Injury-to-Admission Delay Beyond 4 Hours Is Associated with Worsening Outcomes for Traumatic Brain Injury in Cambodia

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BACKGROUND: **In Cambodia, the most common victims of traumatic brain injury (TBI) are men 20–30 years of age involved in motor vehicle collision. Secondary injury sustained by these patients occurs during the time period between initial insult and hospital admission. Strengthening prehospital systems for TBI in low- and middle-income countries (LMICs) such as Cambodia is therefore a key element of the development agenda for universal health equity. We report a retrospective analysis of the relationship between prehospital delays and TBI outcomes among patients from a large government hospital in Cambodia.**

METHODS: **Data were collected from 3476 patients with TBI admitted to a major government hospital in Phnom Penh, Cambodia, from June 2013 to June 2018. Patients with missing data or those admitted >8 hours postinjury were excluded. Statistical analyses examined associations between injury-to-admission delay (IAD) and outcomes such as Glasgow Outcome Scale (GOS) score and length of stay (LOS).**

RESULTS: **A total of 2125 patients with TBI (76.85% men) were included. The median age was 27 years (interquartile range, 22–37 years). Injury severity at presentation included 1406 mild (66%), 464 moderate (22%), and 240 severe cases (11%). No Glasgow Coma Scale (GCS) data were available for 15 patients (1%). We found an inverse relationship between IAD and GOS score, most evidently for mild and moderate TBI (n = 1870; 88%). Regression analysis revealed a marked decrease in GOS score at the IAD >4-hour threshold. Each 30-minute delay in IAD was correlated with >2-hour increase in LOS for mild ($P < 0.001$) and moderate TBI ($P < 0.001$).**

CONCLUSIONS: **In a retrospective cohort of >2000 patients with TBI from Cambodia, we found that increasing IAD was associated with worsening outcome, especially beyond the 4-hour threshold. These data should inform development of prehospital guidelines for TBI care in LMICs.**

INTRODUCTION

Traumatic brain injury (TBI) is a neurological disorder of global epidemiologic importance. According to the World Health Organization, TBI has made road traffic accidents the number one cause of death among those 15–29 years of age, killing as many as half a million pedestrians, cyclists, and motorcyclists annually.[1] Indeed, a growing body of research highlights that, particularly in low- and middle-income countries (LMICs), such as Cambodia, the prototypical victim of TBI is a

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- Global health
- Global neurosurgery
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- LMIC
- Prehospital care
- Sustainable development
- TBI

Abbreviations and Acronyms
CI: Confidence interval
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
IAD: Injury-to-admission delay
LMIC: Low- and middle-income country
LOS: Length of stay
OR: Odds ratio
TBI: Traumatic brain injury

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young man in his 20s or 30s who has suffered a motor vehicle accident.[2] This demographic profile is particularly alarming for LMICs in the midst of a demographic transition, where the economic productivity of young members of the population is a vital component of upward socioeconomic mobility.[3] In an era where poverty reduction, road safety, and universal health coverage figure into the global agenda for sustainable development, decreasing the rates of death and disability from TBI becomes a major priority.[4,5]

In a visionary editorial describing key aspects of the full spectrum of trauma care in LMICs, Mock et al.[6] addresses the critical importance of expedient prehospital care. Citing data showing that 59% of trauma-related mortality in high-income countries occurred at the geographic site of injury, these mortality figures were shown to exceed 70% and 80% in LMIC contexts from Latin America and Sub-Saharan Africa.[7] In addition to the disease burden of TBI in LMICs, the pathophysiology of TBI further underscores the urgent need to strengthen prehospital care systems for TBI in these countries. Secondary insults in TBI, such as increased intracranial pressure, cerebral dysautoregulation, and cerebral edema, are independent predictors of poor outcome in TBI. The mitigation and prevention of these insults requires responsive and effective emergency medical services.[8]

The World Health Organization recommendations for prehospital trauma systems provide a useful point of departure for the organization of emergency medical services, especially in LMICs. Although TBI-specific recommendations are limited to neurologic monitoring and the provision of oxygenation and blood pressure support for the first 5 hours after TBI, the authors state the limitations of this consensus-based document. They highlight the insufficiency of evidence for most prehospital care interventions in contemporary use, suggesting a need for more data to guide future efforts around prehospital trauma system strengthening.[9] Focusing on a large government hospital in Cambodia, an LMIC in Southeast Asia, the current report presents data on prehospital delays to hospital admission from a retrospective cohort of patients with TBI. The specific aim of our study was to analyze the data to see if a clear threshold for the delay time can be identified after which point the outcomes worsen. Data of this nature can indicate specific opportunities for health care system—level interventions that strengthen TBI capacity in similar settings.

