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Models to predict expansive intracranial hematomas occurrence for adult traumatic brain injury patients presenting at Accident and Emergency Department at Mulago National referral Hospital in Uganda

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Abstract

Background: A timely and accurate surgical decision regarding expansive intracranial hematomas (EIH) is crucial in clinical practice and patient outcomes, particularly in resource-limited settings. Although several predictive models exist, their utility in forecasting EIH remains underexplored, often neglecting the evolving nature of intracranial hemorrhage.

Aim: Study determined the models that can be used to predict the EIH occurrence for patients with TBI in Uganda.

Methods: A cross sectional study was conducted to determine characteristics of patients with EIH which was then used to identify applicable models for predicting EIH occurrence among TBI patients. Adult TBI patients with intracranial hematoma undergoing surgical evacuation between June 16, 2021, and December 17, 2022, were included. Participants were categorized based on EIH presence or absence, determined by hematoma volume changes. Logistic regression analyzed factors influencing EIH, including demographics, neurological assessment, hematological parameters, and neuroimaging.

Results: Of the total 324 enrolled patients with intracranial hematomas, 59.3% (n=192) developed EIH, resulting in a proportion of 0.59 (95% CI: 0.54 to 0.65). The final model incorporated age, systolic and diastolic blood pressure, subdural hematoma (SDH), diffuse axonal injury (DAI), skull fracture, and an interaction term between skull fracture and SDH. Each unit increase in systolic blood pressure raised EIH odds by 1.045, while diastolic blood pressure increase lowered odds to 0.942. SDH increased odds by 6.286, and DAI by 4.024. However, in cases of skull fracture, SDH reduced odds to 0.0676. The model's five-fold cross-validated average area under the receiver operating curve (AUC) was 0.722, with 64.5% accuracy.

Conclusion: EIH is common among TBI patients in Uganda with a prevalence of 59.3%. When systolic blood pressure and diastolic are raised by 1 unit from the baseline, having SDH, DAI and skull fracture, the bigger odds of having EIH it becomes. These new models can inform policy and future interventions to predict earlier EIH occurrence and build off the effective treatment modalities for such patients.

Introduction

Expansive intracranial hematoma (EIH) remains a challenge among traumatic brain injury (TBI) patients often leading to increased morbidity and mortality worldwide especially in low-middle income countries (1). The survival and better outcomes after severe TBI depend on the therapeutic window that is clinically difficult to predict the trends (1). The benefits of identification of a subset of traumatic brain injury patients who are at high risk of developing expansive intracranial hematoma (EIH) and in whom the risk-benefit ratio of new therapeutic options has not been well reported (2). Previous reports and observations have reported several factors contributing to EIH following TBI including old age, mechanism of trauma, hypoxia, pre-hospital systolic blood pressure, initial hematoma volume and location such as subdural hematoma (SDH), subarachnoid haemorrhage, hyperglycaemia, antiplatelet medication use, low platelet count, etc. (3-6). However, large clinical trials have shown unclear effective therapy for EIH and many patients still experience poor prognosis (7-11). This fact is not reliable in terms of prediction of the best therapeutic action. Increased EIH among TBI patients admitted to the emergency Unit at Mulago National Referral Hospital (MNRH) as well as to hospitals across Uganda as a result of RTA, assaults, and falls was observed in earlier studies and observations (12). Due to inadequate healthcare facilities, restricted access to the operating rooms, lack of ICU beds, inadequate postoperative care, shortage of neurosurgical workforce and anesthesiologists, duration in decision-making with a lack of evidence-based protocol on the management of such patients can lead to inefficient and unsafe management. Several TBI patients with EIH succumb to death before or during an intervention is instituted in Uganda as well as in other LMIC (1, 13, 14). Given the faster course to deleterious form of brain hematoma, it is clinically relevant to make an appropriate, trustworthy, and quick surgical decision based on predictive models of EIH (15-18). Accurate predictive models for EIH could be derived from early biological markers of injury severity. It might offer a practical tool to enhance resource allocation in remote settings with limited resources (15-18). There have been many described predictive models; however, they do not employ frequently the outcomes (15-18). The evolutionary character of cerebral bleeding is not taken into account by the majority of models (19). Furthermore, the models were established on small samples, many were methodologically flawed, and few were validated in external populations(19). Few others were neither presented in a clinically practical way, nor were they established in populations from LMIC, where 93% of TBI occur (20). The study determined the common demographic characteristic, healthy post American Society of Anesthesia (ASA), neurological assessment, laboratory, and CT findings as well as developed models to predict EIH occurrence in TBI patients.

Methods

Study Design

A cross-sectional study was conducted among TBI patients with intracranial hematoma between the 16th of June 2021 and the 17th of December 2022. Patients presenting with expansive hematomas at MNRH were recorded as well as their

corresponding risk factors for EH following intracranial hematomas.

Study Setting

Study was conducted at Mulago National Referral Hospital (MNRH), Kampala, Uganda. TBI patients were recruited on admission at the Accident and Emergency Department, then followed up in the operative theatres and the neurosurgery ward.

Study Population

TBI patients aged 18 years and above, had two positive CT scan examinations for expansive hematoma as defined by an increase in acute intracranial traumatic hematoma volume >33% or absolute hematoma growth >6ml from the initial scan within 72 hours of injury during the study period and who met the inclusion and exclusion criteria were recruited in the study.

Sample Size & determinism

The sample size was calculated using Kish Lesley formula, where p is the true proportion (30%), Z is the desired confidence interval at 95% (Z=1.96) and e the desired precision (5%). Therefore, the calculated sample size was 324.

