Traumatic Brain Injury in the Intensive Care Unit: association between the Glasgow Coma Score and the Intensive Care Unit mortality; the Botswana experience

Submitted as part of structured Masters

MSC in Clinical Epidemiology

Division of Epidemiology and Biostatistics

Department of Global Health

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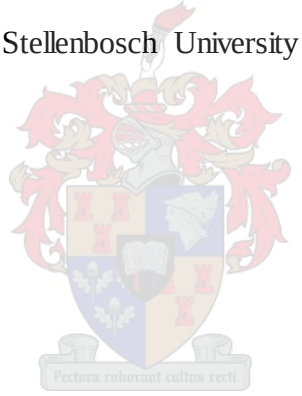

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Traumatic Brain Injury in the Intensive Care Unit: association between the Glasgow Coma Score and the Intensive Care Unit mortality; the Botswana experience (pages 4 to 19)

Traumatic Brain Injury in the Intensive Care Unit: association between the Glasgow Coma Score and the Intensive Care Unit mortality; the Botswana experience

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ABSTRACT

Background

Traumatic brain injury prevalence in Botswana is high and this, coupled with a small population, may reduce productivity. There is no previous study on the association between mortality in traumatic brain injury and the Glasgow coma score in Botswana although global literature supports its existence.

Objectives

Our primary aim was to determine the association between the initial Glasgow Coma scale score and the time to mortality of adults admitted with TBI at the Princess Marina Hospital, Botswana, between 2014 and 2019. Secondary aims were to assess the risk factors associated with time to mortality and to estimate the mortality rate from TBI.

Methods

This was a retrospective cohort design, medical record census conducted from 1st January 2014 to 31st December 2019.

Results

In total, 137 participants fulfilled the inclusion criteria and majority, 114 (83.2%) were male with mean age 34.5 years. The initial GCS score and time to mortality were associated (aHR: 0.69; 95% CI: 0.508-0.947). Other factors associated with time to mortality included constricted pupil (aHR: 0.12; 95% CI: 0.044-0.344), temperature (aHR: 0.82; 95% CI: 0.727-0.929), and subdural haematoma (aHR: 3.41; 95% CI: 1.819-6.517). Most cases of TBI, 74 (54%) were due to road crashes. Mortality was 48, 35% (95% CI: 27.1% to 43.6%) and entirely from severe TBI.

Conclusion

The study confirmed significant association between Glasgow coma score and mortality. Males were mainly involved in TBI. These findings lacked external validity due to a small sample size and therefore a larger multi-centre study is required for validation.

Introduction

Traumatic brain injury (TBI) is defined as physical injury to the head due to mechanical energy, which results in damage to brain tissue. [1,2] Worldwide, 69 million people suffer TBI annually but it is the Low and Middle Income Countries that have the highest incidence of road traffic related TBI.[1] In 2016, there were 12 941 TBI cases in Botswana. The age standardised rate was 675 per 100 000 which had risen by 16% between 1990 and 2016. [1] Therefore, the burden of TBI in Botswana is high given a population of 2.1 million.[3] Mortality from TBI in Africa remains high as well.[4, 5] For survivors, the number of years lived with disability can be high and this amounted to 8.1 million in 2016. Global productivity diminishes because relatively young people are involved. [6]

The three classes of TBI are: mild, Glasgow Coma Scale (GCS) score 13-15, moderate, 9-12 and Severe, 3-8. The GCS is a standardised tool for assessing the level of consciousness widely used since 1974[7]. It is based on three responses, namely: eye opening (4), best verbal response (5) and best motor response (6) points with 15 maximum and 3 minimum points. **[8]** Coma is categorised as absent eye opening, failure to obey commands and no word verbalisations (GCS score 3-8 points). The ICU admission policy varies between centres considerably. [9]

The association between mortality and the GCS score has been explored extensively including its combination with pupillary reaction to predict mortality in severe TBI with increased sensitivity.[10-11] Precise combinations of GCS for predicting mortality have been identified [12] and they contribute to the "sum score differentially across the spectrum of consciousness." [13] Nevertheless, a GCS of ≤8 predicts mortality better in TBI than non-TBI participants.[14] but a simple GCS-Age Prognosis score can predict outcomes reliably in geriatrics.[15] The length of stay (LOS) has implications on mortality as severe TBI and a space-occupying lesion prolong LOS in the ICU. [16] Observer variability may affect the reliability of the GCS but it may be improved through training, education and standardization of assessments. [17, 18] Factors associated with poor outcomes in traumatic brain injury include a low GCS score and absence of pupillary light reaction. [19]

There is a pre-hospital service (called 997) that works in tandem with PMH to resuscitate and transfer patients to hospital from the accident scene. They are taken to the Accident and Emergency unit for further resuscitation and onward transfer to the ICU directly or via operating theatre. In the ICU, patients are artificially ventilated, given analgesia and sedation and monitored both invasively and non-invasively. For TBI patients with raised intracranial pressure mandatory decompressive craniectomy is done before ICU admission. The exception is lack of capacity to monitor intracranial pressure. Use of the neck collar in TBI is a standard procedure.

In Botswana, TBI in the ICU has not been previously reported on. Mortality is an outcome measure of ICU performance where critically ill people such as those with severe TBI are managed. Since critical illness is associated with high mortality, the timing, the delivery and the type of intervention are key to ICU outcomes. Therefore, there is need for quality improvement activities that are geared towards better ICU outcomes with regard to TBI. These activities come at a certain cost. This study seeks to provide preliminary knowledge regarding ICU mortality with respect to TBI.

Our primary aim was to assess the association between the admission GCS score and the time to mortality of adult participants admitted to ICU with TBI from 1st January 2014 to 31st December 2019. The secondary aims were to assess the association between selected risk factors and time to mortality over the same period, as well as to estimate the ICU mortality rate.

Methods

A retrospective cohort study was conducted at Princess Marina Hospital (PMH). It is the main referral and teaching hospital in Botswana with a catchment area in both northern and southern regions, and has a bed capacity of 567, including 8 ICU beds. At PMH, neurosurgery is one of the subspecialties and there were three neurosurgeons at the time of the study. Children over one month old, besides adults, were admitted to ICU.

We included adults, 16 years of age or more, with TBI, either sedated, non-sedated or paralysed, admitted from 1st January 2014 to 31st December 2019, and excluded participants who met inclusion criteria but were transferred to other hospitals. Three research assistants extracted data from de-identified medical records.