CAMBODIA BACKGROUND

Cambodia is located on the southern border of the Indochina Peninsula adjacent to Thailand, Laos, and Vietnam. The country's complex history plays a major role in its current health care capacity. This began with French colonial rule that prevented development of local government health care infrastructure up until Cambodian independence in 1953. Subsequently, a bloody civil war and genocide from 1975 to 1979 under the Khmer Rouge regime took the lives of nearly 2 million people and left the country with a paucity of medical professionals.[10] This shortage continued during the Vietnamese-Cambodian conflict and occupation which lasted up until 1993. Therefore, it has only been in the last 3 decades that there has been significant opportunity for development of health care workforce and infrastructure.

Currently, Cambodia is considered an LMIC country, by World Bank designation, showing signs of rapid economic growth and improvements in health care provision.[2] Its current population is approximately 16.2 million, with 1 in 5 Cambodians being between the ages of 15 and 24 years, and nearly two thirds of the population being between 15 and 30 years of age.[11,12] The regional physician density is 0.14 per 1000 population, which is quite low in comparison with neighboring Laos and Vietnam, with 0.49 and 0.82 physicians per 1000 population, respectively.[11] Therefore, as a result of its very young demographic profile and its relatively low availability of health care provision, Cambodia is a country that is highly susceptible to the economic and societal pitfalls of inadequate TBI care.

METHODS

This study was ethically approved by the National Committee for Health Research and the National Institute of Public Health of Phnom Penh, Cambodia. The procedures for collection of the original data have been previously described.[2,13] Informed consent was obtained from each patient prior to data collection at the time of admission. Briefly, this was a retrospective analysis of data collected from the medical records of patients with TBI admitted to a major government hospital in Phnom Penh, Cambodia, for the period between June 2013 and June 2018.

During this time interval, 3476 patients with TBI were admitted the facility. For each patient, recorded data included the demographics, region of residence, date and time of injury, date and time of admission to the hospital, Glasgow Coma Scale (GCS) score at presentation, main diagnosis, subsequent surgical procedure when performed, and Glasgow Outcome Scale (GOS) score at discharge. We excluded from our analysis all patients lacking records about time of admission or missing information regarding date or time of injury.

For each patient included in this study, we estimated the injury-to-admission delay (IAD), defined here as the difference between the time of injury and the time of admission. For the purpose of our study, we decided to include only patients having an IAD of $\leq$8 hours. This decision is based on clinical reasoning and the literature that patients with acute, traumatic intracranial lesions would need treatment within a maximum 4- to 6-hour time frame after injury to optimize outcome and minimize mortality.[14-16] Given the absence of data on mortality that occurred during the prehospital phase of TBI care, we reasoned that surviving patients admitted to the hospital >8 hours after initial insult would self-select for positive outcome, which would confound interpretation of the impact of prehospital care delays on more severely injured patients. We therefore excluded from this analysis 661 patients with IAD >8 hours, leaving 2320 patients at this stage of analysis.

Our primary outcome for this study was the GOS score at discharge. Additional outcomes evaluated included hospital length of stay (LOS) and patients requiring surgical intervention. GOS score of 1 was assigned to all patients with in-hospital mortality. There were 186 patients excluded from the study because of missing GOS data and 9 patients excluded who were missing LOS data, leading to a final number of 2125 included patients. For statistical purposes, we defined GOS score of 1—3 as a poor outcome and GOS score of 4–5 as a good outcome, considering that GOS score of 3 is the boundary for severe disability (see Statistical Methods section).

Patients were further divided by severity at presentation, according to the GCS score recorded at the time of hospital admission, with mild being a GCS score of 14–15, moderate being a GCS score of 9–13, and severe being a GCS score of ≤8. Using the statistical analysis subsequently described, we investigated the association between the IAD and the outcomes (GOS, LOS, and probability of having surgery) for all patients with TBI and then each subgroup.

Statistical Methods

Continuous data are presented as mean and SD or median and interquartile range as appropriate, whereas categorical data are presented as frequency and percentage. The association between IAD and TBI outcomes were assessed using a regression model. Logistic regression modeling was used to analyze the patient-level data on the probability of undergoing surgery and observing a GOS score of ≥3.

Logistic regression models were used to derive odds ratios (ORs), 95% confidence intervals (CIs), and P values. ORs and 95% CIs corresponding to a 30-minute increase in IAD are presented. Because of nonnormality of LOS, quantile regression modeling on the median (median regression) was used to obtain a less biased regression coefficient and more robust results in the analysis of the association between IAD and LOS. Coefficient estimates on the median, 95% CI, and P value were obtained from the quantile regression modeling.

Regression modeling was performed in the set of all patients, and in sensitivity analyses among patients with mild, moderate, and severe TBI, separately. Clinically relevant cutoff values for IAD duration were considered, and the χ^2 test was used to assess the association between IAD and GOS score for each threshold that was considered. To examine the change in GOS score before and after IAD threshold values, segmented regression modeling was implemented to test the change in the slope before and after each threshold. To confirm the normality in the distribution of the GOS variable, we performed a Shapiro-Wilk test of normality on our data.

