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Original Article

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Predictors of Conversion to Dementia in Patients With Mild Cognitive Impairment: The Role of Low Body Temperature

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Abstract

Background: Subjects with mild cognitive impairment (MCI) can progress to dementia. Studies have shown that neuropsychological tests, biological or radiological markers individually or in combination have helped to determine the risk of conversion from MCI to dementia. These techniques are complex and expensive, and clinical risk factors were not considered in these studies. This study examined demographic, lifestyle and clinical factors including low body temperature that may play a role in the conversion of MCI to dementia in elderly patients.

Methods: In this retrospective study, a chart review was conducted on patients aged 61 to 103 years who were seen at the University of Alberta Hospital. Information on onset of MCI and demographic, social, and lifestyle factors, family history of dementia and clinical factors, and current medications at baseline was collected from patient charts on an electronic database. The conversion from MCI to dementia within 5.5 years was also determined. Logistic regression analysis was conducted to identify the baseline factors associated with conversion from MCI to dementia.

Results: The prevalence of MCI at baseline was 25.6% (335/1,330). During the 5.5 years follow-up period, 43% (143/335) of the subjects converted to dementia from MCI. The factors that were significantly associated with conversion from MCI to dementia were family history of dementia (odds ratio (OR): 2.78, 95% confidence interval (CI): 1.56 - 4.95, P = 0.001), Montreal cognitive assessment (MoCA) score (OR: 0.91, 95% CI: 0.85 - 0.97, P = 0.01), and low body temperature (below 36 °C) (OR: 10.01, 95% CI: 3.59 - 27.88, P < 0.001).

Conclusion: In addition to family history of dementia and MoCA, low body temperature was shown to be associated with the conversion from MCI to dementia. This study would help clinicians to identify patients with MCI who are at highest risk of conversion to dementia.

Keywords: Mild cognitive impairment; Dementia; Low body temperature; Clock drawing; Family history; Risk factors

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Introduction

The prevalence of cognitive impairment in the general population increases with age [1]. As life expectancy continues to climb, so will the prevalence of cognitive impairment. Mild cognitive impairment (MCI) is a stage where individuals experience trouble recalling details, learning new information, and concentrating on tasks. This stage, which lies between normal cognitive decline related to aging and dementia, can remain undetected in older adults. Patients diagnosed with MCI often progress to dementia [1]. Dementia is a condition characterized by a progressive decline in cognitive function that can affect a patient's day to day functioning. In addition, dementia is a heavy burden on caregivers and family members living with the patient. In fact, the total annual cost for managing individuals with cognitive impairment globally has reached nearly $244 billion [2].

Studies have been conducted to determine the factors that play a role in the conversion of MCI to dementia [2]. Multiple factors including age, educational level, physical activity, lifestyle behaviors, and chronic diseases have been associated with cognitive decline [3]. Radiological, brain function and cerebrospinal fluid (CSF) tests have been useful in determining those who are likely to convert from MCI to dementia. These radiological markers include entorhinal atrophy, hippocampal atrophy and white matter disease seen on computed tomography (CT) and magnetic resonance imaging (MRI). Additionally, decreased glucose metabolism in Lewy body dementia can be seen with positron emission tomography (PET) [4, 5]. Some studies have shown that biomarkers, such as amyloid-beta and tau proteins in CSF, predict conversion as well [6, 7]. Certain neuropsychological tests may also help to predict conversion [8]. In addition, some studies have shown that these markers in combination can be used to predict conversion to dementia [9]. While these markers may be useful for patients able to do

more advanced testing, there are common medical factors that can be collected on history and physical exam in clinic that may also contribute to conversion.

Temperature regulation is a vital body function and can serve as a marker for other physiological changes that occur as part of the normal aging process in the elderly. The normal range of body temperature is 36 - 38 °C. Hypothermia is defined as a body temperature below 35 °C, and low body temperature is defined as below 36 °C. Low body temperature is commonly seen in geriatric patients [10]. The temperature ranges between 35 and 36 °C, which we have defined as subnormal low body temperature, has not been studied in the literature. Body temperature has been postulated to be a risk factor for Alzheimer's disease (AD) and may also be implicated in the pathophysiology of dementia [11]. There is some evidence in the literature regarding the effect of hypothermia and heat stroke on cognitive decline, but research on low body temperature, especially subnormal low body temperature and its affect on cognition, is lacking [12].

