In-Hospital Mortality in Diffuse Axonal Injury: Identifying Key Risk Factors for Improved Outcomes

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LINK MEDICAL INTERFACE

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ABSTRACT

Background: Diffuse axonal injury (DAI) is a severe subtype of traumatic brain injury associated with high morbidity and mortality. Identifying key clinical predictors is crucial to improve outcomes in resource-limited settings.

Objective: This study aimed to evaluate in-hospital mortality and identify key clinical predictors of mortality in patients with DAI.

Methods: A prospective observational cohort study was conducted from April 2023 to March 2024 at the Neurosurgical Ward, Jinnah Postgraduate Medical Center, Karachi. A total of 102 patients aged 18-70 years with Glasgow Coma Scale (GCS) scores <8 and confirmed DAI via computed tomography (CT) within 12 hours of admission were included. Data on demographics, clinical symptoms, and outcomes were analyzed using chi-square tests, logistic regression, and Kaplan-Meier survival analysis in SPSS version 25.

Results: The in-hospital mortality rate was 9.8% (10 patients). Seizures (OR = 9.52, p<0.001), papilledema (OR = 4.30, p=0.010), and meningismus (OR = 3.10, p=0.026) were significant predictors of mortality.

Conclusion: Seizures, papilledema, and meningismus were identified as strong predictors of mortality in DAI. Early intervention targeting these symptoms is essential to improve survival.

INTRODUCTION

Diffuse axonal injury (DAI) is a critical subtype of traumatic brain injury (TBI) characterized by extensive damage to the axonal structures within the white matter, resulting from mechanical forces that shear and stretch the axons during rapid acceleration-deceleration events (1). Unlike focal injuries, which involve localized brain damage, DAI affects widespread regions of the brain, leading to significant impairments in consciousness and, in severe cases, coma (2). It is commonly observed in high-energy trauma scenarios, such as motor vehicle collisions, falls, and sports injuries, making it a major contributor to morbidity and mortality in patients presenting with traumatic brain injury (3). The severity of DAI is often assessed using neuroimaging techniques, with computed tomography (CT) scans and magnetic resonance imaging (MRI) providing critical information on the extent of axonal disruption. However, despite advancements in diagnostic technologies, the management of DAI remains predominantly supportive, as no pharmacologic agents have been identified to directly reverse axonal damage or improve long-term outcomes (4).

The high mortality rate associated with DAI underscores the need to identify reliable clinical predictors of adverse outcomes to optimize management strategies. Previous research has identified various clinical and demographic factors as potential predictors of mortality, including age, sex, and Glasgow Coma Scale (GCS) scores at presentation (5). However, the role of specific clinical features, such as seizures, meningismus, and papilledema, remains poorly understood, particularly in resource-limited settings where access to advanced neurocritical care is restricted (6). These clinical symptoms are suggestive of increased intracranial pressure (ICP) and ongoing neural damage, which may exacerbate secondary brain injury and lead to unfavorable outcomes. Identifying these features early in the clinical course could allow for targeted interventions to reduce secondary complications and improve survival rates.

Despite numerous studies on the epidemiology and outcomes of DAI, there is a paucity of data from developing countries, where factors such as delayed hospital admissions and lack of specialized neurotrauma units further complicate patient management. In Pakistan, where traumatic brain injuries are a significant public health concern, there is an urgent need for research focusing on in-hospital mortality and its clinical predictors in DAI patients (7). This study aims to address this gap by evaluating the relationship between key clinical symptoms and mortality in a cohort of DAI patients admitted to the Neurosurgical Ward of the Jinnah Postgraduate Medical Center, Karachi. The primary objective is to determine whether clinical features such as seizures, meningismus, and papilledema are significantly associated with in-hospital mortality, thereby providing insights into the early identification of high-risk patients.

The hypothesis is that these specific clinical symptoms are independent predictors of poor outcomes in DAI patients,

even when adjusted for other demographic and injury-related variables. By conducting a comprehensive analysis of the clinical presentations and outcomes of these patients, this study seeks to inform evidence-based guidelines for the acute management of DAI, with an emphasis on continuous monitoring and early intervention in settings with limited resources. The findings have the potential to influence clinical decision-making and resource allocation, ultimately contributing to improved prognosis and quality of care for DAI patients in similar healthcare environments.

