

Prevalence and risk factors of ischemic stroke in the young; a regional Australian perspective

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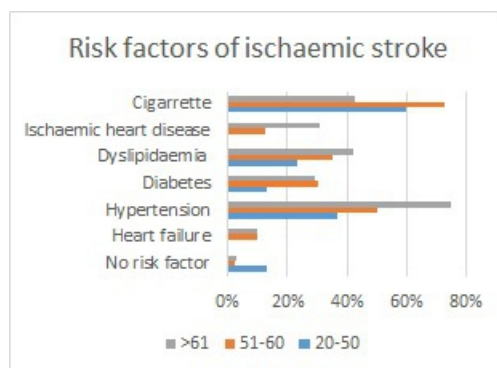
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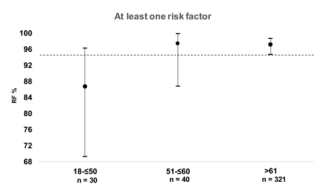
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Table 1: Demographic data

Age group	Total (N)	Males (N)	Females (N)
18-≤50	30 (7.7)	16 (53.3)	14 (46.7)
51-≤60	40 (10.2)	26 (65.0)	14 (35.0)
≥61	321 (82.1)	181 (56.4)	140 (43.6)
Total	391	223	168

Table 2: Traditional vascular risk factors of ischemic stroke

	18-≤50 (N=30)	51-≤60 (N=40)	≥61 (N= 321)	18-≤50 vs ≥61 (P value)	18-≤50 vs 51-≤60 (P value)	51-≤60 vs ≥61 (P value)
At least one risk factor	26 (86.7)	39 (97.5)	312 (97.2)	0.018	0.157	1
Heart failure	0 (0)	4 (10)	31 (9.8)	0.092	0.13	1
Ischaemic heart disease	0 (0)	5 (12.5)	97 (30.6)	<0.001	0.066	0.024
Hypertension	11 (36.7)	20 (50)	237 (74.8)	<0.001	0.334	0.003
Diabetes mellitus	4 (13.3)	12 (30)	93 (29.3)	0.086	0.151	0.856
Dyslipidaemia	7 (23.3)	14 (35)	133 (42)	0.078	0.43	0.49
Cigarette smoking	18 (60)	29 (72.5)*	135 (42.6)*	0.082	0.31	0

Bold values represent statistical significance

*Missing data for 42 patients 61 and over, and 4 patients 51-60 inclusive

Table 3: Causes/mechanisms of ischemic stroke by age group

	18-≤50	51-≤60	≥61	18-≤50 vs ≥61	18-≤50 vs 51- ≤60	51-≤60 vs ≥61
	(N=30)	(N=40)	(N= 321)	(P value)	(P value)	(P value)
Large-artery atherosclerosis	2 (6.7)	9 (22.5)	60(18.7)	0.132	0.1	0.528
Cardioembolism	7 (23.3)	11 (27.5)	139 (43.3)	0.035	0.78	0.062
Small-artery occlusion	8 (20)	9 (22.5)	58 (18.07)	0.624	0.54	0.82
Other determined origin	3 (10)	1 (2.5)	6 (1.9)	0.033	0.307	0.564
Cryptogenic	14 (46.7)	11 (27.5)	57 (18.1)	0.001	0.132	0.138

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Table 4: Sub-analysis of 'other' and 'cryptogenic strokes' in those under 60

Age group	Thrombophilia	Carotid artery dissection	MELAS	2 or more causes	ESUS	Incomplete investigations	True cryptogenic
20-≤50	1 (3.3%)	1 (3.3%)	1 (3.3%)		4 (13.3%)	6 (20%)	4 (13.3%)
51-≤60		1 (2.5%)		2 (5%)	6 (15%)	3 (7.5%)	
Total	1	2	1	2	10	9	4

Abstract

Objective: There is no universally accepted age cut-off for defining young strokes. We aimed to determine, based on the profile of young stroke patients in our regional center, an appropriate age cut-off for young strokes. **Methods:** A retrospective analysis of all ischaemic stroke patients admitted to our center from 2015-2017. We identified 391 ischaemic stroke patients; 30 patients between the ages of ≤ 50 , 40 between 51-60 inclusive, and 321 ≥ 61 years of age. We collected data on demographic profiles, risk factors and stroke classification using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. **Results:** We found significant differences between the ≤ 50 and ≥ 61 age groups for most of the risk factors, and similarities between the 51-60 inclusive and ≥ 61 age groups. At least one of the six risk factors assessed in the study was present in 86.7% of the youngest group, 97.5% of the intermediate age group and 97.2% in the oldest group. In terms of the mechanisms of stroke, the youngest and oldest age groups in our study differed in the prevalence of cryptogenic, cardioembolic and other causes of stroke. The middle and older age groups had similar mechanisms of stroke. **Conclusions:** The prevalence of vascular risk factors and mechanisms of stroke likewise differed significantly across age groups. This study suggests that 50 years is an appropriate age cut-off for defining young strokes, and reinforces the importance of primary prevention in all age groups.