Study participant selection criteria

Inclusion

Participants were TBI patients aged 18 years and above, post resuscitation GCS of 4 to14, with evidence of EIH on two CT scans (increase in hematoma volume >33% or absolute hematoma growth > 6ml from the initial scan) exclusively, eligible for cranial surgery and enrolled in the study within 24 hours of initial presentation to hospital. A written signed informed consent from the patient or their next of kin was obtained.

Exclusion

Patients with (1) known pre-thrombocytopenia, (2) a history of coagulation disorders, and (3) used anticoagulants, (4) pregnancy, (5) and those with the inability to consent before surgical intervention were excluded from the study.

Sampling procedure

Consecutively sampling method was used and TBI patients who met the inclusion criteria and had expansive intracranial hematomas were enrolled in this study.

Study procedures

Patients were recruited from their admission at the Accident and Emergency Department of the MNRH. After the initial trauma assessment and resuscitation, a Brain CT scan was obtained. Hematoma on brain CT findings and measurement were obtained from the neuro-radiologists. Follow-up brain CT scans were obtained at different timing within 72 hours as maximum from the time between the TBI and initial brain CT hours and based on neurosurgeons' recommendations. The date, time and results of initial and all subsequent scans were recorded. The patients were monitored clinically and radiologically for the hematoma enlargement until surgical evacuation decision making.

Study variables

Patient demographic characteristics, healthy pre and post ASA, neurological assessment, laboratory, and brain CT findings were

extracted from captured using the Research Electronic Data Capture (Redcap) system. These included age, sex, educational level, residence type, occupation, marital status, previous comorbidities (diabetes mellitus, hypertension, coagulopathies), history of alcohol and substance abuse, time and date of injury, time and date of hospitalization, previous history of TBI, injury type and mechanism, intention of injury, multi-trauma, pre-hospital (pre and post-injury ASA), neurological assessment (GCS, pupil examination) blood pressure(Systolic and diastolic, mean arterial pressure), findings on brain CT scans, scalp injuries (location, length), skull fracture (simple vs. compound, number, location, side), the types of traumatic expansive intracranial hematoma EIH (epidural, subdural, intra-cerebral, contusion, diffuse axonal injury), their location, size, diameter, presence of midline shift/ herniation syndrome, patency of basal cisterns, and presence of Swirl sign.
The independent variables were presence or absence of EIH. Secondary outcomes control variables were the socio-demographic, healthy pre and post ASA, clinical, laboratory and radiological findings.

Statistical data analysis

Data was submitted to the secure Redcap system of the Uganda Cancer Institute (UCI) and analysis was performed by the department of statistic within Duke Global Neurosurgery and Neurology (DGNN). R 4.1.2 and SPSS version 26 were utilized for statistical analysis in this study. Logistic regression was used to explore the factors that significantly influence EIH, due to the dichotomy of the outcome. The four major factor categories explored includeddemographical information (e.g. age, occupation, etc.), neurological assessment (e.g. GCS), lab and blood results, and neuroimaging patterns (e.g. Subdural Hematoma). Thus, model selection was conducted in order to achieve better interpretability. Variables were selected manually from each category, based on neurological knowledge. Then, variables that "best" fit the outcome (EIH) were selected by choosing the model with the lowest AIC during a backward stepwise selection. Finally, all selected variables were pooled from each category to fit the final logistic regression model. The final model was selected based on the same criteria, but the predictive performance on the validation dataset was undesirable. Therefore, the model was manually tweaked to achieve better accuracy, AUC in both validation dataset and five-fold cross-validation. Levels of $p < 0.05$ were considered statistically significant.

Ethical approval and consent

Agreement for conducting this study was obtained from the Makerere University School of Medicine Research Ethics Committee (SOMREC), recorded as Mak_SOMREC-2020-38. All study methods were carried out in conformity with Ugandan laws and regulations, the Good Clinical Practice guidelines, and the Helsinki Declaration.

Informed consent

Prior to surgery, informed consent was gained from patients with a stable high-level of consciousness and not in pain, and the research assistants then gave them an interviewer-guided questionnaire. After providing the surgical evacuation intervention, participants who were seriously ill or experiencing excruciating pain

or discomfort gave their permission and were recruited. A written signed informed consent from the patient or their next of kin was obtained from each participant.

Consent for publication

Not applicable.

Results

Study flow of the participants

During the study period, a total of 1500 patients were eligible for enrollment into the study between 16 th June 2021 to 17 th December 2022 (figure 1). Out of these, 21.6% (n=324) were enrolled into the study. One thousand one hundred and seventy-six patients were excluded because they did not fulfill the inclusion criteria or did not give consent. In a cohort of 324 patients with intracranial hematomas, 59.3% (n=192) had expansive intracranial hematomas indentified on CT scan (figure 1).

Proportion of traumatic brain injury patients presenting with expansive hematomas

Of the 324 patients with intracranial hematomas, 59.3% (n=192) had expansive hematomas identified on 2 CT scan resulting in a proportion of 0.59 (95% CI: 0.54 to 0.65).

