COGNITIVE IMPAIRMENT AND NEUROPSYCHIATRY MANIFESTATION FOLLOWING MILD AND MODERATE TRAUMATIC BRAIN INJURY AT 3 MONTHS AND 6 MONTHS

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LIST OF ABBREVIATIONS

1.	TBI	TRAUMATIC BRAIN INJURY
2.	GCS	GLASGOW COMA SCALE
3.	CI	COGNITIVE IMPAIRMENT
4.	NM	NEUROPSYCHIATRY MANIFESTATION
5.	MoCA	MONTREAL COGNITIVE ASSESSMENT
6.	GHQ-12	GENERAL HEALTH QUESTIONAIRE - 12
7.	MINI	MINI INTERNATIONAL NEUROPSYCHIATRY INTERVIEW
8.	ICU	INTENSIVE CARE UNIT
9.	NAICU	NATIONAL AUDIT ON ADULT INTENSIVE CARE UNITS
10.	ICP	INTRACRANIAL PRESSURE
11.	CT	COMPUTED TOMOGRAPHY

ABSTRAK

Latar Belakang dan Objektif

Kemerosotan kognitif dan manifestasi neuropsikiatri adalah komplikasi yang sedia maklum di kalangan pesakit kecederaan trauma otak. Untuk pengetahuan kita, hubungan antara kecederaan otak disebabkan oleh trauma dengan kemerosotan kognitif dan manifestasi neuropsikiatri masih belum dikaji di Malaysia. Objektif utama kajian kami adalah untuk menentukan i) kelaziman kemerosotan kognitif dan manifestasi neuropsikiatri dalam pesakit yang mengalami kecederaan otak tahap ringan dan sederhana ii) hubungan antara pesakit yang mengalami kecederaan otak tahap ringan dan sederhana dengan kemerosotan kognitif dan manifestasi neuropsikiatri dan iii) hubungan antara risiko-risiko dengan kemerosotan kognitif dan manifestasi neuropsikiatri.

Kaedah

Pesakit (n = 54) dibahagikan kepada kumpulan ringan dan sederhana. Kedua-dua kumpulan ringan (n = 26) dan sederhana (n = 28) telah diperiksa pada bulan ketiga dan bulan ke enam selepas berlakunya kecederaan otak. Diagnosis kemerosotan kognitif dibuat menggunakan Penilaian Kognitif Montreal (MoCA) manakala saringan bagi manifestasi neuropsikiatri dibuat dengan menggunakan Soal Kesihatan Umum 12 (GHQ-12) diikuti oleh MINI International Interview Neuropsychiatry (MINI) untuk tujuan pengesahan. Data dianalisa menggunakan *Chi square tests* dan *multiple logistic regression*.

Keputusan

Kami mendapati sebanyak 5 pesakit (19.2%) dari kumpulan ringan mengalami kemerosotan kognitif dan 5 pesakit (19.2%) mengalami manifestasi neuropsikiatri pada bulan ketiga. Pada bulan keenam pula, hanya seorang pesakit (3.8%) sahaja yang masih mengalami kemerosotan kognitif sementara yang lain pulih sepenuhnya. Bagi kumpulan sederhana pula, sebanyak 11 pesakit (39.3%) mengalami kemerosotan kognitif dan 7 pesakit (25%) mengalami manifestasi neuropsikiatri pada bulan ketiga. Pada bulan keenam pula, tiada seorang pesakit pun yang mengalami kemerosotan kognitif atau manifestasi neuropsikiatri. Umur ($p<0.05$, OR 0.678, CI 0.463 – 0.995) dan tekanan darah ($p< 0.05$, OR 1.223, CI: 1.001 – 1.495) merupakan faktor yang signifikan bagi pesakit untuk mengalami kemerosotan kognitif atau manifestasi neuropsikiatri pada 3 bulan selepas kecederaan otak.

Kesimpulan

Kajian ini menunjukkan kepentingan saringan bagi kemerosotan kognitif dan manifestasi neuropsikiatri di kalangan pesakit kecederaan otak trauma pada bulan ketiga dan keenam. Hasil saringan adalah sangat penting bagi membantu pesakit dalam merancang proses rehabilitasi kelak.