A predefined and validated data collection tool was used to capture data from each patient record. We conducted a pilot test of the instrument before it was adopted for this study. Data entry was done by the principal investigator (PI) into an excel spreadsheet on a secure laptop computer. Original source documents were used to corroborate data entry. Access to this computer and a separate server, was limited to the PI and authorized personnel including a data analyst. Stata 15.1 (StataCorp LLC, College Station, TX) was used for data analysis.

The independent variables were demographic and social factors such as age, sex, past medical history of TBI, education level and employment status. Others were TBI severity, initial GCS score, ICU LOS, and the mechanism of injury. We categorised the GCS score on admission consistent with mild, moderate or severe TBI. We, also, categorised pupillary size and light reaction as either reactive or non-reactive, dilated or fixed and unilateral or bilateral respectively. The outcome variables were the occurrence of death in the ICU and time to death following ICU admission.

To address the primary aim, the independent variable was GCS score, as a quantitative variable, and the outcome as time to mortality. We computed the ICU length of stay (LOS) as days from the admission to the exit date. A same day admission and exit were computed as half a (0.5)-day LOS.

We used the Cox proportional hazard (PH) model to model the relationship between independent variables and time to mortality. [20] All variables which were significantly associated with time to mortality at $p<0.05$ in bivariate Cox regression analysis were entered into a multivariable Cox regression model to estimate the adjusted Hazard Ratios (aHR). Data were checked for the presence of multicollinearity, normality of data, and proportionality of hazards over time. The proportional hazards assumption was checked by the application of statistical and graphical diagnostics based on the Schoenfeld residuals that are independent of time. [20] We set the level of statistical significance at $p<0.05$.

Our study relied on hospital records to capture patient data without participant contact. For this reason, we obtained a waiver for informed consent. However, patient data was safeguarded as per

data management plan. Permission from the Health Research Ethics committee of the Stellenbosch University, the Ministry of Health and Wellness (MoHW) in Botswana and the PMH ethics committee was obtained. There was no conflict of interest in this study.

Results

In total, 137 participants met the inclusion criteria over the selected six-year period. Besides the ventilated patient care bundle (includes head-up tilt and sedation hold), all participants received seizure prophylaxis, analgesia and end-tidal carbon dioxide monitoring. [21] The mean (SD, range) age was 34.5 (12, 18 to 88) years and participants were predominantly (83.2%, n=114) male. The male to female ratio was 5:1. By GCS category, 91.2% (n=125) of participants suffered severe TBI while 7.3% (n=10) suffered moderate TBI and 1.5% (n=2) mild TBI. The mean (SD) for the mean arterial pressure (MAP) was 87.6 (21.6) mmHg and for the initial temperature was 35.5(2.4)^{0}C; (95% CI: 35.073-35.869). All participants were artificially ventilated. Among the listed modes, 32.1% (n=44) of participants received the Volume Assist Control (VAC) and 27.7% (n=38) the Pressure Synchronised Intermittent Mandatory ventilation (PSIMV) mode. Likewise, all participants had a brain scan on admission to ICU. On brain scan, 38.7% (n=53) of participants suffered a subdural haematoma (SDH) and 27% (n=37), a skull base fracture. By mechanism of injury, 54% (n=74) of the TBIs were caused by road traffic crashes (RTCs) and 33.4% (n=46) by assault. The overall ICU mortality was 35% (n=48) (95% CI: 27.1% - 43.6%). All deaths, 38.4% (n=48) were attributed to severe TBI. The characteristics of study participants are shown in Table 1.

We found that the initial GCS was statistically significantly associated with time to mortality (HR: 0.68; 95% CI: 0.532-0.856; p=0.001). For every one unit increase in GCS, the hazard of mortality decreased by 32%. Other statistically significant factors in the bivariate analysis included age (HR: 1.03; 95% CI: 1.001-1.051; p=0.039); MAP (HR: 0.98; 95% CI: 0.963-0.989; p<0.001), temperature (HR: 0.86; 95% CI: 0.791-0.935; p<0.001), dilated pupil (HR: 3.56; 95% CI: 1.949-6.510; p<0.001), fixed pupil, (HR: 1.90; 95% CI: 1.07-3.40; p=0.030), normal pupil (HR 0.42, 95%CI 0.21 – 0.88, p=0.021); constricted pupil (HR: 0.21; 95% CI: 0.084-0.539; p=0.001) and SDH (HR: 2.20; 95% CI: 1.229-3.952; p=0.008).

Factors independently associated with time to mortality in the final multivariable model were initial GCS (aHR: 0.69; 95% CI: 0.508-0.947; p=0.002), age (aHR:1.03; 95% CI: 1.001-1.056; p=0.042); MAP (aHR: 0.98; 95% CI: 0.971-0.998; p=0.029); constricted pupil (aHR: 0.12; 95% CI: 0.044-0.344; p<0.001), temperature (aHR: 0.82; 95% CI: 0.730-0.929; p=0.002), and SDH (HR: 3.44; 95% CI: 1.819-6.517; p<0.001). The hazard of death increased by 3% for every one-year increase in age and increased by 3.44 times for those who had subdural haematoma. Conversely, the hazard of death decreased by 88% for those with constricted pupils and by 18% for every degree centigrade rise in temperature. It decreased by 2% for every millimetre of mercury (mmHg) rise in mean arterial pressure. Table 2 shows both crude and adjusted estimates of the hazard ratios, and their 95% confidence intervals.

The ICU LOS varied from 0.5 to 1103 days. In ascending order, the median LOS along with the corresponding 25^{th} and 75^{th} percentiles for the mild, moderate and severe TBI severity categories was (1.5: 0, 3), (3.5: 2, 7) and (6: 2, 19) days respectively, however the difference in LOS between the categories of GCS was not statistically significant (p=0.150). The overall median (IQR) LOS was (6: 2, 17) days. The mortality rate based on cumulative at-risk time of 3 999 days was 12 per 1000 (95% CI: 8.61-15.40) person days with a median survival time of 41 days.