In this study, we hypothesized that low and subnormal body temperature, along with other risk factors, play a role in the conversion of MCI to dementia. Orthostatic and postural hypotension (OH and PH) are disabling conditions that are associated with cognitive decline in geriatric patients [13]. Hearing impairment, depression, vascular risk factors, family history of dementia, low education, and living alone are other potential risk factors that have also been shown to be associated with dementia. Epidemiological studies have shown that about 15% of patients diagnosed with MCI progress to dementia annually [14]. Thus, patients with MCI represent a high-risk group for the development of dementia and would be ideal targets for interventions related to modifiable risk factors [15]. A better understanding of factors that influence conversion from MCI to dementia is needed to inform these interventions. Given the importance of behavioral health integration in physician practice, this study may shed light on these other less emphasized aspects of dementia management [16]. The objectives of this study are firstly to assess the prevalence of MCI, secondly to determine the proportion of patients that convert from MCI at baseline to dementia during the follow-up period of 5.5 years and lastly to determine demographic, social, lifestyle and clinical factors that were associated with conversion from MCI to dementia.

Materials and Methods

This study is based on a retrospective chart review of 1,330 patients aged 61 to 103 years at the Kaye Edmonton Senior's Clinic in the University of Alberta Hospital. Information on onset of MCI, demographic, social, lifestyle and clinical risk factors, as well as current medications at baseline was collected from an electronic database with patient charts. The baseline period was defined as January 2015 to July 2018 and was considered the entry point of patients into our study. Patients with MCI were then followed until the end of our study in July 2021 to determine the developments of dementia. Ethics approval was obtained from the ethics committee at the University of Alberta Hospital. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Inclusion and exclusion criteria

Subjects who had been diagnosed with MCI at baseline were included in the study. MCI diagnoses were made based on medical history, physical and neurological examinations, cognitive testing, and brain imaging with CT by geriatricians who were familiar with MCI and dementia diagnostic criteria. Subjects with dementia and those without a cognitive assessment at the baseline were excluded.

Diagnosis of MCI

The standards of practice which recognize the cognitive stages of MCI and dementia were based on Petersen's/European Consortium Criteria and DSM IV or DSM V criteria. MCI is defined as the presence of subjective and objective cognitive impairment without functional decline, hence not meeting the criteria for dementia. The clinical diagnosis of MCI is very similar to that of dementia. MCI was diagnosed according to the European Consortium on Alzheimer's disease criteria, which is the currently available standard test to diagnose MCI. The Consortium criteria include: 1) cognitive complaints coming from the patients or their families, 2) the reporting of a decline in cognitive functioning relative to previous abilities during the past year by the patient or informant, 3) cognitive disorders as evidenced by clinical evaluation (impairment in memory or in another cognitive domain, which in this study was assessed by Montreal cognitive assessment (MoCA) and mini-mental status exam (MMSE)), 4) absence of major repercussions on daily life, and 5) absence of dementia criteria [17, 18]. The Peterson's criteria for MCI include: 1) impaired memory usually corroborated by an informant, 2) objective memory impairment for the patient's age, and 3) intact functional activities. Petersen divided MCI into two categories: 1) amnestic MCI, where there is evidence of memory domain impairment only, and 2) non-amnestic MCI, where there is a single non-memory cognitive domain impairment [17, 18].

In this study, impairment in memory or in another cognitive domain was assessed by MoCA, and absence of major limitations on daily life was measured using Katz activities of daily living (ADL) and Lawton's instrumental activities of daily living (IADL). Dementia was ruled out by using DSM IV or DSM V criteria.

Diagnosis of dementia

The diagnosis of dementia, and screening for depression, was made according to DSM IV or DSM V criteria [19]. Functional information on daily activities was collected using Katz basic activities of daily living (BADL) and Lawton IADL question-

naires [20, 21]. Patients were followed for a period of 3 to 5.5 years, depending on when their baseline assessment was completed, for the development of dementia according to the diagnostic criteria described above.

Measurement of clinical risk factors

Information on the presence of low body temperature, OH, hearing impairment, vascular risk factors and current medications was determined from geriatric assessments completed in the Kaye Edmonton Senior's clinic at baseline, which we defined as the period from January 2015 to July 2018. Other demographic information was also obtained from the electronic charts, such as age, sex, and smoking status.