ABSTRACT

Background and Objective

Cognitive impairment (CI) and neuropsychiatry manifestation (NM) are known complications among patients with traumatic brain injury (TBI). However, the clinical correlation of mild and moderate TBI with CI and NM have not been extensively studied in Malaysia. Our objectives were to determine i) the prevalence of CI and NM in mild and moderate TBI, ii) association between mild and moderate TBI with CI and NM and iii) association between risk factors with CI and NM.

Methods

Patients (n=54) were divided into mild and moderate TBI. Both mild (n=26) and moderate (n=28) TBI were assessed at 3 months and 6 months post trauma for the same measures. Diagnosis of CI was made by using The Montreal Cognitive Assessment (MoCA) while NM screening was done using General Health Questionnaire-12 (GHQ-12) followed by MINI International Neuropsychiatry Interview (MINI) for diagnostic purpose. Univariate analyses were done using chi square tests and multivariate analysis with multiple logistic regression test.

Results

We found 5 patients (19.2%) with mild TBI had CI and 5 patients (19.2%) had NM at 3 months. Only 1 patient (3.8%) persistently has CI at 6 months while the rest recovered. As for moderate TBI, 11 patients (39.3%) had CI and 7 patients (25%) had NM at 3 months but none had persistent CI or NM at 6 months. Age Umur ($p<0.05$, OR 0.678, CI 0.463 – 0.995) and blood pressure were significant risks (($p< 0.05$, OR 1.223, CI: 1.001 – 1.495) for CI and NM at 3 months.

Conclusion

This study highlighted the importance of screening for both CI and NM following mild and moderate TBI at 3 months and 6 months. These data are essential to help treating clinicians identifying potential risk factors among post head trauma patients. Therefore, early recognition facilitates effective rehabilitation programs planning hence improve prognosis in the future.

1. INTRODUCTION & LITERATURE REVIEW

Traumatic brain injury (TBI) is a leading cause of death and disability in the world. An estimated 10 million people will be affected annually by TBI by the year 2020. TBIs can cause damage to the structure and certainly the function of the brain. Damage structures include skull fractures, extradural hematoma, subdural hematoma, brain contusion or diffuse axonal injury. These usually prompt urgent treatment either via medical or surgical intervention. While damage to the function of the brain are rather insidious as it manifests gradually where neuropsychiatric manifestation and cognitive impairment are such examples. Looking at the gravity of the situation in CI and NM patients after TBI towards quality of life which indirectly affect the economy intrigued us to study the prevalence of neuropsychiatry manifestation and cognitive impairment in Malaysia via screening tools. We wanted to determine whether CI and NM has any relation to the severity of traumatic brain injury especially in mild and moderate group. Understanding the demographics will have an impact on healthcare planning and the provision of resources, and may help us meet the unique needs of these patients.

2. STUDY PROTOCOL

This is a prospective cohort study that was conducted from October 2018 till October 2019. Ethics approval obtained from Ministry of Health ethics committee prior to study. The study was carried out in accordance with Malaysian Guidelines for Good Clinical Practice (GCP) as required by the Ministry of Health Malaysia and the World Medical Association Declaration of Helsinki as adopted by the 59th WMA General Assembly, Seoul, October 2008.

This study was carried out in major neurosurgery based hospital in Klang Valley particularly Hospital Kuala Lumpur. The rationale behind it is because Hospital Kuala Lumpur is the main referral centre for head injury cases with psychiatric and rehabilitation support services.

Study population is focus on traumatic brain injury patients and subjects were recruited from Hospital Kuala Lumpur. Subjects recruited from clinic during their first follow up visit at 6 weeks post discharge and followed by 3 months and subsequently was assessed again at 6 months visit.

The inclusion criteria were:

i) Traumatic brain injury

ii) Glasgow coma scale on admission >8 (mild and moderate head injury)

iii) Age more than 18 years' old

The exclusion criteria were:

i) Glasgow coma scale <8 (severe head injury)

ii) Penetrating brain injury

iii) Other underlying comorbid or cognitive impairment

iv) Premorbid diagnosis of other neurological disease (i.e stroke, dementia) or psychiatry illness

v) Any history of traumatic brain injury

vi) No informed consent

TITLE PAGE

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3.2 Abstract

Background and Objectives

Cognitive impairment (CI) and neuropsychiatry manifestation (NM) are known complications among patients with traumatic brain injury (TBI). However, the clinical correlation between mild and moderate TBI with CI and NM have not been extensively studied in Malaysia. Our objectives were to determine i) the prevalence of CI and NM in mild and moderate TBI, ii) association between mild and moderate TBI with CI and NM and iii) association between risk factors with CI and NM.

