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Full Title: Incidence, predictors and cognitive dysfunction in post-traumatic epilepsy following a traumatic brain injury: A study protocol

Short Title: Epilepsy and cognitive dysfunction in traumatic brain injury

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24 traumatic brain injury: A study protocol

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26

27 **Competing interests:**

28 The authors have declared that no competing interests exist.

29

30 **Abstract:**

31 Approximately 69 million people worldwide are annually affected by traumatic brain

32 injury (TBI). In Malaysia, the traumatic injury was the leading cause of hospital

33 admission and death, accounting for one in three emergency visits. Among the most

34 recognised complication of TBI is post-traumatic epilepsy (PTE), which is an essential

35 contributor to morbidity and mortality. However, there is a lack of local epidemiological

36 data on PTE in Malaysia. This study aims to describe the incidence and predictors of

37 PTE among TBI patients admitted to a tertiary healthcare centre in Kuala Lumpur,

38 Malaysia. We hypothesised that increases in age, race, and severity of brain injury

39 are among the main potential predictors of PTE. It will also provide evidence that

40 patients with epilepsy following TBI are associated with significant impairment in

41 cognitive performance than TBI patients without epilepsy. An analysis of a two years

42 retrospective cohort will be employed, of which adults with a history of admission for

43 TBI in 2019 and 2020 will be contacted, and the development of epilepsy will be

44 ascertained using a validated tool and confirmed by our neurologists during visits. The

45 patients will then be grouped into two, with PTE and without PTE, and assessed their

46 cognitive performance by clinical psychologists. Given that the management of TBI

47 and PTE patients involves a multidisciplinary team, the findings might be significant to

48 many healthcare providers in determining policy and strategise a better treatment.

49

50 **Introduction:**

51 At least 10 million people sustain head trauma every year [2,3], making

52 traumatic brain injury (TBI) one of the leading global causes of death and disease

53 burden [1]. One of TBI's major complications but poorly understood sequelae is post-

54 traumatic epilepsy (PTE) [4–6]. PTE is a significant form of symptomatic epilepsies

55 resulting from various brain insults [6]. In the general population, it causes 10–20% of

56 symptomatic epilepsy and 5% of all epilepsy [7].

57 PTE poses significant health and socio-economic problem worldwide [8].

58 People with epilepsy are three times more likely to die prematurely than the general

59 population, with the absolute number of deaths increasing by 39% [1]. Post-traumatic

60 epileptic seizures are distinguished from non-epileptic post-traumatic seizures (PTS)

61 by their etiology and timing after the trauma. Late seizures, occurring more than a

62 week after the initial event, characterise PTE. [9]. The time between a TBI and the

63 onset of the first seizure varies greatly [10]. In about 80% of cases, the first seizure

64 following PTE occurs within the first year, and more than 90% of cases occur by the

65 end of the second year [11]. Eighty-two percent of patients who experienced a late-

66 onset seizure (more than a week after injury) also experienced a second seizure within

67 the following two years [8]. Although a seizure during the first week after injury (early

68 PTS) is linked to a higher incidence of late PTS (after the first week of injury), having

69   a late PTS is correlated with an even higher risk of seizure recurrence [12–14]. The

70   likelihood of seizures following a TBI has been predicted mathematically by several

71   authors, but their clinical applicability for the majority of brain-injured people has not

72   been tested [13]. Researchers have tried to pin down the true prevalence of PTE for

73   decades, and their findings have yielded a wide range of reported numbers, from 1.3%

74   to 53.3% [15–17]. This variation may be attributable to differences in the severity of

75   the initial TBI. The cumulative incidence of PTE was reported to be 4.4 per 100 people

76   with mild TBI, 7.6% per 100 people with moderate TBI, and 13.6 per 100 people with

77   severe TBI in a three-year population-based study conducted in the United States [4].

78   In most TBI cases, cognitive difficulties are the most prominent impairments

79   [18]. However, little is known about how PTE can exaggerate neuropsychological

80   deficits. Preclinical TBI studies provided scientific proof that PTE may further

81   deteriorate cognitive performance. This comorbidity is also reported in other

82   secondary epilepsies, such as post-stroke epilepsy [19]. Cognitive performance

83   includes motor function, memory, intelligence, attention or concentration, processing

84   speed, language, and visual-spatial abilities [20]. Researchers found that mice

85   induced with TBI followed by electroconvulsive shock seizures performed worse in the

86   Barnes maze than mice who underwent TBI alone [21]. These findings on the "double

87   hit" mice were related to increased glial activation.

