

Current status of traumatic brain injury research in Malaysia: A systematic review

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Abstract: Traumatic brain injury (TBI) is a major cause of death and disability worldwide. In 2009, the National Trauma Database Malaysia reported that nearly 80% of traumas in the population were caused by road traffic accidents, with 64% of these cases related to TBI. Despite these concerning reports, TBI reporting systems and research are still limited in Malaysia. Thus, this systematic review aimed to identify and evaluate the available literature on TBI in Malaysia in order to uncover the status of TBI research in Malaysia. A comprehensive literature search was performed on four databases (PubMed, Embase, Medline and Scopus) regarding TBI in Malaysia. Critical evaluation of 60 relevant articles after application of inclusion and exclusion criteria have indicated that TBI research in Malaysia may have significant limitations in representing the actual TBI population and was lacking in basic TBI research. Thus, there is a dire need for government and private institutions to provide support for the advancement of TBI reporting and the progression of basic, clinical and translation TBI research in Malaysia. This will create a deeper understanding of TBI, contributing to global TBI knowledge, and advancing the development of efficient interventions for Malaysians with its population heterogeneity taken into consideration.

Keywords: population studies; long-term outcomes; basic research; ethnicity

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1.0 INTRODUCTION

Traumatic brain injury (TBI) is not just a single event, but a disorder with a high mortality and morbidity rate worldwide (Hyder et al., 2007; Rubiano et al., 2015). In 2018, a paper in the Journal of Neurosurgery referred TBI as a 'silent epidemic', and their model estimated that annually around 64 to 74 million new TBI cases were reported worldwide (Dewan et al., 2018). Interestingly, they showed that the major risk factor for TBI was road traffic accidents, which were greatest in Southeast Asian and African countries (56% of global TBI

cases, respectively) (Dewan et al., 2018). Although global mortality and morbidity rates are yet to be accurately determined, the Centre for Disease Control and Prevention (CDC) reported that an average of 155 people in the USA dies daily from TBI (Centers for Disease Control and Prevention, 2019).

Despite these alarming figures, the multidimensional cascades of secondary injury pathologies of TBI, which include but are not limited to neuroinflammation, mitochondrial dysfunction, and glutamate

excitotoxicity, still lack sufficient understanding, thus leading to ineffective treatment and prevention strategies ([Pavlova et al., 2018](#)). These secondary injury mechanisms of TBI may often persist for months to years later and are often associated with the later development of a range of neurological disorders such as Alzheimer's disease ([Fleminger et al., 2003](#); [Nemetz et al., 1999](#)), Parkinson's disease ([Gardner et al., 2015](#)), Amyotrophic Lateral Sclerosis ([Chen et al., 2007](#)) and even neuropsychological disorders ([Fann et al., 2009](#)). Thus, TBI may not only affect the quality of people's lives, but it also may create a substantial economic burden as well ([Coronado et al., 2012](#)), especially when accounting the cost associated with their long-term outcomes. Middle-income countries like Malaysia are especially more prone to these burdens, given the high incidence rate of traffic accidents coupled with the possibility of inadequate trauma care facilities especially in district general hospitals ([Sethi et al., 2002](#)), leading to poorer outcomes post TBI ([MaHTAS, 2015](#)).

In Malaysia, TBI was deemed as one of the top three common admissions reported in intensive care units ([Rai et al., 2017](#)), which was not surprising given the number of road traffic accidents reported annually. Nevertheless, actual nationwide incidence rate and statistics on TBI remain underreported, especially when accounting for non-road accident TBI cases, such as falls or abuse. The National Trauma Database Malaysia (NTrD) governed by the Ministry of Health, took the initiative to report TBI cases in Malaysia annually. However, only 4 reports, thus far, have been published, with the last report only updated in the year 2011. Furthermore, these reports only included major trauma cases, that were identified by 8 participating hospitals in Malaysia, and consisted of various types of traumas, instead of being TBI specific. Underreporting of the actual number of trauma cases was even recognized as a limitation by the report, but a solution to this problem was not discussed. In brief, the 2011 report showed that in the year 2009, nearly 80% of trauma cases in Malaysia were due to road traffic accidents, which mainly affected many younger (15-24, 34%) males (87%) ([Jamaluddin et al., 2011](#)). These figures are likely still valid to this day. Although the survival rate may be higher than the death rate among Malaysian trauma patients ([Jamaluddin et al., 2011](#)), follow up studies have yet to be effectively established or recorded, to determine the long-term outcomes post-TBI, despite the recovery in these patients.

Similar to the reports on TBI statistics, TBI research in Malaysia is still very scarce. Given the vast diversity in culture, ethnicity and genetic heritage among a multiracial country like Malaysia, this knowledge gap on the prevalence of TBI in Malaysia, and research on post-injury secondary outcomes and interventions that are catered for Malaysian citizens, requires urgent attention. Therefore, this systematic review aimed to elucidate and critically evaluate the current status of TBI research in Malaysia, in hopes to create and increase awareness for TBI research in Malaysia, as well as identify areas of improvement in Malaysian TBI research for the benefit of its people.

2.0 METHODOLOGY

2.1 Literature Search

A systematic literature search was conducted to identify and extract all currently available literature related to traumatic brain injury in Malaysia. The search was limited to the data available until 10th June 2020. The search terms ["traumatic brain injury" OR "TBI" OR "concussion"] AND ["Malaysia"] were used in four databases: PubMed, EMBASE, Medline, and Scopus. The Boolean operator "AND" was used to link both the search terms together on all databases. Embase Subject Heading (Emtree) terms were used for searches on EMBASE with '/exp' used to explore the terms and capture all related articles to the terms. Title, abstract and keyword search of the terms or similar relevant variations of them were used on Pubmed, Medline and Scopus, with ALL search performed for the term 'Malaysia' in order also to capture articles with institutional affiliations in Malaysia. Articles were first screened through their titles and abstracts, before proceeding with the full-text screening of relevant articles.

2.2 Study Selection and Inclusion Criteria

The following inclusion criteria were applied during study selection: 1) peer-reviewed original research articles that investigate traumatic brain injury within Malaysia only, 2) articles with full-text availability. The following exclusion criteria were applied as well: 1) articles labelled as symposiums, editorials, book chapters, conference papers, case reports, reviews and systematic reviews, 2) articles which were not in the English language, 3) duplicated articles, 4) articles that did not focus its investigation on traumatic brain injury, and 5) articles that did not have an association with Malaysia in terms of research or a Malaysian institutional affiliation. The selection of studies was conducted as per the Preferred Reporting Items for

Systematic Reviews and Meta-Analysis (PRISMA) guidelines ([Moher et al., 2015](#)).

2.3 Quality Appraisal

The quality of the selected articles included in this systematic review was assessed using different tools. The prospective and retrospective studies were appraised using the Quality Assessment Tool for Quantitative Studies by The Effective Public Health Practice Project (EPHPP) ([Project, 1998](#)) (Table S1). The cross-sectional studies were evaluated using the recently introduced but validated Appraisal tool for Cross-Sectional Studies (AXIS tool) ([Downes et al., 2016](#))

(Table S2). Critical Appraisal Skills Programme (CASP) tool was used to evaluate the case-control studies ([CASP, 2018](#)) (Table S3), while the Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to appraise randomized clinical/controlled trials (RCTs) studies ([Higgins et al., 2011](#)) (Table S4). The quality and risk of bias of the selected animal studies included in this systematic review were assessed using the Systematic Review Centre for Laboratory animal Experimentation Risk of Bias (SYRCLERoB tool) ([Hooijmans et al., 2014](#)) (Table S5). Unfortunately, currently, there is no well-validated critical appraisal tool for the validation and computational studies included in this review.