Methods

The patients (n=54) were divided into mild and moderate TBI. Both mild (n=26) and moderate (n=28) TBI were assesed at 3 months and 6 months post trauma for the same measures. Diagnosis of CI made by The Montreal Cognitive Assessment (MoCA) while NM screening done using General Health Questionnaire-12 (GHQ-12) followed by MINI International Neuropsychiatry Interview (MINI) for diagnostic. Univariate analysis done using Chi Square test and multivariate analysis with multiple logistic regression test.

Results

We found 5 patients (19.2%) with mild TBI had CI and 5 patients (19.2%) had NM at 3 months. Only 1 patient (3.8%) persistently has CI at 6 months while the rest recovered. As for moderate TBI, 11 patients (39.3%) had CI and 7 patients (25%) had NM at 3 months but none had persistent CI or NM at 6 months. Age ($p<0.05$, OR 0.678, CI 0.463 – 0.995) and blood pressure were significant risks (($p<0.05$, OR 1.223, CI: 1.001 – 1.495) for CI and NM at 3 months.

Conclusion

This study highlighted the importance of screening for both CI and NM following mild and moderate TBI at 3 months and 6 months. These data are essential to help treating clinicians identifying potential risk factors among post head trauma patients. Therefore, early recognition facilitates effective rehabilitation programs planning hence improve prognosis in the future.

Keywords

Traumatic brain injury, mild, moderate, cognitive impairment, neuropsychiatry manifestation, MoCA, GHQ-12, MINI

3.3 Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in the world. It contributed around 30% of all injury death[1]. An estimated 10 million people will be affected annually by TBI, and by the year 2020, it will surpass many diseases as the major cause of death and disability[2]. In Malaysia, total of 166,768 trauma patients were admitted to the Emergency Department in 2009 according to National Trauma Database. Out of that, 2061 were major trauma and 76.8% were attributed to road traffic accidents[3]. Head injury was the commonest diagnosis leading to intensive care unit (ICU) admission in 2008 based on The National Audit on Adult Intensive Care Units (NAICU) report.

TBI can be divided into primary and secondary brain injury. The primary injury occurred as a consequence of the initial physical insult hence the extent of damage will largely depended on the nature, intensity, and duration of the impact. Microscopically there will be cell wall disruption and increased membrane permeability disrupting ionic homeostasis making axonal tissue particularly susceptible to injury. Post insult, neurological injury progressed over hours and days, resulting in a secondary injury. Inflammatory and neurotoxic processes result in vasogenic edema within the brain leading to raised intracranial pressure (ICP), hypoperfusion, and cerebral ischemia. Subsequently, secondary injury occurs as a result of further physiological insults such as hypoxia, hypotension, hypercapnia or hypocapnia, hyperglycemia or hypoglycemia[4]. In terms of severity, TBI can be classified into mild, moderate and severe. The most useful classification of severity is based on the level of consciousness as assessed by the Glasgow Coma Scale (GCS) after resuscitation. The GCS comprises the sum score of the values from three components: eye, motor, and verbal scales and scored as mild (GCS 14–15), moderate (GCS 13–9), and severe (GCS 8). However, factors such as hypoxia,

hypotension, and alcohol intoxication affect GCS, leading to diagnostic confusion. Therefore, the patient should be resuscitated and reversible causes need to be corrected before any GCS assessment. The ability to assess eye opening and verbal response is influenced by sedative agents or tracheal intubation, leading some to suggest the use of the motor score alone[5].

It is important to appreciate that TBIs not only damage brain structure but affect the brain function as well. Damage to the structures include skull fractures, extradural hematoma, subdural hematoma, brain contusion or diffuse axonal injury[6]. These usually prompt urgent treatment via medical or surgical intervention. While damage to the function of the brain are rather insidious as it manifests gradually where neuropsychiatric manifestation and cognitive impairment are such examples[7]. Consequences following head trauma may lead to significant morbidity and mortality both in acute setting as well as long term sequelae. Therefore, it is imperative that clinicians be able to recognize and treat these conditions in order to more effectively manage head trauma, improve outcome, and care for patients. Despite the emphasis placed upon physical deficits during the early stages of recovery from TBI, cognitive and behavioural deficits gave rise to the major morbidity which most impairs the capacity to return to work and maintain social activities[8].