88   Meanwhile, in a study by Shultz and colleagues [22] comparing rats that did or

89   did not develop PTE at six months post-injury, no significant differences between the

90   groups were observed in Morris water maze (MWM) performance. The few preclinical

91   studies that evaluated the impacts of PTE on cognitive functions have yielded

92   inconclusive results. In some studies, temporal complexities may contribute to the

93   failure to distinguish between PTE versus non-PTE groups of post-TBI rats. One

4

94 previous study found an alarming statistic: half of the people with epilepsy exhibit

95 cognitive dysfunctions in multiple domains, including learning, memory, attention, and

96 executive functioning [23]. Memory loss, however, is far more common [24]. As a

97 result, it is prudent to postulate that epilepsy resulting from TBI adds deficits to an

98 individual with TBI, thereby worsening neuropsychological performance.

99 This study involves two parts. Part I of the study is to determine the etiology of

100 PTE in TBI individuals to quantify the incidence rate and stratify risks for developing

101 PTE. Part II of the study examines the cognitive comorbidity of PTE in a diverse multi-

102 ethnic population. Previously, several authors [5,6,13,25,26] had analysed predictors

103 for PTE in a large sample of TBI people. Unfortunately, the geographical limitation

104 prevents the broad generalisation of the results of these investigations. To the best of

105 our knowledge, this study represents the first investigation in Malaysia with multi-

106 ethnicity and various demographical backgrounds who were retrospectively reviewed

107 for up to 2 years after brain injury. The results of this study are intended to add to the

108 emerging body of knowledge for both professionals and the general public. Individuals

109 with TBI and PTE face unique challenges that healthcare providers will consider. Due

110 to this, better services and strategies to enhance these people's lives could be created.

111 Additionally, people with PTE and their families may be better prepared to deal with

112 upcoming issues such as memory deficit, driving limits, intelligence, and the effect on

113 caregivers, family members, and significant others. Furthermore, reducing the burden

114 of comorbidities linked with decreased cognitive abilities and PTE would substantially

115 impact the individual, society, and the economy.

116

117 **Significance of the study**

118   Despite a wealth of epidemiological data, there are still many questions regarding the

119   epidemiology and determinants of outcomes of TBI patients with no definitive answers

120   and no robust evidence base to guide their management. There is a relative lack of

121   data on PTE in Malaysia. As a consequence, it has become an underappreciated

122   condition. Patients with similar injuries may receive very different opinions about their

123   likely prognosis and the best treatment, depending on their unit and the surgeon who

124   treats them. Once a risk has been unequivocally associated with PTE, a logical final

125   step is targeting those individuals with specific predictors in advocating a policy that

126   aims to strategise the pharmacological or non-pharmacological treatment toward

127   preventing epilepsy and its cognitive comorbidity. The findings can be used to plan

128   and evaluate strategies to prevent further deterioration and guide the management of

129   patients whom PTE has already developed, thereby helping to lighten the burden of ill

130   health upon the individual and the community.

131

132   **Aim and objectives**

133   *Study aim:*

134   This project aims to describe the incidence and predictors for PTE among TBI in a

135   tertiary care center in Malaysia and generate evidence on the cognitive burden of PTE.

136   *Study objectives:*

137   a. To estimate the incidence of PTE among TBI patients attending Universiti

138   Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, between

139   2019 to 2020.

140   b. To identify potential predictors of PTE among TBI patients in UKMMC, Kuala

141   Lumpur.

142   c. To determine the association between PTE and cognitive impairment in the

143   study population

144

145 **Research Question**

146   i. What is the incidence of PTE among the TBI patients attending UKMMC, Kuala

147   Lumpur, between 2019 to 2020?

148   ii. What are the potential predictors of PTE among the TBI population in UKMMC,

149   Kuala Lumpur?

150   iii. Does PTE correlate with cognitive impairment in TBI patients?

151

152 **Materials and method**

153 *Study design and setting:*

154 This retrospective cohort study will take place in UKMMC, Kuala Lumpur, from March

155 2022 until March 2024. All TBI patients admitted from 2019 to 2020 to UKMMC that

156 meet the inclusion criteria will be retrieved from the hospital ward census.

