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Research Article

Clinical Outcomes of Ischemic Stroke in Indigenous Populations: A Systematic Review and Meta-analysis

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Abstract

Background: The burden and outcome of stroke in -Iindigenous populations is less well understood. This review evaluates ischemic stroke outcomes in Indigenous populations as compared to the general population in the context of recent advances in ischemic stroke therapy. **Method:** The OVID Medline and EMBASE databases were searched for this review. Clinical outcome was measured and compared using standardized outcome scale following stroke intervention in Indigenous as compared to non-Indigenous adult populations. Associated risk factors were also collected and compared. **Results:** 897 studies were identified, with 4 studies included in the final analysis. A total of (n=68895) patients were included who underwent thrombolysis. Study populations from Australia, New Zealand, United States, and Canada comprised of (n=2012) Indigenous patients. Mortality was significantly higher in Indigenous populations as compared to non-Indigenous (Odds Ratio-1.28, 95% CI-1.12; 1.46). The odds ratios of atrial fibrillation (1.26, 95% CI-1.12;– 1.41), diabetes (1.43, 95% CI- 1.27; 1.62), hypertension (1.33, 95% CI- 1.17; 1.51) and IHD (0.71, 95% CI- 0.62; 0.81) in Indigenous patients was significantly higher than in non-Indigenous patients. **Conclusion:** Indigenous populations undergoing stroke therapy have significantly higher mortality compared to non-Indigenous populations. Comorbidities including diabetes, atrial fibrillation, and hypertension are more prevalent in Indigenous populations.

Keywords: Stroke; Ischemic stroke; Clinical outcome; Indigenous population

Introduction

Stroke is the second most common cause of both death and disability globally with over 80 million cases occurring in 2016 [1]. Ischemic stroke accounts for over 84% of the total case burden and is the second most common cause of long-term disability globally having significantly increased in the period from 1990 to 2016 [1]. While the epidemiology, risk factors, and outcomes related to stroke in the general population have been extensively studied, the burden and outcome of stroke in Indigenous populations is less well understood.

The global Indigenous population is estimated to be approximately 370 million people spread across 90 countries who experience lower standards of health relative to surrounding populations [2]. While there is no universally accepted definition of Indigenous populations, the World Health Organization (WHO) generally defines Indigenous populations as those who descend from communities present prior to the emergence of modern nation states and who self-identify and are recognized as members by their communities [3]. Indigenous populations throughout the world exhibit significant diversity both within populations and around the world. Poor health outcomes persist in Indigenous communities regardless of income status of the surrounding nation [2,4]. Stroke in Indigenous populations tends to occur at a significantly younger age when compared to the general population [5,6]. Stroke risk

factors including diabetes, smoking, hypercholesterolemia, and hypertension are up to 5 times more prevalent in Indigenous compared to non-Indigenous patients [7]. The burden of stroke, in terms of disability adjusted life years (DALY) is approximately 3 times higher than non-Indigenous populations reflecting the significant burden of ischemic stroke [8]. While such studies hint at the elevated incidence and burden in the Indigenous population, there is limited data on stroke in the global Indigenous population. A protocol for a systemic review investigating stroke incidence in Indigenous population has recently been undertaken to assess stroke incidence in Indigenous populations [9].

Intravenous thrombolytics (IVT) and endovascular thrombectomy (EVT) are two treatments for acute ischemic stroke that have shown significant improvement in functional outcomes when used in the acute setting. However, access to care and outcomes of acute ischemic stroke among Indigenous populations has not been studied. The goal of this review is to provide a comprehensive evaluation of outcomes following ischemic stroke and associated risk factors in Indigenous populations as compared to the general population in the context of recent advances in ischemic stroke therapy.

Methods

The OVID Medline and EMBASE databases were searched for the purposes of this review. A librarian [JL] with over 20 years of experience working in Indigenous health designed a comprehensive search strategy using keywords and subject headings for Indigenous people, inclusive of the term "Indigenous" used globally, and keywords for Indigenous People in Canada, the United States, Australia, and New Zealand. Searches were run in OVID Medline and EMBASE. Articles were limited to those published in English and indexed as of June 2021.