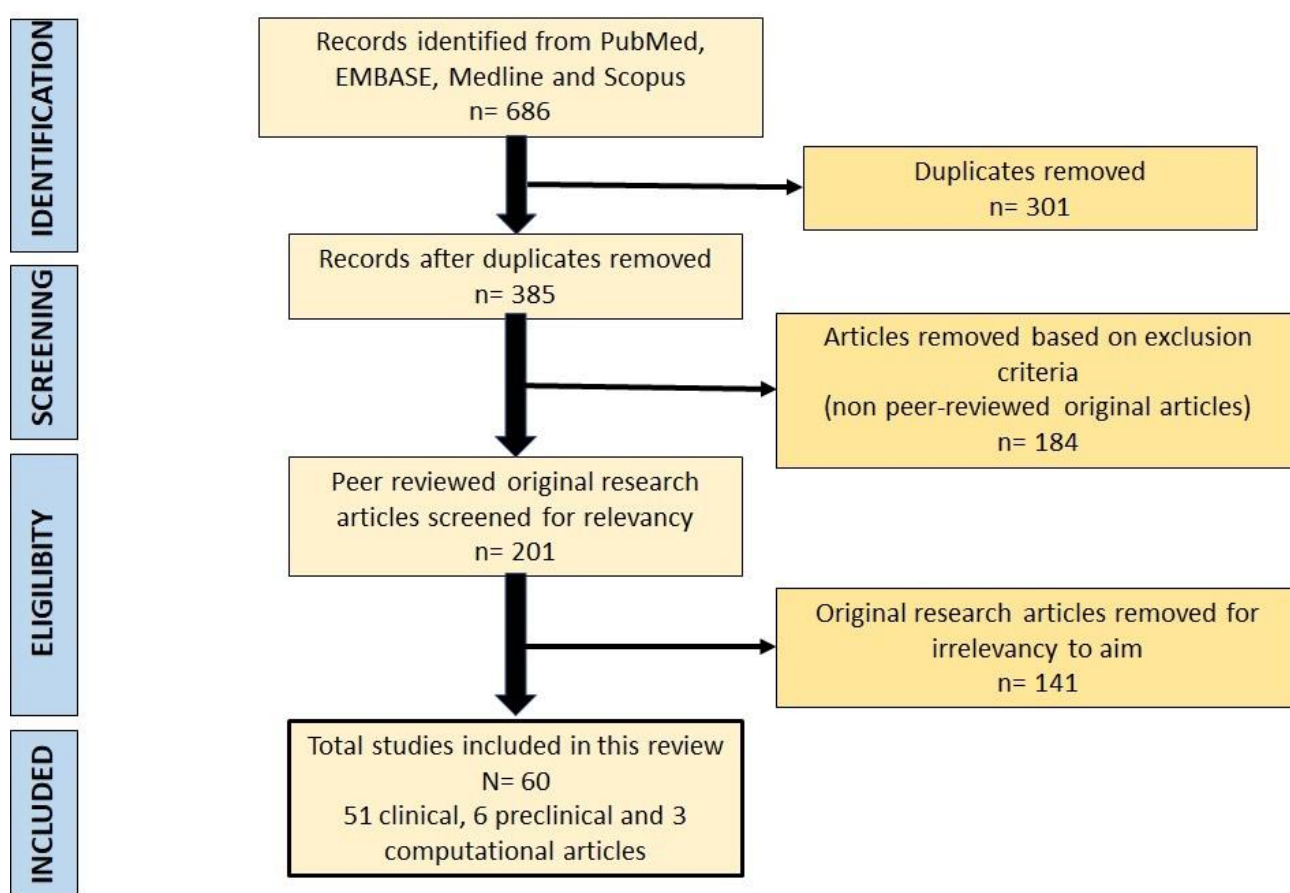


Figure 1. Study selection based on PRISMA guidelines.

3.0 RESULTS

The initial literature searches retrieved 686 articles: 89 articles from PubMed, 186 articles from EMBASE, 316 articles from Scopus and 95 articles from Medline. Three hundred and one duplicated articles were removed, and 385 articles were screened based on the exclusion criteria for peer-reviewed original research articles only. Finally, the abstracts of the 201 articles were screened for relevancy, where 141 articles were found to be irrelevant to the aim of this systematic

review; their investigation was not focused on traumatic brain injury and was not investigated in Malaysia. To be noted, there were 5 case reports identified (before the exclusion criteria) that were relevant to the aim of this review but were not included for critical appraisal as case reports provide bias and insufficient information for effective evaluation of the findings.

Thus, a total of 60 studies were selected for critical appraisal as per PRISMA guidelines (Figure 1) and were

systematically evaluated in this review. The 60 articles were further categorized into 17 clinical, 34 epidemiology studies, 6 preclinical animal studies and 3 computational model studies for ease of evaluation. The characteristics and significant findings of the selected studies were summarized in Table 1.

3.1 Publication Overview of Population Studies

The human/population studies included 34 epidemiological studies which can be further characterized into 3 case-control, 7 prospective cohorts, 6 prospective longitudinal, 7 retrospective and 11 cross-sectional studies, as well as 17 clinical studies which included 7 randomized controlled trials (RCT), 9

prospective observational and 1 validation studies (Table 1). There was a wide range in the type of population studies conducted in Malaysia, with epidemiological studies, mainly cross-sectional studies, is the most sought-after form of study methodology and clinical studies, especially validation studies, being the least investigated thus far (Figure 2B). Population-based research on TBI in Malaysia has increased at an exponential rate every 5 years (Figure 2A), starting with the first publication recorded in 1988 by Pratap-Chand and his colleagues, that investigated the diagnostic usage of cognitive evoked potential to determine cognitive dysfunction after a concussion ([Pratap-Chand et al., 1988](#)) (Table 1).