Discussion

In our study, the GCS was an independent predictor of mortality in the best-fit cox regression model. Others included subdural haematoma, constricted pupil, temperature, age and mean arterial pressure. Interestingly, the HR for the GCS did not change when adjusted for the other factors associated with time to mortality. This suggests that it is a stable measurement of risk of mortality on its own, without taking the other factors into account. Although there are other scoring systems such as APACHE II as well as the increased use of machine learning approach, the GCS remains popular because of its simplicity and widespread application. The GCS, unlike the machine learning approach, does not require any equipment. [22] A review paper that reported on the early management of TBI revealed a quasi-exponential relationship with a decrease in mortality coupled with an increase in the GCS score from 3 to 8. [23] The prediction of mortality may contribute to the judicious use of intensive care resources through the application of ICU protocols thus redirecting resources to where they are most beneficial. However, there have been arguments in support of initial aggressive management even in severe TBI because, first, it is difficult to predict

outcome within six hours of presentation of TBI and second, good functional outcome may be possible in some severe TBI cases. [16, 24] The findings of our study are consistent with other studies in which a GCS score below 8 was associated with mortality. [25, 26] This underscores the role of GCS as a bedside clinical tool in predicting mortality that is applied in all settings.

The initial temperature was subnormal (35.5°C) and statistically significant (p=0.002) with an 18% reduction in the hazard of death for every one degree Celsius increase in temperature. A recent systematic review reported positive outcomes in terms of reduced length of stay and mortality in adults where fever is averted. [27] There was no use of induced hypothermia in our patients and this was axillary temperature.

A constricted pupil demonstrated a protective effect which was statistically significant (p<0.001) with 88% reduction in the hazard of death. Other studies have reported statistically significant findings for pupillary reactivity (p=0.011) but not pupillary size. [21, 26]

The overall mortality in our study was 35% (n=48) with all deaths due to severe TBI. Our findings are consistent with literature demonstrating that the majority of deaths are due to severe TBI. [21, 24, 27] In our study, the mean age for TBI was 34.5 years with 83.2% of the participants being male while the commonest mechanism of injury was RTC at 74%. This is consistent with other studies regarding the age and mechanism of injury. [21, 27] These studies, also suggest that, it is the male youth who are mainly affected by TBI.

Another predictor of mortality we found to be consistent with other studies was the SDH. [20, 27] In our study, the hazard of death in participants who had SDH was more than 3 times those who did not. The development of SDH is directly linked to a raised intracranial pressure, reduced cerebral perfusion pressure and hypoxia, leading to low GCS scores. [28, **29, 30**] The hazard ratio for SDH increased by more than 50% with adjustment.

Limitations

Our study had limitations. The first is missing data, which is common in studies of this nature. We collected a data set for every participant who met inclusion criteria in the first hour of ICU admission. If the data for the first hour was missing then we extracted data for the second hour for the same participant. This was done in approximately 0.5% of the participants but it had no

effect on our calculations. Our study was limited to one centre in Botswana, which implies that our findings may not be generalised to the rest of Botswana and, additionally, we had a small sample size and thus power was diminished. This was evident in our computation of magnitudes of effect, some of which had wide confidence intervals though they were statistically significant. We lacked data from invasive monitoring such as intracranial pressure measurements that are critical in traumatic brain injury management.

Conclusion

In spite of its limitations, our study confirmed the association between GCS and mortality found in other larger studies. Some of the factors associated with mortality were found in other studies as well. Although our mortality rate does not differ markedly from other resource-limited settings in Africa, we have room for improvement. This study has demonstrated, to a limited extent, a gap in knowledge about traumatic brain injury approaches in the PMH ICU. The male youth bears the burden of traumatic brain injury, largely due to road traffic crashes. A larger study is required to validate the findings in our study.

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TABLES

Table1 Demographic and clinical characteristics of Traumatic Brain Injury participants

Variable	**N=137**	
Age, mean (SD, range) years	34.5 (12, 18 to 88)	
Sex, n (%)		
Male	114 (83.2)	
Female	23 (16.8)	
Initial Glasgow Comma Score[§], n (%)		
Mild TBI	2 (2)	
Moderate TBI	10 (7)	
Severe TBI	125(91)	
Vital Signs, mean (SD)		
Mean Arterial Pressure (MAP) mmHg	87.6 (21.6)	
Saturation %	98.2 (3.5)	
Heart rate (beats per minute)	104.2 (26.1)	
Temperature (^{0}C)	35.5 (2.4)	
Initial pupillary reaction, n (%)	Left eye	Right eye
Dilated pupil	44 (32.1)	47 (34.3)
Fixed pupil	60 (43.8)	58(40.9)
Constricted pupil	36 (26.2)	35 (25.6)
Normal pupil	45 (32.8)	43 (31.4)
Mechanical ventilation, n (%)		
Continuous Positive Airway Pressure	8 (5.8)	
O_2/face mask	2 (1.5)	
Pressure Assist Control	9 (6.6)	
Pressure Synchronised Intermittent Mandatory Ventilation	38 (27.7)	
Spontaneous	2 (1.5)	
T-piece	5 (3.7)	
Volume Assist Control	44 (32.1)	
Volume Synchronised Intermittent Mandatory Ventilation	29 (21.2)	
Radiology: brain scan, n (%)		
Skull base fracture	37 (27)	
Depressed skull fracture	13 (9.5)	
Non-depressed skull fracture	2 (1.5)	
Sub-dural haematoma	53 (38.7)	
Extra-dural haematoma	6 (4.4)	
Diffuse axonal injury	12 (8.8)	
Mechanism of injury, n (%)		
Road traffic accident (RTA)	74 (54)	
Assault	46 (33.4)	
Other	10 (7.3)	
Fall from height	6 (4.4)	
Blunt force trauma	1 (0.7)	
ICU LOS, median (IQR; range) days	6 (15; 0 – 1,103)	
Discharge, n (%)		
Alive	89 (65)	
Died	48 (35)	

Table 2 Univariate and multivariable Cox regression analysis of factors associated with time to mortality in traumatic brain injury participants