Models leading to expansive intracranial hematoma development following TBI

The selected variables from each of the categories that were used in the model included demographical information, neurological assessment, biochemical findings, blood pressure, and imaging (Figure 2). The selection was based on AIC. The model with the lowest AIC was further selected. The following were the variables that were selected from each category including demographical information: (age, residence, habit, pre-injury ASA, post-injury ASA, and admission time from injury to hospital); neurological assessment:(GCS, pupils' examination); biochemical parameter (Sodium [Na+]), and blood pressure: (systolic blood pressure, diastolic blood pressure and mean arterial pressure); Imaging: (skull fracture, epidural hematoma, subdural hematoma, diffuse axonal injury, and scalp injuries)

After selecting these variables above, another logistic regression model was fit using the selected variables. This was the final selection and it was based on AIC, generalized Variance Inflation Factor and neurological knowledge. The final selected model was further included with the following variables like age, systolic blood pressure, diastolic blood pressure, skull fracture, subdural hematoma, diffuse axonal injury, skull fracture, and subdural hematoma (interaction term) (Figure 3). The model coefficients and their significance level were obtained and interpreted as the significant coefficients. Among the variables, Subdural hematoma showed the highest risk to EIH with odds of 6.2860509 (Table 1).

Models leading to expansive intracranial hematoma development following TBI

At multivariate logistic regression for EIH, the initial model included the following variables: outcomes (presence or absence of developing EIH), demographic characteristics such as age, sex, education, occupation etc. After AIC-based model selection, the model had these selected variables (Table 2).

