Best Evidence Topic

Identification of associations and distinguishing moyamoya disease from ischemic strokes of other etiologies: A retrospective case-control study

Cori Xiu Yue Sutton, Enrique Carrazana, Catherine Mitchell, Jason Viereck, Kore Kai Liow, Arash Ghaffari-Rafi

Keywords: Moyamoya disease, Cardiovascular, Socioeconomic, Ischemic stroke, Migraines

Abstract

Introduction: Better characterizing moyamoya disease (MMD) from ischemic strokes of other etiologies may facilitate earlier diagnosis by raising suspicion for a diagnostic work-up.

Methods: To identify associated variables, MMD cases (n = 12) were compared against three sets of controls: age-, sex-, and race-matched controls of patients with general neurological disorders (n = 48), unmatched general controls (n = 48), and unmatched non-MMD ischemic stroke controls (n = 48).

Results: MMD patients were 32 years (p < 0.0001) younger than ischemic stroke controls. Relative to non-MMD ischemic strokes, MMD patients had greater odds of presenting with visual field defects (OR: 9.13, p = 0.09) or dizziness (OR: 9.13, p = 0.09), as well as being female (OR: 8.04, p = 0.02), having migraines (OR: 21.61, p = 0.005), epilepsy (OR: 6.69, p = 0.01), insomnia (OR: 8.90, p = 0.099), and a lower Charlson Comorbidity Index (CCI; p = 0.002). Patients with MMD, compared to non-MMD ischemic strokes, also had a 4.67 kg/m² greater body mass index (BMI) and larger odds (OR relative to normal BMI: 21.00, p = 0.006) of being from obesity class III (>40 kg/m²), yet reduced odds of diabetes mellitus type 2 (OR: 10.07, p = 0.007) and hypertension (OR: 7.29, p = 0.004).

Conclusion: MMD not only has a unique clinical presentation from other ischemic strokes, but also unique comorbidities, which may facilitate earlier work-up and treatment.

1. Introduction

Moyamoya disease (MMD) is a chronic progressive occlusion of the circle of Willis and surrounding vessels, causing the formation of weak collaterals with increased stroke [1]. Given the identical clinical presentation of ischemic stroke secondary to MMD versus other etiologies (non-MMD ischemic stroke), up to 62.0% of MMD goes misdiagnosed, with delay of diagnosis greater than three years in 42.6% of MMD patients [2]. Yet, unlike the vast majority of ischemic strokes, patients with MMD can be treated with revascularization surgery—hence, promptly diagnosing MMD patients becomes imperative, provided the available treatment options [3-6]. One method to facilitate earlier MMD diagnosis is by identifying variables that distinguish MMD from non-MMD ischemic strokes, therefore helping raise a clinician’s suspicion to conduct a MMD diagnostic work-up.

To better characterize and distinguish MMD, we conducted a retrospective case-control study comparing patients with MMD against those with non-MMD ischemic strokes, as well as patients with general neurological disorders. The study also examined numerous socioeconomic variables and medical comorbidities, with the ancillary goals of investigating potential healthcare disparities in MMD, along with the role of modifiable risk factors [7,8].

Abbreviations: ACA, Anterior Cerebral Artery; CCI, Charlson Comorbidity Index; NHPI, Native Hawaiian or Other Pacific Islander; ICD-9, International Classification of Diseases 9th Edition; ICD-10, International Classification of Diseases 10th Edition; MCA, Middle Cerebral Artery; MMD, Moyamoya Disease; TIA, Transient Ischemic Attack; PCA, Posterior Cerebral Artery.

* Corresponding author. 651 Ilalo Street, Honolulu, HI, 96813, USA.
E-mail address: arashgr@hawaii.edu (A. Ghaffari-Rafi).

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2. Methods

2.1. Study design and setting

Prior to study initiation, institutional review board exemption was obtained from the University of Hawai‘i at Manoa, Office of Research Compliance (protocol number: 2020–01010). Utilizing electronic medical records at a large neuroscience institute in Hawai‘i (Hawai‘i Pacific Neuroscience), MMD patients with only ischemic strokes were retrospectively identified, between January 1st, 2009 to February 13, 2021, via International Classification of Diseases 9th or 10th Revisions, Clinical Modification (ICD-9 or ICD-10) codes for MMD: ICD-9 (437.5); ICD-10 (I67.5) [9]. Only patients who met the Research Committee on Spontaneous Occlusion of the Circle of Willis Guidelines for MMD diagnosis were included [10].

2.2. Predictor and outcome variables

For cases, recorded data included sex, age at diagnosis, clinical presentation (ischemic stroke, transient ischemic attack [TIA], visual field defect, dizziness), ischemia location (middle cerebral artery [MCA], anterior cerebral artery [ACA], posterior cerebral artery [PCA], multiple large vessels, lacunar/small vessel), ischemia laterality (left, right, bilateral), and self-identified race (White, Hispanic, Asian, Native Hawaiian or Other Pacific Islander [NHPI]).

Numerous socioeconomic variables and medical comorbidities were collected (Table 1). As described in a prior study, socioeconomic variables included health insurance type and the Zone Improvement Plan (ZIP) code of the patient’s residence, with ZIP code serving as a proxy for other variables [7,9]. Charlson Comorbidity Index (CCI) score for each subject was also determined; the CCI is a validated tool used to predict 10-year survival probability by measuring 17 comorbidities [11,12].

2.3. Controls

To maximize statistical power, four controls were selected per each case (n = 12) [13]. Three sets of 48 randomly selected controls were attained from the institute’s total patient pool from January 1st 2009 to February 13th 2021 (n = 29,965). The first set involved unmatched controls, for studying differences in age, sex, and race, between cases and the general population of patients with neurological disorders [9]. The second set of controls was matched by age, sex, and race, thus utilized to investigate socioeconomic and medical comorbidities in relation to MMD, relative to the general population of patients with neurological disorders (general controls). The third set of controls represented the non-MMD ischemic stroke population (ischemic stroke controls), which was unmatched and randomly selected utilizing the ICD-9 (434.91) and ICD-10 (I63.9) codes for patients with ischemic stroke.

2.4. Statistical analysis

Continuous nonparametric variables were analyzed using the independent Wilcoxon rank sum test. Categorical variables were assessed via the Pearson’s chi-squared test or Fisher’s exact test of independence, with Haldane-Anscombe correction. Univariate and multivariable logistic regression, with Firth correction, were performed to identify strongest predictors associated with MMD diagnosis [9,14]. The study was registered with Center for Open Science (UIN: mw746), found at https://osf.io/mw746, and was reported in accordance with STROCSS 2021 guidelines [15].

