%)**
Pedestrian	271 (48.4)
Boda No Helmet	36 (6.4)
Cyclist	18 (3.2)
Boda Helmet unknown	11 (2.0)
Car No Seatbelt	7 (1.3)
Fall	7 (1.3)
Car Seatbelt Unknown	2 (0.4)
Boda w/ Helmet	1 (0.2)
Unknown	13 (2.3)
Did not have Road Traffic Accident	194 (34.6)
Associated injuries	**N (%)**
No	367 (65.5)
Yes	51 (9.1)
Unknown	3 (0.5)
N/A	139 (24.8)
Unequal Pupils	**N (%)**
No	438 (78.2)
Yes	25 (4.5)
Unknown	97 (17.3)
Pupil Size	**N (%)**
Both Constricted	7 (1.3)
Both Dilated	16 (2.9)
Both Normal	421 (75.2)
Unknown	116 (20.7)
Motor Exam	**N (%)**
Normal	341 (60.9)
Single sided weakness	42 (7.5)
Both sided weakness	10 (1.8)
Unknown	167 (29.8)
Seizures	**N (%)**
No	452 (80.7)
Yes	94 (16.8)
Unknown	14 (2.5)
Incontinence	**N (%)**
No	500 (89.3)
Yes	11 (2.0)
Unknown	49 (8.8)
Nasal Cannula Oxygen Support	**N (%)**
No	456 (81.4)
Yes	96 (17.1)
Unknown	8 (1.4)
Intubation or Tracheostomy	**N (%)**
No	544 (97.1)
Yes	6 (1.1)
Unknown	10 (1.8)
ICU Care	**N (%)**
No	432 (77.14)
Yes	39 (7.0)
Unknown	89 (15.9)
Infection	**N (%)**
No	531 (94.8)
Yes	29 (5.2)
Injury to Admission (in hours)	**Mean (SD)**
	4.3 (26.2)
Comorbidities	**N (%)**
None	496 (89.1)
Unknown	57 (10.2)
Yes	4 (0.7)

*SD=Standard deviation

Table 2. Pattern and Mechanism of Traumatic Brain Injury

The overall mortality rate for our cohort was 7.1% (n=40). GOS at discharge was primarily 5 (good recovery) (n=428, 76.4%) and 4 (moderate recovery) (n=29, 5.2%) with only 3 (0.5%) patients discharged with a GOS of 3 (severe disability). From admission to any outcome, the average time in the hospital was 9.2 days (*SD*=22.4 days).

Admission GCS	N (%)
Mild (13-15)	240 (42.9)
Moderate (9-12)	80 (14.3)
Severe (6-8)	88 (15.7)
Critical (3-5)	14 (2.50)
Unknown	138 (24.6)
Management	**N (%)**
Conservative	473 (84.5)
Surgical	87 (15.5)
Discharge GCS	**N (%)**
Mild (13-15)	447 (92.4)
Moderate (9-12)	13 (2.7)
Severe (6-8)	2 (0.4)
Critical (3-5)	8 (1.7)
Unknown	14 (2.9)
Outcome	**N (%)**
Discharged	484 (86.4)
Died	40 (7.1)
Absconded	31 (5.5)
Referred	4 (0.7)
Transferred internally	1 (0.2)
CT Completed	**N (%)**
No	253 (45.2)
Yes	307 (54.8)
CT Findings	**N (%)**
Bleed only	37 (9.6)
Skull Fracture only	70 (18.2)
Edema/Contusion only	74 (19.3)
Any Positive Finding	148 (38.5)
Other	17 (4.4)
Normal	38 (9.9)
Midline Shift	**N (%)**
No	296 (85.1)
Yes	52 (14.9)
Basal Cisterns Status	
Absent	12 (3.7)
Compressed	53 (16.1)
Open	264 (80.2)

Reason for no CT	N (%)
Patient Unable to Pay	84 (37.3)
Patient arrived w/CT result	80 (35.6)
CT Not Needed	52 (23.1)
Patient Unstable	3 (1.3)
Equipment Not Functional	1 (0.4)
Other	5 (2.2)
Discharge GOS	**N (%)**
5 (Good Recovery)	428 (76.4)
4 (Moderate Disability)	29 (5.2)
3 (Severe Disability)	3 (0.5)
1 (Dead)	40 (7.1)
Unknown	60 (10.7)
Admission to Outcome (in Days)	**Median (IQR)**
	5 (2-9)