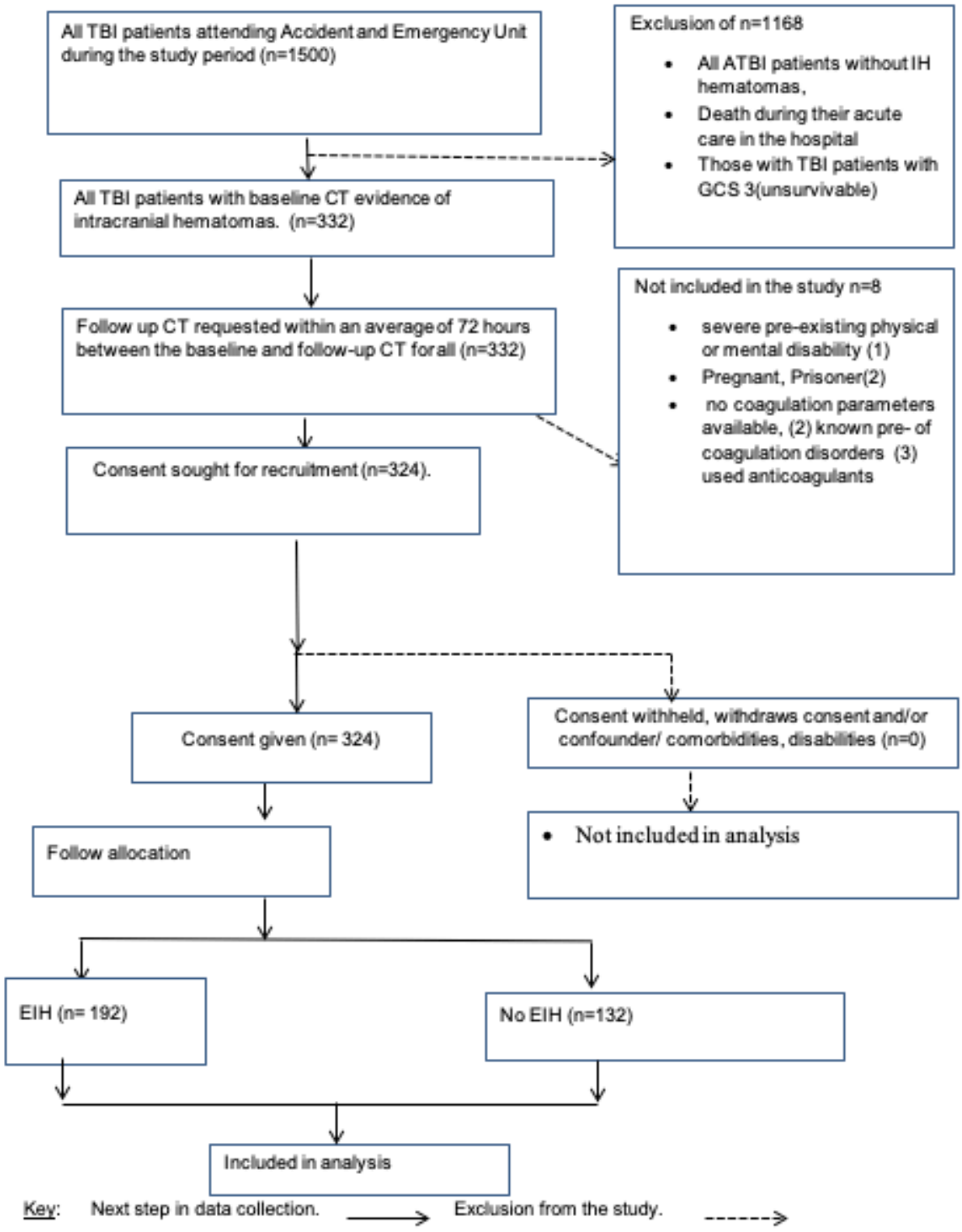

Figure 1. Flow chart of patient's recruitment

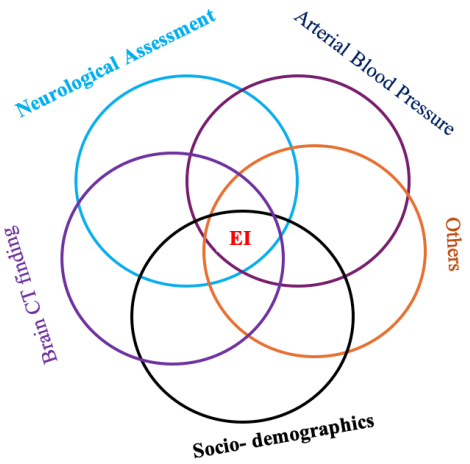

Figure 2. Modelling mathematical same-size circle design

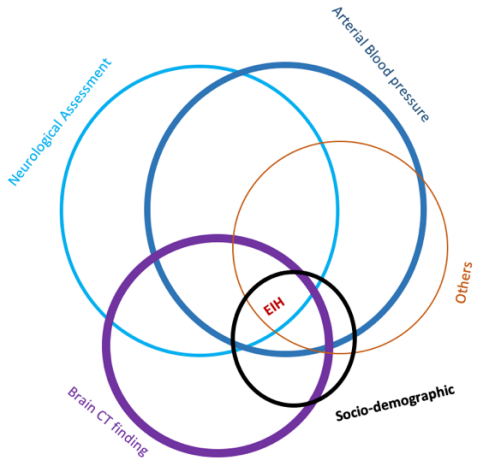

Figure 3. Modelling mathematical circles with different weight

	Odds Ratio	Pr(>|z|)
(Intercept)	0.1432344	0.1931110
Age 18 to 30	0.4644902	0.1493704
Age 31 to 45	0.9938626	0.9918531
Systolic blood pressure	1.0451607	0.0062050
Diastolic pressure	0.9419734	0.0069345
Skull fracture	1.8982746	0.2802460
Subdural hematoma	6.2860509	0.0038340
Diffuse axonal injury	4.0244741	0.0081517
Skull fracture and subdural hematoma	0.0675804	0.0026879

Table 1. Model coefficients for expansive intracranial hematomas including demographic, blood pressure, imaging characteristic of patients with traumatic brain injury and their significance level

Coefficients	Estimate Std.	Error z	value	Pr (>|z|)
Intercept	1.6727	0.7687	2.176	0.029562 *
Age 18 to 30	-4.0024	0.8268	-4.841	1.29e-06 ***
A ge 31 to 45	-3.0463	0.8416	-3.620	0.000295 ***
Age 46 to 60	-2.3090	0.8343	-2.768	0.005644 **

Education Higher	1.4596	0.5678	2.571	0.010153 *
Education intermediate	1.0487	0.4198	2.498	0.012475 *
Education Unknown	0.4462	1.2674	0.352	0.724814
Mild post ASA	-2.4651	1.1697	-2.107	0.035075 *
Severe post ASA	-0.7016	1.0169	-0.690	0.490265
Age 18 to 30 post ASA mild	3.4414	1.7610	1.954	0.050672.
Age31 to 45 post ASA mild	4.4123	1.6923	2.607	0.009126 **
Age 46 to 60 post ASA mild	4.5016	1.6402	2.745	0.006060 **
Age 18 to 30 post ASA severe	4.6783	1.2432	3.763	0.000168 ***
Age 31 to 45 post ASA severe	2.8103	1.3179	2.132	0.032971 *
Age 46 to 60: post ASA severe	3.0769	1.2692	2.424	0.015342 *
Education Higher post ASA mild	-1.3501	1.8682	-0.723	0.469864
Education Intermediate post ASA mild	-0.7939	1.2985	-0.611	0.540917
Education unknown post ASA mild	16.4733	1029.1236	0.016	0.987229
Education Higher post ASA severe	13.1020	820.8092	0.016	0.987264
Education intermediate post ASA severe	-2.0572	0.8663	-2.375	0.017560 *
Education Unknown post ASA severe	-2.1391	1.7774	-1.204	0.228766

Table 2. Multivariate logistic regression analysis of socio-demographic and Post-injury ASA (American Society of Anesthesia) characteristics of patients with EIH

Key codes : 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1---- Statistical significance at 95% CI.

Summary of the logistic regression models of neurological assessment where the Null deviance is 294.49 on 216 degrees of freedom; AIC of 241.48; number of Fisher Scoring iterations of 22 and deviance residuals with min of -1.3422; 1Q of -1.0061; median of -0.8127; 3Q of 1.3590, Max of 1.5928 (Table 3).

Coefficients	Estimate Std.	Error z	value	Pr (>|z|)
Intercept	768.5554	62738.0760	0.012	0.9902
Age 18 to 30	-770.5037	62738.0760	-0.012	0.9902
Age 31 to 45	-768.8803	62738.0760	-0.012	0.9902
Age 46 to 60	-768.8688	62738.0760	-0.012	0.9902