3. Results

3.1. General characteristics of moyamoya disease

The prevalence of MMD amongst the institute’s population was 40

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Table 1

| Category                          | Moyamoya Disease | General Controls | Ischemic Stroke |
|----------------------------------|------------------|------------------|-----------------|
| Age (years)                      | 12               | 48*              | 48              |
| Sex                              |                  |                  |                 |
| Female                           | 10               | 24*              | 18              |
| Male                             | 2                | 24*              | 30              |
| Race                             |                  |                  |                 |
| Asian                            | 7                | 13*              | 13              |
| Hispanic                         | 0                | 5*               | 3               |
| NHPI                             | 3                | 7*               | 13              |
| White                            | 2                | 23*              | 19              |
| Median Household Income          | 12               | 48               | 48              |
| Income Quartiles                 |                  |                  |                 |
| Quartile 1                       | 2                | 9                | 5               |
| Quartile 2                       | 2                | 16               | 11              |
| Quartile 3                       | 4                | 12               | 13              |
| Quartile 4                       | 4                | 11               | 19              |
| Overall Poverty Level in Municipality | 12      | 48               | 48              |
| Poverty Level for Ages 18-64     | 12               | 48               | 48              |
| Poverty Level for Ages 65 and Older | 12       | 48               | 48              |
| Geographic Origin                |                  |                  |                 |
| Urban                            | 5                | 32               | 34              |
| Suburban                         | 7                | 16               | 14              |
| Insurance Type                   |                  |                  |                 |
| Medicare                         | 4                | 8                | 31              |
| Medicaid                         | 3                | 17               | 6               |
| Private                          | 5                | 20               | 11              |
| Military                         | 0                | 3                | 0               |
| Employment Status                |                  |                  |                 |
| Employed                         | 5                | 33               | 4               |
| Retired                          | 2                | 4                | 35              |
| Not Able to Work                 | 4                | 6                | 3               |
| Unemployed                       | 1                | 2                | 2               |
| Homemaker                        | 0                | 1                | 1               |
| Marital Status                   |                  |                  |                 |
| Divorced                         | 0                | 5                | 7               |
| Married                          | 6                | 27               | 23              |
| Single                           | 5                | 13               | 6               |
| Widowed                          | 1                | 2                | 10              |
| Smoking Status                   |                  |                  |                 |
| Smoker (>100 Cigarettes)         | 3                | 17               | 17              |
| Non-Smoker (<100 Cigarettes)     | 9                | 31               | 31              |
| Alcohol Use Screen (AUDIT-C)     |                  |                  |                 |
| Positive Screen                  | 2                | 8                | 4               |
| Negative Screen                  | 10               | 40               | 44              |
| Anxiety                          |                  |                  |                 |
| Anxiety                          | 1                | 15               | 5               |
| No Anxiety                       | 11               | 33               | 43              |
| Depression                       |                  |                  |                 |
| Depression                       | 3                | 17               | 14              |
| No Depression                    | 9                | 31               | 34              |
| Attention Deficit Hyperactivity Disorder (ADHD) | 1 | 2 | 0 |
| No ADHD                          | 11               | 46               | 48              |
| Bipolar Disorder                 | 0                | 2                | 1               |
| No Bipolar Disorder              | 12               | 46               | 47              |
| Insomnia                         | 2                | 9                | 1               |
| No Insomnia                      | 10               | 39               | 47              |
| Illicit Drug Use                 |                  |                  |                 |
| Drug Use                         | 0                | 9                | 4               |
| No Drug Use                      | 12               | 39               | 44              |
| Body Mass Index                  | 12               | 48               | 44              |
| Weight Class                     |                  |                  |                 |
| Underweight                      | 0                | 3                | 1               |
| Normal                           | 1                | 20               | 14              |
| Overweight                       | 4                | 14               | 16              |

*unmatched controls for analysis relative to HPH population of patients with general neurological disorders.
per 100,000 patients. Of the MMD cases, ischemic stroke was first presenting symptom for 60.0% of cases, followed by TIA (8.3%), visual field defect (8.3%), and dizziness (8.3%). Regarding ischemic vessel location, the MCA was the most common at 58.3%, followed by multiple vessels at 25.0%, ACA at 8.3%, and lacunar infarcts at 8.3%. For laterality, 41.6% of ischemia was on the left hemisphere, 25.0% on the right, and 33.0% bilateral.

Compared to ischemic stroke controls, MMD patients had 9.13 (95% CI: 0.46, 557.97; \( p = 0.090 \)) fold greater odds of presenting with either a visual field defect or dizziness. MMD patients meanwhile had a reduced odds of presenting with an ischemic stroke (0.32, 95% CI: 0.049–2.45, \( p = 0.16 \)). When comparing ischemia location, MMD patients experienced 8.50 (95% CI: 0.43–518.11, \( p = 0.10 \)) fold greater odds of ACA involvement. For ischemia laterality, MMD patients experienced a 2.87 (95% CI: 0.50–14.93, \( p = 0.21 \)) fold greater odds of bilateral symptoms, compared to non-MMD ischemic stroke patients (Tables 2 and 3).

### 3.2. Patient age, sex, and race

MMD patients had a median age at diagnosis of 42 years (25th-75th Quartiles [IQR]: 32.5, 43.5), an estimated 21 years (95% CI: 9.00, 32.00; \( p = 0.002 \)) younger than the institute’s general population, and 32 years younger (95% CI: 24.00, 42.00, \( p < 0.0001 \)) than ischemic stroke controls (Table 2). Relative to general unmatched controls and non-MMD ischemic stroke controls, odds of females being diagnosed with MMD were 4.88 (95% CI: 0.90, 50.45; \( p = 0.052 \)) and 8.04 (95% CI: 1.48, 83.86; \( p = 0.008 \)) fold greater than males, respectively (Table 2). Regarding race, Asian patients experienced 3.68 (95% CI: 0.84–17.59; \( p = 0.087 \)) fold greater odds of MMD diagnosis than both the general and ischemic stroke controls.

### 3.3. Socioeconomic variables

Several socioeconomic variables were examined, including the patient’s median household income, poverty level in the municipality of residence, insurance type, and marital status, however due to a small sample size statistically significant was not appreciated in most variables (Tables 2 and 3).

MMD patients had a median population size of 45208 (25th–75th Quartiles: 36361, 51534), an estimated 4543 less than general controls (95% CI: \(-1.15 \times 10^{-3}, 9532; \ p = 0.11 \)) and 4583 less than ischemic stroke controls (95% CI: \(-7.50 \times 10^{-1}, 13511; \ p = 0.083 \)). When comparing geographic origin, those living in suburban areas had 2.74 (95% CI: 0.64, 12.88; \( p = 0.18 \)) and 3.32 (95% CI: 0.76, 15.78; \( p = 0.09 \)) fold greater odds of MMD diagnosis compared to general and ischemic stroke controls, respectively (Tables 2 and 3).