*IQR=Inter-quartile range

Table 3. GCS, Management, and Outcomes

Clinical Variables Impacting Outcomes

After initial analysis age, admission GCS, presence of unequal pupils, differing pupillary sizes, deficit present on the motor exam, presence of seizures, incontinence, need for nasal cannula oxygen support, intubation or tracheostomy, need for ICU care, infection, presence of midline shift on CT, and basal cisterns status on CT were included in a multivariate logistic regression model. The greatest odds of an unfavorable outcome were associated with pupillary exam findings (e.g. bilaterally abnormal pupils (OR 22.39, 2.98-168.11 CI, p-value 0.003)), incontinence (OR 19.01, 5.37-67.33 CI, p-value <0.001), basal cisterns status classified as absent on CT (OR 14.33, 3.08-66.66, p-value 0.001), need for ICU care (OR

12.17, 5.47-27.08 CI, p-value <0.001), and severe GCS on admission (OR 11.25, 4.01-31.58 CI, p-value <0.001) (Table 4).

Variables	Odds ratio	95% CI	p-value
Age (years)			
0-4	4.31	1.45-12.81	**0.008**
5-9	Ref		
10-14	2.37	0.65-8.62	0.191
15-18	3.75	1.16-12.12	**0.027**
Admission GCS			
Mild (13-15)	Ref		
Moderate (9-12)	2.47	0.65-9.45	0.185
Severe (6-8)	11.25	4.01-31.58	**<0.001**
Critical (3-5)	47	11.92-185.32	**<0.001**
Unequal Pupils			
No	Ref		
Yes	14.63	6.07-35.23	**<0.001**
Pupil Size			
Both Normal	Ref		
Both Constricted	16.79	3.49-80.68	**<0.001**
Both Dilated	22.39	7.54-66.44	**<0.001**
Motor Exam			
Normal	Ref		
Both sided weakness	4.63	0.52-40.99	0.169
Single sided weakness	5.63	1.75-18.08	**0.004**
Seizures			
No	Ref		
Yes	3.24	1.64-6.42	**0.001**
Incontinence			
No	Ref		
Yes	19.01	5.37-67.33	**<0.001**
Nasal Cannula Oxygen Support			
No	Ref		
Yes	12.11	6.15-23.83	**<0.001**
Intubation or Tracheostomy			
No	Ref		
Yes	6.66	1.18-37.52	**0.032**
ICU Care			
No	Ref		

Yes	12.17	5.47-27.08	**<0.001**
Infection			
No	Ref		
Yes	5.4	2.23-13.06	**<0.001**
CT Complete			
No	Ref		
Yes	0.46	0.24-0.87	**0.018**
CT Findings			
Normal	Ref		
Bleed only	0.27	0.04-1.77	0.171
Skull Fracture only	0.14	0.02-0.90	**0.038**
Edema/Contusion only	0.20	0.04-1.08	0.061
Combo Positive Findings	0.45	0.11-1.77	0.114
Midline Shift			
No	Ref		
Yes	5.8	2.12-15.82	**0.001**
Basal Cisterns Status			
Open	Ref		
Absent	14.33	3.08-66.66	**0.001**
Compressed	3.51	0.96-12.90	0.059

*CI=Confidence Interval

Table 4. Binary Logistic Regression for Poor Outcome

Discussion

Mitigating the impact of pediatric TBI is an important global health concern. In most places, particularly in LMICs where pTBI outcome data is lacking, the foundational step is to describe current outcomes to illuminate what can be done. In this study, we describe a prospectively collected cohort of pTBI patients in Western Uganda and detail the drivers of TBI and the factors linked to unfavorable outcomes. Our study adds to the limited literature available about pTBI in LMIC settings and represents one of the largest cohorts described to date.