Data were analyzed using Excel 2016 version 15.40 for Mac (Microsoft Inc., Redmond, Washington, USA). All statistical analyses were performed using R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata 15.0 (StataCorp, College Station, Texas, USA). A 2-sided alpha level of 0.05 was implemented to determine statistical significance. Average values were used for the GOS analysis given normality of distribution.

RESULTS

Demographic data are presented in Table 1. In total, there were 2125 patients who presented with TBI; of these, 76.85% were mem. The median age for this cohort was 27 years, and the interquartile range for age was 22–37 years (Table 1), confirming a demographic trend of young male victims of TBI that is seen in many LMICs.[17-20] Among the 2125 patients with TBI, most presented with mild TBI severity (n = 1406; 66%), whereas 464 cases (22%) were of moderate severity and 240 cases (11%) presented with severe TBI. No GCS data were available for 15 of these patients (1%). Table 2 summarizes the raw data, demonstrating the spectrum of IAD time periods, average GOS score per IAD category, and number of patients requiring surgical intervention during the hospital stay.

Table 1. Patient Demographics

Characteristic	Value
Sex	
Male	1633 (76.85)
Female	492 (23.15)
Age (years)	
Mean	31.30
Median	27
IQR	14
Range	14–98
Residing province	
Battambang	3 (0.14)
Kampong Cham	122 (5.74)
Kampong Chhnang	36 (1.69)
Kampong Speu	335 (15.76)
Kampong Thom	83 (3.91)
Kampot	87 (4.09)
Kandal	231 (10.87)
Kep	1 (0.05)
Koh Kong	17 (0.80)
Kratie	10 (0.47)
Phnom Penh	862 (40.56)
Preah Sihanouk	28 (1.32)
Preah Vihear	2 (0.09)
Prey Veng	82 (3.86)
Pursat	5 (0.24)
Siem Reap	3 (0.14)
Stung Treng	1 (0.05)
Svay Rieng	28 (1.32)
Takeo	186 (8.75)
Not reported	3 (0.14)

Values are number of patients (%) or as otherwise indicated.
IQR, interquartile range.

Figure 1 demonstrates scatterplots of the mean GOS score (y axis) plotted as a function of increasing IAD (x axis), and for each category of TBI severity. IAD is numbered by hourly intervals of delay, where 1 represents the first time interval from 00:00 to 00:59, 2 represents the second time interval from 1:00 to 1:59, and so forth (Table 2 and Figures 1 and 2). The curves

Table 2. Raw Data for All Patients

All Patients				Mild TBI			
I-A Interval (hours)	Number	Qty Having Surgery (%)	Mean GOS ± SD	I-A Interval (hours)	Number	Qty Having Surgery (%)	Mean GOS ± SD
0:00—0:59	175	24 (13.71)	4.06 ± 0.66	0:00—0:59	133	8 (6.02)	4.28 ± 0.67
1:00—1:59	464	76 (16.38)	3.98 ± 0.87	1:00—1:59	324	17 (5.25)	4.29 ± 0.57
2:00—2:59	405	99 (24.44)	3.85 ± 0.93	2:00—2:59	260	30 (11.54)	4.20 ± 0.65
3:00—3:59	368	84 (22.83)	3.93 ± 0.84	3:00—3:59	241	22 (9.13)	4.24 ± 0.56
4:00—4:59	263	56 (21.29)	3.87 ± 0.88	4:00—4:59	172	14 (8.14)	4.18 ± 0.63
5:00—5:59	198	41 (20.71)	3.81 ± 0.92	5:00—5:59	128	13 (10.16)	4.15 ± 0.64
6:00—6:59	130	30 (23.08)	3.69 ± 0.92	6:00—6:59	77	6 (7.79)	4.09 ± 0.67
7:00—8:00	122	26 (21.31)	3.70 ± 0.90	7:00—8:00	71	4 (5.63)	4.06 ± 0.53
Total	2125	436 (20.52)	3.89 ± 0.89	Total	1406	114 (8.11)	4.22 ± 0.61
Moderate TBI				**Severe TBI**			
I-A Interva l (hours)	Number	Qty Having Surgery (%)	Mean GOS ± SD	I-A Interval (hours)	Number	Qty Having Surgery (%)	Mean GOS ± SD
0:00—0:59	29	10 (34.48)	3.66 ± 0.67	0:00—0:59	11	6 (54.55)	2.55 ± 1.21
1:00—1:59	92	31 (33.70)	3.58 ± 0.76	1:00—1:59	45	28 (62.22)	2.64 ± 1.19
2:00—2:59	88	33 (37.50)	3.64 ± 0.59	2:00—2:59	53	34 (64.15)	2.47 ± 1.17
3:00—3:59	75	26 (34.67)	3.67 ± 0.58	3:00—3:59	50	36 (72)	2.94 ± 1.24
4:00—4:59	64	26 (40.63)	3.63 ± 0.70	4:00—4:59	26	16 (61.54)	2.50 ± 1.21
5:00—5:59	44	13 (29.55)	3.57 ± 0.82	5:00—5:59	23	13 (56.52)	2.30 ± 0.82
6:00—6:59	37	13 (35.14)	3.43 ± 0.80	6:00—6:59	16	11 (68.75)	2.38 ± 0.81
7:00—8:00	35	11 (31.43)	3.34 ± 0.84	7:00—8:00	16	11 (68.75)	2.94 ± 1.34
Total	464	163	3.58 ± 0.71	Total	240	155	2.62 ± 1.16