Regarding employment status, relative to general controls, odds of employment for MMD patients was reduced (0.29, 95% CI: 0.060, 1.27; \( p = 0.11 \)), but increased relative to ischemic stroke controls (6.96, 95% CI: 1.19–45.23, \( p = 0.015 \)). Compared to ischemic stroke controls, MMD patients also experienced greater odds of not being able to work (7.00, 95% CI: 1.31, 37.45; \( p = 0.01 \)) and reduced odds of being retired (0.061, 95% CI: 0.0056, 0.35, \( p = 0.002 \)).

Medicare beneficiaries had 0.28 (95% CI: 0.054–1.23, \( p = 0.090 \)) fold reduced odds of MMD diagnosis compared to ischemic stroke controls. Lastly, regarding marital status in relation to non-MMD ischemic stroke, single patients were at 4.60 (95% CI: 0.86–24.60, \( p = 0.066 \)) fold greater odds MMD diagnosis, while divorced patients were at 0.23 (95% CI: 0.0053, 1.70; \( p = 0.19 \)) fold reduced odds (Tables 2 and 3). Per the logistic regression, with married as the reference, unadjusted odds of being single amongst MMD patients was greater (3.19, 95% CI: 0.72, 14.15; \( p = 0.01 \)), relative to ischemic stroke controls (Table 3).

### Table 1 (continued)

| Moyamoya Disease | General Controls | Ischemic Stroke |
|------------------|------------------|-----------------|
| Obesity Class 1  | 2                | 6               | 8               |
| Obesity Class 2  | 2                | 3               | 3               |
| Obesity Class 3  | 3                | 2               | 2               |
| Hyperlipidemia   | 6                | 11              | 25              |
| Hyperlipidemia   | 6                | 37              | 13              |
| Type 2 Diabetes Mellitus | 5 | 3  | 17 |
| Diabetes Mellitus | 7 | 45 | 31 |
| Hypertension     | 8                | 10              | 34              |
| No Hypertension  | 4                | 38              | 14              |
| Coronary Artery Disease or Myocardial Infarction (CAD/MI) | 0 | 0 | 12 |
| Atrial Fibrillation (Afb) | 1 | 1 | 11 |
| No Afb           | 11               | 47              | 37              |
| Autoimmune Disease | 0 | 3 | 1 |
| Autoimmune Disease | 12 | 45 | 47 |
| Thyroid Disease  | 0                | 1               | 4               |
| No Thyroid Disease | 12 | 47 | 44 |
| Obstructive Pulmonary Disease (Assma or COPD) | 2 | 11 | 10 |
| Bidateral        | 4                | 7               | 6               |
| Left             | 5                | 22              | 22              |
| Right            | 3                | 13              | 13              |
| Bilateral        | 4                | 10              | 10              |
| Moyamoya or Ischemic Stroke Clinical Presentation | 8 | 43 | 48 |
| Ischemic Stroke  | 8                | 43              | 48              |
| Visual Field Defect | 1 | 5 | 5 |
| Dizziness        | 1                | 0               | 0               |

(Tables 2 and 3).
Table 2
Crude odds of sociodemographic and medical comorbidities.

|                                | Moyamoya Disease vs. General Population | Moyamoya Disease vs. Ischemic Strokes |
|--------------------------------|----------------------------------------|---------------------------------------|
|                                | Median (25% Quartile, 75% Quartile)    | Wilcoxon Rank Sum Test (estimated difference between groups) |
|                                | Median (25% Quartile, 75% Quartile)    | Wilcoxon Rank Sum Test (estimated difference between groups) |
|                                | 42 (32.5, 43.5)                        | 42 (32.5, 43.5)                        |
|                                | 21.00 (95% CI: 9.00, 32.00), p = 0.0020| 32.00 (95% CI: 24.00, 42.00), p = 2.21 × 10⁻⁴ |
| Income                           | controls                               | moyamoya disease vs. general population |
| Median Household Income          | 55.5 (45.25, 73)                       | 5.67 × 10⁻⁶                          |
| MMD                              | 2.87 (0.50, 14.93)                     | 1.00 (0.22, 10.02)                   |
| Ischemia Location                | squamous                               | military                             |
| Middle Cerebral Artery           | 1.64 (0.38, 7.56)                     | 0.00 (0.00, 2.12)                    |
| Anterior Cerebral Artery         | 8.50 (0.43, 51.81)                    | 0.00 (0.00, 2.45)                    |
| Posterior Cerebral Artery        | 0.62 (0.01, 5.57)                     | 0.25 (0.0053, 2.03)                  |
| Lacunar                          | 0.25 (0.00, 6.45)                     | 0.71 (0.00, 0.71)                    |
| Multiple Vessels                 | 1.26 (0.19, 9.07)                     | 0.16 (0.049, 2.45)                   |
| Moyamoya or Ischemic Stroke      | 0.32 (0.049, 2.28)                     | 0.86 (0.017, 9.07)                   |
| Clinical Presentation            | 0.86 (0.01, 9.76)                     | 0.57 (0.01, 14.23)                   |
| Ischemia Stroke                  | 9.13 (0.46, 557.97)                   | 0.66 (0.14, 2.82)                    |
| Laterality                       | 9.13 (0.46, 557.97)                   | 0.67 (0.10, 3.20)                    |
| Left                             | 0.66 (0.14, 2.82)                     | 0.78 (0.50, 14.93)                   |
| Right                            | 0.67 (0.10, 3.20)                     | 0.75 (0.01, 0.75)                    |
| Bilateral                        | 2.87 (0.50, 14.93)                    | 0.74 (0.01, 0.74)                    |
| Medicaid                         | 102242 (90250, 102972)                | 102242 (90250, 102972)                |
| Quartile 1                       | 0.87 (0.079, 5.26)                    | 0.10 (0.001, 1.11)                   |
| Quartile 2                       | 0.41 (0.039, 2.25)                    | 1.70 (0.14, 12.45)                   |
| Quartile 3                       | 1.48 (0.28, 6.88)                     | 0.68 (0.06, 3.95)                    |
| Quartile 4                       | 1.67 (0.31, 7.81)                     | 1.34 (0.25, 6.12)                    |
| Geographic Origin                | 0.36 (0.078, 1.57)                    | 1.70 (0.14, 12.45)                   |
| Urban                            | 0.36 (0.078, 1.57)                    | 0.68 (0.06, 3.95)                    |
| Suburban                         | 2.74 (0.64, 12.88)                    | 1.34 (0.25, 6.12)                    |
| Sex                              | 0.00 (0.00, 10.02)                    | 1.34 (0.25, 6.12)                    |
| Female                           | 4.88 (0.90, 50.45)                    | 3.00 (0.06, 1.31)                    |
| Male                             | 0.20 (0.02, 1.11)                     | 1.00 (0.06, 1.31)                    |
| Race                             | 0.22 (0.022, 1.21)                    | 0.30 (0.06, 1.31)                    |
| White                            | 0.22 (0.022, 1.21)                    | 0.80 (0.012, 0.68)                   |
| Asian                            | 3.68 (0.84, 17.59)                    | 0.31 (0.030, 0.19)                   |
| Native Hawaiian or Other Pacific Islander | 1.93 (0.27, 10.77) | 3.68 (0.84, 17.59) |
| Hispanic                         | 0.00 (0.00, 4.48)                     | 0.90 (0.14, 4.40)                    |
| Employment Status                | 0.51 (0.00, 0.51)                     | 0.63 (0.013, 0.57)                   |
| Status                           | 0.51 (0.00, 0.51)                     | 0.63 (0.013, 0.57)                   |
| Employed                         | 0.29 (0.060, 1.27)                    | 6.96 (1.19, 45.23)                   |
| Unemployed                       | 1.97 (0.031, 41.21)                   | 1.97 (0.030, 40.30)                  |
| Retired                          | 20.1 (0.17, 16.97)                    | 0.61 (0.0056, 0.25)                  |
| Not Able to Work                 | 3.25 (0.55, 17.86)                    | 0.19 (0.00018, 0.0013)                |