Blood pressure measurement

Blood pressures were measured in the supine and standing position after 3 min. These measurements were taken by trained clinical nurses during patient's baseline geriatric assessments. OH was defined as a systolic blood pressure drop of greater than or equal to 20 mm Hg or a diastolic drop of greater than or equal to10 mm Hg [22].

Temperature measurement

Temperature was measured once between 8 am and 4 pm during the clinic hours. Among types of temperature measurement techniques, rectal temperature is the most accurate. Oral and tympanic temperatures are acceptable and often more practical in clinical settings [23]. Skin and axillary temperature measurements have some limitations [24]. In this study, tympanic temperatures were taken in all subjects. The normal range of body temperature is 36 to 38 °C [25]. We have defined low body temperature as less than 36 °C and subnormal body temperature as ≥ 35 °C and < 36 °C.

Cognitive and executive function testing

Standardized MMSE and MoCA scores were used to measure global cognitive function and clock drawing was used for executive function testing [26-28].

Statistical analysis

Baseline characteristics were compared between those who converted from MCI to dementia and those who did not to convert in the univariate analysis. The factors that were significant in the univariate analysis were then considered in the multivariable logistic regression to identify the factors individually associated with conversion to dementia. All analysis was performed using STATA. Statistical significance was set at $P < 0.05$ for all statistical tests.

Results

After a search for patient encounters at the Kaye Edmonton Senior's Clinic during the period of January 2015 to July 2018, we were able to retrieve 1,330 patient charts. Of these patients, 335 had a diagnosis of MCI at baseline, resulting in a prevalence of 25.6%. The mean age of patients with MCI at baseline was 76.5 years (standard deviation (SD): 7.2) with the range being 61 to 103 years. The proportion of females in this study was slightly greater than that for males (54.6% vs. 45.4%). The proportion of patients who converted to dementia from MCI was 42.7% (143/335) over the follow-up period of 5.5 years. Mean time to conversion in this study was 2.14 years (SD: 1.34) with the range being 0.15 to 5.3 years. The proportion of polypharmacy seen was 58.5% (196/ 335). The proportion of subjects with low body temperature (temperature less than 36 °C) was 13.5% (44/326) and the proportion of subjects with subnormal body temperature (≥ 35 °C and < 36 °C) was 12.6% (41/326). There were only three subjects with a temperature less than 35 °C.

Baseline characteristics of non-converters and converters from MCI to dementia are shown in Table 1. There were significant differences between non-converters and converters in mean age ($P = 0.04$), mean MoCA score ($P = 0.001$), and in the proportion of patients with a family history of dementia ($P < 0.001$), abnormal clock drawing ($P = 0.004$), polypharmacy ($P = 0.003$), overweight/obesity ($P = 0.03$), body mass index (BMI) ($P = 0.001$) and low body temperature ($P < 0.001$). Age, sex, smoking history, family history of dementia, IADL, MoCA, polypharmacy and low body temperatures were taken into consideration for the multivariable logistic regression analysis. Abnormal clock drawing was excluded from the multivariable logistic regression because of the high correlation with MoCA.

As shown in Table 2, factors that were significantly associated with conversion from MCI to dementia in the multivariable logistic regression were family history of dementia (odds ratio (OR): 2.78, 95% confidence interval (CI): 1.56 - 4.95, $P = 0.001$), MoCA score (OR: 0.91, 95% CI: 0.85 - 0.97, $P = 0.01$), and low body temperature (below 36 °C) (OR: 10.01, 95% CI: 3.59 - 27.88, $P < 0.001$). Although age, sex, smoking history, IADL, BMI and polypharmacy were not significant in the multivariable logistic regression, they were not removed from the multivariable regression as they were considered as potential confounders.

A sensitivity analysis was conducted to determine characteristics that were significantly different between the patients with low and normal body temperature. Patients with low body temperature were taking fewer number of medications (45.5% vs. 61.4%, $P = 0.05$) and less likely to be overweight or obese (45.5% vs. 61.4%, $P = 0.02$).