Residence Urban	1.1279	0.4097	2.753	0.0059**
Habit Smoke	-721.7209	63023.7735	-0.011	0.9909
Pre_ASA mild	-72.4522	6051.8892	-0.012	0.9904
Pre_ASA severe	34.2440	45383.5973	0.001	0.9994
Post_ASA mild	-683.2496	56030.9510	-0.012	0.9903
Post_ASA severe	-782.6557	62148.0370	-0.013	0.9900
Admission_time	-17.0507	1407.0242	-0.012	0.9903
Age18 to 30 habit Smoke	721.0271	63023.7735	0.011	0.9909
Age31 to 45 habit Smoke	720.8889	63023.7735	0.011	0.9909
Age 46 to 60 habit Smoke	721.8548	63023.7735	0.011	0.9909
Age18 to 30 post_ASA mild	742.9351	59224.5757	0.013	0.9900
Age31 to 45 post_ASA mild	703.1359	57048.8784	0.012	0.9902
Age46 to 60 :post_ASA mild	860.0512	77237.7297	0.011	0.9911
Age18 to 30 post_ASA severe	786.1386	62148.0370	0.013	0.9899
Age31 to 45 post_ASA severe	783.3970	62148.0370	0.013	0.9899
Age46 to 60 post_ASA severe	748.1735	71382.4677	0.010	0.9916
Age18 to 30 admission_time	17.0528	1407.0242	0.012	0.9903
Age31 to 45 admission_time	16.7452	1407.0242	0.012	0.9905
Age46 to 60 admission_time	17.0939	1407.0242	0.012	0.9903
Residence Urban post_ASA mild	-41.3748	7367.2762	-0.006	0.9955
Residence Urban post_ASA severe	-1.5756	1.1407	-1.381	0.1672
Habit Smoke post_ASA mild	-80.8060	31953.5340	-0.003	0.9980
Habit Smoke post_ASA severe	-15.0738	18800.6825	-0.001	0.9994
Pre_ASA mild admission_time	19.1221	1476.9911	0.013	0.9897
Pre_ASA severe :admission_time	18.1437	14006.9610	0.001	0.9990

Key codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 ---- ---- Statistical significance at 95% CI

Table 3. Multivariate logistic regression analysis of socio-demographic and Post-injury ASA (American Society of Anesthesia) characteristics of patients with expansive intracranial hematomas

Coefficients	Estimate Std.	Error z	value	Pr (>|z|)
Intercept	-0.4173	0.1721	-2.425	0.0153 *
GCS_eye_open None	0.7968	0.3990	1.997	0.0458 *
GCS_eye_open To pain	-0.5210	0.4292	-1.214	0.2248
GCS_eye_openTo speech	0.2838	0.4044	0.702	0.4829

Key codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 --- ---- Statistical significance at 95% CI

Table 4. Multivariate logistic regression analysis of sociodemographic and Post-injury ASA (American Society of Anesthesia) characteristics of patients with expansive intracranial hematomas

Summary of the logistic regression models of CT imaging findings where the Null deviance is 257.54 on 188 degrees of freedom; residual deviance of 233.59 on 184 degrees of freedom; AIC of 243.59; number of Fisher Scoring iterations of 5 and deviance residuals with min of -1.7242; 1Q of -0.9656; median of-0.7095; 3Q of 1.1460; max of 1.9491 (Table 5).

Coefficients	Estimate Std.	Error z	value	Pr (>|z|)
Intercept	-6.841e+00	2.648e+00	-2.583	0.00978 **
Sodium Na+	2.099e-02	1.767e-02	1.188	0.23493
Systolic blood pressure	5.152e+04	2.397e+04	2.150	0.03158 *
Diastolic blood pressure	1.030e+05	4.794e+04	2.150	0.03158 *
Mean arterial pressure	-1.546e+05	7.191e+04	-2.150	0.03158 *

Key codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 ---- ---- Statistical significance at 95% CI

Table 5. Multivariate logistic regression analysis of socio-demographic and Post-injury ASA (American Society of Anesthesia) characteristics of patients with expansive intracranial hematomas

Summary of the logistic regression models including factors from demographic, lab and CT imaging findings where the null deviance is 216.21 on 156 degrees of freedom; residual deviance of 180.32 on 146 degrees of freedom ; AIC of 202.32; number of Fisher Scoring iterations of 4 and deviance residuals with min of -1.7728 ; 1Q of -0.7953 ; median of -0.4560 ; 3Q of 0.8401; max of 2.2309 1.9491; Area under the curve: 0.7081 (Table 6)

Coefficients	Estimate Std.	Error z	value	Pr (>|z|)
Intercept	-2.7604	0.7322	-3.770	0.000163 ***
Skull fracture	1.0048	0.9775	1.028	0.303959

Epidural hematoma	1.8740	0.6627	2.828	0.004688 **
Subdural hematoma	2.9560	0.7024	4.208	2.57e-05 ***
Diffuse axonal injury	2.6817	1.0235	2.620	0.008790 **
Scalp injuries	-0.9347	0.8075	-1.158	0.247049
Skull fracture :epihematoma	-1.4064	0.9919	-1.418	0.156232
Skull fracture :subdhematoma	-2.5384	0.9187	-2.763	0.005728 **
Skull fracture :Scalpinjuries	2.0230	1.0511	1.925	0.054275.
Epihematoma: diffuse axonal injuries	-2.1427	1.0722	-1.998	0.045668 *
Subdhematoma: diffuse axonal injuries	-1.7742	1.1025	-1.609	0.107565

Key codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 ----- ---- Statistical significance at 95% CI

Table 6. Multivariate logistic regression analysis of CT imaging findings of patients with expansive intracranial hematomas

Summary of the logistic regression models including factors from demographic, blood pressure measurement and CT imaging findings where the null deviance is 197.06 on 142 degrees of freedom; residual deviance of 155.46 on 134 degrees of freedom; AIC of 173.46; number of Fisher Scoring iterations of 4 and average of accuracy from cross validation mean of 0.6445048; average AUC from cross-validation mean of 0.7216186 (table 7).