Characteristic	**Crude HR**	**95% CI**	**p-value**	**Adjusted HR**	**95% CI**	**p-value**
Initial GCS Score	0.68	0.532 – 0.856	0.001	0.69	0.508 – 0.947	0.002
Age	1.03	1.001 – 1.051	0.039	1.03	1.003 – 1.058	0.029
Mean arterial pressure (MAP)	0.98	0.963 - 0.989	<0.001	0.98	0.971 – 0.999	0.035
Pulse oximetry (SPO2)	0.93	0.870 - 1.001	0.054	-	-	-
Heart rate	1.00	0.990 - 1.013	0.811	-	-	-
Temperature	0.86	0.791 - 0.935	<0.001	0.82	0.727 – 0.929	0.002
Dilated pupil	3.56	1.949 – 6.510	<0.001	1.32	0.634 – 2.780	0.453
Fixed pupil	1.90	1.066 – 3.404	0.030	0.88	0.426 – 1.810	0.724
Normal pupil	0.42	0.205- 0.877	0.021	0.58	0.246 – 1.373	0.216
Constricted pupil	0.21	0.084 – 0.539	0.001	0.12	0.043 – 0.342	<0.001
Mechanism of injury Assault (reference) Road traffic accident Other	 0.73 1.05	 0.394 – 1.332 0.418 – 2.649	 0.300 0.110	 - -	 - -	 - -
Extradural haematoma	0.43	0.059 – 3.143	0.407	-	-	-
Subdural haematoma	2.20	1.229 – 3.951	0.008	3.41	1.788 – 6.533	<0.001
Depressed skull fracture	0.91	0.324 – 2.540	0.853	-	-	-
Non-depressed skull fracture	2.57	0.351– 18.904	0.353	-	-	-
Diffuse axonal injury	0.64	0.227 – 1.791	0.393	-	-	-

Appendix A

Author Guidelines

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

Scope of the Journal.

This Journal publishes scientific articles related to multidisciplinary critical and intensive medical care and the emergency care of critically ill humans.

To submit a manuscript, please proceed to the *SAJCC* Editorial Manager website:

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Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions. Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that

both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript an accompanying documentation. A copy of the ethics approval letter must be uploaded as a supplementary file.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki (2013), and should include a statement on independent ethical review. Where appropriate, a statement must be made that informed consent was taken from human participants, and/or whether the need for informed consent was waived.

Please also refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Protection of rights to privacy

Research Participants

Information that would enable identification of individual research participants should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed

written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAJCC*.

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will not be made available to any third party without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAJCC* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note thatit is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, submissions may include an anonymized version of the manuscript.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- Medical drugs should be referred to by their generic name although the trade name may be used in brackets in the text once if unique.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The title of the manuscript should concisely describe the study but should not include the outcome. The

introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. At the end of the introduction clearly state the aim or objective of the study. The primary and secondary outcomes should be specified.

In the Methods section describe in sufficient detail so that others would be able to replicate the study should they need to. Sections of the methods that have been described in previous publications need only be referenced. The statistical methods should be described. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered.

Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

The discussion should be confined to an interpretation of your results with respect to your stated aim and if applicable, a comparison to the results of similar studies. The strengths and weaknesses of your study should be discussed.

The conclusion should be confined to an interpretation of the results of the study and a recommendation if applicable.

- May include up to 6 illustrations or tables.
- References should only include the most recent and relevant articles. A maximum of 30 references is advised.

Structured abstract

- This should be no more than 250 words, with the following headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the research tools/instruments, any specific analyses that were done on the data.

- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, and be aligned with the conclusion in the main text.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

***Scientific letters*/short reports**

These are shorter length, scholarly research articles of no more than 1500 words, and include case reports.

Guideline word limit: 1500 words

- Abstract: Structured, maximum 250 words, with the following headings: Background, Objectives, Methods, Results, and Conclusion.
- May include only one illustration or table
- A maximum of 15 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience

- observational studies
- trials
- systematic reviews.

Review articles

Narrative review articles should always be discussed with the Editor prior to submission. (Structured reviews or meta-analyses' need not be).

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a précis of reviews published in the international literature

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJCC or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.

- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
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Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. DOI:10.1000/hgjr.182

- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAJCC requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
    - Anonymous manuscript (unless otherwise stated)
    - Author Agreement form
    - Manuscript
    - Ethics Approval form (for research articles)
    - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
    - Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been

appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by two of the editors and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by two reviewers selected on the basis of their expertise in the field.

A double blind review process is followed at SAJCC. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion

Article Processing Charges

There is currently no article-processing charge (APC), also known as page fees, for the publication of manuscripts. The publication costs are supported by the Critical Care Society of Southern Africa and advertisements in the print version.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is currently applicable.

Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

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Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

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Published articles are covered by the following major indexing services. As such articles published in the *SAJCC* are immediately available to all users of these databases, guaranteed a global and African audience:

- DOAJ
- AIM
- AJOL
- Scopus
- EBSCO
- EMBASE

- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact the editor for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published, nor is it before another journal for consideration.
2. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
3. The manuscript is in Microsoft Word format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
4. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (Jpeg). These must be submitted as 'supplementary files' (not in the manuscript).
5. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
6. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
7. An abstract has been included where applicable.
8. The research was approved by a Research Ethics Committee (if applicable)
9. Any conflict of interest (or competing interests) is indicated by the author(s).

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STUDY PROTOCOL

Traumatic Brain Injury in the Intensive Care Unit: association between the Glasgow Coma Score and the Intensive Care Unit mortality; a Case of Botswana

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TABLE OF CONTENTS

ABSTRACT

The traumatic brain injury (TBI) prevalence in Botswana is high and this together with a small population also reduces the productivity of this country. Furthermore, the number of years lived with disability contribute to reduction in the productivity of Botswana as it is mainly young males who are involved. There is no previous study on TBI in intensive care unit (ICU) mortality in Botswana and this study aims to fill that gap.

Specific aims:

Primary aim;

1. To determine the association between admission Glasgow coma scale (GCS) score and the time to mortality of adult patients admitted to ICU with TBI from 1st January 2014 to 31st December 2019.

Secondary aims;

1. To determine the mortality incidence rate and incidence risk (95% confidence interval) of adult patients with TBI in the ICU from 1st January 2014 to 31st December 2019.
2. To assess the association between length of stay in ICU (LOS) and the incidence of mortality following TBI among adult patients.

Study setting

This study will be conducted at Princess Marina Hospital (PMH) ICU, the largest referral hospital in Botswana.

Study design

This is a retrospective cohort design, medical record review looking at the association between mortality and the Glasgow coma scale among adult ICU patients with TBI.

Methods

Eligibility criteria

Inclusion Criteria

1. All Adults, 16 years of age and above, with TBI, neither sedated nor paralysed, both males and females admitted to ICU from 1st January 2014 to 31st December 2019.

Exclusion criteria

1. Adult patients with TBI who are transferred to other hospitals.

Variables:

Explanatory variables include age, sex, GCS, LOS and education level. Response or outcome variables include time to mortality, and death incidence rate in the ICU.