157 *Inclusion criteria:*

158 Inclusion criteria are (a) above 18 years old, (b) patient or guardian able to understand

159 and speak English/Malay, and (c) with a history of admission to the Neurosurgery ward

160 in UKMMC for traumatic brain injury caused between 2019 to 2020.

161 *Exclusion criteria:*

162 Patients are excluded if (a) the patient or guardian does not understand Malay/English,

163 (b) declines to participate, (c) individuals with pre-existing epilepsy before TBI, (d)

164 brain disorder that may cause epilepsy, e.g., brain tumor, stroke, meningitis, dementia.

165

166   *Sample and sampling:*

167   We will approach All TBI patients meeting the inclusion criteria retrieved from the

168   ward census.

169

170   **a) <u>Study Part I: Determine the incidence and predictors of PTE</u>**

171   *Sample size calculation:*

172   The reported incidence of PTE range from about 1% to 18.5% in year 1 [8,27–30].

173   Hence for a cumulative incidence of 18.5%, the sample size for 95% CI is 232 with an

174   alpha error of 5% (https://www.openepi.com/SampleSize/SSPropor.htm). Assuming

175   a drop out of 10%, thus 232+ 23= 255, rounded off to 260. Therefore, the TBI subjects

176   to be recruited are 260.

177

178   *Data collection process:*

179   The study flowchart is depicted in Fig 1. A TBI database will be formed based on the

180   list. The patient's medical records in UKMMC will be retrieved from the medical record

181   unit to find related demographic and clinical information, which are:

182   • Demographic and basal variables:

183   Age, gender, ethnicity, comorbid illness, and medical history focus on

184   neurological conditions.

185

186   • TBI characteristics during admission:

187   Glasgow Coma Scale (GCS), loss of consciousness, vomiting, post-traumatic

188   seizure (PTS), cranial surgery, and neuroimaging (looking for different

189   aspects, such as subdural hematoma (SDH), subarachnoid hemorrhage

8

190   (SAH), extradural hemorrhage (EDH), Intraparenchymal hemorrhage (IPH),

191   midline shift, hydrocephalus, cerebral edema, and skull fracture).

192

193   •   Seizure and epilepsy evaluation:

194   Seizures occurrence in-ward (if any), type, duration of seizure episode, EEG

195   monitoring for evidence of epileptogenesis, epilepsy diagnosis, and anti-

196   seizure medication.

197

198 An invitation letter that mentions the researcher's background, the study's aims, and

199 the design will be sent to the patients' home addresses. Next, patients will be

200 contacted by telephone to ascertain their epilepsy using a validated instrument

201 adapted from a study by Ottman et al. [31] and the Malay version by Fong et al. [32].

202 Permission to use the original screening instruments has been obtained from both

203 authors.

204 We made some modifications to the scoring system as below. We classified the

205 response as positive having epilepsy following TBI if the subject answered as:

206   i.   Q1 and Q3d: "No" or "don't know" and

207   ii.   Any Q2, Q3a, b, c, e, f, g: "Yes" or "possible."

208 The following questions were also asked of patients with positive symptoms.

209 Responses were recorded in a subject data sheet (APPENDIX III).

210   i.   Before the TBI, did the patient experience seizures or epilepsy?

211   ii.   Have the most recent seizure(s) occurred more than seven days after the

212   TBI?

9

213   iii.   Has the patient been diagnosed with epilepsy or a seizure disorder since

214   the TBI diagnosis? If so, when was the date of diagnosis, and which

215   clinician/hospital made the diagnosis?

216   iv.   Any anti-seizure /anti-epileptic medication received?

217

218 All screened cases will be discussed with a consultant neurologist. Patients who

219 declared having symptoms of PTE but have not sought any treatment determined by

220 a record of follow-up in UKMMC will be directed to a neurologist for clinical observation

221 and further treatment. Electroencephalography (EEG) will be used as an adjunct

222 diagnostic tool. Then, patients who consented to cognitive assessment will be

223 grouped into two, with PTE and without PTE. The cognitive assessment will be

224 performed by our clinical psychologist and trained researcher at Neurology Clinic

225 UKMMC or by home visit.

226 *Consent taking:*

227 The consent-taking process will be done verbally at the beginning of the phone call

228 (APPENDIX IV). First, the researcher will introduce herself and explain the purpose

229 of the phone call. Then, the researcher will play a pre-recorded Patient Information

230 Sheet (PIS) script to ensure transparency (APPENDIX V). The patient/ guardian will

231 be given sufficient time to think and ask questions afterward. Next, verbal consent

232 from the patient or guardian will be taken before the interview, and the process will be

233 recorded. The phone call will be discontinued if no permission is given. Suppose the

234 patient is not fit to be interviewed (e.g., hearing impairment or cognitively not fit to

235 answer); in that case, the patient's guardian will be contacted.