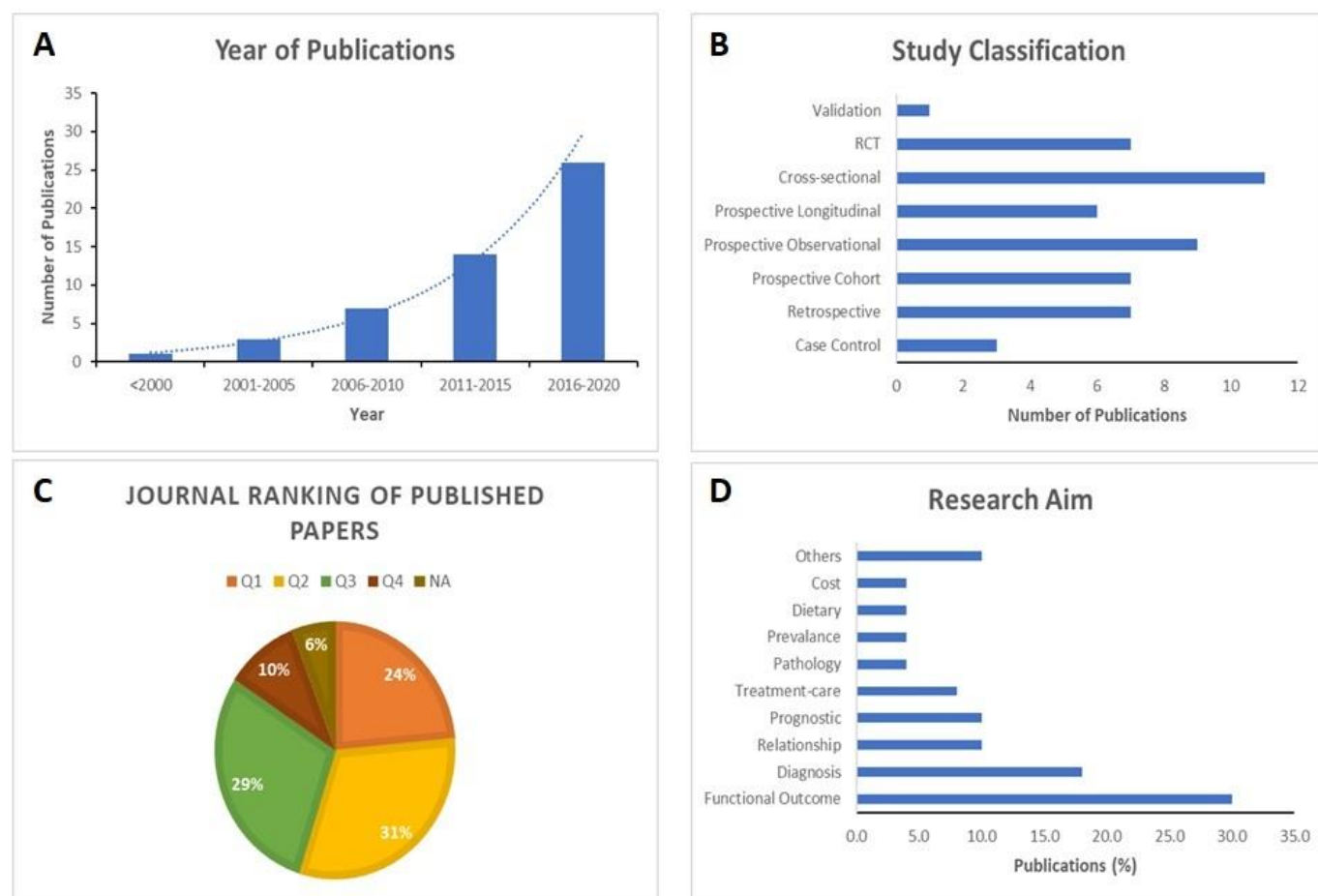


Figure 2. Publication characteristics. **(A)** A bar chart showing the number of publications produced each year, grouped every 5 years with an exponential line; **(B)** A bar chart showing the types of population based studies performed in Malaysia; **(C)** A pie chart showing the percentage of publication published within each SCImago journal ranking; **(D)** A bar chart showing the different research aims explored by the publications in percentage.

Most researchers chose to focus their investigations on the functional outcome post TBI (30%), followed by diagnostic (18%), prognostic (10%) and relationship (10%) studies and finally an almost equal spread in all

other areas of investigations (Figure 2D). Studies whereby their aim of investigation was in rehabilitation, quality of life of patients or caregivers, epidemiology and tool assessment, had only a single study in each

Table 1. Study characteristics and the significant findings of articles included in this systematic review.

Type of study	Research aim	Sample	TBI characteristics	Significant findings	References
Case Control	Functional Outcome	8-14 years; 29M, 6F	Moderate and Severe	Gait performance under dual task affected post TBI	(Abdul Rahman et al., 2018)
	Functional Outcome	8-14 years; 31M, 7F	Moderate and Severe	Concurrent task affects postural control performance in TBI children	(Abdul Rahman et al., 2019)
	Quality of Life (QoL)	18-65 years; 54M, 10F	Mild, Moderate and Severe	Post-TBI olfactory dysfunction significantly lowered QoL	(Ahmedy et al., 2020)
Prospective Longitudinal	Rehabilitation service	18 below years; unspecified	Mild-to-Moderate and Severe	Poor paramedical, medical and rehabilitation care slows down recovery post TBI in children and leads to persistent neuropsychological deficits	(Abdullah et al., 2005)
	Functional Outcome	18-53 years; 69M, 11F	Mild	Significant use of DTI as an imaging biomarker and indicator of white matter damage occurring in the context of mild TBI	(Veeramuthu et al., 2015)
	Pathology	18-53 years; 42M, 6F	Mild	BDNF rs6265 Val66Met polymorphism influences specific neurocognitive outcomes in patients with mild TBI	(Narayanan et al., 2016)
	Relationship	18 above years; 36M, 5F	Mild	The presence of MF injury without any intracranial traumatic lesions in patients with mild TBI increases the risk of short- and long-term neurocognitive derangements	(Veeramuthu et al., 2016)
	Functional Outcome	18 above years; 54M, 7F	Mild	Complicated mild TBI recovered with time while uncomplicated mild TBI showed slower recovery in memory, visuospatial processing, and executive functions	(Veeramuthu et al., 2017)
	Pathology	18 above years; 37M, 24F	Mild	The ratio of NAA and NAAG has potential to serve as a biomarker as it discriminates between the complicated and uncomplicated cases of mild TBI	(Veeramuthu et al., 2018)
Cross sectional	Prognostic	13-81 years; 21M, 10F	Moderate and Severe	No direct correlation between predictors on the first CT scan and the follow-up	(Kiflie et al., 2006)
	Prognostic	14-72 years; 70M, 11F	Mild, Moderate and Severe	Early detection of (10%) DTICH and (42%) PTBI in older age group patient	(Jeng et al., 2008)
	Prognostic	2-16 years; 123M, 23F	Severe	Hyperglycaemia, prolonged PT ratio and leucocytosis were associated with poorer outcome post TBI	(Kan et al., 2009)
	Diagnosis	0-3 years; ratio M>F	Moderate and Severe	Retinal haemorrhages and seizures were common physical signs related to the non-accidental as compared to the accidental TBI	(Hafiz & Saffari, 2011)