Cognitive impairment (CI) is a common consequence of TBI. Impairment is particularly prominent in terms of information processing speed and attention, memory, and executive functioning. Cognition is seen markedly impaired around 1-month post injury[9]. Similar observation was found by author that CI manifest between 48 hours and 1 month after trauma. CI typically resolve in 80-85% of cases of uncomplicated mild

TBI within 3-6 months[10]. Another study showed that most CI tend to disappear beyond 1 month post trauma, but some do persist, thus suggesting different recovery patterns[11]. Nonetheless, studies have also found that about 5– 10% of individuals experience the presence of persistent and atypical cognitive deficits up to 1 year[12]. On the other hand, for moderate TBI survivors approximately 65% report to have long-term problems with cognitive functioning[13]. These symptoms persist longer than mild TBI from several months up to several years after the trauma[14] and lead to a less favourable recovery[15]. Factors that may influence cognitive outcome according to current literatures include demographic or premorbid characteristics, severity of injury, type and location of lesions, early cognitive functioning, or event of posttraumatic amnesia (PTA)[16].

Neuropsychiatry manifestation (NM) is not uncommon after TBI. The term neuropsychiatry is a discipline that focuses on the relationship between the brain and its role in thinking, emotions, and behaviour. Sequelae such as mood and anxiety disorders, post concussive syndrome, personality change, aggression, and psychosis are among the most common problems after TBI. Ciurli and colleagues[17] in their study reported the prevalence of psychiatric symptoms found in 120 persons with TBI are apathy (42%), irritability (37%), dysphoria/depressed mood (29%), disinhibition (28%), eating disturbances (27%), and agitation (24%)[18]. In one study of 939 TBI patients, the prevalence of any psychiatric illness in the 1st year was 49% following moderate to severe TBI and 34% following mild TBI[19]. Another study found out that the prevalence of depression after TBI was approximately 30%. Based on their findings, on average 27% met criteria for depression 3 to 6 months from injury; 32% at 6 to 12 months; and 33% beyond 12 months[20]. Anxiety disorders on the other hand frequently coexist with depressive disorders. Prevalence of anxiety disorders has been reported ranging from 18%

to 60% and generalized anxiety disorder (GAD) is the most commonly reported anxiety disorder after mild and moderate TBI ranging from 24% - 27%[21]. Risk factors for neuropsychiatry manifestation included female gender, younger age, lower education, and preinjury unemployment[22]. On top of that, other factors like increasing age, arteriosclerosis, and alcoholism increased the risk of neuropsychiatry manifestation[23]. Surprisingly, the effects of severity of TBI either mild or moderate TBI are uncertain. Studies using the Glasgow Coma Scale (GCS) score to estimate severity have generally not found an association between mild or moderate TBI to later psychiatric symptoms[24].

The reason for both impairments could be explained by understanding the pathophysiology of brain injury which can be viewed consist of three components according to Ann et. al[25]; 1) macroscopic pathophysiological events or primary brain injury; 2) microscopic pathophysiological events which are part of secondary brain injury consisting of intracranial hypertension, cerebral ischaemia and hypoxia, and electrographic seizures and finally 3) ultramicroscopic events which are also part of secondary brain injury processes including cascades of glial cells and molecular events, microvascular dysfunction, blood brain barrier (BBB) disruption, inflammatory cells recruitment and reactivation, and immunological response. These alterations will end up with fewer axonal connections throughout their brains and less efficient electrophysiological function of at least some of the axonal connections that are present which may lead to neuropsychiatry consequences later. Warren in his review[26] brought about the concept of power function, a term that refers to the basic capacity of the brain to engage efficiently in any cognitive task, regardless of what that task may be. It consists of two critical components which are arousal and channel capacity. The overall loss of

mental “power” after TBI can be seen as a direct consequence of the widespread reduction in axonal performance resulting from traumatic brain injury.