There is a consistent male predominance within TBI in LMIC settings and this trend appears within those impacted by pTBI.[22–25] In our cohort, males predominated with a 1.4:1 (male: female) ratio in the 0-5 age group with this trend increasing to a 10:1 (male: female) ratio in the 15-18 age group. RTAs are a primary driver of TBI worldwide and significantly contribute to pTBI cases.[26] In LMIC settings, a multitude of drivers exists for RTAs including road infrastructure, increased motorization, laws and regulation, and safety of vehicles on the road.[27,28] Motorcycles, which are commonly used as taxis in places like Uganda, contribute significantly to TBI and within our cohort, over 25% of pTBI cases were related to motorcycles.[29,30] Pediatric populations are impacted by RTAs typically as passengers or pedestrians in the younger age groups, and then as vehicle operators in the older age groups.[31] Nearly 50% of patients in our study were pedestrians that sustained their injury by being hit or run off the road by a motorized vehicle while walking. It has been previously documented that many of these children are unsupervised when they incur their injury.[7] Our finding highlights the need for improved road infrastructure and public health policy that allows for adequate space for pedestrians to reduce the number of pTBI cases.

TBI in pediatric populations differs in many significant ways from TBI in adults given that pediatric patient's brains are actively developing.[32] Differences include different durations of physiological impacts, age-specific cerebral responses, increased risk of early posttraumatic seizures, and delayed impairment of neuronal activation with potential diminution of plasticity. [33] These differences are important given the large distribution of severity within pTBI populations. In most studies, typically ~70% of pTBIs are characterized as mild TBI and then 30% moderate and severe. Our study severity is reflective of this spread with 60% with mild TBI and 40% moderate and severe. Severe TBI management is best provided in an ICU setting.[31] Only 39 patients in our cohort were treated in the ICU despite 102 patients arriving with an admission GCS of less than 8. Only 38% of those that met ICU criteria were admitted to the ICU due to MRRH's 8-bed ICU capacity which led to a lack of open beds, no resources for children below 20 kgs in the ICU, and a lack of general resources in the ICU. Surgery was provided to 87 (15.5%) of the cohort, which is an operative rate aligned with other studies in LMICs and HICs.[34–36] Importantly, the mortality rate in our cohort was only 7.1% which is as good as or better than other studies both in LMICs and HICs.[37–39] Our mortality rate reflects an interesting finding given that limited resources led to patients that would have otherwise been managed in the ICU being managed elsewhere without a significant impact on mortality. This finding warrants further exploration to understand the current management practices within the ward that lead to severe pTBI patients having favorable outcomes.

Unfavorable outcome predictors in our study all reflect TBI severity on presentation (e.g. pupillary response, motor exam findings, signs of raised intracranial pressure, and positive CT findings). Usage of limited resources for the sickest patients, like management in ICU, nasal cannula oxygen, and intubation were all associated with unfavorable outcomes. This combination of TBI severity on presentation and usage of resources illustrates the importance of triage decision-making in the casualty ward.[40] Fortunately, most of the patients in our cohort made it to the casualty ward within 4 hours of injury and nearly all made it within 1 day. Time to presentation was not found to be correlated with unfavorable outcomes in our cohort, but prior work has shown the impact that time delays have on TBI outcomes.[41,42]

Limitations

Our study has many strengths and is one of the largest cohorts that exists for pTBI in LMIC settings. An important limitation is that our cohort is from only one regional referral center thus limiting the generalizability of our results. Importantly, our mortality rate is comparable to published literature, but we are missing data from pediatric patients who died on the scene or during transit. Thus, we have a bias in our dataset that can not be fully accounted for. Despite this fact, our in-hospital outcomes compare favorably with other settings with similar pre-hospital resource constraints. Additionally, estimation of the GCS by different and at times junior staff could have impacted the results given the necessary training and expertise required to assess GCS in pediatric populations. We would also like to highlight that our study only focused on short-term in-hospital outcomes and long-term outcomes are important in pediatric populations. The next step for our study team is to follow our pTBI cohort for 6-months to 2 years to determine long-term outcomes.

Conclusion

Our study utilizes a prospectively collected pTBI cohort in Uganda to illustrate pTBI in an LMIC setting. Demographic characteristics reflected similar trends to other studies around the world and highlighted that RTA, specifically pediatric patients as pedestrians, is a major driver of pTBI cases. TBI severity on presentation correlated with unfavorable outcomes reinforcing the need for rapid triage protocols and access to the necessary human and physical resources to appropriately manage pTBI. Investment in governmental policies that improve road infrastructure, hospital policies on triage, and hospital access to needed resources have the ability to improve pTBI in LMIC settings.

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