Sampling technique

All ICU medical records of adult patients 16 years and above admitted with the diagnosis of TBI or head injury will be used for enrollment in the study. To facilitate this process, two research assistants will be recruited and trained in data extraction for this study.

Time frame

IRB clearance from PMH and Ministry of Health and Wellness of Botswana (MoHW) from September 2019 to December 2020. Data collection will be done by May-June 2020, then analysis will follow in July 2020 and by December 2020 the study report should be ready for dissemination.

Key words: Adults, Botswana, Glasgow coma scale, ICU, Mortality, Traumatic Brain Injury.

Title

Traumatic Brain Injury in the Intensive Care Unit: association between the Glasgow Coma Score and the Intensive Care Unit mortality; a Case of Botswana

2.0 Background and rationale

2.1 Background

Traumatic brain injury (TBI) or head injury may be defined as physical injury to the head due to mechanical energy which results in shearing and compression of neuronal and vascular tissue[1-3]. TBI is classified as: Mild Glasgow Coma Scale (GCS score) 13-15, Moderate GCS score 9-12 and Severe GCS score less than or equal to 8. The GCS is easy to use and provides a standardised way of assessing the level of consciousness in traumatic brain injury.

Worldwide, it is estimated that 69 million people (95% confidence interval, 64-74 million) suffer from traumatic brain injury (TBI) annually from all causes[4]. However, the Southeast Asian and the West Pacific regions have the highest burden of TBI[4]. Similarly, the Low and Middle Income Countries (LMICs) have the highest incidence of road traffic related traumatic brain injury[4].

The prevalence of TBI in Botswana in 2016 was reported as 12, 941 (range 12,262-13,600), age standardised rate as 675 (range 643-706) per 100,000 and percentage change in age standardised rates from 1990-2016 as 8.3 (range 6.5 to 10.2)[5]. The burden of TBI in Botswana is therefore high given a low population[6]. Mortality from TBI in Africa remains high as well[7,8].

For those who survive TBI, the number of years lived with disability (YLDs) increases as it is a quantitative measure of disability. Globally, TBI caused 8.1 million (95% confidence interval 6.0-10.4 million) YLDs in 2016, which corresponds to age standardized rates of 111 (range 82-141) per 100,000. This has implications on the productivity of the worldwide workforce since relatively young individuals are affected[5].

The Glasgow coma scale (GCS) has been widely used to assess patients with traumatic brain injury since its introduction in 1974. The scale is used to assess three responses namely, the eye opening (E) (4 points), verbal (V) (5 points) and motor (M) (6 points) hence summing up to a maximum of 15 points[9]. Coma is categorized as no eye opening, no ability to follow commands, no word verbalizations (GCS 3-8 points).

Regarding ICU admission policy, there is a considerable variation between centres for mild TBI while for moderate and severe TBI 63% and 98% of the patients were admitted respectively[10]. Patients with mild TBI may be admitted for observation into the ICU in selected cases.

The association between ICU mortality from TBI and the GCS has been studied extensively. The results have been mixed. In recent times the GCS has been combined with pupillary reaction to predict mortality in severe traumatic brain injury patients with increased sensitivity[11]. Furthermore, the three most precise combinations of GCS for predicting mortality are eye and verbal (E + V), motor and verbal (M + V) and motor (M) scores[12].

Similarly, the GCS components contribute differentially across the spectrum of consciousness to the sum score with each having the highest and lowest effects[13]. Nevertheless a GCS of ≤ 8 predicts mortality better in TBI than non-TBI patients[14]. If this is so why are there questions about the performance of the GCS in predicting mortality? Finally for geriatric patients, a simple GCS-Age Prognosis (GAP) score can predict outcomes reliably[15].

The length of stay (LOS) in the ICU has implications on mortality from traumatic brain injury as well. Patients with severe TBI have a prolonged LOS in the ICU. Similarly patients with an intracranial lesion on a head computed tomography with mass effect have been found to have a prolonged LOS in the ICU[16].

In spite of its widespread application, the GCS has limitations. A case in point is the observer variability in assessing impaired consciousness and coma[17]. Another one is the limited predictive value of the GCS even with early application[18]. Consequently, the GCS has been compared with scales such as APACHE II to predict outcomes in traumatic brain injury patients[19].

The comparison of the GCS and the APACHE II found the latter to be superior in predicting mortality. This comparison is well founded for two reasons. First the APACHE II scale has been in use in the ICU since 1985. Second the APACHE II Scale has a physiological component while the GCS does not**.** Alternatively the pupillary light reactivity may be combined with the GCS as well to predict mortality[20].

Despite these limitations, the GCS is still the most widely used assessment scale in both trauma and non-trauma conditions by all cadres of health care workers including nurses, General practitioners and specialists alike[21].

2.2 Rationale

In summary, the background has given an indication of what is already known locally and internationally. First the burden of TBI is a public health problem and it is worldwide. Secondly it is young males who are predominantly involved.

Thirdly, the cost of managing long-term complications of TBI is high. In particular there is prolonged disability after TBI which essentially translates into years lived with disability. There is reduced productivity during prolonged disability. Fourthly, mortality from severe TBI is associated with road traffic accidents especially in the low and middle-income countries (LMICs) including Botswana.

There is no previous study that has been done on TBI in the ICU in Botswana. Hence there is no data on TBI ICU mortality. In view of the high cost of ICU services, knowledge of the ICU TBI mortality will be invaluable in helping with planning and implementation of new policies and interventions in ICU care. This study seeks to close this gap.

3.0 Research Question:

In adults with traumatic brain injury admitted to intensive care, is the Glasgow Coma Score (GCS Score) on admission associated with Intensive Care Unit (ICU) mortality?

3.1 Overall aim**:**

To assess the association between ICU mortality and the admission GCS score following traumatic brain injury.

3.2 Specific aims:

Primary aim;

1. To determine the association between the admission GCS score and the time to mortality of adult patients admitted to ICU with traumatic brain injury from 1st January 2014 to 31st December 2019.

Hypothesis;

Null hypothesis (H_0)

H_0: There is no association between the GCS score and the time to mortality of adult patients with TBI from 1st January 2014 to 31st December 2019.

Alternative hypothesis (H_1)

H_1: There is an association between the GCS score and the time to mortality of adult patients with TBI from 1st January 2014 to 31st December 2019.

Secondary aims;

1. To determine the incidence rate and incidence risk (95% confidence interval) of adult patients with TBI who died in the ICU from 1st January 2014 to 31st December 2019.