Discussion

MCI is the prodromal phase of dementia [27]. A study by Espinosa et al examined different risk factors that played a role in subsequent conversion to dementia [29]. In our study, low MoCA score, family history of dementia and low body temperature were the three risk factors that played a significant role in the conversion of MCI to dementia in the final multivariate

Table 1. Baseline Characteristics of MCI Converter and MCI Non-Converter Groups

Variables	MCI non-converters (n = 192)	MCI converters (n = 143)	P-value
Personal, lifestyle, and social characteristics			
Age (mean ± SD, range) years	75.7 ± 7.3, 61 - 93	77.4 ± 7.1, 62 - 103	0.04
Sex			0.34
Female	52.4	57.6	
Male	47.6	42.4	
Current or past smoker	39.3	54.2	0.17
Alcohol intake	42.9	50.7	0.16
Living alone	31.9	29.2	0.59
Family history of dementia	21.1	42.6	< 0.001
Dependent on ≥ 1 ADL	22.3	22.4	0.99
Dependent on ≥ 1 IADL	64.9	73.6	0.09
Clinical characteristics			
Abnormal clock drawing	36.2	52.6	0.004
MoCA (mean ± SD)	22.3 ± 3.9	20.8 ± 4.3	0.001
Low temperature (below 36 °C)	2.7	27.7	< 0.001
Polypharmacy (≥ 5 medications)	65.5	49.3	0.003
Sodium ≤ 135 mmol/L	10.5	8.33	0.51
eGFR ≤ 60 mL/min/1.73 m^2	31.4	36.1	0.37
TSH (mean ± SD)	2.3 ± 1.9	2.5 ± 2.6	0.38
Taking sedatives	24.6	21.5	0.51
Taking hypothyroidism medication	27.8	33.3	0.27
Taking depression medication	38.2	32.6	0.58
Autonomic factors			
Loss of hearing	33.0	32.6	0.95
Orthostatic hypertension	20.9	24.1	0.50
Vascular factors			
Overweight/obese	76.2	65.0	0.03
Body mass index (kg/m^2) (mean ± SD)	28.9 ± 6.0	26.9 ± 4.7	0.001
Hypertension	60.2	64.6	0.41
Diabetes	25.7	20.8	0.30
Coronary artery disease	17.3	14.6	0.51
Cerebrovascular disease	13.1	13.2	0.98
Other factors			
Atrial fibrillation	12.0	10.4	0.64
Heart failure	4.71	3.47	0.58

Percentages are given in the table for categorical variables and, means and standard deviations are given for continuous variable. MCI: mild cognitive impairment; SD: standard deviation; ADL: activities of daily living; IADL: instrumental activities of daily living; MoCA: Montreal cognitive assessment; eGFR: estimated glomerular filtration rate; TSH: thyroid-stimulating hormone.

analysis model.

MoCA score

MoCA is one of the screening tests to assess for MCI. It measures cognitive domains like abstraction and executive function which are not normally measured by MMSE. It has been shown to have excellent psychometric properties, such as internal consistency and test-retest reliability [26, 27]. In addition, the MoCA test is effective at discriminating between patients with normal cognition and MCI. The European Consortium Criteria

Table 2. Risk Factors for Conversion of MCI to Dementia: Results From the Multiple Logistic Regression Analysis

Variables	Odds ratio	95% confidence interval	P-value
Age	1.03	(0.99 - 1.09)	0.10
Sex (reference: male)	1.04	(0.60 - 1.81)	0.88
Current or past smoker	1.38	(0.80 - 2.40)	0.25
Family history of dementia	2.78	(1.56 - 4.95)	0.001
Dependent on ≥ 1 IADL	1.63	(0.90 - 1.01)	0.11
MoCA score	0.91	(0.85 - 0.97)	0.007
Body mass index	0.95	(0.90 - 1.00)	0.07
Polypharmacy (≥ 5 medications)	0.59	(0.34 - 1.03)	0.06
Low temperature (at or below 36 °C)	10.01	(3.59 - 27.88)	< 0.001

IADL: instrumental activities of daily living; MCI: mild cognitive impairment; MoCA: Montreal cognitive assessment.

diagnosis for MCI in elderly needs a detailed clinical history which is not available most of the time [17, 18]. This makes the MoCA score a quick and useful assessment in practice to determine if a patient is exhibiting some cognitive deficits.

In this study, low MoCA score at baseline was a predictor of conversion to dementia. As expected, subjects with higher global cognitive function as measured by MoCA were less likely to progress to dementia.