The clinical presentations of cognitive impairment and neuropsychiatric manifestations are subtle. Unfortunately, it is indeed a monumental challenge to spend extra time in clinic for a thorough evaluation due to the sheer number of patients in head injury clinics and the lack of manpower. On top of that, no specific radiological imaging may aid to clinch the diagnosis. Therefore, if the presentation is not obvious, most of the time, doctors would have missed the diagnosis. It is time consuming to perform sufficient assessment in a busy clinic due to the length of its screening tools. Hence, it is important to elicit symptoms that may suggest any cognitive or neuropsychiatry manifestation prior to detailed assessment. A collection of symptoms for neurocognitive include deficits in executive functioning, learning, memory, attention, processing speed, increased irritability, depression, anxiety, and sleep disturbance[27].

The Montreal Cognitive Assessment (MoCA) tool is utilized for detailed evaluation of cognitive impairment. It is a comprehensive cognitive instrument used to assess the level of impairment in neurological populations[28]. MoCA evaluate neuropsychological functioning across its five domains (executive function, working memory, short-term memory, language and visuospatial ability). Executive function is assessed using trail-making, phonemic fluency, and verbal abstraction tasks. Working memory is assessed using sustained attention, serial subtraction, and digit span forward/backward tasks. Short-term memory is assessed through the delayed recall of five nouns. Language is assessed using naming (low familiarity animals), sentence repetition, and the phonemic fluency task. Visuospatial ability is assessed using clock-drawing and cube-copying tasks.

It is quick and reasonably sensitive (87.9%) and specific (66.7%) test for cognitive impairment following mild TBI and is a good screening tool for assessment of cognitive function[29]. Another study by Chu Wong et al[30] showed that MoCA is a useful and psychometrically valid tool for the assessment of gross cognitive function in traumatic brain injury and have a significant correlation with other comprehensive neuropsychological assessments and the Mini Mental State Examination (MMSE). MoCA has been translated to Malay language and a few studies showed the validity of the translated version for assessment of cognitive function and in fact it's superior than Malay Mini Mental State Examination (M-MMSE). To date, there is no study available to evaluate the reliability of Malay MoCA among TBI patient.

The GHQ-12 is an instrument in identifying states of psychiatric morbidity, anxiety and depression. It detects the form of psychiatric disorder which may be relevant to a patient's presence in a medical clinic and focuses on psychological compounds of ill health[31]. It has been widely used and developed in Western countries and therefore a translated version of GHQ-12 has been made and validated to the local population for psychiatric disorder assessment[32]. Study by Saiful and his colleague looking into the sensitivity, specificity and positive predictive value of Malay version GHQ-12 showed that it is comparable with other validated studies. Sensitivity and specificity and reliability were reported as 81.3% and 75.3% respectively with positive predictive value of 62.9% as well as having area under curve more than 0.7[33]. The 12-item GHQ-12 is simple, short and only requires less than 10 minutes to be filled by respondents. However, GHQ-12 is only as good as a screening tool for psychiatric morbidity and a second-stage of assessment is needed to confirm the diagnosis hence the usage of a MINI International Neuropsychiatric Interview (MINI).

The MINI is compatible with international diagnostic criteria, including the International Classification of Disease (ICD-10) as well as the Diagnostic and Statistical Manual of Mental Disorders (DSM)[34]. It is useful in clinical psychiatry as well as in research settings and the present study showed that the MINI is a useful instrument with good psychometric qualities in a real world setting when used by layman interviewers to conduct a large scale epidemiological survey. Firdaus Mokhtar and his colleagues conducted a preliminary study[35] to evaluate the Malay version of the MINI in term of its reliability and validity but only focus on two only two diagnoses (Major Depressive Disorder and Generalized Anxiety Disorder). They found out Malaysian Version of MINI, especially for Major Depressive Disorder and Generalized Anxiety Disorder, can be used by academic researchers and layman interviewers (with adequate training) for rapid screening of homogenous samples for clinical trials and epidemiology studies.

We are well aware that mild and moderate TBI are the leading cause of morbidity in adults during their most productive years. In addition, they are at risk for considerable loss of earning potential and costs associated with providing long term care due to the young age of occurrence. Delayed diagnosis of neuropsychiatry and cognitive impairment will eventually lead to burden of cost, morbidity and quality of life. Amongst the many sequalae of mild and moderate TBI, CI and NM may be paramount in relation to its contribution to long term dysfunction. CI after TBI has major detrimental effects on functional ability, as demonstrated by a study by Whitnall et. al[36]. This result in long term functional impairment and decrease in quality of life. NM like major depression after TBI may have severe consequences for rehabilitation outcomes which in turn significantly affect interpersonal, occupational, and social functioning. Eventually, it impairs activities

of daily living and overall quality of life as well as increase the risk for suicide[37]. As a result, the average healthcare costs of the TBI group were 76% higher than those without TBI 3 years after injury. Surprisingly, the costs of treating psychiatric illnesses in mild and moderate TBI were more than double the total cost for nonpsychiatric patients[38].