Hypothesis;

Null hypothesis (H_0)

H_0: There is no difference in the incidence rate and incidence risk among adult patients with TBI who died in the ICU from 1st January 2014 to 31st December 2019.

Alternative hypothesis (H_1)

H_1: There is a difference in the incidence rate and incidence risk among adult patients with TBI who died in the ICU from 1st January 2014 to 31st December 2019.

2. To compare the LOS and the Incidence of mortality following TBI among adult patients admitted to ICU.
   Hypothesis;

   Null hypothesis (H_0)

   H_0: There is no association between the LOS and the Incidence of mortality following TBI among adult patients admitted to ICU.

   Alternative hypothesis H_1

H_1: There is an association between the LOS and the Incidence of mortality following TBI among adult patients admitted to ICU.**4.0** Study design and methods:

4.1 Study design:

This will be a retrospective cohort study design. This entails going back in time and picking a cohort of patients that is then followed over time[22], (Aldous 2013). Hence the data collection is also backwards in time. This design was chosen for the following reasons:

1. It is suitable for calculating incidence rates, relative risks and 95% confidence intervals.
2. Since exposure precedes outcome, problems of temporality do not arise.

A data capture tool will be used to extract data from the ICU medical records. This will include socio-demographic and as well as clinical parameters.

4.2 Study population and sampling

4.2.1 Study setting

This study will be conducted at the PMH ICU. PMH is the main referral and teaching hospital in Botswana with a catchment area in both the Northern and the Southern parts of Botswana. This is so despite the fact that there is another referral hospital in the North, Nyangabgwe referral hospital. The bed capacity of the Princess Marina hospital is 567. PMH has major specialties including medicine, surgery, orthopaedics, paediatrics, obstetrics and gynaecology. There are surgical and medical subspecialties as well. On the other hand, the Intensive care unit is mixed i.e. both children over a month old and adults are admitted. It has a capacity of eight beds and patients from within and without Botswana are admitted.

4.2.2 Sampling technique

All ICU medical records of adult patients 16 years and above admitted with the diagnosis of TBI or head injury will be used for enrolment in the study. To facilitate this process, two research assistants will be recruited and trained in data extraction for this study.

Participants:

There will be no human contact or identifiers involved and instead medical records from the hospital will be used with codes to identify TBI patients admitted to ICU from 1st January 2014 to 31st December 2019. A waiver of informed consent for these patients will be applied for.

4.2.3 Selection criteria**;**

4.2.3.1 Inclusion criteria

All Adults, 16 years of age and above, with TBI, neither sedated nor paralysed, both males and females admitted to ICU from 1st January 2014 to 31st December 2019.

4.2.3.2 Exclusion criteria;

Adult patients with TBI who are transferred to other hospitals.

4.3 Measures

Explanatory (or independent) variables include demographic and social factors among others age, sex, participant and family history of TBI, education level and employment status of the participants. Others are the severity of the TBI and the initial GCS assessment score at the ICU, and length of stay in ICU. The type of TBI, place, cause and the mechanism of injury, and the presence or absence of extra-cranial injury will be noted[23].

Demographic factors: These factors include age, gender, and marital status.
Socioeconomic factors: This will include the following variables; education: primary, high school, college or university.
Occupation: professional or non-professional.

Employment status: unemployed, employed, casual worker or student.
Traumatic brain Injury: Cause: assault, road traffic accident. Type: open or closed,
GCS score on admission: consistent with either, mild, moderate or severe TBI.
Pupillary size and reaction: reactive or non-reactive or fixed and dilated unilateral or bilateral.
Brain scan: Done or not done, findings of brain scan reported or not reported.

The response (outcome) variables include; time to death following ICU admission, the incidence rate and the incidence risk of death for this cohort of ICU patients.

4.4 Data management Plan

4.4.1 Data collection:

Two trained study assistants who are nurses will do the collection of data. The principal investigator (PI) will be involved in data collection as well as well cross–checking the study assistants' entries in the data capture tool. A validated data collection tool will be used to capture data from each patient record. The collected data will cover the period from 1st January 2014 to 31st December 2019. The data collection will be done at the PMH medical records department.

4.4.2 Data tool validation:

This is a predefined form that will be used to capture both clinical and non-clinical data from the patient ICU medical records. A pilot test will done before it is adopted for this study. The tool is based on the recommendations of the Demographics and clinical assessment international working group on neurotrauma[23]

4.4.3 Data entry, validation and storage: Data organization

Following data collection, data entry will be made consistently by the PI into an excel spread sheet on a secure laptop computer. Each spread sheet will be rectangular in shape. There will be one data item entry in each cell. We will ensure that all cells are filled. A data dictionary will be created. This dictionary will be used to explain all the variables. It will also be used for data analysis. The primary data file will not be used for calculations.

It will be separately write-protected and stored. Instead a copy of the primary data file will be used for calculations and graphs. A daily data backup will be done on a separate but secure server [24] to avoid data entry error, validation will be done using the Excel software. Original source documents will be used to corroborate data entry if required. Common codes such as hyphen will be used for missing data. Where possible imputation of missing values will be done from available data[25].

This computer as well as a separate server, will be accessible to the PI and authorized personnel including a data analyst. The Stata 15.1 software will be used for data analysis.

4.5 Statistical considerations

4.5.1 Sample size Consideration

All available records from participants that meet the inclusion criteria will be included in the study. A census approach will be used, and therefore sample size calculation is not required. According to the records, 150 are expected in the selected study period from January 2014 to December 2019.

4.5.2 Data analysis

4.5.2.1 To determine the association between the GCS score and the time to mortality of adult patients with severe TBI from 1st January 2014 to 31st December 2019.

Descriptive and univariate analysis:

The independent variables is the GCS score and the dependent variable the time to mortality.

Data will be coded and keyed into a password excel spreadsheet and cleaned using STATA v15.1. All assumptions were checked using STATA version v15.1. The presence of multicollinearity, normality of data, and proportionality of hazards over time have been checked.

Time to mortality is the time to event variable. Hence the descriptive analysis of time to mortality will be Kaplan-Meier survival analysis. The GCS score is a categorical one based on an ordinal scale that is the Glasgow coma scale. On an ordinal scale a unit has no intrinsic meaning. The score 3-8 is categorised as severe TBI, 9-12 as moderate TBI and 13-15 as mild TBI. It will be described using frequency, relative frequency (%), confidence interval and bar chart[26].