The results of the searched records were stored in the Covidence platform to facilitate selection and Zotero during preparation of the manuscript. Prior to the selection process, duplicated records were removed with a combination of automated screening and manual removal.

The process of article screening was performed using the Covidence platform. Titles and abstracts from the search articles were reviewed by two independent reviewers (JD and RT). Using this process, the articles were independently flagged as "Yes", "No" or "Maybe". Decisions in the screening stage were based on inclusion and exclusion criteria summarized in (Table 1).

Inclusion/Exclusion Criteria
Inclusion Criteria
Inclusion of an Indigenous population
Patients experienced ischemic stroke
Article reports on acute stroke therapies patients accessed
Clinical outcomes for patients in the study are recorded for at least 90 days
Exclusion Criteria
Abstracts only without full text publication, Abstracts from oral presentations or poster presentations
Studies with less than 5 participants
Studies with non-adult populations (Eg. < 18 years old)

Table 1: Inclusion and exclusion for screening of studies included in the systematic review and meta-analysis.

Data collection and Data items- Data extraction was performed on the screened articles identified using the above criteria. A predefined spreadsheet was used for data entry, which contained year of publication, publication, Indigenous population, control population if present, sex ratio, age, stroke interventions, and clinical outcome. In addition, data regarding stroke risk factors including hypertension, diabetes, ischemic heart disease, atrial fibrillation, and associated treatments were recorded. This included rates of antiplatelet and anticoagulation use. Data extraction was performed by the study investigators (JD and RT).

Outcomes and prioritization- Primary outcomes were measured as clinical outcomes using a standardized outcome scale (eg. modified Rankin Score [mRS]) following stroke intervention in Indigenous as compared to non-Indigenous adult populations. Mortality as an outcome was encompassed within the clinical outcome scale.

Secondary outcomes included relative prevalence of IVT vs EVT in Indigenous as compared to non-Indigenous populations and comparative prevalence of stroke related risk factors in the study populations.

Risk of bias analysis was performed for all papers included in the systematic review and meta-analysis. The Cochrane risk of bias assessment tools was used for evaluation of studies at the data collection stage. In particular, the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool was applied [Cochrane].

Statistics

The results of the systematic review are presented both quantitatively and qualitatively. A meta-analysis was undertaken after completion of the systematic review. Effects were summarized using both fixed effects and random effects models. Heterogeneity was quantified using the I2 statistics. Statistical analysis was performed with Revman (Version 5.4), which was used to generate meta-analysis and forest plots. Pooled estimates and confidence intervals were calculated using Revman software.

Results

A total of 897 records were identified using search criteria. The PRISMA diagram of the included articles is shown in (Figure 1). Studies were included only when they compared the stroke outcomes and associated risk factors between Indigenous and non-Indigenous population. Articles were excluded for two primary reasons: a lack of information regarding stroke treatment and a lack of any clinical outcome measures.