Family history of dementia

In practice, a detailed family history of dementia may have similar utility to blood-based biomarkers. However, tests to screen for these biomarkers are costly and invasive. A good understanding of family history can shed light on genetic risk and susceptibility for a dementia diagnosis. As seen in the literature, an individual's risk of developing dementia increases with a positive family history [30, 31]. The lifetime risk for developing dementia when having a first degree relative with an AD diagnosis ranges from 25% to 40% [30, 31]. Additionally, previous research has shown that patients with a maternal history had a higher risk of progression to dementia [32]. Although our study confirmed the role that family history plays in conversion of MCI to dementia, it did not distinguish between paternal and maternal family history.

Low body temperature

This study has shown that lower body temperature was associated with increased risk of conversion from MCI to dementia. Age-associated decrease in body temperature in the elderly is well documented in the literature [33]. Low body temperature in the elderly could be due to decreased production of heat by low basal metabolic rate, decreased blood flow due to changes in vasculature and increased heat loss due to thinner skin and less subcutaneous fat. Animal and human studies have shown that elderly body temperature can be lower than 37 °C [10, 34]. Core body temperature, or temperature of vital organs, including the brain, is not well understood and thermoregulation plays a major role in maintaining it. Thermoregulation is less efficient at regulating core body temperature in older adults [34, 35]. In spite of external temperature variations, body temperature is maintained in a tight range by homeostatic mechanisms. Neurohormonal control of body temperature plays a large part in thermoregulation, and in the elderly these mechanisms begin to deteriorate. The inability to regulate body temperature is known as poikilothermia. Other factors that can affect thermoregulation and cause low body temperature include cardiovascular, neurological, and endocrine conditions [34, 35]. Mental illness, alcohol and recreational drug use can also impact thermoregulation. As medications can also disrupt thermoregulation, our study accounted for this by adjusting for polypharmacy in statistical analyses. Impaired thermoregulation with aging increased the incidence of hypothermia, and this may be a risk factor for AD [34, 35]. Hypothermia may also be iatrogenic or secondary to medical conditions, such as diabetes or use of anesthesia [36, 37]. Hypothermia is commonly seen during surgery. In an animal study, intraoperative hypothermia caused hippocampal damage and led to postoperative cognitive dysfunction (POCD) [36]. An animal study using transgenic mice demonstrated that mice with low temperature have more abnormal tau proteins and a loss of synaptic proteins, both of which are pathological markers of AD [38]. Additionally, when environmental temperature was elevated by even 1 °C, there was a decrease in brain plaques and memory test results were comparable to normal mice. In another study, La Freche et al reported increased tau protein levels in the brain after anesthesia-induced hypothermia [39]. A different animal study showed that for each °C below normal body temperature, there was an 80% increase in tau protein phosphorylation [40].

Although our finding regarding low body temperature being a risk factor for conversion of MCI to dementia is novel, there are some studies that may explain this phenomenon. Holtzman et al have hypothesized that low body temperature over long periods may accelerate pathology and progression of AD [11]. This lower-than-normal body temperature may even be prodromal, as a case report has shown low body temperature can be seen several years prior to the onset of AD [42]. In a small human study, low nocturnal core body temperature seen

in Lewy body dementia was shown to be a biomarker of neurodegeneration [42]. Additionally, Whittington et al suggested a neuropathological link between low temperature and AD [43]. A recent human study in cognitively normal adults showed low body temperature may be associated with increased tau pathology [44]. Carrettiero et al proposed that temperature abnormalities can affect tau regulation of microtubule function [45]. Low temperature causes destruction of microtubules, loss of synaptic function, and a decrease in neurotransmitter levels [46, 47]. The hippocampus can be affected by these mechanisms, which can lead to problems with memory.

Homeostasis is maintained in large part by the autonomic nervous system, which is intimately linked to temperature control. An inadequate autonomic response to physiological stressors can contribute to lower body temperature and affect cognitive performance. Autonomic dysfunction is common in dementia, which affects core vital functions including temperature control. AD is the most common neurodegenerative dementia with pathology involving tau proteins and microtubules. Tau forms insoluble aggregates and causes neurotoxicity by affecting neuronal microtubule stability. These microtubules play a significant role in neuronal function and may be implicated in the autonomic dysfunction seen in dementia [48, 49]. In fact, autonomic dysfunction can occur with normal aging, and aging itself is a risk factor for dementia [47, 50]. In this way, the novel risk factor of body temperature at or below 36 °C in our study may simply be an indicator of autonomic dysfunction in MCI patients. Thus, these MCI patients would be more likely to progress to dementia. In our study, we used infrared tympanic membrane temperature measurements. Anatomically, the tympanic membrane is close to the hypothalamus, which is the main thermoregulatory center [48].