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Table 2 (continued)

| Moyamoya Disease vs. General Population | Moyamoya Disease vs. Ischemic Strokes |
|----------------------------------------|---------------------------------------|
| Median (25% Quartile, 75% Quartile)   | Wilcoxon Rank Sum Test (estimated difference between groups) |
| Homemaker                             | 1.86 (0.031, 37.24) p = 0.52           |
| Marital Status                        |                                       |
| Homemaker                             | 1.82 (0.030, 36.41) p = 0.52           |
| Divorced                               | 0.35 (0.0078, 2.71) p = 0.45           |
| Married                                | 0.74 (0.17, 2.24) χ² = 0.019, p = 0.89 |
| Single                                 | 1.84 (0.39, 8.26) χ² = 0.43, p = 0.56 |
| Widowed                                | 2.02 (0.032, 42.12) p = 0.50           |
| Smoking Status                        |                                       |
| Smoker                                 | 0.61 (0.094, 2.91) p = 0.73            |
| Non-Smoker                             | 1.63(0.34, 10.63) p = 0.73             |
| Alcohol Use Screen (AUDIT-C)           |                                       |
| Positive Screen                       | 1.00 (0.090, 6.24) p = 1.00            |
| Negative Screen                       | 1.00 (0.16, 11.11) p = 0.59            |
| Illicit Drug Use                      | 0.46 (0.056, 5.77) p = 0.59            |
| Drug Use                               | 0.46 (0.0099, 3.73) p = 0.68           |
| Anxiety                               | 0.46 (0.0099, 3.73) p = 0.68           |
| Anxiety                               | 0.46 (0.0099, 3.73) p = 0.68           |
| Depression (PHQ-9 Positive)           | 0.50 (0.12, 65.90) p = 0.10            |
| Depression                             | 0.50 (0.12, 65.90) p = 0.10            |
| Attention Deficit Hyperactivity Disorder (ADHD) | 2.06 (0.033, 43.02) p = 0.49 |
| ADHD                                  | 8.50 (0.43, 518.11) p = 0.10           |
| No ADHD                                | 0.12 (0.0019, 2.35) p = 0.10           |
| Bipolar Disorder                      | 1.94 (0.032, 38.82) p = 0.50           |
| Depression                             | 0.41 (0.026, 31.37) p = 0.50           |
| Bipolar Disorder                      | 0.41 (0.026, 31.37) p = 0.50           |
| No Bipolar Disorder                   | 0.10 (0.097, 54.50) p = 1.00           |
| Insomnia                              | 0.89 (0.079, 5.27) p = 1.00            |
| No Insomnia                           | 8.90 (0.43, 563.46) p = 0.099          |
| Body Mass Index (kg/m²)               | 0.89 (0.079, 5.27) p = 1.00            |
| MMD                                   | 1.15 (0.19, 12.64) p = 0.30            |
| Median (25% Quartile, 75% Quartile)   | 1.59 (0.18, 76.60) p = 0.50            |
| Wilcoxon Rank Sum Test (estimated difference between groups) | 1.59 (0.18, 76.60) p = 0.50 |
| Wilcoxon Rank Sum Test (estimated difference between groups) | 1.59 (0.18, 76.60) p = 0.50 |
| Matched Controls                      | 30.73 (27.75, 40.30) p = 0.0078        |
| Odds Ratios                           | 6.10 (95% CI: 4.00, 10.01) p = 0.0078  |
| Chi-Square Test or Fisher Exact Test  | 31.28 (28.31, 34.12) p = 0.0078        |
| Weight Class                          | 30.73 (27.75, 40.30) p = 0.0078        |
| Normal                                | 0.13 (0.0028, 1.03) p = 0.057           |
| Overweight                            | 0.88 (0.060, 8.13) p = 0.057           |
| Obesity Class 1                       | 1.00 (0.91, 9.46) p = 0.057            |
| Obesity Class 2                       | 1.00 (1.00, 1.00) p = 0.057            |
| Obesity Class 3                       | 0.09 (0.01, 0.91) p = 0.057            |
| Hyperlipidemia                        | 1.94 (0.032, 38.82) p = 0.50           |
| No                                    | 0.10 (0.025, 0.63) p = 0.50            |
| Hyperlipidemia                        | 0.10 (0.025, 0.63) p = 0.50            |
| Type 2 Diabetes Mellitus              | 0.20 (0.0042, 1.28) p = 0.26           |
| Diabetes Mellitus                     | 1.03 (0.009, 9.46) p = 0.060           |
| No Diabetes                           | 1.00 (1.00, 1.00) p = 0.057            |
| Coronary Artery Disease or Myocardial Infarction (CAD/MI) | 1.10 (1.58, 80.19) p = 0.0058 |
| CAD/MI                                | 1.30 (0.28, 5.62) p = 0.0058           |
| Atrial Fibrillation (Afib)             | 0.77 (0.18, 3.58) p = 0.0058           |
| No Afib                               | 0.77 (0.18, 3.58) p = 0.0058           |
| Autoimmune Disease                    | 0.83 (0.18, 4.37) p = 0.74             |
| No Autoimmune                         | 0.83 (0.18, 4.37) p = 0.74             |
| Thyroid Disease                       | 1.21 (0.22, 5.47) p = 0.74             |
| No Thyroid Disease                    | 1.21 (0.22, 5.47) p = 0.74             |
| Traumatic Brain Injury (TBI)           | 0.70 (0.0045, 0.94) p = 0.0058         |
| TBI                                   | 1.30 (0.0045, 0.94) p = 0.0058         |
| (continued on next page)              | (continued on next page)               |
### Table 2