Within the Malaysian context, data of the expenditure profiles of TBI and epidemiology of neuropsychiatry and cognitive impairment in TBI are currently lacking hence it's difficult to gauge the consequences of this problem. We wanted to determine whether CI and NM has any relation to severity of traumatic brain injury especially in mild and moderate group. Understanding the demographics will have an impact on healthcare planning and the provision of resources, and may help us meet the unique needs of these patients. Long-term outcomes of these patients are important for clinicians to assist patients and their families in formulating rehabilitation intervention and reducing secondary complications

3.4 Methodology

3.4.1 Research design

This was a prospective cohort study which was conducted from October 2018 till October 2019.

3.4.2 Research location and duration

This study was carried out in a major neurosurgery based hospital in Klang Valley at Hospital Kuala Lumpur.

3.4.3 Study population

Study population was focused on traumatic brain injury patients and subjects were recruited from Hospital Kuala Lumpur. Subject recruited from clinic during first follow up visit at 6 weeks post discharge followed by subsequent visit at 3 months and re-assessed again at 6 months visit.

3.4.4 Method of research

This study was approved by National Medical Research Register (NMRR- 18-1844-42388). Written consent was obtained from patients.

1. Participant

Fifty four patients recruited from Neurosurgery Clinic Hospital Kuala Lumpur, Malaysia. A purpose-designed questionnaire was used to collect information during interviews in the following areas: age, gender, race, educational status, civil status, employment status, smoking, alcohol, mechanism of trauma, Glasgow Coma Scale, CT brain findings and surgical procedure. First contact with subjects was during their immediate follow up 6 weeks post discharge from neurosurgical ward. Our inclusion criteria were i) patient must be a traumatic brain injury case, ii) patient's Glasgow Coma Scale on admission was more than 8 and iii) patient age was more than 18 years old and iv) patient must be able to complete the screening process. Any cases with GCS less than 8, penetrating brain injury, previous underlying psychiatry or cognitive impairment condition or any neurological

disease, history of traumatic brain injury before or not consented for the study will be excluded. Subjects were divided into mild and moderate group based on their admission GCS. Both mild and moderate TBI were assessed at 3 and 6 months.

2. Cognitive measures

Cognitive status was assessed in both mild and moderate TBI patients using The Montreal Cognitive Assessment (MoCA) questionnaire. This set of questionnaire has been translated into Malay language and validated as mentioned in the literature review. MoCA was used to assess neuropsychological functioning across its five domains (executive function, working memory, short-term memory, language and visuospatial ability). Executive function was assessed using trail-making, phonemic fluency, and verbal abstraction tasks. Working memory was assessed using sustained attention, serial subtraction, and digit span forward/backward tasks. Short-term memory was assessed through the delayed recall of five nouns. Language was assessed using naming (low familiarity animals), sentence repetition, and the phonemic fluency task. Visuospatial ability was assessed using clock-drawing and cube-copying tasks. Any patient with score less than 26 will be regarded as having cognitive impairment and further referred to neurorehabilitation unit for detail assessment and intervention.

3. Neuropsychiatry measures

Neuropsychiatry assessment was performed in two stages for both mild and moderate TBI patients. Firstly, all consented patients were screened with General Health Questionnaire, 12-item version. Subjects who scored 4 or more on General Health

Questionnaire will be followed by MINI International Neuropsychiatry Interview (MINI) which was compatible with international diagnostic criteria, including the International Classification of Disease (ICD-10) as well as the Diagnostic and Statistical Manual of Mental Disorders (DSM). In this study, our focused was on neuropsychiatric diseases like Major Depression Disorder (MDD), Panic Disorder and Generalized Anxiety Disorder. For any patient with scores to suggest any of the neuropsychiatry disease were then further referred to Psychiatry clinic for detailed assessment and management.