I-A, injury-to-admission interval in hours; Qty, quantity; GOS, Glasgow Outcome Scale.

of best fit for Table 1 enable visualization of changes in the slope describing the relationship between IAD and GOS score. In the mild and moderate categories of TBI, which represent 88% of the cohort (n = 1870), this change appears to be most evident beyond a 4-hour duration in IAD. Multiple logistic regression analyses were conducted to further explore this relationship and the overall impact of the IAD on the clinical outcomes of interest.

Exploration of GOS Score Around the 4-Hour Time Point

Given the appearance of marked change in slope at the 4-hour time point for patients with mild and moderate TBI (Figure 1), we performed segmented regression analysis and χ^2 hypothesis testing for IAD versus GOS score before and after the 4-hour time point to explore this time point as a threshold for predicting significantly worsening GOS score (see Statistical Methods section). Segmented regression analysis revealed that the apparent slope changes observed in the best fit curve around the 4-hour time point for moderate TBI was statistically significant. For the mild group, the values of the 95% CI for the relationship tested by segmented regression analysis were −0.07 to 0.03; the change in slope at the 4-hour time point for the mild group was therefore not statistically significant (Figure 2). Chi-square hypothesis testing demonstrated that among all patients with an IAD of ≥4 hours, there was an approximate 8% increase in the quantity of patients with an unfavorable GOS score of ≤3 compared with patients with an IAD of <4 hours, and this finding was statistically significant (Table 3). The trend was maintained for subgroup analysis of patients with mild TBI and IAD of 4—8 hours, revealing an estimated 5% increase in the unfavorable outcome (i.e., GOS score ≤3) compared with patients with mild TBI arriving in <4 hours. For the moderate and severe TBI groups, similar trends were observed; however, the sample sizes were too small to achieve statistical significance (Table 4).

Combining our data from Figure 2 and Table 3, we observed that for the mild TBI group, a statistically significant difference in outcome was evident depending on whether patients where