	Functional Outcome	18 above years; 73M, 27F	Mild, Moderate and Severe	Extracranial concomitant injuries AIS grade ≥ 3 influenced the long-term functional outcome at 18 months	(Leong et al., 2013)
	Functional Outcome	15-60 years; 31M, 9F	Mild and Moderate-to-Severe	Cognitive dysfunction prevalent in TBI patients and is dependent on severity of TBI	(Ali et al., 2013)
	Caregivers	18 above years; 139M, 143F	Mild, Moderate and Severe	High risk of strain due to lower income and care for patients with significant cognitive and neurobehavioral disturbances	(Mazlan et al., 2016)
	Functional Outcome	18 above years; 85M, 16F	Mild, Moderate and Severe	Duration of injury was associated with depression while mechanism of trauma was associated with anxiety in TBI	(Abdullah et al., 2018)
	Prevalence	16-84 years; 133M, 76F	Mild	Less than 10% of patients with mild TBI had PCS after 6 months' following trauma	(Balakrishnan et al., 2019)
	Functional Outcome	18 above years; 85M, 16F	Mild, Moderate and Severe	The Malay version of HADS is a valid screening tool for depression and anxiety among Malaysian TBI population	(Abdullah et al., 2019)
	Dietary	20-60 years; 28M, 22F	Mild and Moderate	Hospitalized TBI patients were at risk to develop malnutrition	(Abdullah et al., 2020)
Prospective cohort	Prevalence	14-72 years; 1251M, 328F	Moderate and Severe	Contrecoup injury is not uncommon in cases of temporal bone fracture, and is significantly associated with petrous temporal bone fracture	(Asha'Ari et al., 2011)
	Diagnosis	18-65 years; 244M, 50F	Mild, Moderate and Severe	Isolated TBI alone may cause a significant elevation in blood glucose levels which was a predictor of poorer outcomes	(Haron et al., 2011)
	Diagnosis	18 above years; 37M, 7F	Severe	CSF NOx levels may be used to predict ICP readings as well as CT scan severity of patients with severe TBI	(Kandasamy et al., 2013)
	Prognostic	18 above years; 94M, 16F	Severe	Postoperative hypoxia, unmaintained cerebral perfusion pressure and unstable blood pressure are independent predictors of poor outcome in severe TBI after decompressive craniectomy	(Sharda et al., 2014)
	Functional Outcome	13-65 years; 19M, 2F	Mild	The visuospatial and sensory motor domain of cognitive deficits persist over time and possibly modulated by ApoE e4	(Veeramuthu et al., 2014)
	Functional Outcome	18 above years; 22M, 14F	Mild	The latency of P300 was significantly prolonged in early mild TBI patients who improved over time	(Nandrajog et al., 2017)
	Functional Outcome	16-73 years; 27M, 6F	Severe	The logistic regression model, length of stay in intensive care unit and duration on ventilator were good predictors of the functional outcomes post TBI	(Ludin et al., 2019)
Prospective Observational	Functional Outcome	6-13 years; 27M, 9F	Mild, Moderate and Severe	Midline shift, duration of coma and duration of transport were found to be significant variables associated with bad outcome	(Kumaraswamy et al., 2002)

	Treatment-care	12-30 years; 69M, 13F	Severe	Significant difference in proportions of good outcomes between the multimodality group, patients that underwent a single intracranial-based monitoring method and the group that received no monitoring	(Isa et al., 2003)
	Cost	18-75 years; 57M, 5F	Severe	The application of M3 for severe TBI was more cost-effective than BNM	(Ibrahim et al., 2007)
	Prognostic	17-69 years; 47M, 5F	Severe	The outcome at 6 months post treatment between the two modality groups was not statistically significant	(Idris et al., 2007)
	Functional Outcome	18 above years; 61M, 11F	Severe	Higher risk of mortality, worse GCS improvement upon discharge and longer ICU stays in ICP group compared to Intubation group	(Liew et al., 2009)
	Functional Outcome	2-87 years; 137M, 20F	Mild, Moderate and Severe	Younger and intubated patients were at a higher risk of developing early post-traumatic seizures	(Chan et al., 2010)
	Diagnosis	18 above years; 227M, 52F	Mild	Patients with mild TBI and a normal neurological examination, a repeat cranial CT is not indicated unless the repeat head CT worsens	(Sharifuddin et al., 2012)
	Treatment-care	14-74 years; 27M, 5F	Severe	Direct regional brain hypothermia appears safe, feasible and maybe beneficial in treating severely head-injured patients	(Idris et al., 2014)
	Diagnosis	14-60 years; 12M, 8F	Mild	P ₃₀₀ latency and amplitude is a sensitive measure of cerebral dysfunction in concussive head injuries.	(Pratap-Chand et al., 1988)
RCT	Functional Outcome	16-55 years; 18M, 1F	Mild and Moderate	No clear relationship between possession of the $\epsilon 4$ allele and poorer neuropsychological performance in small group of Malaysians with mild-to-moderate TBI	(Shadli et al., 2011)
	Diagnosis	16-50 years; 15M, 15F	Mild, Moderate and Severe	Variations in the levels of protein signature can be used to differentiate the severity of head injury	(Anada et al., 2018)
	Diagnosis	18 above years; 18M, 7F	Moderate	Data from moderate TBI cases was explored to refine the decision boundary (hyperplane) by anomaly support vectors (ASVs)	(Rasheed & Tang, 2020)
	Diagnosis	18-65 years; unspecified	Moderate	CNN is a potential substitution for EEG machine learning application which required complex procedure for preprocessing of the signals and feature extraction	(Lai et al., 2020)

	Dietary	15-75 years; 33M, 3F	Moderate and Severe	These findings indicate the potential of immunonutrition reducing cytokines and increasing antioxidant indices in patients with TBI	(Rai et al., 2017)
	Treatment-care	18 above years; 55M, 8F	Severe	BF therapy showed better effects in maintaining higher electrolyte parameters and reducing the trend toward hyperchloremic metabolic acidosis than the NS therapy during prolonged fluid therapy for postoperative TBI patients	(M. H. Hassan et al., 2017)
	Treatment-care	18-60 years; 89M, 21F	Severe	TIVA/TCI propofol anaesthesia was comparable in the outcome parameters with sevoflurane anaesthesia	(W. M. N. W. Hassan et al., 2017)
Retrospective	Cost	18-54 years; 45M, 4F	Mild, Moderate and Severe	The mean cost of treatment for traumatic head injury is high compared to the per capita income of RM37,900 in 2016	(You et al., 2018)
	Relationship	18 above years; 304M, 44F	Mild	Facial injuries were significantly associated with mild TBI	(Razak et al., 2017)
Retrospective cohort	Diagnosis	18 below years; 199M, 75F	Mild	Headache, dizziness and scalp haematoma were identified as important clinical variables that can be used to predict TBI on a CT scan of paediatric minor head injury	(Song, Ahmad, Siti-Azrin, et al., 2019)
	Relationship	18 below years; 100M, 35F	Mild	Paediatric patients who present with non-isolated vomiting symptoms post minor blunt head trauma were at higher risk of developing TBI and thus require immediate CT scan	(Song, Ahmad, Hamid, et al., 2019)
Retrospective cross sectional	Relationship	1-86 years; 381M, 87F	Mild, Moderate and Severe	Patients with maxillofacial injuries with or without facial fractures are at risk of acute or delayed traumatic brain injury	(Rajandram et al., 2014)
	Epidemiology	0-19 years; 594M, 148F	Mild, Moderate and Severe	Most brain injuries occurred among older male children, with traffic, specifically motorcycle-related, accidents being the main mode of injury	(Tay et al., 2016)
Retrospective Observational	Relationship	12-78 years; 41M, 3F	Severe	Leucocytosis on admission was associated with poor outcomes where patients with higher total white counts on presentation attaining lower GOS-E scores	(Vijian et al., 2020)
Validation	Assessment Tool	18 above years; 93M, 21F	Mild	S-NAB is an acceptable and reliable screening tool for the measurement of mild cognitive deficits in mTBI population of Malaysia	(Hamzah et al., 2019)
Preclinical Animal	Intervention	11-13 weeks; 60M	Weight drop model; Severe	PX-coated PLGA nanoparticles effectively delivered BDNF into the brain, and improved neurological and cognitive deficits post TBI	(Khalin, Alyautdin, et al., 2016)