| Moyamoya Disease vs. General Population | Moyamoya Disease vs. Ischemic Strokes |
|----------------------------------------|--------------------------------------|
| Median (25% Quartile, 75% Quartile)    | Wilcoxon Rank Sum Test (estimated difference between groups) |
| No TBI                                 | 0.29 (0.0066, 2.18) |
|                                         | 3.00 (4.06, 152.49) |
|                                         | 0.46 (0.0099, 3.73) |
|                                         | 2.17 (0.27, 100.75) |
| GERD                                   | 0.64 (0.013, 6.22) |
|                                         | p = 1.00 |
|                                         | 0.78 (0.015, 8.15) |
|                                         | p = 1.00 |
| No GERD                                | 1.56 (0.16, 78.74) |
|                                         | 1.27 (0.12, 65.90) |
| Migraine                               | 0.84 (0.16, 3.69) |
|                                         | p = 1.00 |
|                                         | 21.61 (1.85, 1170.81) |
|                                         | p = 0.0045 |
| No Migraine                            | 1.20 (0.27, 6.23) |
|                                         | 0.046 |
|                                         | (0.00085, 0.54) |
| Epilepsy                               | 5.63 (1.16, 28.85) |
|                                         | χ² = 5.16, p = 0.023 |
|                                         | χ² = 6.26, p = 0.012 |
| No Epilepsy                            | 0.18 (0.035, 0.87) |
|                                         | 0.15 (0.028, 0.75) |

### Table 3

| Moyamoya Disease vs. General Population | Moyamoya Disease vs. Ischemic Stroke |
|----------------------------------------|--------------------------------------|
| Unadjusted Odds Ratios (95% Confidence Interval) | Best Fit Model: Adjusted Odds Ratios (95% Confidence Interval) |
| Age at                                  | 0.84 (0.75, 0.86) |
| Presentation                           | 0.93 (0.97, 0.99) |
| Ischemia Vessel Location               | 0.000097 |
| Middle Cerebral                        | 0.014 |
| Anterior Cerebral Artery               | 193.88 (1.19 × 10⁻⁷, 3.15 × 10⁻⁷) |
| Artery                                 | p = 1.00 |
| Posterior Artery                       | 0.53 (0.033, 2.19) |
| Lacunar Artery                         | p = 0.09 |
| Multiple Vessels                       | 0.94 (0.20, 4.42) |
| Moyamoya or Ischemic Stroke Clinical Presentation | p = 0.94 |
| Ischemic Stroke                        | Referent |
| Left                                   | 1.08 (0.11, 10.47) |
| Right                                  | p = 0.95 |
| Transient                              | 2.86 (0.60, 13.59) |
| Bilateral                              | p = 0.19 |
| Visual Field                           | 8.33 (1.63, 42.99) |
| Defect                                 | p = 0.011 |
| Ischemia Laterality                    | Referent |
| Male                                   | 0.94 (0.20, 4.47) |
| Female                                 | 4.7, p = 0.94 |
| Sex                                    | 2.86 (0.60, 13.59) |
| Sex                                    | p = 0.19 |
| Race                                   | 8.33 (1.63, 42.99) |
| White                                  | p = 0.011 |
| Asian                                  | Referent |
| Hispanic                               | 0.94 (0.20, 4.47) |
| NIHPI                                  | 4.7, p = 0.94 |
| Hispanic                               | 12.11, p = 0.99 |
| Median                                 | 2.19 (0.32, 15.00) |
| Household Income                       | p = 0.42 |
| Median                                 | 1.00 (1.00, 1.00) |
| Overall Poverty Level                  | 1.00 (p = 0.74) |
| Income                                 | 1.00, p = 0.24 |
| Median                                 | 1.00 (1.00, 1.00) |
| Household Income                       | 1.00, p = 0.74 |
| Overall Poverty Level                  | 1.00, p = 0.24 |
| Income                                 | 1.00 (1.00, 1.00) |
| Overall Poverty Level                  | 1.36 (3.04 × 10⁻⁵, 6.11 × 10⁻¹) |
| Income                                 | p = 0.97 |
| Poverty Level                          | 1.34 (9.92 × 10⁻⁴, 1.81 × 10⁻¹) |
| Medians                                | p = 0.28 |
| Median                                 | 5.00 (10⁻⁶, 10⁻³) |
| Median                                 | 5.00 (10⁻⁶, 10⁻³) |
| Median                                 | p = 0.28 |
| Poverty Level                          | 5.00 (10⁻⁶, 10⁻³) |
| Media Age                              | 1.34 (9.92 × 10⁻⁴, 1.81 × 10⁻¹) |
| Median                                 | p = 0.28 |
| Poverty Level                          | 5.00 (10⁻⁶, 10⁻³) |
| Age                                    | 0.99 (0.0048, 5.22) |
| Median                                 | p = 0.22 |
| Poverty Level                          | 4.99 × 10⁻¹ |
| Media Age                              | X² = 0.004 (0.19) |
| Median                                 | p = 0.04 |
| Poverty Level                          | 4.99 × 10⁻¹ |
| Media Age                              | X² = 0.004 (0.19) |
| Median                                 | p = 0.04 |
| Origin Population                      | 1.00 (1.00, 1.00) |
| Size                                   | 1.00 (p = 0.54) |
| Origin Population                      | 1.00, p = 0.31 |
| Geographic Origin                      | Referent |
| Urban                                  | 2.80 (0.77, 10.22) |
| Suburban                               | p = 0.12 |
| Suburban                               | 2.80 (0.77, 10.22) |
| Suburban                               | p = 0.12 |