3.4.5 Statistical analyses

The recorded data were analysed using the SPSS (version 22, SPSS Inc., IBM, Chicago, IL, USA) statistical software. Univariate analysis such as Chi Square test used and logistic regression for multivariate analysis. Statistical significance was defined as $p<0.05$ for all analyses, unless otherwise stated.

3.5 Results

A total of fifty four patients were recruited in which mild TBI were 26 patients (48.1%) and moderate TBI were 28 patients (51.9%). Their median age group were 27 years old (inter quartile range 21-38) for mild TBI and 26 years old (inter quartile range 23-34) for moderate TBI. Majority were male in both groups with male to female ratio of 3:1 for mild TBI and 2:1 for moderate TBI. Majority of the mechanism of injury were motor vehicle accident where highest for both groups involving motorcyclists; 76.9% for mild TBI and 71.4% for moderate TBI respectively. Information pertaining to demographic details and injury-related characteristics of the patients for both mild and moderate TBI were presented in Table 1.

Subjects were divided into mild and moderate TBI and evaluated twice at interval of 3 months and 6 months. In mild TBI (N=26), we found that 5 patients (19.2%) had CI and 5 patients (19.2%) had NM at 3 months. However, upon second assessment at 6 months, only 1 patient (3.8 %) persistently had CI in mild TBI.

As for moderate TBI (N=28), 11 patients (39.3 %) had CI and 7 patients (25%) had NM at 3 months but none had it persistent at 6 months for both mild and moderate TBI.

3.5.1 Relation of severity of traumatic brain injury with CI and NM

A univariate analysis was carried out comparing the presence of CI and NM at 3 months and 6 months as a dependent variables and severity of GCS as independent

variables. Severity of GCS either mild or moderate TBI does not contribute significantly (p=0.26) towards CI and NM at 3 months and 6 months.

3.5.2 Relation of risk factors with CI and NM

Multiple logistic regression analyses were carried out by using the presence of CI and NM at 3 months and 6 months as a dependent variables and the following risk factors as covariates: age, gender, employment status, income status, blood pressure on admission, CT brain findings either normal or abnormal and surgical status either treated conservatively or operated. According to the logistic regression analyses, there was a statistically significant association between blood pressure and manifestation of CI at 3 months with $p < 0.05$.

There are statistically significant risk factors for CI in systolic blood pressure (OR: 1.223, CI: 1.001-1.495, p-value 0.049) and diastolic blood pressure (OR: 1.215, CI: 1.016-1.454, p-value 0.033) at 3 months. We found that an increase in a unit of systolic or diastolic blood pressure leads to the odds of the occurring of CI by 1.223 time for systolic and 1.215 for diastolic respectively. As for NM at 3 months' assessment, age was associated with increased risk of NM (OR: 0.678, CI: 0.463 – 0.995, p-value 0.047). An increase in a unit of age leads to the odds of the occurring of NM by 0.678 time.

There were no statistically significant risk factors in both CI and NM at 3 and 6 months. The results were tabulated in table 3.

3.6 Discussion

This study aimed at evaluating the presence of cognitive impairment (CI) and neuropsychiatry manifestation (NM) following mild and moderate traumatic brain injury (TBI) at 3 months and 6 months. In addition, our study wanted to determine any association between risk factors with cognitive impairment and neuropsychology manifestation.

The main result showed that mild and moderate TBI does not have any significant effect (p=0.26) on CI and NM hence we were unable to reject our null hypothesis. Our findings are contradicting with similar study conducted where they evaluated 12 patients with mild and moderate TBI post 1 year injury and demonstrated that CI does correlate with severity of GCS[39].

These contradicting findings are attributed to the different sets of assessment tool used which may influence the detection rate. We chose MoCA as our sole assessment tool because it's a brief tool and require less than 10 minutes to complete the assessment hence its suitable for a busy outpatient neurosurgery clinic. It was reported to be a useful and psychometrically valid tool for the assessment of gross cognitive function in TBI patients[40]. On another note, we used mostly (81.4%) translated Malay MoCA for our assessment as Malay language is our national language. The original English version of the MoCA was translated into Malay language and has been validated for cases like stroke[41] and even though characteristic for CI of post-stroke and TBI appear similar in certain aspects[42] no study was done among TBI population using Malay MoCA.