236

10

237 **b) Study Part II: Cognitive assessments**

238 *Sample size calculation:*

239 The next part of the study is the sub-analysis of cognitive performance. The ratio of

240 individuals from Part I in the PTE group to individuals in the non-PTE group (as the

241 control group) to be recruited is 1:3. The number of PTE patients depends upon the

242 incidence within the sample of 260. For example, the incidence of PTE is 18.5% which

243 means 48, so 48 subjects in the PTE group vs. 144 subjects in the non-PTE group.

244 The control group will be age-matched and gender-matched with the study group.

245

246 *Data collection process:*

247 The following is the cognitive assessments and anxiety/depression test involved:

248   i.   Addenbrooke's Cognitive Examination-III (ACE-III) test [33] with both

249   English and Malay versions [34].

250   ii.   Wechsler Adult Intelligence Scale (WAIS-IV) subtest: symbol search and

251   coding [35].

252   iii.   Comprehensive Trail Making Test (CTMT) [36,37].

253   iv.   Depression, Anxiety and Stress Scale (DASS 21) [38,39].

254

255

256 *Data analysis:*

257 Statistical analysis will be performed using SPSS 28.0. Chi-square test or Fisher exact

258 test will be conducted to compare categorical data, independent sample t-test for

259 continuous variables, and ANOVA with repeated measures to study between subjects'

260 factor group, within subjects' factor time, and post-doc tests with Bonferroni correction

11

261   method. Pearson correlations and logistic regression analysis will determine if the

262   variables are significantly related. The cognitive score difference between the two

263   groups will be analysed using SPSS.

264

265   *Ethics approval:*

266   This study has been approved by the Research Ethics Committee, The National

267   University of Malaysia (UKM PPI/111/8/JEP-2022-072).

268

269   *Status and timeline of study:*

270   The TBI patients' database has been formed, and participant recruitment is in

271   progress. The study is expected to be completed by June 2023. The data analysis

272   will be performed by July 2023, and the research article will be completed by

273   September 2023.

274   **Discussion:**

275   This study will benefit a multidisciplinary team involved in managing TBI patients, like

276   critical care physicians, neurosurgeons, neurologist rehabilitation specialists, and

277   clinical psychologists. The results will help clinicians to understand the best way to

278   treat TBI and PTE cases and serve as a source of information to support care

279   decisions in designing therapies that would improve the quality of life of TBI patients.

280   There are several limitations of this study. It is a single-center study; thus, the

281   sample may not represent all geographic regions of Malaysia. Nonetheless, to our

282   knowledge, our study constitutes the first analysis of PTE incidence in Malaysia. As

283   with the other retrospective study designs, the results will rely on whatever information

284   is available in the medical record during data collection. Thus, there might be

285   unrecorded or unavailable information. To deal with it, we will try to capture important

286   details such as the patients' TBI history, education level, and any signs and symptoms

287   of seizure/epilepsy during the phone interview session.

288   We anticipate that patients willing to come for cognitive assessment might be

289   cognitively well, thus leading to the skewness of results. We offer a home visit for

290   individuals with ambulatory problems to minimise bias.

291   Another challenge is that the contacts provided may no longer be in service.

292   The previous study shows that some may not want to answer calls due to business or

293   worry about answering unknown phone numbers [40]. To reduce this problem, we will

294   send a letter to the individual's home address to mention our study purpose and action

295   plan to contact them. In the letter, we will provide the team telephone numbers and a

296   Q.R. code linked to Whatsapp so they can propose their preferred date and time for a

297   phone interview. A token of RM20 will also be provided to cover the petrol cost of

298   patients participating in the cognitive assessments.