The categories of GCS will be used as factors in the Kaplan-Meier survival analysis and log rank tests will be used to compare the time to mortality between the categories. Life table, Kaplan-Meier (KM) survival, and hazard functions will be applied to estimate the probability of survival from TBI and Log-rank test will be used to compare the KM curves for two or more categories of GCS scores.

Adjusted analysis

Cox proportional hazard model will be used to determine the relationship between independent variables and the outcome variable (time to death from TBI). First, bivariate Cox-regression analysis will be done to estimate the crude hazard ratios (HR). Every independent variable will be tested against the dependent variable and variables significant at $P<0.05$ in bivariate analysis and those which were significant predictors in the most studies will be taken to the multivariate Cox regression model.

Second, multivariate Cox-regression analysis will be performed to estimate the adjusted Hazard Ratios (aHR). The aHR with 95% Confidence Interval (CI) will be used to measure the association between dependent and independent variables.

4.5.2.2 To compare the LOS and the Incidence of mortality following TBI among adult patients in the ICU.

Descriptive analysis:

The length of stay (LOS) is calculated in days from the date of admission to the date of exit from the ICU. Same day admission and exit is considered zero (0) LOS. This is a numerical variable and will be described using the median interquartile range (IQR), range (R), box and whisker plots. The incidence of mortality is a numerical variable and will analysed as such[26].

Adjusted Analysis:

Cox regression analysis will be used to estimate the hazards ratio associated with an increase in LOS on time to mortality while adjusting for other confounders including GCS. Stata v15.1 will be used[27] for all statistical analysis. P-values <0.05 will be considered statistically significant.

5.0 Ethical considerations:

The retrospective cohort study design is appropriate for this study. This study will rely on hospital medical records to capture patient data. We shall have no contact with patients. For this reason, we shall seek a waiver for informed consent. However patient data shall be safeguarded as described in section 4.2.2 in the data management plan. The collected data will be used to meet the objectives of this study. Any benefits accruing from this study will not benefit previous but future patients through appropriate policies.

There will be no human contact or identifiers involved and instead medical records from the hospital will be used with codes to identify TBI patients admitted to ICU from 1st January 2014 to 31st December 2019. A waiver of informed consent for these patients will be applied for.

We shall apply for Institutional Review Board (IRB) permission to undertake this study. First, we will seek permission from the ethics committee of the Stellenbosch University. Secondly we will seek permission from the Ministry of Health and Wellness (MoHW) in Botswana. Thirdly we shall seek the same from the PMH ethics committee. We declare no conflict of interest in this study.

6.0 Data dissemination plan

We have planned to disseminate this data in the following manner:

In conference proceedings and with the MoHW in Botswana. Likewise we intend to have it published in peer-reviewed journals. At hospital meetings we shall present to the staff and colleagues particularly at PMH. The PMH administration will be briefed as well. Last but not least the University of Stellenbosch will be part of this process of dissemination.

Our dissemination plan is underpinned by principles of communication. The message to be communicated will be defined. This will be followed by defining the source and channel of communication. The target audience for communication will then be identified. Lastly the setting in which the communication is to be delivered will also be defined[28]. This will translate into effective communication by which our message will reach the target audience.

7.0 Project time line and responsible persons

Study Timeline

Calendar Year	2019				2020											
Month	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Literature review protocol development	X	X														
Apply for funding			NA	NA												
Submission to HREC (SU)			X	X												
Submission to PMH IRB			X													
Training of study assistants and preparation of study material.					X											
Data collection and data entry						X	X									
Data cleaning and analysis								X	X	X	X					
Manuscript preparation and publication.												X	X	X	X	

Figure 1 above shows the project time line for this study.

8.0 study feasibility and limitations

Data capture tools will be refined to test their validity. A pilot study will done on ten randomly selected files whose data will be extracted using the study tool. Thereafter analysis will be done and refining of the tool made where appropriate.

We will use patient medical records for this study and therefore missing files or missing data is an issue to content with. Secondly we will include patients with multiple injuries because TBI rarely occurs in isolation. Thirdly, since PMH is a tertiary referral hospital we admit patients whose initial assessment was done elsewhere. The latter is a limitation to due to interrater variation.

9.0 Research Environment and infrastructure

The Stellenbosch University through the strategic Office of Research Development and Support (ORDS) is well endowed with resources. It therefore provides a platform upon which students aspiring to do world class research can achieve their dreams. There is a well-resourced and elaborate grant scheme for research. This is open to most students with a few exceptions. We are taught how to motivate for and use grants. It is a process which has been on-going for years, making Stellenbosch University one of the institutions spear heading research not just on the continent but across the world. Through partnerships established with local and global organizations, Stellenbosch University has established itself as a centre for research and knowledge exchange. We intent to tap into this resource.

10.0 Budget and budget justification.

Table 2: TBI Study Budget

MSc Project Budget	Period September 2019 to December 2020
Personnel compensation	
1. Research assistant-1	ZAR 2,000
2. Research assistant-2	ZAR 2,000
Consultation Services	
1. Biostatistician	ZAR 2,000 (waived for student Research)
Other direct costs	
1. Telephone, cell phone and Fax	ZAR 2,500
2. Internet & e-mail	ZAR 1,500
3. Office supplies	ZAR 1,000
4. Printing & copying	ZAR 1,000

5. Staff training	ZAR 1,200
Equipment	
1. Laptop	ZAR 4,000
2. Backup device	ZAR 2000
TOTAL COST	ZAR 23,200 (BwP 16,250)

Table 2 is an illustration of the budget estimate. The Principal Investigator (PI) of this study will meet the bill. Therefore, we shall not apply for a study grant.

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APPENDIX B

PLOT 1836 HOSPITAL WAY
TELEPHONE: 3621400
FAX: 3973776

REPUBLIC OF BOTSWANA

PRINCESS MARINA HOSPITAL
P. O. BOX 258
GABORONE
BOTSWANA

11th March 2020

Dr. Jack Mokubwa
Princess Marina Hospital
P.O. Box 258
Gaborone

Dear Dr. Mokubwa

RE: REQUEST FOR CONSENT WAIVER: DR. JACK MOKUBWA.

STUDY: TRAUMATIC BRAIN INJURY IN THE INTENSIVE CARE UNIT: ASSOCIATION BETWEEN GLASGOW COMA SCORE AND THE INTENSIVE CARE UNIT MORTALITY: A CASE OF BOTSWANA

The PMH IRB has reviewed and granted a waiver of consent for the above study following your application for a waiver of consent.