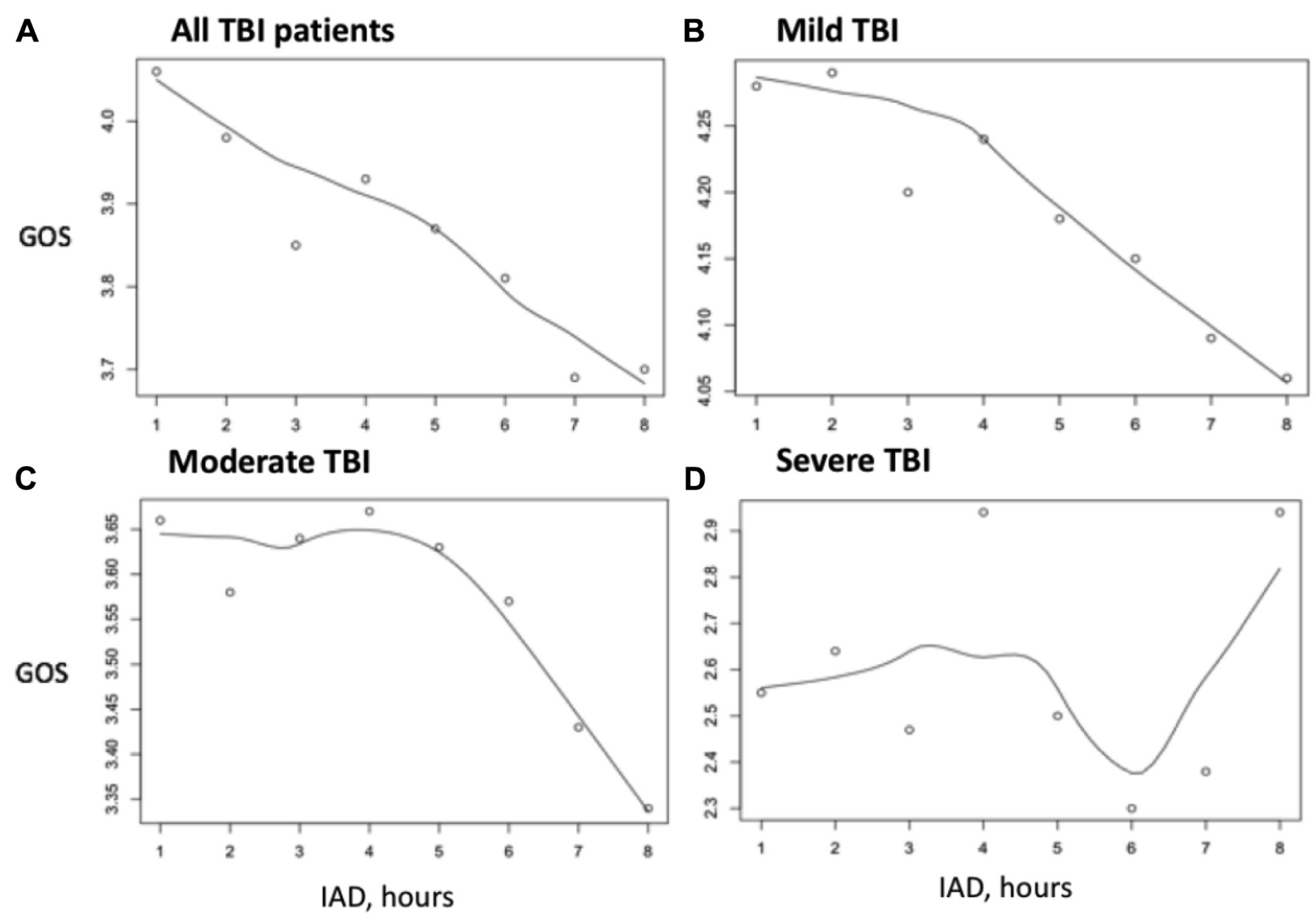

Figure 1. Scatterplots with best curve fitting to demonstrate changes in mean Glasgow Outcome Scale (GOS) score with increasing injury-to-admission delay (IAD) at each hour beyond time of injury, up to 8 hours. (**A**) IAD in hours versus mean GOS score at each hour for all patients in the cohort (n = 2125). (**B**–**D**) The relationship for patients with mild (n = 1406), moderate (n = 464), and severe (n = 240) traumatic brain injury, respectively. TBI, traumatic brain injury.

admitted in <4 hours after their injury versus >4 hours. Change in slope of GOS score as a function of IAD for mild TBI at precisely the 4-hour mark was, however, not statistically significant, which indicates that although GOS score does appear to steadily decline with increasing IAD, the magnitude of decline as observed at the 4-hour time point was not great enough to support the hypothesis at this time threshold. In the case of moderate TBI, however, the hypothesis of 4-hour threshold is supported by a significant change in slope observed by segmented regression analysis, indicating that the change in GOS score versus IAD was greater for this group than it was for the mild TBI group. The χ^2 testing for the moderate TBI group, on the other hand, did not support the 4-hour hypothesis, which is a likely result of inadequate sample size for statistical power in this group.

GOS Score at Discharge

The logistic regression model found an inverse relationship between favorable outcome (i.e., GOS score >3) and increasing delay between time of injury and admission (IAD). For each 30-minute increase in IAD, favorable outcome was associated with an OR of <1 (OR, 0.96; 95% CI, 0.93–0.98; $P = 0.001$) in all analyzed intervals (0–8 hours), and this association was statistically significant. This inverse relationship between favorable outcome and IAD was maintained in subgroup analysis of patients with mild TBI (n = 1406; OR, 0.94; 95% CI, 0.90–0.99; $P = 0.01$). For the moderate (n = 464) and severe (n = 240) subgroup analyses, this relationship was not maintained (Table 3).

IAD versus Surgical Intervention

To explore potential relationships between IAD and odds of undergoing a surgical intervention, we performed logistic regression conducted across all time intervals (Table 5). The overall association tended toward statistical significance (OR, 1.03; 95% CI, 1.00–1.06; $P = 0.057$) (Table 5). Subgroup analyses by TBI severity failed, however, to reject the null hypothesis. In other words, no