In pertaining to MoCA as an assessment tool, studies reported that the significant of the scores were strongly dependent on educational level. They found that when applying the MoCA test on individuals, those with lower educational level seem to display higher rates of CI. It was suggested in the study that different cut-off values were required in order to better distinguish normality from CI in the lower educational level group[43]. In this study, 92.3% of mild TBI and 82.1% of moderate TBI received secondary to tertiary education hence made the assessment valid in this population.

However, the trend of our data appeared similar with other studies. We found the presence of CI at 3 months among mild and moderate TBI patients were 19.2%-39.3%. This finding was consistent to what was reported by Nygren-de Boussard et. al. where they found that 30% of their patients persisted to have CI at 3 months following mild TBI[44]. Skandsen et. al. found 43% of moderate TBI had CI at 3 months post injury[45]. Furthermore, at 6 months following mild and moderate TBI, nearly all patients (75%) recover except 1 patient persist to have CI. Similar findings were reported where one third of mild TBI patients continue to experience CI post 3 months injury and nearly 80%-85% of them resolved fully within 6 months[46].

As for NM, Jorge et al.[47] assessed 91 consecutive TBI patients (44% mild, 32.5% moderate and 23.2% severe) admitted to general hospital at 3, 6, 9, and 12 months post injury. Evaluation was done by psychiatrist and they found that in the TBI sample, 46.7% in mild TBI and 40% in moderate TBI had depression. Other study by Levin et al.[48] looked into depression at 3 months post mild and moderate TBI found out 18% of mild TBI and 11% of moderate TBI had depression. Their patients were evaluated using structured psychiatric interviews and Diagnostic and Statistical Manual (DSM) criteria

for diagnosis. In this study, we found that 19% of mild TBI and 39.3% of moderate TBI had depression which is similar range of percentage with both studies. Unfortunately, we couldn't get any significant association between severity GCS and NM. We postulate that it may be affected by the fact that our interview session was set in a less conducive setup because of high number of patients in neurosurgical clinic. Therefore, the result may appear under reported.

In this study, we found that systolic and diastolic blood pressure correlate significantly with CI at 3 months post injury regardless of either mild or moderate brain injury. There's no recent study to highlight the association of elevated blood pressure in TBI patients with CI. Nikolet et al.[49] in their animal study managed to show the significance of this factor pertaining to CI in TBI rodents. They found out in the TBI sample with hypertension showed impaired learning and memory two weeks after mild TBI. Both condition eventually leads to persistent disruption of the blood-brain barrier, which was associated with accumulation of toxic blood borne substances in the brain parenchyma, neuroinflammation and cognitive decline amongst the animals.

We also found that the risk of having NM at 3 months post injury is higher with increasing age. Similar finding was reported with previous literature by Glenn et al.[50]. Glenn found that NM particularly depression increases with age after injury. Based on their cohort, 41 patients (56% mild, 17% moderate and 27% severe TBI) with the mean age of 43.6 year old was evaluated using Beck Depression Investory-II (BDI-II) by three clinician investigators showed significant correlation between depression and increasing age. Another study by Levin et al.[51] showed similar significant association between increasing age and depression. Out of 41 patients with mild and moderate TBI, 31% were

depressed at 1 month with mean age of 40 year old. Both studies share the same range of age for their cohort but compared to our study, our median age for mild and moderate TBI are younger ranging between 26-27 year old hence it's difficult to conclude despite its statistically significant. This does not entirely sure to indicate age is associated with depression, but rather suggest that it would take a larger sample size to determine this with greater certainty.

3.7 Study Limitations

To our knowledge, this is the first study in Malaysia looking into association of traumatic brain injury with CI and NM. Despite other reason stated above, another limitation of this study including limited sample size and inter interviewer factor as all interviews were conducted by a single researcher. In the future, we suggest to recruit larger sample size and to use additional assessment tool besides MoCA alone. Multiple researchers especially during assessment should be assembled to prevent any bias to the outcome.

3.8 Conclusion

TBI is common among young adults in Malaysia and little attention has been paid to the significant morbidity which may interfere with rehabilitation due to CI and NM as a consequence of TBI. While this study does not offer a conclusive answer pertaining to association of mild and moderate TBI with CI and NM but it does provide some findings

to enlighten treating clinicians. Regardless, future research should aim to replicate results in a larger sample with multiple assessment tools.

3.9 References

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