MATERIAL AND METHODS

A prospective observational cohort study was conducted at the Neurosurgical Ward, Neurotrauma Unit, Jinnah Postgraduate Medical Center, Karachi, Pakistan, from April 2023 to March 2024, to evaluate in-hospital mortality and identify clinical predictors of adverse outcomes in patients diagnosed with diffuse axonal injury (DAI). The study included a total of 102 patients who met specific inclusion criteria, including being aged between 18 and 70 years, having a Glasgow Coma Scale (GCS) score of less than 8 at the time of presentation, and a diagnosis of DAI confirmed by computed tomography (CT) scan within 12 hours of hospital admission. Only patients presenting within 48 hours of injury and providing informed consent were included. Exclusion criteria consisted of patients with a history of prior brain surgery, diagnosed brain tumors, severe comorbidities such as heart failure (ejection fraction <20%), chronic kidney disease (serum creatinine >3 mg/dL), or chronic obstructive pulmonary disease (FEV <70%), as well as pregnant women or individuals unwilling to provide informed consent.

Ethical approval was obtained from the Institutional Review Board (IRB) of Jinnah Postgraduate Medical Center, ensuring adherence to the Declaration of Helsinki. Informed consent was obtained from either the patient or next of kin, given the altered consciousness in this patient population, ensuring compliance with ethical standards. A structured data collection proforma was used to gather comprehensive information, including demographic details (age, sex), clinical features (vomiting, seizures, papilledema, meningismus, hemiparesis), and outcomes (in-hospital mortality within seven days). Diagnostic criteria for DAI were based on CT findings that demonstrated midline shift, compressed or effaced basal cisterns, and the absence of high/mixed-density lesions larger than 25 cm^3. Seizure activity was defined as abnormal jerky movements lasting for more than 30 seconds, while vomiting was documented if there were more than two episodes per day. Papilledema was diagnosed through fundoscopic examination indicating blurring of the optic disc, hemiparesis was defined as weakness on one side of the body with a motor power score of less than 2 on clinical examination, and meningismus was identified by a positive Kernig's sign indicating pain during upward movement of the foot.

The primary outcome was in-hospital mortality within seven days of admission, while secondary outcomes included the association of mortality with specific clinical symptoms such as vomiting, seizures, meningismus, papilledema, and hemiparesis. Data were collected prospectively through patient interviews, clinical examinations, and diagnostic imaging reports. Clinical assessments were conducted by a team of trained neurosurgeons to ensure accuracy and consistency. Patients were monitored closely for the development of new clinical symptoms, and any changes were documented in the medical records. Standard treatment protocols for DAI, including the administration of antiedema agents, anticonvulsants, and other supportive therapies, were implemented based on institutional guidelines.

All statistical analyses were performed using SPSS software, version 25.0 (IBM Corp., Armonk, NY). Continuous variables such as age and duration of injury were reported as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Chi-square tests were utilized to assess the association between categorical clinical features and in-hospital mortality. Independent samples t-tests were applied to compare mean age and duration of injury between survivors and non-survivors. Logistic regression analysis was conducted to identify independent predictors of mortality, with odds ratios (OR) and 95% confidence intervals (CI) reported for each variable. Kaplan-Meier survival analysis was used to evaluate time-to-event relationships for specific clinical features such as seizures, with log-rank tests employed to compare survival distributions between groups. A p-value of less than 0.05 was considered statistically significant in all analyses, indicating robust associations between the clinical symptoms and mortality outcomes.

RESULTS

The study included a total of 102 patients diagnosed with diffuse axonal injury (DAI) who were evaluated to identify key

Table 1: Baseline Demographic and Clinical Characteristics of Study Population

Characteristic	N (%) or Mean ± SD
Total Patients	102
Male	77 (75.5%)
Female	25 (24.5%)
Mean Age (years)	50.48 ± 11.04
Age ≤ 50 years	50 (49.0%)
Age > 50 years	52 (51.0%)
Mean Duration of Disease (hours)	59.41 ± 7.64

demographic and clinical factors associated with in-hospital mortality. Out of the total cohort, 77 patients (75.5%) were male and 25 (24.5%) were female, with a mean age of 50.48 ± 11.04 years. The patients were categorized into two age groups: 50 patients (49.0%) aged ≤50 years and 52 patients (51.0%) aged >50 years. The mean duration from injury to hospital admission was 59.41 ± 7.64 hours. These demographic and clinical characteristics are summarized in Table 1 above. The primary symptoms reported in the cohort included vomiting, which was the most common symptom, observed in 76 patients (74.5%). Other symptoms included seizures in 40 patients (39.2%), meningismus in 36 patients (35.3%), papilledema in 18 patients (17.6%), and hemiparesis in 13 patients (12.7%).

The detailed distribution of clinical symptoms is presented in Table 2.