	Functional Outcome	11-13 weeks; 62M	Weight drop model; Severe	Cognitive disorders in mice with severe closed head injury could be detected using passive avoidance test on day 7 after injury	(Khalin, Jamari, et al., 2016)
	Intervention	11-13 weeks; 60M	FPI; unspecified	DA levels consistently increased at all stages due to NBOT which also controls oxidative damage and over activation of glutamate	(Muthuraju et al., 2014)
	Intervention	11-13 weeks; 38M	FPI; unspecified	FPI mice with IE showed less dead cells as compared to FPI mice without IE, with a complete restoration in locomotive activity	(Muthuraju et al., 2012)
	Intervention	11-13 weeks; 54M	FPI; unspecified	TBI group showed severe morphological changes and neuronal damage as compared to the TBI group exposed to NBO for 3 h	(Muthuraju, Pati, et al., 2013)
	Intervention	11-13 weeks; 96M	FPI; unspecified	Immediate exposure to NBOT improved LA in terms of reduced cell death and improved receptor expression as compared to FPI.	(Muthuraju, Taha, et al., 2013)
Computational	Diagnosis	NA	Mathematical Model; NA	The proposed predictive model improves the predictive performance of TBI	(Alanazi et al., 2018)
	Functional Outcome	NA	Mathematical Model; NA	This study shows that a simple linear mathematical model can be used to investigate the important parameters during soccer heading that affect the brain displacement and acceleration,	(Taha et al., 2015)
	Diagnosis	NA	Mathematical Model; 5 different impact velocities	The proposed Finite Element software may predict the head injury mechanism (magnitude of total deformation, maximum principle stress) on TBI patients skull using computed impact velocity	(Norli et al., 2018)

Note: M: Male, F: Female, TBI: traumatic brain injury, DTI: diffuse tensor imaging, BDNF: brain derived neurotrophic factor, MF: maxillofacial, NAA: N-acetylaspartate, NAAG: N-acetylaspartylglutamate, CT: computed tomography, DTICH: Delayed traumatic intracranial haemorrhage, PTBI: progressive traumatic brain injury, PT: Prothrombin Time, GCS: Glasgow Coma Scale, AIS: Abbreviated Injury Scale, PCS: Postconcussion Syndrome, HADS: hospital anxiety and depression scale, CSF: Cerebrospinal fluid, NOx: nitric oxide, ICP: intracranial pressure, ApoE: Apolipoprotein E, M3: multimodality monitoring, BNM: baseline neuromonitoring, CNN: convolutional neural network, FPI: fluid percussion injury, ICU: intensive care unit, EEG: electroencephalography, BF: Balanced Fluid, PLGA: Poly (lactic-co-glycolic acid), PX: poloxamer 188, DA: dopamine, S-NAB: Neuropsychological Assessment Battery–Screening Module, GOSE: Glasgow Outcome Scale-Extended, NS: Saline-Based Fluid, TIVA: total intravenous anaesthesia, TCI: target-controlled infusion, IE: IntelliCage Exposure, NBOT: Normobaric hyperoxia treatment, NBO: normobaric hyperoxia, LA: Locomotor Activity.

research aim category, and thus were pooled together under the category 'Others'. Interestingly, only five TBI studies had a follow up extending more than a year; 18 months ([Leong et al., 2013](#)) or around 2 years ([Abdul Rahman et al., 2019](#); [Abdul Rahman et al., 2018](#); [Ahmedy et al., 2020](#); [Kumaraswamy et al., 2002](#)), which aimed at investigating the functional outcome in patients post TBI, and only one study that investigated the impact on caregivers of TBI patients, with a follow up for more than 5 years ([Mazlan et al., 2016](#)). Majority of the studies looked at acute (24-72 hours) or subacute (weeks) effects of TBI, especially those with research aimed at diagnosis after TBI.

Nearly 25% of the population studies were published in Malaysian journals such as Malaysian Journal of Medical Sciences, and more than 50% of the population studies were published in high ranking journals; Q1 and Q2 journals, according to SCImago journal ranking (Figure 2C). There was no observable correlation between type of study or research aim with the publication journal ranks. Quality assessments on the publications revealed that the population-based studies had five studies (3 cross-sectional and 2 RCTs) which may be biased due to lack of blinding and sample size justification, while quality assessment of the rest of the population based studies and preclinical animal studies showed unbiased methodology and reporting of their results (see Supplementary S1-S5).

3.2 Population Sample Overview

Most of the studies have sampled the adult population (18 years and above); 21 studies had a population average age in their 30s, 15 studies in their 20s and only 1 study had a mean population age of 46.13 years (Figure 3A). Ten studies investigated TBI in children or in a paediatric population (18 years and below). Four of the population studies had an undefined mean population age, but stated their population age range to be 18 years and above. In most of the studies with a wide age range for participant recruitment, participants in their 20s to 30s reported the most TBI cases, especially due to road accidents, which accounts for around 70-90% of all TBI cases in nearly all the selected population studies. One study by Sharda et al (2014), found that road traffic accidents, especially those involving motorbikes, was the most common cause of TBI among the 12-30 years old age group ([Sharda et al., 2014](#)). While the younger population were at higher risk of attaining TBI, some of the selected studies suggested that there was a negative correlation between the outcomes of TBI (especially cognitive effects) and age ([Asha'Ari et al., 2011](#); [Sharifuddin et al., 2012](#);

[Veeramuthu et al., 2014](#); [Vijian et al., 2020](#)). In contradiction, some studies also suggested no significant effect between age and functional outcome or prognosis ([Abdullah et al., 2005](#); [Abdullah et al., 2018](#); [Kan et al., 2009](#); [Kiflie et al., 2006](#); [Ludin et al., 2019](#)).

Interestingly, when calculating and stratifying the number of participants in each of the studies sample population according to gender, a large gender difference was noticed in the age groups 10s, 20s and 30s, with males predominating the population by more than 1000 participants in the 20s and 30s age group (Figure 3B). Females were clearly underrepresented in the Malaysian population TBI studies. Nevertheless, a number of studies indicated no significant relationship between gender differences and measures of TBI, except a recent study by Abdullah et al. (2020) that witnessed male TBI patients having a higher calorie intake than their female counterpart at discharge day ([Abdullah et al., 2020](#)).

As for racial representation, most of the TBI population studies had a 6:2:1:1 ratio of Malays: Chinese: Indian: Other minorities, respectively. Cumulatively, the Malay population represented 62% of the pooled sample of all the population studies, with Chinese following at 16% of the pooled sample, Indians at 12% and finally the other minority ethnicities such as the indigenous Malaysians making up the remaining 10% of the pooled sample (Figure 3C). Only one study utilized religion as a characteristic of their sample ([Abdullah et al., 2018](#)). Twenty-six studies did not identify the ethnicity of their population, while 7 studies had an unequal representation of the Malaysian population ethnicity; only had one or two of the ethnicities represented. Among the studies that had a good ethnicity representation, only two studies suggested that ethnicity heterogeneity had a significant influence on the TBI outcome ([Ali et al., 2013](#); [Jeng et al., 2008](#)).

Type of TBI severity was fairly well investigated in the population studies, with severe TBI (GCS <8) investigated in 36% of studies, followed by mild TBI (GCS 13-15) and lastly by moderate TBI (GCS 9-12) (Figure 3D). Only thirteen studies investigated all three TBI severities within their population sample and showed that TBI severity affects the functional outcome and diagnosis post TBI, whereby severe TBI showed poorer outcomes.