(continued on next page)
Table 3 (continued)

| Income Quarters (Middle Class) | Unadjusted | Best Fit | Unadjusted | Best Fit |
|-------------------------------|------------|----------|------------|----------|
| Homemaker                    | 0.42 (0.044, 40.37), p = 0.100 | 0.021 (1.79, 10^{-3}), 818.86, p = 0.99 | 0.012 (1.79, 10^{-3}), 818.86, p = 0.99 | 0.00018 |
| Employed Status               |            |          |            |          |
| Married                       | Referent   | Referent | Referent   | Referent |
| Divorced                      | 0.27 (3.73, 68.97), p = 0.099 | 0.44 (0.051, 3.72), p = 0.99 | 0.44 (0.051, 3.72), p = 0.99 | 0.013 |
| Widowed                       | 2.25 (0.17, 29.06), p = 0.53 | 0.38 (0.041, 3.61), p = 0.40 | 0.38 (0.041, 3.61), p = 0.40 | 0.013 |
| Smoking Status (Current/Former) | Referent   | Referent | Referent   | Referent |
| Never Smoker                  | 0.60 (0.14, 2.55), p = 0.50 | 0.61 (0.14, 2.55), p = 0.50 | 0.61 (0.14, 2.55), p = 0.50 | 0.013 |
| AUDIT (Alcohol Abuse)         | Referent   | Referent | Referent   | Referent |
| Negative                      | 1.00 (0.18, 5.46), p = 1.00 | 2.20 (0.35, 13.73), p = 0.40 | 2.20 (0.35, 13.73), p = 0.40 | 0.013 |
| No Drug Use                   | Referent   | Referent | Referent   | Referent |
| Drug Use                      | 0.010 (1.75, 62.15), p = 0.57 | 0.010 (2.58, 10^{-3}, 42.17), p = 0.99 | 0.010 (2.58, 10^{-3}, 42.17), p = 0.99 | 0.013 |
| Anxiety                       | Referent   | Referent | Referent   | Referent |
| No Anxiety                    | 0.20 (0.024, 1.69), p = 0.14 | 0.78 (0.083, 7.39), p = 0.83 | 0.78 (0.083, 7.39), p = 0.83 | 0.013 |
| Depression (PHQ-9)            | Referent   | Referent | Referent   | Referent |
| No Depression                 | 0.61 (0.14, 2.55), p = 0.50 | 0.81 (0.19, 3.44), p = 0.77 | 0.81 (0.19, 3.44), p = 0.77 | 0.013 |
| Bipolar Disorder              | Referent   | Referent | Referent   | Referent |
| No Bipolar Disorder           |            |          |            |          |
| Disorder                      | 0.010 (3.49 × 10^{-3}, 3.50, p = 0.0045) | 0.010 (3.49 × 10^{-3}, 3.50, p = 0.0045) | 0.010 (3.49 × 10^{-3}, 3.50, p = 0.0045) | 0.013 |
| | 0.010 (3.49 × 10^{-3}, 3.50, p = 0.0045) | 0.010 (3.49 × 10^{-3}, 3.50, p = 0.0045) | 0.010 (3.49 × 10^{-3}, 3.50, p = 0.0045) | 0.013 |
| Type 2 Diabetes Mellitus      | Referent   | Referent | Referent   | Referent |
| No Diabetes                   | Referent   | Referent | Referent   | Referent |
| Mellitus                      | 10.71 (2.08, 5.90, 1.30 (0.36, 55.12), p = 0.47, p = 0.69 | 0.0044 | 0.0044 | 0.0044 |
| Hypertension                  | Referent   | Referent | Referent   | Referent |
| No Hypertension               | Referent   | Referent | Referent   | Referent |
| Hypertension                  | 7.60 (1.90, 3.42, 0.82 (0.21, 3.04), p = 0.44, p = 0.78 | 0.0042 | 0.0042 | 0.0042 |
| History of Atrial Fibrillation or Flutter (AFib) | Referent | Referent | Referent | Referent |
| No Afb                        | Referent   | Referent | Referent   | Referent |
| Afb                           | 4.27 (0.25, 73.75), p = 0.32 | 0.31 (0.035, 2.64), p = 0.28 | 0.31 (0.035, 2.64), p = 0.28 | 0.013 |
| Autoimmune Disease            | Referent   | Referent | Referent   | Referent |
| No Autoimmune Disease         | Referent   | Referent | Referent   | Referent |
| Autoimmune                    | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.013 |
| Thyroid Disease               | Referent   | Referent | Referent   | Referent |
| No Thyroid Disease            | Referent   | Referent | Referent   | Referent |
| Thyroid Disease               | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.013 |
| Obstructive Pulmonary Disease (Asthma or COPD) | Referent | Referent | Referent | Referent |
| No Obstructive Pulmonary Disease | Referent | Referent | Referent | Referent |
| Obstructive Pulmonary Disease (Asthma or COPD) | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.010 (2.58 × 10^{-3}, 40.70), p = 10^{-5}, 31.12, p = 0.99 | 0.013 |

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3.4. Medical risk factors

3.4.1. Cardiovascular

Nine cardiovascular risk factors were examined. Median BMI was estimated 6.10 kg/m² greater (95% CI: 1.68, 11.83; p = 0.008) amongst MMD patients (30.73 kg/m², IQR: 27.75, 40.30) than general controls, and 4.67 kg/m² greater (95% CI: 0.68, 10.95; p = 0.03) than ischemic stroke controls (Table 2).

Following CDC obesity classification guidelines, MMD patients were at 7.29 (95% CI: 0.73, 99.15; p = 0.050) fold greater odds of being in obesity class III (BMI >=40 kg/m²), and 0.13 (95% CI: 0.0028, 1.03; p = 0.042) fold reduced odds of being normal weight (BMI 18.5-25.9 kg/m²), relative to general population controls. Compared against non-MMD ischemic strokes, MMD patients were at 6.66 (95% CI: 0.66, 90.93; p = 0.06) fold greater odds of being in obesity class III, and 0.20 (95% CI: 0.0042-1.63; p = 0.015) fold reduced odds of being normal weight. Per logistic regression, with normal BMI as the reference, MMD patients were at a significantly increased odds of being in obesity class III (21.00, 95% CI: 1.40, 314.04; p = 0.03), relative to ischemic stroke patients (Table 3).

Relative to general population controls, MMD patients had greater odds of being comorbid with type 2 diabetes mellitus (10.07, 95% CI: 1.58, 80.19; p = 0.006), hypertension (7.28, 95% CI: 1.58, 40.28; p = 0.004), and hyperlipidemia (3.28, 95% CI: 0.72, 15.25; p = 0.13). Meanwhile, relative to ischemic stroke controls, MMD patients had a reduced odds of coronary artery disease or myocardial infarction (0.13, 95% CI: 0.0029, 0.86; p = 0.024).

3.4.2. Miscellaneous

The role of numerous other medical variables was also assessed. MMD patients for insomnia and ADHD were at respectively, 8.90 (95% CI: 0.43, 563.46; p = 0.099) and 8.50 (95% CI: 0.43, 518.11; p = 0.10) folds greater odds, relative to ischemic stroke controls. Meanwhile, for epilepsy, odds amongst MMD patients were increased relative to both general (5.63, 95% CI: 1.16, 28.85; p = 0.02) and ischemic stroke (6.69, 95% CI: 1.33, 35.94; p = 0.01) controls. Regarding migraines, odds were also greater (21.61, 95% CI: 1.85, 1170.81; p = 0.005) amongst MMD patients, compared to ischemic stroke controls.

When examining the composite comorbidity index, the CCI of MMD patients was an estimated 1.00 higher (95% CI: 1.00, 3.00, p = 0.004) than general controls, while 3.00 lower (95% CI: 1.00, 4.00, p = 0.002) than ischemic stroke controls (Table 2).