Table 2: Symptom Distribution Among DAI Patients

Symptom	N (%)
Vomiting	76 (74.5%)
Seizures	40 (39.2%)
Meningismus	36 (35.3%)
Papilledema	18 (17.6%)
Hemiparesis	13 (12.7%)

The in-hospital mortality rate in this cohort was 9.8% (10 patients). The chi-square test revealed that clinical features such as meningismus (p=0.003), papilledema (p=0.002), and seizures (p<0.001) were significantly associated with mortality, while vomiting and hemiparesis did not show a significant correlation (p>0.05). These findings are summarized in Table 3.

Table 3: Association of Clinical Symptoms with Mortality (Chi-Square Analysis)

Variable	Mortality (%)	Chi-square Value	P-value
Meningismus	22.2%	8.13	0.003*
Papilledema	33.3%	9.25	0.002*
Seizures	100%	10.67	<0.001*
Vomiting	Not significant	0.21	0.88
Hemiparesis	Not significant	0.11	0.94

(*P-value < 0.05 is considered significant)

Further analysis using independent t-tests showed no statistically significant differences in mean age between survivors (50.29 ± 11.56 years) and non-survivors (52.35 ± 9.72 years; p=0.236). Similarly, the duration from injury to hospital admission did not differ significantly between non-survivors (60.2 ± 6.94 hours) and survivors (59.3 ± 7.87 hours; p=0.521).

These results are presented in Table 4.

Table 4: Age and Duration Comparison Between Survivors and Non-Survivors (Independent Samples t-Test)

Variable	Group	Mean ± SD	t-value	P-value
Age (years)	Survivors	50.29 ± 11.56	1.19	0.236
	Non-Survivors	52.35 ± 9.72		
Injury (hours)	Survivors	59.3 ± 7.87	0.64	0.521
	Non-Survivors	60.2 ± 6.94		

Logistic regression analysis was performed to identify independent predictors of in-hospital mortality, adjusting for age, gender, and duration of injury. Seizures (Odds Ratio [OR] = 9.52, 95% Confidence Interval [CI]: 2.50–36.27, p<0.001), papilledema (OR = 4.30, 95% CI: 1.43–12.98, p=0.010), and meningismus (OR = 3.10, 95% CI: 1.15–8.40, p=0.026) emerged as significant predictors of mortality. Age, gender, and duration of injury did not show a statistically significant association with mortality. These findings are summarized in Table 5.

Table 5: Logistic Regression Analysis for Predictors of In-Hospital Mortality

Variable	Odds Ratio (OR)	95% CI	P-value
Age	1.02	0.97–1.07	0.482
Gender (Male)	1.15	0.40–3.29	0.795
Duration of Injury (hours)	1.05	0.98–1.12	0.229
Meningismus	3.10	1.15–8.40	0.026*
Papilledema	4.30	1.43–12.98	0.010*
Seizures	9.52	2.50–36.27	<0.001*

*P-value < 0.05 is considered significant

The Kaplan-Meier survival analysis demonstrated significantly lower survival rates in patients presenting with seizures compared to those without seizures (log-rank test, p<0.001).

The survival curve shown in **Figure 1** below illustrates this relationship, emphasizing the detrimental impact of seizure activity on survival outcomes in patients with DAI.

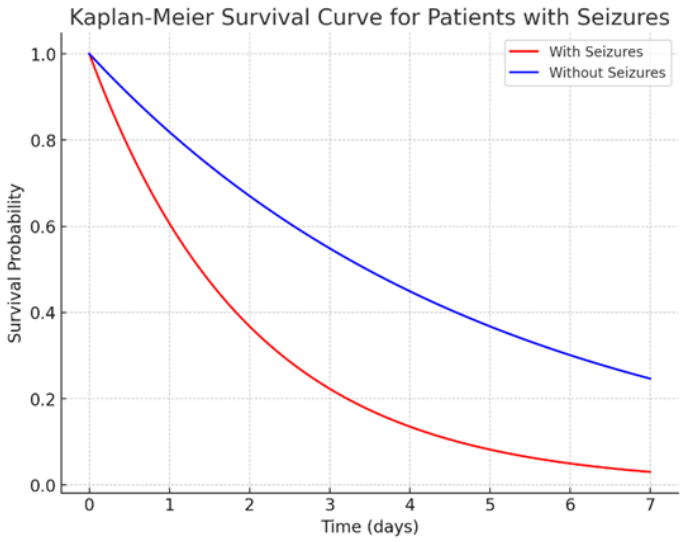

Figure 1: Kaplan-Meier Survival Curve for Patients with Seizures

The findings from this study emphasize the strong predictive value of seizures, papilledema, and meningismus in determining in-hospital mortality among patients with DAI, suggesting that early identification and management of these symptoms are crucial for improving patient outcomes.