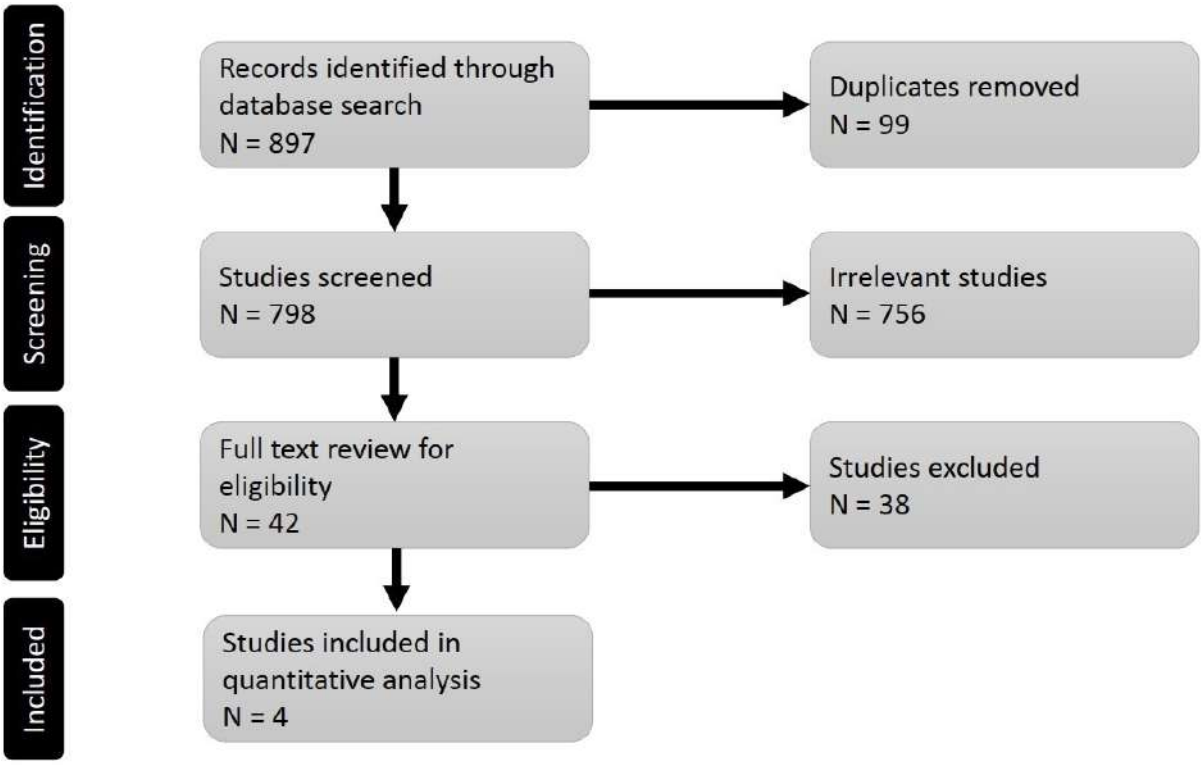

Figure 1: Flow chart demonstrating search and screening process (PRISMA chart).

A total of 4 studies were included in the analysis. A summary of study characteristics is provided in (Table 2). A total of (n=68895) patients were included in the analysis who underwent combinations of thrombolysis with or without mechanical thrombectomy. A small number of patients may have received mechanical thrombectomy alone. There was a total of 32750 (47.5%) female patients with age ranging from 59 years to 79 years. As defined by the authors of each study, there was a total of (n= 2012) Indigenous patients included in this study. Study populations were located in Australia, New Zealand, United States, and Canada [10-13]. Data extracted from the studies is shown in (Table 3).

Outcome Data						
Study	**Design**	**Location**	**mRS at 90 days**	**mRS any time**	**Mortality**	**Partial discharge data**
Dos Santos et al	Prospective Cohort	Australia		X	X	
Samuels et al	Retrospective Cohort	New Zealand	X		X	
Nasr et al	Retrospective Cohort	United States			X	
Kapral et al	Retrospective Cohort	Canada			X	X

Table 2: Characteristics of studies included in the systematic review and meta-analysis.

Indigenous									
Study	**N**	**Age**	**Female**	**Atrial Fib**	**HTN**	**DM**	**IHD**	**IVT**	**Mortality**
Dos Santos et al	26	62	10	6	23	12	9	2	0
Samuels et al	124	61	58					134	10
Nasr et al	1248	69	627	487	945	364	277	1248	183
Kapral et al	536	63	287					30	64
Non-Indigenous									
Study	**N**	**Age**	**Female**	**Atrial Fib**	**HTN**	**DM**	**IHD**	**IVT**	**Mortality**
Dos Santos et al	1163	74.4	490	359	930	277	304	74	14
Samuels et al	243	75	90					243	21
Nasr et al	36988	70.2	17829	12355	25978	8354	10771	36988	4475
Kapral et al	28338	74	13274					2765	2409

Table 3: Summary of data extracted from included studies including data regarding comorbidities and clinical outcomes.