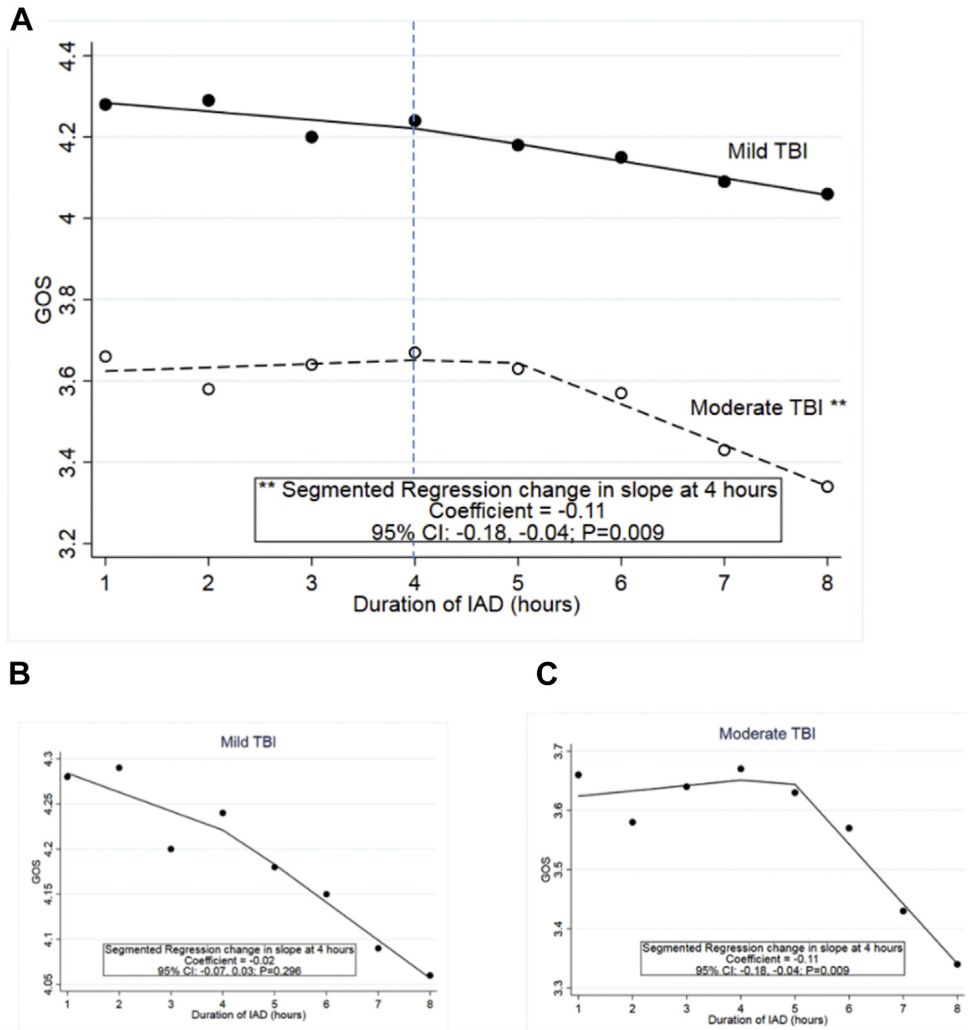

Figure 2. Segmented regression analyses. (**A**) Segmented regression of the best fit curve for the scatterplot of patients with mild traumatic brain injury (TBI), with a *dotted line* at the 4-hour mark to facilitate visual inspection of this threshold (compare with **B** and **C**). (**B** and **C**) Curves for mild and moderate TBI, separately. CI, confidence interval; GOS, Glasgow Outcome Scale; IAD, injury-to-admission delay.

evidence was found to support a meaningful relationship between IAD and odds of undergoing a surgical intervention.

Hospital LOS

The quantile regression performed to evaluate the relationship between IAD and hospital LOS found a positive correlation between these 2 parameters (Table 6). Considering all patients with TBI, each 30-minute increase in IAD was associated with a statistically significant increase in LOS of 0.18 days (4.5 hours) in all studied time intervals ($P = 0.00001$). We observed similar findings in subgroup analysis of patients with mild TBI specifically, with an increase in 0.13 days (3 hours and 7 minutes) for every 30-minute increase in IAD ($P = 0.0006$). For patients with moderate and severe TBI, quantile regression was not able to estimate a unique solution given the limited number of cases available in these subgroups.

DISCUSSION

In this retrospective analysis of prehospital care timelines for patients with TBI in Cambodia, there was an inverse correlation of delay in prehospital time course (IAD) and GOS score. This correlation was statistically significant for all patients presenting with craniocerebral trauma, and the relationship was maintained for subgroup analysis of patients with mild TBI. Moreover, our findings regarding the relationship of IAD to our secondary outcomes, such as impact on hospital LOS, and other clinical implications of

Table 3. 2 × 2 Tables Constructed for Pearson χ^2 Test for Dichotomized Glasgow Outcome Scale Score versus Injury-To-Admission Delay of <4 or 4–8 Hours