Coefficients	Estimate Std.	Error z	value	Pr (>|z|)
Intercept	-1.943273	1.493182	-1.301	0.19311
Age 18 to 30	-0.766815	0.531861	-1.442	0.14937
Age 31 to 45	-0.006156	0.602920	-0.010	0.99185
Systolic blood pressure	0.044171	0.016140	2.737	0.00620 **
Diastolic blood pressure	-0.059778	0.022140	-2.700	0.00693 **
Skull fracture intermediate	0.640945	0.593596	1.080	0.28025
Subdural hematoma	1.838333	0.635770	2.892	0.00383 **
Skull fracture_subd hematoma	-2.694437	0.897743	- -3.001	0.00269 **

Key codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 ---- ---- Statistical significance at 95% CI

Table 7. Multivariate logistic regression analysis of demographic, blood pressure and CT imaging findings of patients with EIH

Discussion

Several predictive models for EIH following TBI have been described with limited information on their use in predicting EIH. The prevalence of EIH among TBI patients presenting at Accident and emergency unit at MNRH was 59.3% among adult TBI patients and this differed according to the time of their presentation at the unit. The findings were consistent with previous studies which showed that the rate of EIH following TBI ranged from 38 to 59% of cerebral hemorrhages (6, 21-24), but was lower than a study by Adatia and colleagues (75%) (2). These variations may, in part, have resulted from the absence of a common definition of EH in the literature (25-27). The timing between baseline (first scan at initial presentation at the Accident and emergency unit) and follow-up scans, research inclusion criteria, and various hematoma volume measuring techniques, on the other hand, could all contribute to this variation in proportion among studies (2). In addition, age, systolic blood pressure, diastolic blood pressure, subdural hematoma (SDH), diffuse axonal injury (DAI), skull fracture, and an interactive term of skull fracture and SDH were found to be independly associeted with EIH in the final model (Table 1). These findings concur with previous studies which reported that SDH, skull fracture are risk factors to EIH (2, 26, 28-30). Some studies have linked the evolution of intracranial hematomas with factors such as age greater than 61 (2, 26, 31-33) and elevated admission systolic blood pressure (2, 34, 35). However, this study didnot find subarachnoid hemorrage(SAH) among risk factors as reported by Allison et al.(26) but added new risk factors such as DAI and increment in diastolic blood pressure show an association with EIH. However, it is unknown why these seven risk factors for EIH are independent of one another, but in constrat with previous report (26), this study revealed that an interactive term of skull fracture and SDH decreases the odds of EIH to 0.0676 times, thus a protective effect. These findings limit the ability to confirm if a cumulative brain injury in which patients who also experience skull fractures and SDH in addition to DAI suffered more brain damage due to EIH than those who only had DAI. The average area under the receiver curve (AUC) from a five-fold cross-validation was 0.722, while the average accuracy was 64.5%. The AUC of the current study seven-point models agree with models developped by Cepata et al (0.72) (6), but lower than a simple four-point predictive score reported by Allison et al.(0.77) (26).

Holding the rest of variables constant, increasing systolic blood pressure by 1 unit from the baseline would make the odds of getting EIH become 1.045 times. Similarly, increasing diastolic blood pressure by 1 unit from the baseline would make the odds of getting EIH become 0.942 times. Although some research, including this study, have corrolated this observation with high mean arterial pressure (MAP) which was positively corrolated to EIH (5, 36, 37) and patients with post-admission SBP of more than 160 mmHg have a substantially higher risk of expansive hemorrhages (P = 0.0074) (36, 38). The ongoing rupture and bleeding of small veins may help to explain this and managing blood pressure early could be one of the possible therapy goal. Additionally, people with a previous history of hypertension are four times more likely than those without a history of the condition to develop an enlargement of a cerebral hematoma (table 1). In patients with persistent hypertension, endovascular dysfunction and

cerebrovascular remodelling were seen. These alterations could be linked to increased blood-brain barrier permeability following TBI (2, 39).

Holding the rest of variables constant, having SDH would make the odds of getting EIH become 6.286 times. This finding is in line with previous studies where ASDH may progress overtime especially when the Hounsfield unit and bleeding depth are higher (40).

Holding the rest of variables constant, having DAI (severe deep white matter shear injuries) would make the odds of getting EIH become 4.024 times. DAI is one of the two most serious brain injuries which is more common in car accidents and cases of falling from a great height (41).

Finally, holding the rest of variables constant, given a patient has Skull fracture (bone plate), having SDH would make the odds of getting hematoma become 0.0676 times. Previous studies have shown a connection between the enlargement of cerebral hematomas and the impact sites, such as the frontal and temporal skull fractures, rupturing of cortical veins etc. (26, 27).

Given basic education, healthy post ASA, people in age group 18 to 30, 31 to 45, and 46 to 60 hadve a significantly lower odds of getting Expansive intracranial Hematoma (EIH), compared to people greater than 61. Specifically, the odds of getting an expansive intracranial hematoma become 0.018, 0.048, and 0.099 times the odds for greater than 61, respectively for these three age groups (Table 2). Age-related structural deficiencies in the microvasculature, endothelial loss, and decreased resting CBF are all linked to increased vulnerability to the mechanisms causing cerebral hematoma propagation inside the traumatic penumbra, as has been reported in the previous studies (2, 33, 42, 43). Similar to earlier studies, TBI patients between the ages of 39 and 48 years had a 1.54 times higher chance of developing EH than their counterparts less than 39 years (26, 31-33). Given healthy post ASA, age greater than 61, people with higher or intermediate education have significantly higher odds of getting EIH than the basic education. The odds become 4.3, 2.9 times the odds of basic education (Table 2). Higher or intermediate educated people typically participate in risky behaviors to boost their income, which predisposes them to TBI and subsequently EIH (Table 2). Being educated is related to various activities that demand more financial requirements. So, given age greater than 61, basic education, people having mild or severe post ASA are less likely to have EIH than healthy people. The odds become 0.085 and 0.5 times the healthy odds. Given age between 18 to 30, basic education, having a mild or severe post ASA significantly increases the odds of getting EH, compared to healthy condition. The odds become 3.1 and 10.8 times the healthy, respectively (Table 2). Given age between 31 to 45, basic education, having a mild or severe post ASA significantly increases the odds of getting EIH, compared to healthy condition. The odds become 8.2 and 16.6 times the healthy, respectively (Table 2). Given age between 46 to 60, basic education, having a mild or severe post ASA significantly increases the odds of getting EIH, compared to healthy condition. The odds become 9, 21.9 times the healthy, respectively (Table 2). Although some studies, including this study, have validated this discovery, this conclusion is consistent with previous findings that showed that serious systemic diseases are positively correlated with EIH (37). However, given age greater than 61, intermediate education, having a severe post ASA significantly