3.5. Multivariable analysis

After conducting the univariate logistic analysis, when comparing MMD to the general population controls, the strongest predictor of MMD diagnosis was presence of epilepsy (adjusted odds: 5.71, 95% CI: 1.01, 32.39; p = 0.049). However, when comparing MMD against ischemic stroke controls, the strongest predictor of MMD diagnosis was a younger age (adjusted odds: 0.84, 95% CI: 0.75, 0.93; p = 0.01).

4. Discussion

Notwithstanding the small sample size—secondary to low disease incidence—, this case-control study remained sensitive enough to identify several statistically significant associations with MMD, variables that are not only modifiable risk factors with clinical implications—with regards to prevention and treatment—, but also variables that can heighten clinician awareness to conduct a MMD diagnostic work-up in an ischemic stroke patient [7].

4.1. Overall prevalence

The prevalence of MMD within our institute was 40 per 100,000 neurology/neurosurgery patients. In relation, when considering the general population—which includes patients without neurological disorders—, the national estimate of MMD per 100,000 people is 0.09 in the United States (2005–2008), 3.92 in China (2005–2008), 10.5 in Japan (2002–2006), 16.1 in South Korea (2011) [16–19]. In Hawai’i specifically, estimates of statewide prevalence from 1990 are 1.08 per 100,000 [20].

4.2. Clinical characteristics of moyamoya disease

The most common presenting symptom amongst our MMD cohort was ischemic stroke (60.0%). Regarding ischemia location, the most common vessel amongst our cohort was the middle cerebral artery (58.3%), consistent with literature indicating MMD disproportionately affects the anterior circulation [21]. No cases of isolated posterior circulation MMD were found, congruent with prior studies demonstrating posterior involvement as rare [22]. Unilateral disease (66.7%) was more common than bilateral (33.3%) vessel disease in our population. These observations correlate with other studies; yet notably, when considering unilateral MMD may progress to involve bilateral vessels, the 33.3% bilateral disease could indicate 33.3% of patients within our population experienced a delayed diagnosis [23,24].
Compared to non-MMD ischemic stroke, MMD patients were at greater odds of having atypical presentations (i.e., visual field defects and dizziness; odds ratio OR 9.13, p = 0.09), an ACA stroke (OR: 8.50, p = 0.10), and bilateral vessel disease (OR: 2.87, p = 0.21). The increased odds of ACA vessel disease in MMD does correlate with findings that in the general ischemic stroke population ACA only accounts for 1.3–5.4% of infarctions [25,26]. In summary, ischemic stroke patients experiencing visual field defects or dizziness as the first presenting symptom, ACA vessel infarction, or bilateral vessel disease, may warrant extra scrutiny by undergoing a diagnostic workup for MMD.

4.3. Age

MMD patients at our institute had a median age at diagnosis of 42 years old, corresponding to a 2008–2015 Nationwide Inpatient Sample (NIS) study finding the largest incidence in the 18–44 years old age group [7]. Other United States studies have demonstrated a younger mean age of diagnosis, between 32 and 34.5 years [27,28]. Our cohort’s older age may be secondary to 83.3% of the patients being Asian or NHPI and median age of MMD onset varying with race—in that Asians present at an older age (median: 36 years) than Whites (32 years) [29]. Relative to non-MMD ischemic strokes, MMD patients at our institute presented with symptoms 32 years younger (p < 0.0001). After multivariable logistic regression, younger age remained the strongest predictor of MMD diagnosis (p = 0.014). Hence, ischemic stroke patients presenting between 32.5 and 43.5 years of age or younger, should be considered for MMD diagnostic work-up.

4.4. Sex

Several studies have also found that MMD predominately affects females, with female-to-male incidence ratios ranging between 1.1 and 2.9 [16,29–35]. Regional differences in MMD sex distribution have been identified as well, with the ratio 1.1 in China, while 2.9 in Europe [19,35,36]. Our study identified a female-to-male ratio of 5.0, with divergence from current literature likely related to the small cohort and Hawai’i’s unique demographics.

Relative to non-MMD ischemic strokes, females had an 8.78 (p = 0.004) fold greater odds of MMD. In general, for strokes, females have a lower age-adjusted incidence than men, where ischemic strokes disproportionately affect men at younger ages and women at older ages [37,38]. Therefore, a young female ischemic stroke patient should be considered for MMD diagnostic work-up.

4.5. Race

Our study found that Asian patients were at 3.68 greater odds (p = 0.087) of MMD diagnosis relative to both general and ischemic stroke controls. These findings are similar to other studies in the United States that have found higher incidence in Asians [7,20,29]. Genetic predisposition in certain Asian and Pacific Islander populations has been recognized in MMD [39,40]. A genome wide association study identified RNF213 as highly associated with familial MMD [41].

4.6. Socioeconomic variables

Our small cohort size prevented identification of statistically significant differences in income and poverty levels in MMD patients. From 2020, one American study did identify low-income patients had a higher incidence of MMD (0.514) relative higher income quartiles (0.239) [7]. While no other studies that have examined the role of socioeconomic status on MMD diagnosis, investigations do likewise demonstrate an inverse relationship between socioeconomic status and stroke incidence [42–45].

Relative to non-MMD ischemic strokes, MMD patients were at 3.32 fold greater (p = 0.090) odds of being from suburban areas than urban. Independently, MMD patient are more likely to originate from urban areas, per nationwide data [7].

When examining insurance, employment, and marital status, relative to ischemic stroke controls, MMD patients had 0.28 (p = 0.090) and 0.0061 (p = 0.002) folds reduced odds of being on Medicare and retired, respectively, while a 6.96 (p = 0.02) and 3.19 (relative to being married, p = 0.01) fold increased odds of being employed and single, respectively. These findings are likely secondary to the younger age of MMD patients relative to non-MMD ischemic stroke patients, as older patients are more likely to qualify for Medicare insurance, as well as be retired and married [46].

4.7. Medical comorbidities

4.7.1. Cardiovascular variables

Several studies have also noted an association between cardiovascular risk factors and MMD [28,47–50]. Our investigation identified that patients with a higher BMI (p = 0.008), diabetes mellitus type 2 (OR: 10.07, p = 0.006), hypertension (OR: 7.28, p = 0.004), and hyperlipidemia (OR: 3.28, p = 0.13), all had greater odds of MMD, relative to general controls. Compared to non-MMD ischemic strokes, MMD patients had a 4.67 kg/m² fold greater (p = 0.03) BMI, and were at 21.00 (relative to normal BMI, p = 0.027) fold greater odds to be from obesity class III; while other cardiovascular risk factors were not statistically different, MMD patients were 0.13 (p = 0.02) fold reduced odds of coronary artery disease or myocardial infarction, relative to non-MMD ischemic strokes.