All Patients (N = 2125, *P* < 0.001)				Mild TBI (n = 1406, *P* < 0.001)			
Outcome	**Duration of IAD**			**Outcome**	**Duration of IAD**		
GOS Score ≤3 versus GOS Score >3	**<4 Hours**	**4–8 Hours**	**Total**	**GOS Score≤3 versus GOS Score >3**	**<4 Hours**	**4–8 Hours**	**Total**
GOS score ≤3	284	197	481	GOS score ≤3	66	56	122
GOS score >3	1128	516	1644	GOS score >3	892	392	1284
Total	1412	713		Total	958	448	
Moderate TBI (n = 464, *P* = 0.187)				**Severe TBI (n = 240, *P* = 0.103)**			
Outcome	**Duration of IAD**			**Outcome**	**Duration of IAD**		
GOS Score ≤3 versus GOS Score >3	**<4 Hours**	**4–8 Hours**	**Total**	**GOS Score ≤3 versus GOS Score >3**	**<4 Hours**	**4–8 Hours**	**Total**
GOS score ≤3	101	75	176	GOS score ≤3	112	65	172
GOS score >3	183	105	288	GOS score >3	47	16	63
Total	284	180		Total	159	81	

Among all patients, 20% of patients with duration of IAD <4 hours had GOS score ≤3, as compared with 28% of patients with duration of IAD 4–8 hours ($P < 0.001$). Among patients with mild TBI, 7% of patients with duration of IAD <4 hours had GOS score ≤3, as compared with 13% of patients with duration of IAD 4–8 hours ($P < 0.001$). Among patients with moderate TBI, 36% of patients with duration of IAD <4 hours had GOS score ≤3, as compared with 42% of patients with duration of IAD 4–8 hours, but this did not reach statistical significance ($P = 0.187$). Among patients with severe TBI, 70% of patients with duration of IAD <4 hours had GOS score ≤3, as compared with 80% of patients with duration of IAD 4–8 hours, but this did not reach statistical significance ($P = 0.103$).

TBI, traumatic brain injury; GOS, Glasgow Outcome Scale; IAD, injury-to-admission delay.

these data, warrant careful reflection. Our main parameter under study was the period of elapsed time, denominated as IAD. Using segmented regression modeling and χ^2 hypothesis testing to explore a qualitative change detected, by visual inspection, in the relationship between mean GOS score and IAD in both mild and moderate TBI groups, we found evidence supporting a threshold IAD time point of 4 hours, beyond which patient outcomes for TBI are significantly worse.

The clinical implications of our evidence for the 4-hour threshold should be carefully deduced. Given the expected worsening of outcomes caused by the pathophysiology of secondary insults in TBI, prehospital systems should be structured to expedite the stabilization and transport of patients with TBI to a neurosurgery-capable center as rapidly as possible.[8] Indeed, the principal finding in our analysis was that at all time points studied, GOS score worsened as IAD increased. We therefore interpret the changes observed around the 4-hour time point not as evidence that IAD may safely be lengthened to 4 hours, but rather as evidence that in LMIC environments, such as the Cambodian context studied here, geospatial mapping of access to neurosurgery-capable centers should assure that any patient with TBI is absolutely no more than 4 hours away from a facility with neurosurgical capacity.

Table 4. Logistic Regression Between Injury-to-Admission Delay and Dichotomized Glasgow Outcome Scale Score

Category	OR (30 minutes)	*P* Value	95% CI
Overall	0.96	0.001	0.93–0.98
Mild TBI	0.94	0.01	0.90–0.99
Moderate TBI	0.97	0.2	0.93–1.02
Severe TBI	1	0.999	0.93–1.08

OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury.

Using data based on the time required for a death to occur from postpartum hemorrhage, the Lancet Commission on Global Surgery recommended that a facility capable of performing the Bellwether procedures (i.e., fracture reduction, laparotomy, cesarean section) should be within 2 hours of the population's reach. The authors further note that the precise time window for reduction of morbidity and mortality may be shorter or longer depending on a variety of factors, including the patient's condition and diagnosis.[21] We assert that the findings of our study in Cambodia are aligned with these recommendations, with the following additional observations. First, if cranial procedures for TBI are

Table 5. Quantile Regression: Injury-to-Admission Delay and Length of Stay

Category	LOS Increase (30 minutes)	*P* Value
Overall	0.18	0.00001
Mild TBI	0.13	0.0006
Moderate TBI	—	—
Severe TBI	—	—

LOS, length of stay; TBI, traumatic brain injury.

to be included among the fracture reduction category of Bellwether procedures, then ministries of health may consider the value of including neurotrauma capability among essential surgical services to be offered at the first level or district hospital. If these hospitals meet the targets of preparedness recommended by the Lancet Commission on Global Surgery, then access to essential neurosurgical care for TBI can be reduced to 2 hours, which could markedly improve TBI outcomes for patients such as the cohort under study. Second, if preparedness for neurotrauma care is to be limited to tertiary care facilities, then our data can inform a recommendation that all members of a population in contexts that resemble our cohort's environment should be able to reach such neurosurgically capable facilities within $\leq$4 hours after a TBI incident.