decreases the odds of getting EIH, compared to healthy condition. The odds become 0.13 times the healthy (Table 2). When age is greater than 61, the worse post ASA is, the smaller odds of having EIH becomes. This counterintuitive result is likely to due to the small sample size in the present study.

Study limitation

The present study had limitations including more variables of 824 than the sample size of the study participants and missing values. Thus, the model selection was done to achieve better interpretability of the findings. The model used a 70% and 30% split for the train and test data. A seed was set so that the findings were reproducible. However, the findings show that the selected models were subject to changes when the seed changes, meaning a person who uses a different configuration for the 70%, 30% is likely to get different models. And these findings could be due to the small sample size used in the study. In addition, there was no enough samples to fit a large model with all these factors and their interaction and then do model selection. Therefore, the criteria to include the follow-up process was not standardized since the clinical evolution of patients is not predictable.

Conclusion

EIH is common among TBI patients in Uganda with a prevalence of 59.3%. When systolic blood pressure and diastolic are raised by 1 unit from the baseline, having SDH, DAI and skull fracture, the bigger odds of having EIH becomes. These new models will inform policy and future interventions to predict earlier EIH occurrence and build off the effective treatment modalities for such patients. The Models for EIH for adult traumatic brain injury patients in Uganda will then undergo external validation to determine whether this predictive tool can successfully classify patients into those who are at high and low risk for developing EIH.

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References

1. Maas AI, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. The Lancet Neurology. 2022.
2. Adatia K, Newcombe VF, Menon DK. Contusion progression following traumatic brain injury: a review of clinical and radiological predictors, and influence on outcome. Neurocritical care. 2021;34(1):312-24.
3. Yatsushige H. Surgical Management of a Post-traumatic Intracranial Hematoma. No Shinkei geka Neurological Surgery. 2021;49(5):977-85.
4. Homnick A, Sifri Z, Yonclas P, Mohr A, Livingston D. The temporal course of intracranial haemorrhage progression: how long is observation necessary? Injury. 2012;43(12):2122-5.
5. Rodriguez-Luna D, Rodriguez-Villatoro N, Juega JM, Boned S, Muchada M, Sanjuan E, et al. Prehospital systolic blood pressure is related to intracerebral hemorrhage volume on admission. Stroke. 2018;49(1):204-6.
6. Cepeda S, Gómez PA, Castaño-Leon AM, Martínez-Pérez R, Munarriz PM, Lagares A. Traumatic intracerebral hemorrhage: risk factors associated with progression. Journal of neurotrauma. 2015;32(16):1246-53.
7. Hemphill III JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(7):2032-60.
8. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. The Lancet Neurology. 2008;7(5):391-9.
9. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl j Med. 2013;368:2355-65.
10. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. New England Journal of Medicine. 2016;375(11):1033-43.
11. Hanley DF, Thompson RE, Muschelli J, Rosenblum M, McBee N, Lane K, et al. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. The Lancet Neurology. 2016;15(12):1228-37.
12. Sundstrøm T, Helseth E, Wester KG. Surgical Management of Traumatic Intracranial Haematomas. Management of Severe Traumatic Brain Injury: Springer; 2020. p. 163-72.
13. Kuo BJ, Vaca SD, Vissoci JRN, Staton CA, Xu L, Muhumuza M, et al. A prospective neurosurgical registry evaluating the clinical care of traumatic brain injury patients presenting to Mulago National Referral Hospital in Uganda. PLoS One. 2017;12(10):e0182285.
14. Vaca SD, Kuo BJ, Nickenig Vissoci JR, Staton CA, Xu LW, Muhumuza M, et al. Temporal delays along the neurosurgical care continuum for traumatic brain injury patients at a tertiary care hospital in Kampala, Uganda. Neurosurgery. 2019;84(1):95-103.
15. Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R. The outcome from severe head injury with early diagnosis and intensive management. Journal of neurosurgery. 1977;47(4):491-502.