Dos Santos et al. investigated stroke recognition, risk factors, treatment, and outcomes among Indigenous and non-Indigenous Australians within the Murrumbidgee health district, which encompassed approximately 250000 people [10]. The study was a prospective cohort study. A total of 1843 patients were included in the study, of which 45 identified as Indigenous. Treatment with IVT was performed in 2 (4.4%) of Indigenous and 74 (4.1%) of non-Indigenous patients. Clinical outcomes (mRS scores) at 5-days were available for 19 Indigenous patients and 909 non-Indigenous patients. Favorable outcomes (mRS 0 – 2) were observed in 47% of Indigenous patients and 46% of non-Indigenous patients.

Samuels et al. investigated the stroke reperfusion therapy in mixed urban/rural communities in northern New Zealand in the period Jan 1, 2018 to Sept 30, 2019 [11]. The study was a retrospective cohort study using data from the New Zealand (NZ) stroke registry. There were 124 Indigenous patients treated with IVT and 10 deaths noted at 7 days. Indigenous patients were separated into Māori and Pacific Islander, and both populations had a median mRS of 2 at 90 days. A control population (NZ European/other) included 404 patients undergoing IVT with 33 deaths. The median mRS at 90 days was 2. Similarly, for patients undergoing EVT, there were 78 Indigenous patients and 6 deaths. A median mRS at 90 days of 2 was recorded for both Maori and Pacific Islander populations. Among controls, there were 11 deaths in 151 patients undergoing EVT. The median mRS was also 2 at 90 days.

Nasr et al. investigated IVT utilization, cost, and outcomes using a retrospective cohort methodology based on a national inpatient sample database (2001-2008) in the United States [12]. A total of 1248 Indigenous patients received IVT out of a total of 56428 included in the study. Of the IVT patients, in hospital mortality occurred in (n = 183/609, 14.7%). A total of 36988 control (white caucasian) patients underwent IVT out of a total of 1588267 included in the study. In hospital mortality occurred in (n = 4475/18306, 12.1%) of the control patients. Clinical outcome data were not available.

Kapral et al. investigated ischemic stroke incidence, comorbidities, treatment, and outcomes in Indigenous and non-Indigenous Ontarians (Ontario, Canada) with diabetes mellitus [13]. A retrospective cohort study was conducted using administrative databases as sources during the time period of April 1, 2011 to Mar 31, 2016. A total of 536 Indigenous patients were admitted with ischemic stroke, of which 372 were identified to have ischemic stroke. IVT was performed in 6.3% of patients and the 7-day mortality rate was 12%. A control population of 28338

was identified who experienced 20854 ischemic strokes. Thrombolysis was performed in 11% of patients and mortality occurred in 8.5% of patients. No further specific clinical outcome data was available; however, discharge to inpatient rehabilitation occurred in 31.8% of Indigenous patients as compared to 34.8% of control patients.

Meta-analysis

Out of all the stroke outcomes, only mortality data could be pooled for meta-analysis. The pooled data showed that the mortality was significantly higher in Indigenous populations as compared to non-Indigenous (Figure 2), Odds Ratio 1.28, 95% CI [1.12 – 1.46]). I2 measure was 0% with p = 0.62 suggesting no significant heterogeneity in the included studies.