These data parallel one prior study which also found higher BMI and homocysteine were associated with greater risk for MMD [51]. The

| Variable | Relative to Neurological Disorders | Relative to Ischemic Stroke |
|----------|-----------------------------------|-----------------------------|
| Younger Age of Presentation | ✓ | ✓* |
| Female | √ (p < 0.1) | ✓ |
| Asian | √ (p < 0.1) | ✓ (p < 0.1) |
| Employed | ✓ | ✓ |
| Not Able to Work | √ (p < 0.1) | ✓ |
| Single | ✓ | ✓ |
| Lower Population Density Origin | ✓ (p < 0.1) | ✓ |
| Suburban Origin | ✓ (p < 0.1) | ✓ |
| Greater Body Mass Index | ✓ | ✓ |
| Obesity Class II (30.0–39.9 kg/m²) | ✓ | ✓ |
| Obesity Class III (>40 kg/m²) | ✓ | ✓ |
| Diabetes Mellitus Type 2 | ✓ | ✓ |
| Hypertension | ✓ | ✓ |
| Hyperlipidemia | (p < 0.1) | ✓ |
| Migraine | ✓ | ✓ |
| Epilepsy | ✓* | ✓ |
| Insomnia | ✓ (p < 0.1) | ✓ |
| Higher Charlson Comorbidity Index | ✓ | ✓ |
| Visual Field Defect | ✓ (p < 0.1) | ✓ |
| Dizziness | ✓ (p < 0.1) | ✓ |
| Moyamoya Odds Reduced | ✓ | ✓ |
| Retired | ✓ | ✓ |
| Normal BMI (18.5–24.8 kg/m²) | ✓ | ✓ |
| Coronary Artery Disease or Myocardial Infarction | ✓ | ✓ |
| Lower Charlson Comorbidity Index | ✓ | ✓ |
| Medicare | ✓ (p < 0.1) | ✓ |

*variables determined to be statistically significant after multivariable analysis. Variables with marginal significance (p < 0.1) also presented, as low sample size of moyamoya cases likely limited attainment of significance.
significant association of our MMD cohort obesity class III (BMI >40 kg/m²), has been noted in one case report [52]. Regarding diabetes mellitus, associations between RNF213 and TNFα-mediated inflammation, have been postulated to link insulin resistance and MMD [53]. Finally, while there is a lack of evidence correlating hypertension with adult-onset MMD, 29% of pediatric MMD patients met clinical criteria for hypertension even after surgical correction [54]. Overall, given BMI, hypertension, diabetes, and hyperlipidemia are modifiable risk factors, by intervening on these comorbidities, there is potential to slow progression or medically treat MMD.

4.7.2. Miscellaneous variables

While statistical significance was likely attenuated by the small cohort size, MMD patients were at 8.90 (p = 0.099) fold greater odds of insomnia, compared to ischemic stroke controls. In survivors of ischemic strokes, insomnia has been found to occur in up to 50% of patients [55, 56].

MMD patients were also found to have a greater odds of epilepsy, relative to the general controls (OR: 5.63, p = 0.02) and non-MMD ischemic stroke (OR: 6.69, p = 0.01); after multivariable logistic regression, epilepsy was the strongest predictor of MMD diagnosis (p = 0.049) relative to general controls. While seizures and epilepsy are known associations of ischemic strokes and MMD, frequency of epilepsy between MMD and non-MMD ischemic strokes is unknown [57–59]. Similarly, compared to ischemic stroke controls, MMD patients were at 21.61 (p = 0.005) fold greater odds of having. Although headaches have been linked with MMD, these are associations are mostly case reports and have not been well characterized [60–62]. The pathophysiology behind headaches in MMD remains unclear, but is hypothesized secondary to cerebral hypoperfusion [63,64]. Themselves, migraines are associated with an increased risk for ischemic stroke [65]. Given the significant differences in odds, ischemic stroke patients with a history of migraines or epilepsy should be considered for MMD diagnostic work-up.

Finally, our study also found MMD was associated with a higher CCI (p = 0.004) score than general controls, yet a lower CCI (p = 0.002) than that of ischemic stroke patients. Such indicates, MMD have a reduced life-expectancy relative to the general HPN population, but greater relative to non-MMD ischemic strokes. The difference could be in part due to the increased median age of ischemic stroke patients, thus imparting a higher likelihood of multiple comorbidities.

4.8. Limitations

Several limitations should be noted. First, the study was retrospective, thus requiring reliance on accurate documentation by healthcare providers. Additionally, our small sample size of MMD cases limited the statistical power of the study, thus only allow for appreciation of statistical significance for variables with strong associations. For certain variables, there is also potential of recall bias or patients not being forthcoming, as with smoking, alcohol consumption, and illicit drug use. Furthermore, there may have been administrative errors in working with ICD-CM codes, including data inputting errors and potentially padded data. Therefore, the association of our MMD cohort obesity class III (BMI >40 kg/m²), has been noted in one case report [52]. Regarding diabetes mellitus, associations between RNF213 and TNFα-mediated inflammation, have been postulated to link insulin resistance and MMD [53]. Finally, while there is a lack of evidence correlating hypertension with adult-onset MMD, 29% of pediatric MMD patients met clinical criteria for hypertension even after surgical correction [54]. Overall, given BMI, hypertension, diabetes, and hyperlipidemia are modifiable risk factors, by intervening on these comorbidities, there is potential to slow progression or medically treat MMD.

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5. Conclusion

In summary, this case-control study sought to better characterizing MMD in order to facilitate potential earlier diagnosis (Table 4). Relative to the general population of patients with neurological disorders, MMD patients had increased odds of being younger, female, Asian, not able to work, greater body mass index, obesity class II and III, diabetes mellitus type 2, hypertension, hyperlipidemia, epilepsy, and a higher CCI. When compared against non-MMD ischemic stroke patients, those with MMD had reduced odds of coronary artery disease or myocardial infarction, yet a greater odds of the first clinical presentation being a visual field defect or dizziness, as well as the following variables: younger, female, Asian, employed, not able to work (disabled), single, from a lower population density area, suburban origin, greater body mass index, obesity class III, migraines, epilepsy, and insomnia; hence, ischemic stroke patients presenting with such variables should be considered for MMD diagnostic work-up. These findings highlight not only several unique variables to better recognize MMD from ischemic strokes of other etiologies, but also emphasize the presence of modifiable risk factors being associated with MMD, thus providing the potential for impactful preventative health measures.

Availability of data and material (data transparency)

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Code availability (software application or custom code)

Not applicable.

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All authors contributed equally.

Registration of research studies

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Guarantor

Arash Ghaffari-Rafi.

Declaration of competing interest

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