Wishing you a great success in your study

Yours Sincerely

Dr. Mpapho Joseph Motsumi

Chairperson Princess Marina Hospital IRB Committee
Cell: 00267 72858907
Work: 00267 3621400
Email: josephmotsumi@yahoo.com

Approval Notice

New Application

08/07/2020

Project ID :15132

HREC Reference No: S20/05/113

Project Title: Traumatic brain injury: the effect of Glasgow coma scale score on the mortality in an intensive care unit: The Botswana Experience

Dear Dr Jack Mkubwa

The **Response to Modifications** received on 07/07/2020 was reviewed by members of **Health Research Ethics Committee** via **expedited** review procedures on 08/07/2020 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Date: 8 July 2020

Protocol Expiry Date: 7 July 2021

Please remember to use your Project ID 15132 and Ethics Reference Number S20/05/113 on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Translation of the informed consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Departement of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/15132

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mrs. Ashleen Fortuin
Health Research Ethics Committee 1 (HREC1)

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)•REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; the South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes andStructures (2nd edition)

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

PRIVATE BAG 0038
GABORONE
BOTSWANA
REFERENCE:

REPUBLIC OF BOTSWANA
MINISTRY OF HEALTH AND WELLNESS

TEL: (+267) 363 2500
FAX: (+267) 391 0647
TELEGRAMS: RABONGAKA
TELEX: 2818 CARE BD

REFERENCE NO: HPDME 13/18/1 **20 December 2019**

Health Research and Development Division

Notification of IRB Review: **New application**

Dr Jack Mkubwa
Princess Marina Hospital
P O Box 258
Gaborone

Dear Jack Mkubwa

Protocol Title: **TRAUMATIC BRAIN INJURY IN THE INTENSIVE CARE UNIT: ASSOCIATION BETWEEN THE GLASGOW COMA SCORE AND THE INTENSIVE CARE UNIT MORTALITY; A CASE OF BOTSWANA**

HRU Approval Date:	20 December 2019
HRU Expiration Date:	19 December 2020
HRU Review Type:	Expedited Review
HRU Review Determination:	Approved
Risk Determination:	Minimal risk

Thank you for submitting new application for the above referenced protocol. The permission is granted to conduct the study.

This permit does not however give you authority to collect data from the selected sites without prior approval from the management. Consent from the identified individuals should be obtained at all times.

The research should be conducted as outlined in the approved proposal. Any changes to the approved proposal must be submitted to the Health Research and Development Division in the Ministry of Health for consideration and approval.

Furthermore, you are requested to submit at least one hardcopy and an electronic copy of the report to the Health Research, Ministry of Health and Wellness within 3 months of completion of the study. Copies should also be submitted to all other relevant authorities.

Continuing Review

In order to continue work on this study (including data analysis) beyond the expiry date, submit a Continuing Review Form for Approval at least three (3) months prior to the protocol's expiration date. The Continuing Review Form can be obtained from the Health Research Division Office (HRDD), Office No. 7A.7 or Ministry of Health website: www.moh.gov.bw or can be requested via e-mail from Mr. Kgomotso Motlhanka, e-mail address: kgmmotlhanka@gov.bw As a courtesy, the HRDD will send you a reminder email about eight (8) weeks before the lapse date, but failure to receive it does not affect your responsibility to submit a timely Continuing Report form

Amendments

During the approval period, if you propose any change to the protocol such as its funding source, recruiting materials, or consent documents, you must seek HRDC approval before implementing it. Please summarize the proposed change and the rationale for it in the amendment form available from the Health Research Division Office (HRDD), Office No. 7A 7 or Ministry of Health website: www.moh.gov.bw or can be requested via e- mail from Mr. Kgomotso Motlhanka, e-mail address: kgmotlhanka@gov.bw . In addition submit three copies of an updated version of your original protocol application showing all proposed changes in bold or "track changes".

Reporting

Other events which must be reported promptly in writing to the HRDC include:

- Suspension or termination of the protocol by you or the grantor
- Unexpected problems involving risk to subjects or others
- Adverse events, including unanticipated or anticipated but severe physical harm to subjects.

If you have any questions please do not hesitate to contact Mr. K. Motlhanka at kgmmotlhanka@gov.bw, Tel +267-3632751. Thank you for your cooperation and your commitment to the protection of human subjects in research.

Yours sincerely

SPMo

Ms S. Mosweunyane
for /PERMANENT SECRETARY

MINISTRY OF HEALTH DIVISION
2019 -12- 20
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REPUBLIC OF BOTSWANA

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REPUBLIC OF BOTSWANA

PRINCESS MARINA HOSPITAL
P. O. BOX 258
GABORONE
BOTSWANA

11th March 2020

Dr Jack Mokubwa

Dear Sir,

RE: PERMISSION TO CARRY OUT RESERCH ON: TRAUMATIC BRAIN INJURY IN THE INTENSIVE CARE UNIT: ASSOCIATION BETWEEN GLASGOW COMA SCORE AND THE INTENSIVE CARE UNIT MORTALITY;A CASE OF BOTSWANA

Your application for a research permit for the above research protocol has been approved on 11th March 2020.

You are granted full approval, but you need to note the following:

1. You will not change any aspect of your research without permission from the Princess Marina Hospital.
2. You need to report any unforeseen circumstances including the termination of the study of the Princess Marina Hospital.
3. You must allow Princess Marina Hospital access to the study at anytime for purposes of auditing.
4. This permit is valid for one year from 11th March 2020 to 11th March 2021.
5. The end of the study you should give the Princess Marina Hospital a hard copy and soft copy of your report.

Wishing you a great success in your studies.

Yours faithfully

Dr P. Motlokwa
Secretary PMH REC
For Hospital Superintendent

TBI Data tool v.2

1. Sex

M	F	Other	Unknown

M=Male F=Female

2. Age (years)

3. Educational Level

Tertiary	High school	Primary school	None	Unknown

4. Marital status

Married	Divorced	Single	other	Unknown

5. Employment

Employed	Unemployed	Retired	Other	Unknown

6. Past medical history of TBI

Yes	No

7. Initial GCS score

3-8	9-12	13-15

8. Initial pupillary reaction

Dilated		Fixed		Constricted		Normal	
Left	Right	Left	Right	Left	Right	Left	Right
Yes		Yes		Yes		Yes	
No		No		No		No	