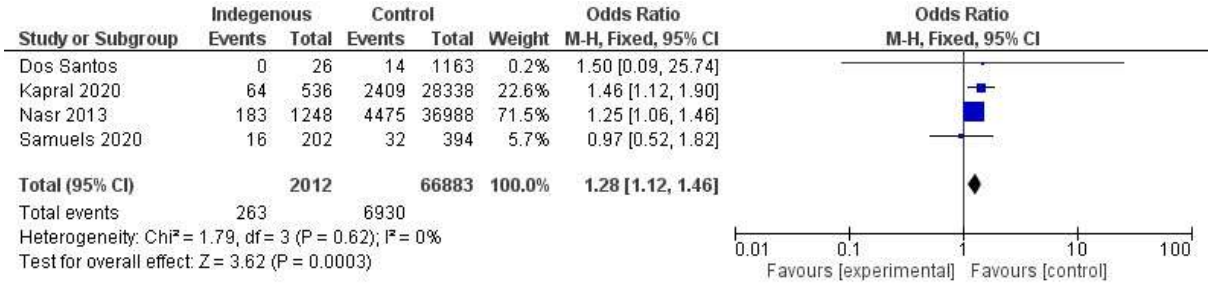

Figure 2: Forest plot showing mortality in Indigenous compared to control populations with ischemic stroke undergoing treatment.

Only two studies included data regarding comorbidities including diabetes mellitus (DM), ischemic heart disease (IHD), hypertension (HTN) and atrial fibrillation (Afib) [10,12]. Only these could be pooled for meta-analysis. Pooled data for common comorbidities showed the odds ratio of atrial fibrillation in Indigenous patients was significantly higher than in non-Indigenous patients (Figure 3), 1.26 95% CI [1.12 – 1.41]). The odds ratio of diabetes was significantly higher in Indigenous patients as compared to non-Indigenous patients (Figure 4), 1.43, 95% CI [1.27 – 1.62]). The odds ratio of hypertension in Indigenous patients was significantly higher than in control patients (Figure 5), 1.33 95% CI [1.17 – 1.51]). The odds ratio for IHD in Indigenous patients was significantly lower than in control patients (Figure 6), 0.71 95% CI [0.62 – 0.81]). Across the four included studies, the odds ratio of being female in Indigenous populations was significantly higher than in control populations (Figure 7), 1.16 95% CI [1.06 – 1.27]).

Figure 3: Forest plot showing atrial fibrillation in Indigenous compared to control populations with ischemic stroke undergoing treatment.

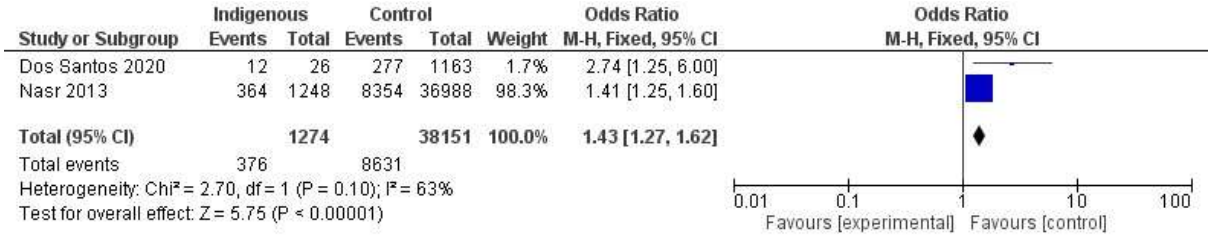

Figure 4: Forest plot showing diabetes mellitus in Indigenous as compared to control populations with ischemic stroke undergoing treatment.

Figure 5: Forest plot showing hypertension in Indigenous as compared to control populations with ischemic stroke undergoing treatment.

Figure 6: Forest plot showing ischemic heart disease in Indigenous as compared to control populations with ischemic stroke undergoing treatment.