According to the 2019 road accident statistics, reported by the Royal Malaysian Police ([PDRM, 2020a](#)), Selangor



Figure 3. Population characteristics. **(A)** A bar chart of population age (mean) group versus number of publications; **(B)** A bar chart of the number of cumulative participants stratified according to gender (M: Male (blue bar), F: Female (orange bar)) within each age group; **(C)** A pie chart showing the distribution of population according to race/ethnicity; **(D)** A pie chart showing the distribution of TBI severity recorded in the TBI population studies.

had the highest number (darkest orange colour) of road accidents cases followed by Johor and then Wilayah Persekutuan (WP) Kuala Lumpur (Figure 4A). However, the TBI participants sampled for the population studies were mainly from areas surrounding WP Kuala Lumpur with 18 studies, followed by Kelantan with 17 studies (Figure 4B). A large proportion of the studies sampled their TBI population from the University Malaya Medical Centre (UMMC) or from the General Hospital Kuala Lumpur (GHKL), both situated in Kuala Lumpur. In Kelantan, the TBI participants was mainly sampled from the University Sains Malaysia (USM) Hospital. Therefore, the publication affiliations for these TBI studies were majorly from USM (Kelantan campus and hospital) with 23 TBI studies published by their researchers, followed by University Malaya researchers publishing 12 TBI population studies in total (Figure 5). Interestingly, although Jeng *et al.* (2008) sampled his population from GHKL, the sample contained TBI patients from various Malaysian states that were part of referrals to GHKL (Jeng *et al.*, 2008). However, the

differences in the Malaysian states were not significantly correlated with the aim of their study.

3.3 Basic Science Research

The literature search revealed that basic science research or preclinical research in the TBI field was very scarce in Malaysia, with only 9 studies; 6 animal studies and 3 computational studies, ever to be published and all only within the last decade (Table 1). The preclinical animal TBI studies were performed only by two research groups; one from University Malaya with articles published by Khalin I. *et al.* and the other from University Sains Malaysia with articles published by Muthuraju S. and his colleagues. Both groups used adult (11-13 weeks of age) male mice to investigate functional outcomes and interventions post TBI (Figure 6). Khalin *et al.* applied the weight drop injury model (Khalin, Alyautdin, *et al.*, 2016; Khalin, Jamari, *et al.*, 2016) while Muthuraju *et al.* applied the fluid percussion injury (FPI) model to inflict TBI in their animals (Muthuraju *et al.*, 2014; Muthuraju *et al.*, 2012; Muthuraju, Pati, *et al.*,

2013; Muthuraju, Taha, et al., 2013). While both groups used similar mice breed as their animal model, Khalin *et al.* used two variations for each of their published studies in 2016; C57BL/6 mice (Khalin, Alyautdin, et al., 2016) and C57BL/6N mice (Khalin, Jamari, et al., 2016), and Muthuraju *et al.* used the C57BL/6 mice consistently in all their published studies (Figure 6). Although Khalin *et al.* claimed that their injury model achieved severe TBI, Muthuraju *et al.* did not specify their injury severity resulted from their injury model. Regardless, all six of the preclinical studies suggested cognitive or motor deficits as well as neuronal damage that were significantly evident post injury, which may be reversed to sham levels, using different interventions such as BDNF (Khalin, Alyautdin, et al., 2016), normobaric hypoxia treatment (Muthuraju et al., 2014; Muthuraju, Pati, et al., 2013; Muthuraju, Taha, et al.,

2013) and enriched environment (Muthuraju et al., 2012).

The preclinical computational studies had no similarities in methodology or in research group. Based on Table 1, Alazani et al. (2018) was focused on a creating a predictive model for TBI disease classification using mathematical formula and equations (Alanazi et al., 2018), while Taha et al. (2015) had proposed a mathematical model that studies the kinematic parameters surrounding the impact of a soccer ball on a head resulting in TBI (Taha et al., 2015). Similarly, Norli et al. (2018) had developed a virtual software (Finite Element) that may be used to understand and predict the mechanics of head injury in patients based on the impact velocity information available on the sustained TBI (Norli et al., 2018).

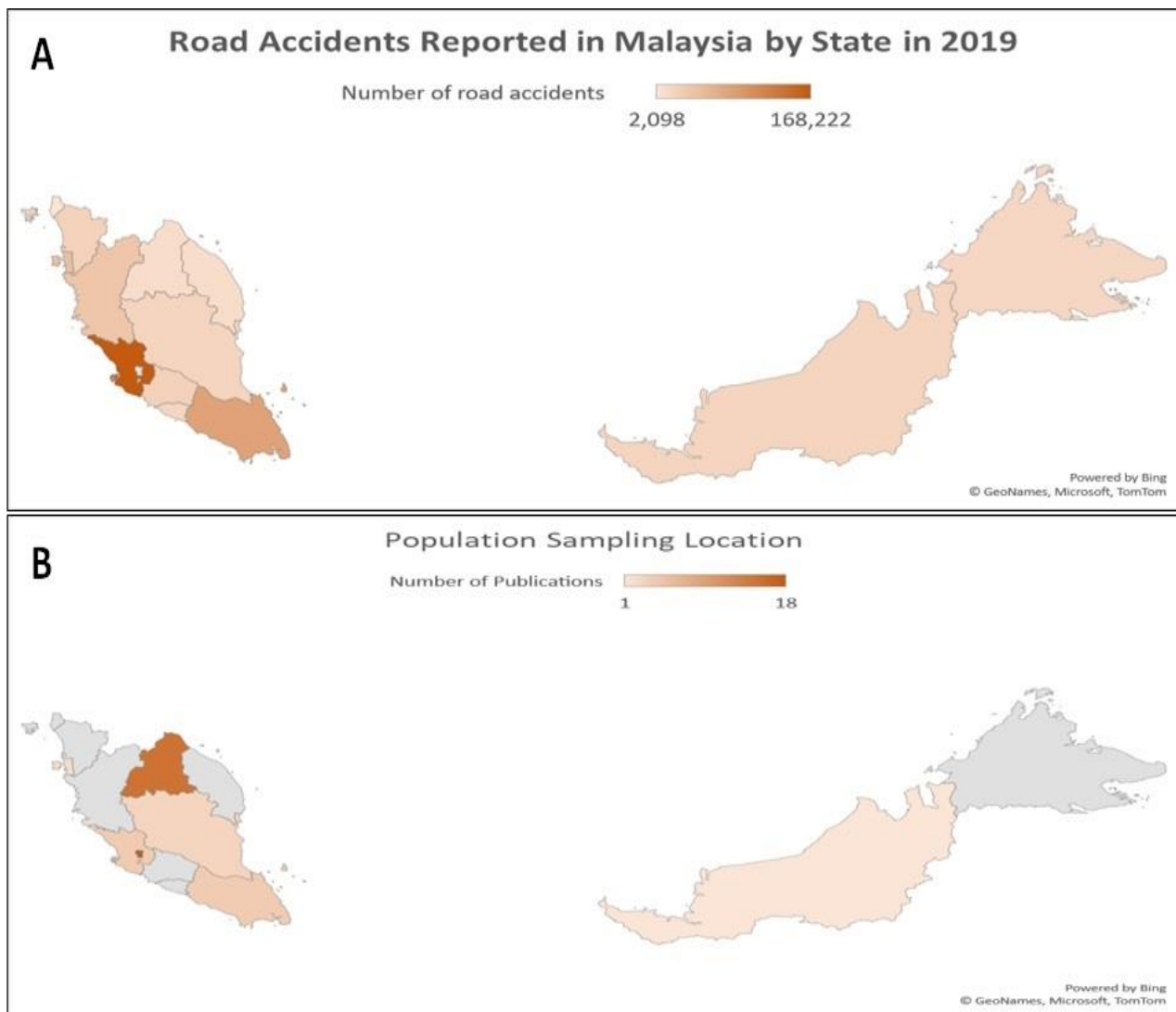


Figure 4. A geographical chart of (A) road accident incidences reported in 2019 and (B) population sampling distributions by publications, in Malaysia. The darker the orange shade, the higher number of (A) incidences or (B) publications. Grey areas signify no incidences or publications recorded.