299   **<u>Author's contributions:</u>**

300   IWN: Data curation, Writing, Investigation, Formal Analysis

301   MFS: Conceptualization, Project Administration, Funding Acquisition

302   DM: Conceptualisation, Formal Analysis, Supervision

303   CSK: Investigation, Supervision

304   WLC: Validation, Supervision

305   AAS: Validation, Supervision

306

307

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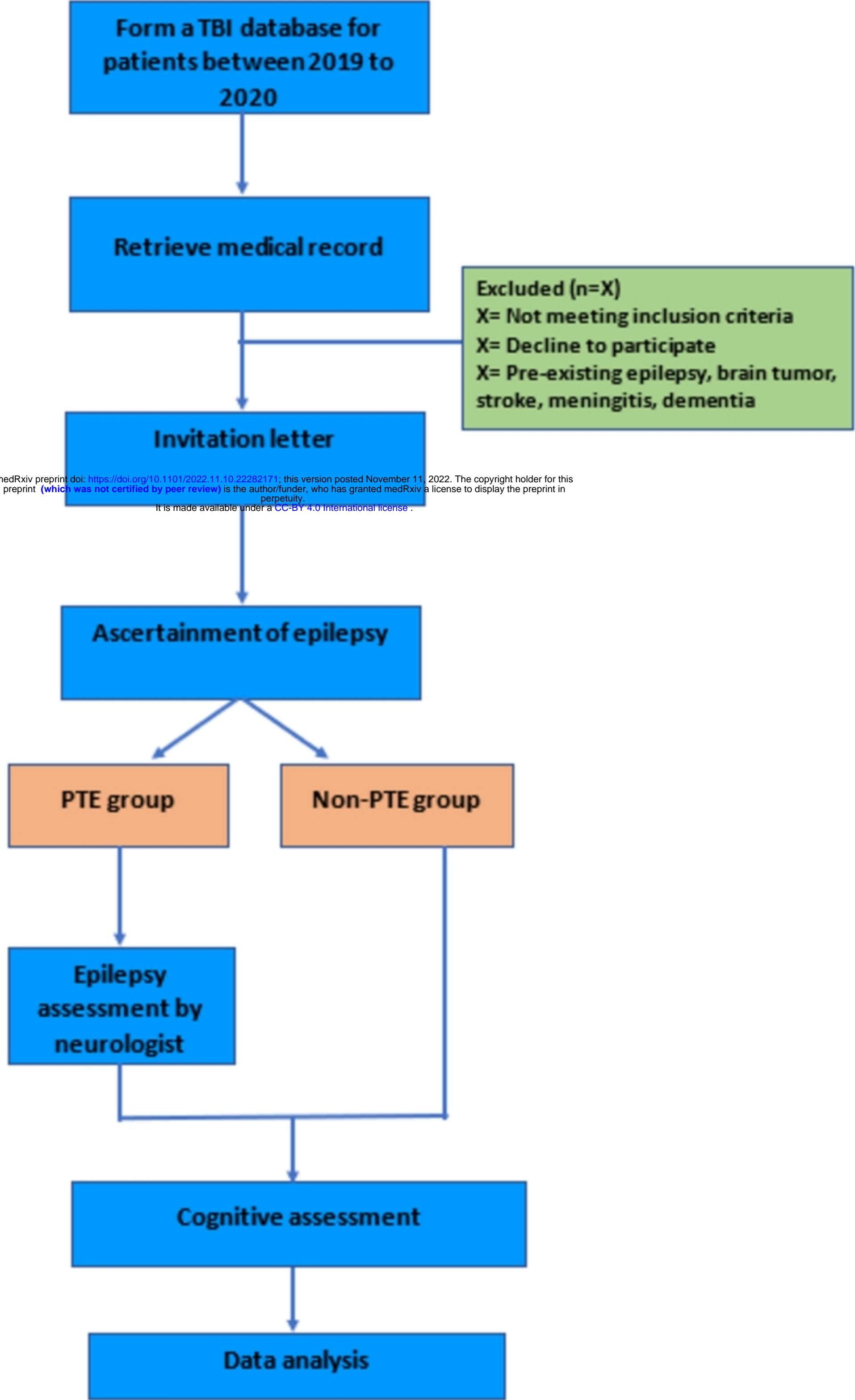
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458

459 **Supporting information:**

460 Appendix I: Ascertainment of epilepsy by Ottomen et al., 2010

461 Appendix II: Ascertainment of epilepsy by Fong et al., 2019

462 Appendix III: Subject data sheet

463 Appendix IV: Telephone script for verbal consent and recruitment

464 Appendix V: Patient Information Sheet (PIS)

465

466

Figure