A few studies, including a recent study in elderly women, have reported that even ambient temperature changes can affect neurocognitive function, including semantic memory and executive function [49, 50]. One study has shown that elevated daytime skin temperature in both AD and elderly controls was associated with more daytime sleepiness in AD subjects [51]. A recent paper by Eggenberger et al measured peak-to-peak body temperature measurements during a 12-h interval, and found that median temperature may be a better predictor of MCI [52]. Even though previous research has shown that low body temperature is associated with both MCI and dementia separately, this study is the first to report an association of low body temperature with conversion to dementia in patients already diagnosed with MCI at baseline. Correcting low body temperature and hypothermia in elderly subjects may prevent or slow down dementia-related cognitive decline [53, 54]. An animal study showed mild hyperthermia with sauna-like treatment in mice reduces tau-phosphorylation [54]. Knekt et al in their study showed frequent sauna bathing in middle-aged men is associated with reduced risk of dementia in later life [54]. Interventions to increase muscle mass, such as regular exercise and reducing sedentary lifestyle can also help to raise body temperature in human subjects [55, 56]. In this sense, low body temperature represents a modifiable risk factor for dementia that can be corrected with appropriate treatment modalities.

Limitations

In this study, most of the baseline diagnoses were amnestic MCI. Secondly, this study is a retrospective chart review of subjects recruited from a single teaching hospital, which may limit the generalizability of the study results. Furthermore, all the temperatures were tympanic in our study, and rectal temperatures may more closely approximate core body temperature. Additionally, the temperature measurements were taken only once at the point of entry of each patient into the study. In addition, it is possible that diet may induce thermogenesis. Body temperature after meal and physical exercise were not measured in the study which may have an influence on the body temperature. Future studies should consider taking multiple temperature measurements to study how core body temperature changes with progression to dementia. Ambient temperature was not recorded in clinic either, which could have affected the body temperature of participants. As previously noted, lower education is a risk factor for dementia. Information on education level was inconsistent during the chart review and was excluded from the analyses. MCI subjects carrying the apolipoprotein E (APOE) epsilon4 allele showed cognitive profile similar to early AD patients. APOE epsilon4 allele genotype was associated with increased prevalence and risk of AD and early-onset of AD with ages at onset less than 60 years [57-59]. In our study, we did not have information on genetic risk factors including APOE.

Conclusions

This study identified risk factors that put patients diagnosed with MCI at higher risk for progression to dementia. Many of these risk factors have been previously established, such as a positive family history, low scores on cognitive assessments, and aging. Emerging risk factors identified in this study, such as low body temperature, may also affect pathological processes that worsen cognition in MCI patients. Identifying and correcting established and emerging modifiable risk factors is crucial for patients diagnosed with MCI. For example, correcting low body temperature in the elderly may be possible with warm blankets, adjusting room temperature, warm liquid consumption, avoiding alcohol, regular exercise, and sauna baths. Knowing which patients diagnosed with MCI are at highest risk for conversion to dementia allows practitioners to identify which patients to more closely monitor and initiate management strategies for cognitive decline. Novel risk factors like low body temperature indicate that autonomic dysfunction may be the driving force for conversion of MCI to dementia. These practical clinical indicators can easily be collected during geriatric assessments and may have similar utility to expensive laboratory and imaging techniques. Integrating body temperature measurements as part of cognitive assessments should be examined in future studies.

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Conflict of Interest

The authors report no conflict of interest in this work.

Informed Consent

Not applicable.

Author Contributions

Kannayiram Alagiakrishnan contributed to the study design, planning and implementation of the study and preparation of the manuscript. Prabhpaul Dhami retrieved the data from the electronic database of patient charts and contributed to the preparation of the manuscript. Ambikaipakan Senthilselvan conducted the statistical analysis and contributed to the preparation of manuscript.

Data Availability

Data were obtained from Alberta Health Services under strict guidelines for the use of the data for this study and authors are not permitted to share the data.

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