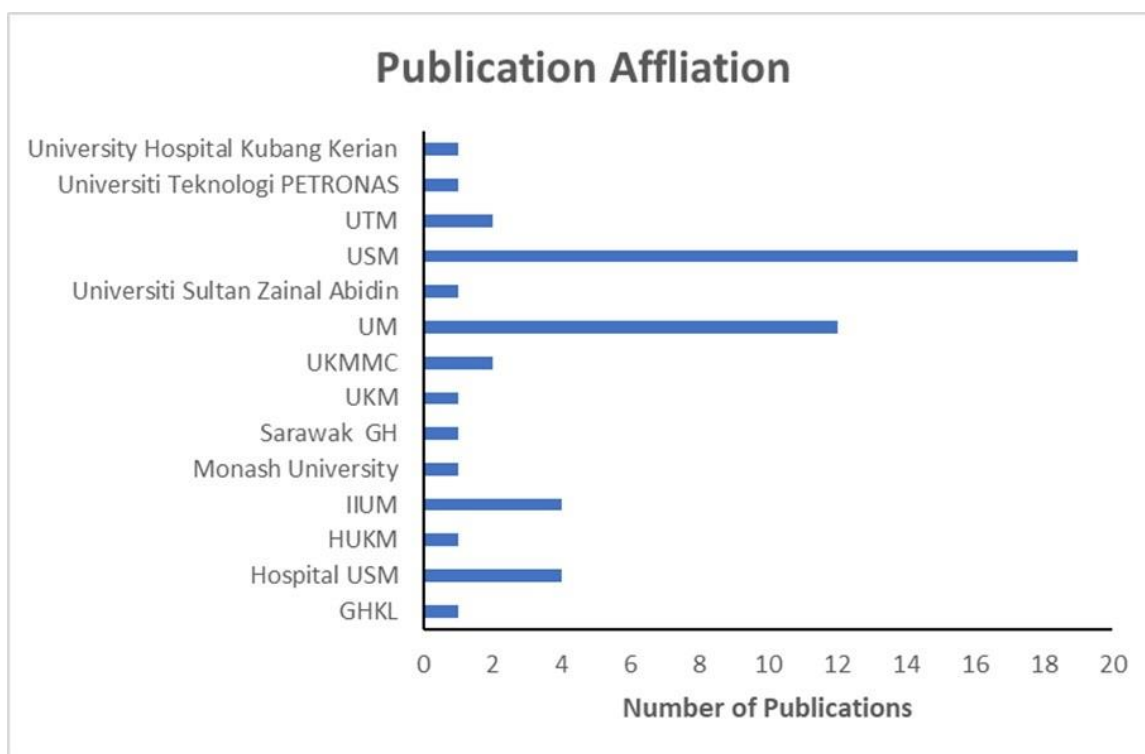


Figure 5. A bar chart of number of publications produced by each institution in Malaysia for population based TBI studies.

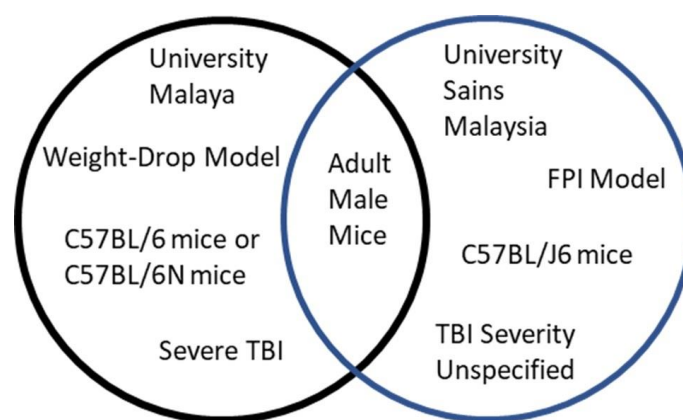


Figure 6. A Venn diagram showing the similarities and differences between the preclinical TBI studies published by two research groups

4.0 DISCUSSION

Overall, this systematic review provides a clear and concise overview on the current status of traumatic brain injury research in Malaysia. Evaluation of the available literature revealed that TBI research in Malaysia were relatively scarce compared to other countries such as US and Europe, and population based TBI research outweighed basic TBI research in Malaysia by roughly a 6 to 1 ratio. Nevertheless, the selected list of literature has cohesively concluded that TBI is a devastating disease in Malaysia, caused predominantly

by motor vehicle accidents, that results in detrimental and often persisting functional outcomes with poor prognosis, which therefore reduces the quality of life in patients and their caregivers. However, under-representation of the actual Malaysian population, small sample size and lack of statistical testing of potential influencing factors such as age, gender and ethnicity, were found to be prominent limitation in many of the selected studies. Similarly, preclinical animal models were only tested by two research groups

which may provide a narrow basic research scope on TBI.

This review observed an exponential increase in TBI publications in Malaysia within the last two decades, which could be a reflection towards the increased awareness of TBI research globally, as well as the increased number of TBI cases in Malaysia ([Jamaluddin et al., 2011](#)). The increment in TBI cases could be an indirect result of Malaysia's economy growth which may enable more Malaysian citizens, especially adolescence, to afford motor vehicles. In conjunction with the increase in TBI cases and awareness, the type of study design and TBI research aims have expanded as well, as more researchers collaborate with hospitals and universities to provide a better understanding of traumatic brain injury within Malaysia and globally. While Malaysian TBI research has been well cited and received in high impact journals, Malaysia is still a couple of steps behind in producing high throughput and high quality TBI research as compared to leading TBI experts in high income countries such as Australia, America, Europe and China ([Tropeano et al., 2019](#)). This is alarming as global TBI incidence reports have stated that countries in Southeast Asia, such as Malaysia have the highest number of reported TBI cases, which are majorly due to motor vehicle accidents ([Dewan et al., 2018](#)). In support, the latest 2019 Malaysian road accident report by the Royal Malaysian Police (PDRM) have shown that the number of road accidents in Malaysia affected about 1.74% of the population every year and at an increasing rate of 10,000 to 20,000 cases yearly ([PDRM, 2020a](#)). Given that the number of TBI fatalities were decreasing in the past years ([PDRM, 2020b](#)), indirectly indicating an increase in TBI survivors, more studies investigating the secondary outcomes post TBI are therefore much needed in Malaysia.