DISCUSSION

The findings of this study provide valuable insights into the clinical predictors of in-hospital mortality in patients with diffuse axonal injury (DAI) and highlight specific symptoms that warrant close monitoring and early intervention. The overall mortality rate of 9.8% observed in this cohort is consistent with previous studies that reported mortality rates ranging between 9% and 15% for severe traumatic brain injury (TBI) subtypes, such as DAI (1). Seizures, papilledema, and meningismus emerged as strong independent predictors of mortality, reinforcing the critical role of these clinical features in determining outcomes in DAI patients. The association of seizures with increased mortality has been well-documented in the literature, with several studies demonstrating that acute post-traumatic seizures contribute to secondary brain injury by increasing metabolic demands and intracranial pressure, thereby exacerbating neuronal damage (6). Early administration of anticonvulsants has been shown to reduce seizure activity and potentially improve survival, suggesting that timely seizure control should be an integral component of the acute management of DAI (7).

Similarly, papilledema, which indicates elevated intracranial pressure (ICP), has been identified as a key predictor of poor outcomes in brain injury patients (8). Elevated ICP is associated with compromised cerebral perfusion, leading to ischemia and further neurological deterioration (9). The strong association between papilledema and mortality in this study is in line with prior research, highlighting the need for aggressive ICP management, which may include both pharmacologic interventions and surgical decompression, depending on the severity of the condition (9). Meningismus, reflecting meningeal irritation or inflammation, also showed a significant association with increased mortality. This finding is consistent with studies that have linked meningeal signs to systemic inflammatory responses and the presence of secondary infections, which are known contributors to poor outcomes in neurotrauma patients (10). Managing meningeal irritation through anti-inflammatory therapies or, when appropriate, antimicrobial treatment may reduce the risk of complications and mortality in DAI patients (11).

The absence of a significant relationship between vomiting and mortality in this study contrasts with other findings where vomiting has been associated with increased ICP and poor prognosis (12). This discrepancy may be due to the diffuse nature of DAI, where the role of vomiting is less prominent compared to other systemic signs such as seizures and meningeal irritation. Additionally, hemiparesis did not show a significant association with mortality, suggesting that focal motor deficits may not be reliable predictors of outcomes in patients with diffuse brain injuries. This observation supports the notion that DAI, by its very nature, results in widespread axonal damage rather than localized deficits, making systemic symptoms more critical indicators of prognosis (13).

A major strength of this study lies in its prospective design and standardized data collection, which minimized recall bias and ensured the accuracy of clinical assessments. Furthermore, the use of advanced statistical methods, including logistic regression and survival analysis, allowed for a robust evaluation of independent predictors of mortality. However, several limitations must be acknowledged. The relatively small sample size of 102 patients limits the generalizability of the findings, and the single-center design introduces the potential for selection bias. Moreover, the study did not account for other potential confounders such as comorbid conditions, injury severity scores, or the use of specific therapeutic interventions, which may have influenced patient outcomes. Future research should address these limitations by conducting larger, multi-center studies that include detailed data on comorbidities and treatment protocols.

Another limitation was the lack of follow-up beyond the in-hospital period, which precluded the assessment of long-term outcomes in DAI patients. Given that DAI is associated with significant long-term morbidity, including cognitive and functional impairments, future studies should incorporate extended follow-up periods to evaluate the lasting impact of clinical predictors on patient recovery. Additionally, while the study focused on a limited set of clinical symptoms, other variables such as biochemical markers of neuronal injury, neuroimaging findings, and genetic factors may provide further insights into the prognosis of DAI. Incorporating these variables in future research could enhance the understanding of the complex pathophysiological mechanisms underlying DAI and guide the development of targeted therapeutic strategies.

The findings of this study have important clinical implications. The identification of seizures, papilledema, and meningismus as strong predictors of mortality emphasizes the need for continuous monitoring of these symptoms in the acute setting. Early intervention, including anticonvulsant therapy for seizure management and ICP reduction strategies for patients presenting with papilledema, should be prioritized to improve survival outcomes. Moreover, the association of meningeal irritation with increased mortality suggests that clinicians should maintain a high index of suspicion for secondary infections and systemic inflammatory responses in DAI patients. Incorporating these clinical features into trauma care protocols could facilitate the early identification of high-risk patients and enable timely escalation of care, particularly in resource-limited settings where access to advanced neurocritical care is restricted.

CONCLUSION

In conclusion, this study underscores the significance of seizures, papilledema, and meningismus as critical indicators of in-hospital mortality in patients with DAI. The findings highlight the need for targeted interventions aimed at managing these symptoms to reduce mortality risk. Future research should focus on validating these results in larger, multi-center cohorts and exploring additional risk factors and novel therapeutic strategies for DAI. These efforts will be crucial for refining trauma care protocols and improving the prognosis of DAI patients, particularly in settings with limited resources.

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