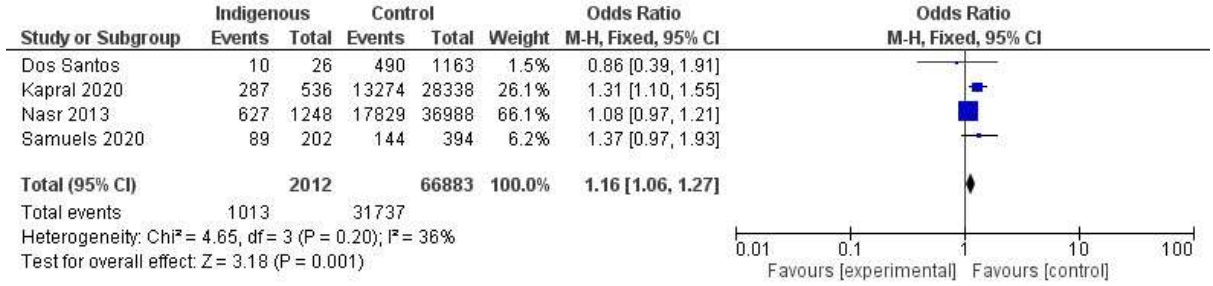

Figure 7: Forest plot showing sex distribution in Indigenous as compared to control populations with ischemic stroke undergoing treatment.

Discussion

To the best of our knowledge, we performed the first systematic review and meta-analysis investigating stroke clinical outcomes in Indigenous populations. There is a paucity of published information regarding the clinical outcomes of stroke in Indigenous populations and there was only a single study which provided data on 90-day clinical outcomes post stroke using a standardized grading scale. Despite limited data, the relative odds of mortality from stroke following intervention were significantly increased to 1.28 in our meta-analysis. There is insufficient data to comment on the comparative clinical outcomes between Indigenous and non-Indigenous populations in light of recent advances in acute stroke therapy.

Consistent with previous reports, mortality in Indigenous populations is higher than non-Indigenous populations [7]. Mortality at 90 days following ischemic stroke intervention in non-Indigenous populations has been reported to range from 14 – 20% at 90 days [14,15]. In this review endpoints were mixed between outcomes at 5 days up to 90 days post stroke. Such early recording of outcomes may underrepresent mortality in Indigenous populations and the associated outcome difference.

A single study, Samuels et al, reported clinical outcome at 90 days following stroke interventions in an Indigenous population. Standardized outcome data has been extensively used to investigate and optimize the use of acute stroke interventions including expanding the time window for mechanical thrombectomy [16]. Such data is lacking for Indigenous populations, limiting the ability to improve care for such populations. In a limited data set, Samuels et al. demonstrated similar clinical outcomes between Indigenous and non-Indigenous populations; however, there remains a significant gap in mortality outcomes. Additional outcome data is necessary to help explain the persistent disparity in mortality and to understand the impact of stroke interventions on 90 day clinical outcomes.

Indigenous populations are more rurally distributed than non-Indigenous populations across geographic regions, whereas advanced stroke treatment resources are usually located in an urban setting. In Western Australia, 40% of the Indigenous population is rurally located as compared to 6% of the non-Indigenous population [5]. Acute stroke interventions are strongly time dependent with improved outcomes being associated with reperfusion within 6 hours of symptom onset, direct arrival rather than transfer, and alteplase administration [14]. Such interventions are generally not available in rural areas, resulting in 31.3% of patients achieving a favorable clinical outcome as compared to 42.5% in an urban population [17]. Similar urban-rural disparity has also been shown in other studies [18]. Recent studies have demonstrated improved clinical outcomes by further shortening times to reperfusion using a direct to angiography suite approach and transfer of neurointerventionalists rather than patients [19,20]. Such approaches are liable to further expand the outcome disparities between urban and rural populations which disproportionately impacts Indigenous populations.

This research will help to promote understanding of ischemic stroke in Indigenous populations and inform the direction of future policy/research initiatives related to stroke therapy.

Conclusion

In the era of thrombolysis and mechanical thrombectomy, there is limited data available documenting clinical outcomes in Indigenous populations. Indigenous populations undergoing stroke therapy had a higher mortality as compared to non-Indigenous populations. Comorbidities including diabetes, atrial fibrillation, and hypertension are more prevalent in Indigenous populations.

Disclosures

No financial disclosures or conflicts of interest to declare except Dr Jai Shankar is the principal investigator of EMMA-Can study in Canada.

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