Secondary outcomes of TBI included cognitive deficits, motor impairments, disease progression such as epilepsy and neuropsychiatric disorders, which have all been reported globally ([Kozlowski et al., 2013](#); [Lucke-Wold et al., 2015](#); [Nicholl & LaFrance, 2009](#); [Rabinowitz & Levin, 2014](#)) and in Malaysia ([Abdul Rahman et al., 2018](#); [Abdullah et al., 2005](#); [Abdullah et al., 2018](#); [Ali et al., 2013](#); [Chan et al., 2010](#); [Kumaraswamy et al., 2002](#); [Liew et al., 2009](#); [Ludin et al., 2019](#); [Nandrajog et al., 2017](#); [Shadli et al., 2011](#); [Veeramuthu et al., 2015](#); [Veeramuthu et al., 2017](#); [Veeramuthu et al., 2014](#)). It is quite well known globally that TBI is not just a static event but an ongoing evolving disease that often leads to functional and psychiatric impairments in the later years following injury ([McKee & Daneshvar, 2015](#)),

despite initial recovery. Thus far, only a limited number of studies have investigated this post injury outcome progression, with 2-3 years being the furthest outcome followed up in TBI patients ([Abdul Rahman et al., 2019](#); [Abdul Rahman et al., 2018](#); [Ahmedy et al., 2020](#); [Kumaraswamy et al., 2002](#)). Thus, with mental health problems slowly shedding its taboo coat in Malaysia, emphasis should be given in investigating long term (at least 10 years) cognitive and neuropsychiatric deficits, as well as the later progression into brain diseases after TBI in future studies. Moreover, future retrospective studies on the influence of childhood or young age TBI on the mental health during old age, may shed light on the prevalence of TBI-related mental impairments in Malaysia, which in turn will propagate and mould TBI intervention studies to prevent these secondary outcomes of TBI.

Marching forward, TBI research in Malaysia should also cautiously and statistically account the factors that may influence their research hypotheses on TBI. Factors such as age and gender have been reported to significantly affect TBI outcome ([Biswas et al., 2017](#); [Ma et al., 2019](#); [Marquez de la Plata et al., 2008](#); [Munivenkatappa et al., 2016](#)). Some studies have suggested that those 50 years and above ([Biswas et al., 2017](#); [Marquez de la Plata et al., 2008](#)) and children ([Sariaslan et al., 2016](#)) were at higher risk for poorer prognosis post TBI and were more vulnerable to long term impairments, with TBI in children having been related to late development of functional outcomes and neurodegeneration ([Sariaslan et al., 2016](#)). Gender-wise, while males have reported a higher TBI incidences, females have reported a higher fatality rate and poorer TBI prognosis, based on GCS scores, in some studies ([Biswas et al., 2017](#); [Kraus et al., 2000](#); [Munivenkatappa et al., 2016](#); [Wright et al., 2014](#)), despite studies suggesting the neuroprotective effects of female hormones against TBI secondary outcomes ([Deutsch et al., 2013](#); [Ma et al., 2019](#)). Despite these findings, majority of the Malaysian TBI population studies had not taken age (33 articles) or gender (36 articles) differences into statistical account. Among those that did account for age and gender in their results, only age was shown to have significantly affect and negatively correlate with the prognosis and functional outcome in TBI patients, while gender differences were mostly insignificant. The latter could be a result of the small sample size and gender disproportioned recruitment/participation of TBI patients in the studies.

Another factor that may affect TBI measures, which strongly applies to a multiracial country like Malaysia, is

ethnicity. Differences in ethnicities in the Malaysian population may create a great heterogeneity effect in the sample, and therefore may potentially affect the TBI outcome and diagnosis. Ethnicity disparities have been suggested to influence TBI outcomes in western populations ([Arango-Lasprilla & Kreutzer, 2010](#); [Brenner et al., 2020](#); [Sorani et al., 2009](#); [Staudenmayer et al., 2007](#)), thus may be translated in Malaysia ([Ali et al., 2013](#); [Jeng et al., 2008](#)) as well. Genetic diversity and cultural environment differences such as in food, beliefs and lifestyle between the ethnicities, may impact the recovery process post-injury and its functional outcomes ([Lequerica & Krch, 2014](#); [Saltapidas & Ponsford, 2008](#)). The study by Saltapidas and Ponsford (2008) showed that culturally diverse populations exhibited varied understanding of TBI, diverse negative emotions and even scored differently in post-injury outcome measurements, and therefore urged health professionals to understand the differences in beliefs among ethnicities that may impact TBI diagnosis and prognosis ([Saltapidas & Ponsford, 2008](#)). However, like gender, ethnical differences as a confounder was hardly investigated or mentioned in the Malaysian population studies. Only five studies have acknowledged the ethnicity differences in the sample population ([Abdullah et al., 2018](#); [Ali et al., 2013](#); [Jeng et al., 2008](#); [Liew et al., 2009](#); [Sharifuddin et al., 2012](#)), with only one of them statistically proving the significant affect race had on brain injury ([Jeng et al., 2008](#)). Interestingly, the study by Ali et al (2013), showed that one of their cognitive tests, the Rey Auditory Verbal Learning Test (RAVLT) was significantly affected by ethnicity ([Ali et al., 2013](#)), regardless of TBI and urged future TBI research to account ethnicity differences in their cognitive results.

Taken together, the lack of statistical application and accounting of these factors (age, gender and ethnicity) and possibly others such as time since injury and education, may have stunted Malaysian TBI studies. This is because these factors may affect the pharmacokinetics and pharmacodynamics of treatments ([Mangoni & Jackson, 2004](#); [Shah & Gaedigk, 2018](#); [Soldin & Mattison, 2009](#)). Therefore, future TBI studies in Malaysia should account for these factors in order to develop effective precision-based prescriptions to TBI patients, especially since genotype differences between ethnicities may influence treatment strategies. Besides that, future Malaysian TBI studies may also benefit from conducting nationwide TBI sampling and pooling of resources and data across states, which may translate better to the actual TBI population similar to the nationwide PDRM motor vehicle accident reports ([PDRM, 2020a](#)).

The lack of preclinical studies in Malaysia should also be of concern, as basic research may provide a more in depth understanding on the pathophysiology of TBI and the pharmacological aspects of interventions, that may manipulate the pathways of TBI and its secondary outcomes. Moreover, basic animal research may help hasten the investigations on factors, especially age and time since injury, influencing TBI, unlike population studies which requires years to see its effects.

Therefore, more time, effort, collaboration and funding should be placed into TBI research in Malaysia as a whole, in order to curb these issues and solve the annual ongoing problem of TBI cases and their future secondary outcomes, for the benefit of Malaysian road users and other TBI patients.

5.0 CONCLUSIONS

Traumatic brain injury is a devastating disorder that can affect anyone in the world. While the mortality rate reported in Malaysia was low, which may be under-reported, it still may significantly impact the nation, both economically and socially, especially when considering the development of long-term outcomes and mental disorders after physical recovery. Despite this concern, TBI research in Malaysia was still found to be in its infancy, especially in the basic research area. Lack of TBI awareness in the population and unrectified limitations in TBI research in Malaysia, may result in devastating outcomes in the future for the Malaysian population and its economy. Given the yearly rise in TBI cases in Malaysia, more funds and support should be allocated into the TBI field, as there is a dire need for more effective TBI reporting systems as well as basic, translation and clinical research to be carried out in Malaysia, for the betterment of its people.

Supplementary Materials: Table S1: EPHPP tool, Table S2: AXIS tool, Table S3: CASP tool, Table S4: Cochrane RoB 2 tool, and Table S5: SYRCLE tool, are available online at <https://neurosci.ri.cn.org/ojs/index.php/nrnotes/article/view/52>.

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