16. Williams N, O'Connell PR, McCaskie A. Bailey & Love's Short Practice of Surgery: CRC press; 2018.
17. Maas AI, Lingsma HF, Roozenbeek B. Predicting outcome after traumatic brain injury. Handbook of clinical neurology. 2015;128:455-74.
18. Collaborators MCT. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. Bmj. 2008;336(7641):425-9.
19. Dijkland SA, Foks KA, Polinder S, Dippel DW, Maas AI, Lingsma HF, et al. Prognosis in moderate and severe traumatic brain injury: a systematic review of contemporary models and validation studies. Journal of neurotrauma. 2020;37(1):1-13.
20. Khaki D, Hietanen V, Corell A, Hergès HO, Ljungqvist J. Selection of CT variables and prognostic models for outcome prediction in patients with traumatic brain injury. Scandinavian journal of trauma, resuscitation and emergency medicine. 2021;29(1):1-9.
21. Servadei F, Nanni A, Nasi MT, Zappi D, Vergoni G, Giuliani G, et al. Evolving brain lesions in the first 12 hours after head injury: analysis of 37 comatose patients. Neurosurgery. 1995;37(5):899-906; discussion
22. Nasi D, Di Somma L, Gladi M, Moriconi E, Scerrati M, Iacoangeli M, et al. New or blossoming hemorrhagic contusions after decompressive craniectomy in traumatic brain injury: analysis of risk factors. Frontiers in Neurology. 2019;9:1186.
23. Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. The Lancet Neurology. 2006;5(1):53-63.
24. Narayan RK, Maas AI, Servadei F, Skolnick BE, Tillinger MN, Marshall LF, et al. Progression of traumatic intracerebral hemorrhage: a prospective observational study. Journal of neurotrauma. 2008;25(6):629-39.
25. Juratli TA, Zang B, Litz RJ, Sitoci K-H, Aschenbrenner U, Gottschlich B, et al. Early hemorrhagic progression of traumatic brain contusions: frequency, correlation with coagulation disorders, and patient outcome: a prospective study. Journal of neurotrauma. 2014;31(17):1521-7.
26. Allison RZ, Nakagawa K, Hayashi M, Donovan DJ, Koenig MA. Derivation of a predictive score for hemorrhagic progression of cerebral contusions in moderate and severe traumatic brain injury. Neurocritical care. 2017;26(1):80-6.
27. Cepeda S, Gómez PA, Castaño-Leon AM, Munarriz PM, Paredes I, Lagares A. Contrecoup traumatic intracerebral hemorrhage: a geometric study of the impact site and association with hemorrhagic progression. Journal of neurotrauma. 2016;33(11):1034-46.
28. Alahmadi H, Vachhrajani S, Cusimano MD. The natural history of brain contusion: an analysis of radiological and clinical progression. Journal of neurosurgery. 2010;112(5):1139-45.
29. Iaccarino C, Schiavi P, Picetti E, Goldoni M, Cerasti D, Caspani M, et al. Patients with brain contusions: predictors of outcome and relationship between radiological and clinical evolution. Journal of neurosurgery. 2014;120(4):908-18.
30. Tong W-s, Zheng P, Xu J-f, Guo Y-j, Zeng J-s, Yang W-j, et al. Early CT signs of progressive hemorrhagic injury following acute traumatic brain injury. Neuroradiology. 2011;53:305-9.
31. Sharma M, Mittal R, Sharma A, Gandhi A. Posttraumatic contusion: clinical and radiologic factors for progression in early postinjury period. Indian Journal of Neurotrauma. 2016;13(01):001-6.

32. Rehman L, Afzal A, Aziz HF, Akbar S, Abbas A, Rizvi R. Radiological parameters to predict hemorrhagic progression of traumatic contusional brain injury. Journal of neurosciences in rural practice. 2019;10(02):212-7.
33. Carnevale JA, Segar DJ, Powers AY, Shah M, Doberstein C, Drapcho B, et al. Blossoming contusions: identifying factors contributing to the expansion of traumatic intracerebral hemorrhage. Journal of neurosurgery. 2018;129(5):1305-16.
34. Qureshi AI, Malik AA, Adil MM, Defillo A, Sherr GT, Suri MFK. Hematoma enlargement among patients with traumatic brain injury: analysis of a prospective multicenter clinical trial. Journal of Vascular and Interventional Neurology. 2015;8(3):42.
35. Kim H, Jin ST, Kim YW, Kim SR, Park IS, Jo KW. Risk factors for early hemorrhagic progression after traumatic brain injury: a focus on lipid profile. Journal of neurotrauma. 2015;32(13):950-5.
36. MARUISHI M, SHIMA T, OKADA Y, NISHIDA M, YAMANE K. Involvement of fluctuating high blood pressure in the enlargement of spontaneous intracerebral hematoma. Neurologia medico-chirurgica. 2001;41(6):300-5.
37. Rodriguez-Luna D, Piñeiro S, Rubiera M, Ribo M, Coscojuela P, Pagola J, et al. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. European journal of neurology. 2013;20(9):1277-83.
38. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke. 2004;35(6):1364-7.
39. Pires PW, Dams Ramos CM, Matin N, Dorrance AM. The effects of hypertension on the cerebral circulation. American Journal of Physiology-Heart and Circulatory Physiology. 2013;304(12):H1598-H614.
40. Lee JJ, Won Y, Yang T, Kim S, Choi C-s, Yang J. Risk factors of chronic subdural hematoma progression after conservative management of cases with initially acute subdural hematoma. Korean Journal of Neurotrauma. 2015;11(2):52.
41. Davceva N, Janevska V, Ilievski B, Petrushevska G, Popeska Z. The occurrence of acute subdural haematoma and diffuse axonal injury as two typical acceleration injuries. Journal of forensic and legal medicine. 2012;19(8):480-4.
42. R Burchell S, Tang J, H Zhang J. Hematoma expansion following intracerebral hemorrhage: mechanisms targeting the coagulation cascade and platelet activation. Current drug targets. 2017;18(12):1329-44.
43. Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. Journal of neurosurgery. 2002;96(1):109-16.