Severity of TBI is assessed based on initial presentation. The value of GCS score in the management of patients with TBI is primarily in its utility as a dynamic marker of patient evolution when performed at repeated intervals, and not necessarily as a prognostic tool when performed at initial presentation.[22] Indeed, despite presenting with mild TBI by initial GCS score, 8.11% (Table 2) of patients with mild TBI in this cohort ultimately underwent neurosurgical intervention. Several mild cases in this cohort may therefore represent the patients who stand to benefit most from emergent neurosurgical intervention, which underscores the importance of IAD as a measure of prehospital care capacity. Prior studies of the target population exhibited a high prevalence of acute cranial epidural hemorrhage, which classically exhibits a lucid interval followed by coma from an expanding hemorrhage.[2] Early detection of this condition is critical for timely surgical management and optimal outcome.[23]

Table 6. Logistic Regression: Injury-to-Admission Delay and Probability of Having Surgery

Category	OR (30 minutes)	*P* Value	95% CI
Overall	1.03	0.057	1.00—1.06
Mild TBI	1.03	0.304	0.98—1.08
Moderate TBI	0.99	0.69	0.94—1.04
Severe TBI	1.02	0.53	0.95—1.10

OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury.

Evidence regarding prehospital delays in TBI is limited, and questions regarding optimal time frames between injury, hospital admission, and neurosurgical interventions are actively debated.[8] A retrospective chart review by Seelig et al.[16] analyzed 366 consecutive patients with nonpenetrating TBI and found that hospital admission within 4 hours of injury reduced mortality from acute subdural hematomas by as much as 60%. More recently, the Société Française d'Anesthésie et de Réanimation made a grade 1 recommendation for managing patients with severe TBI by team-driven prehospital stabilization on scene and subsequent transfer to a neurosurgical referral center as soon as possible.[24] Although these data and recommendations from high-income country contexts have uncertain relevance for LMICs, they merit consideration given common pathophysiology of the various forms of TBI. In particular, the relative incidence of acute subdural versus extradural hemorrhage in LMICs will impact the generalizability of high-income country TBI literature to LMIC populations.[17,25]

Long hospital transport times for TBI are a particular challenge of LMIC environments and represent an important research priority for global TBI.[26] Notably, a recent Ugandan study addressing these concerns found that increasing IAD, defined as the second delay, was positively correlated with mortality.[20] Of note, the authors found a statistically significant difference in mortality outcomes for patients with moderate TBI ($n = 152$) admitted within 4 hours after injury versus 24 hours; however, the study may have been underpowered to demonstrate the same trend for patients with mild and severe TBI. Although our regression model demonstrates continuous worsening in outcomes associated with the increase in delay, the IAD versus GOS score scatterplots and segmented regression analyses (Figures 1 and 2) also highlight a marked decrease in slope of the curve when IAD exceeds the 4-hour threshold. We interpret this change in association as a more rapid worsening in outcomes associated with an increase in IAD beyond the 4-hour time point. Our data therefore corroborate evidence from high-income countries regarding the importance of a 4-hour maximum time frame from injury to hospital admission for patients with TBI and add to a small but growing body of evidence from LMICs that shorter IAD improves TBI outcomes.

Our findings also suggest that in this cohort a 6-hour delay in IAD adds an extra day to LOS. Analysis of the relationship between LOS and IAD by quantile regression revealed that each 30-minute delay in IAD increases LOS by approximately 4 hours and 20 minutes for the overall cohort, and by approximately 3 hours and 7 minutes per 30-minute delay for the mild TBI group. These findings were statistically significant. In LMIC contexts, where prehospital delays can unfortunately exceed 24 or even 124 hours, the economic implications of increasing LOS for surviving patients are also of great importance.[20] Cost of care audits for intensive acre unit stays in another Asian LMIC found per-day costs ranging from $200 to $300 per patient; such costs can be prohibitive in resource-poor settings, and strengthen the economic argument for system-level interventions that can decrease LOS.[27]

This study has important limitations. First, retrospective analysis introduces restrictions and study design such as selection bias, which limits the generalizability of our findings. Second, absence of data on prehospital mortality limits our ability to appreciate the impact of delay or other prehospital factors that may have contributed to mortality prior to admission. Finally, the absence of data on possible confounders, such as socioeconomic status, or on further prehospital variables, such as initial vital signs during prehospital assessment, airway status, and timing of intubation for patients requiring intubation, presents a limitation on the comprehensive analysis of these data that also suggests important areas for further investigation.

CONCLUSIONS

In a retrospective cohort of >2000 patients from Cambodia with TBI, we found that a delay from time of injury to hospital admission beyond a 4-hour threshold was associated with worsening neurologic outcome and increased hospital LOS. These data can inform the development of prehospital guidelines for TBI care in LMICs. Capacity-building efforts around neurosurgery in these contexts should explore trauma system-level interventions that minimize IADs as much as possible, with a recommended 4-hour maximum threshold to optimize patient outcomes.

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