Introduction:

Stroke is the second leading cause of death and third main cause of disability globally, accounting for 6.5 million deaths and 113 million disability-adjusted life years (DALY).¹ The incidence of stroke has increased over the past twenty years and is projected to rise further with the increase in the life expectancy and incidence of modifiable risk factors. Stroke disproportionately affects low-income countries, even when compared to ischaemic heart disease.^{1,2} In Australia and other developed countries, cardiovascular risk factors and the morbidity and mortality related to ischaemic stroke are more common in those of underprivileged socio-economic status.³

Ischaemic stroke in the young population is a common cause of admission to stroke departments.⁴ An estimated 25% of ischaemic strokes occur in working-aged people in high-income countries, and around 10% of all ischaemic strokes occur in those 50 years and under.⁵ Moreover, many epidemiological studies show an increase in the incidence of stroke at younger ages since the 1980s to present.^{1,5,6} The economic implications of this are significant since patients in their most productive working years are left potentially disabled. Despite being more prevalent in older age groups, stroke in the young population is a significant problem.¹

The upper age limit for defining young strokes is unclear, with most published studies defining it as under 45 or 55 years. In clinical practice the upper limit is generally considered 50 years.⁵ In contrast, the World Health Organization (WHO) define young strokes as under 65 in their Global Burden of Disease analyses.^{1,7} A consensus on the definition of young strokes is important for various reasons. The work-up of a stroke patient relies in part on their age, with younger patients often warranting extensive investigations. Therefore, the absence of a uniform definition of young stroke may not only fail to accurately reflect the true magnitude of the problem, it also could lead to unnecessarily costly investigations performed.^{5,7}

The traditional vascular risk factors for ischaemic stroke in older people are also prevalent in younger patients, indicating an important role in the development of stroke.¹ These include hypertension, hyperlipidaemia and diabetes, as well as behavioral risk factors such as smoking, sedentary lifestyle, abdominal obesity, and unhealthy diet.^{5,8} However, the prevalence of vascular risk factors in younger patients does not translate to their associated stroke mechanisms, with large artery atherosclerosis and small vessel disease being uncommon in the younger stroke patients.⁵

Ballarat Health Services (BHS) is a regional health center that provides medical care to a population of approximately 250,000 people, spread over an area of 48,000 km². We conducted a retrospective analysis of patients in BHS to determine the risk factor profile and mechanism of ischaemic stroke across three age groups. In particular, by comparing the three age groups based on risk factors and mechanisms, we sought to determine an appropriate age cut-off for defining young strokes.

Materials and Methods

Study population

We conducted a retrospective audit of ischaemic stroke patients admitted to BHS from 1st of January 2015 to 31st of December 2017, identified on the Australian Stroke Clinical Registry (AuSCR) database. We searched individual patient records to identify the admission of interest and record their demographic details, risk factors and stroke type. We divided the patients into those aged 18 to 50 inclusive, 51 to 60 inclusive, and ≥ 61 years. The exclusion criteria were hemorrhagic strokes, transient ischaemic attacks and stroke mimics. Inclusion criteria was acute ischaemic stroke demonstrated on computed tomography (CT) brain and/or magnetic resonance imaging (MRI) of the brain. The institution's Human Research and Ethics Committee approved the study (LNR/18/BHSSJOB/34).

Risk factors

The risk factors for ischaemic stroke that we assessed were hypertension, past or present cigarette smoking, type 1 or 2 diabetes, dyslipidaemia, ischaemic heart disease and heart failure. We considered a risk factor to be present if documented in the

patient's admission notes, inpatient progress notes, discharge summary or outpatient follow-up notes. Medications started during the admission of interest were not automatically considered indicators for risk factors, with the exception of diabetes. Routine secondary prevention in stroke includes ACE inhibitors and statins and this does not always indicate the presence of hypertension or hyperlipidaemia.

Diagnostic evaluation

We obtained results of CT brain and/or MRI of the brain in all patients, as well as CT angiography, carotid ultrasound, telemetry (minimum 24 hours) and echocardiogram results if available.

In addition, results of routine diagnostic blood investigations were recorded, including fasting lipids, HbA1c and fasting blood sugar levels. In patients ≤ 60 years, we also looked for evidence of a bubble study with their echocardiogram, vasculitic screen, and thrombophilia screen. The thrombophilia screening included Factor V Leiden, plasma homocysteine, prothrombin G20210A gene mutation, anticardiolipin antibodies,

anti-b2 glycoprotein 1 antibodies, lupus anticoagulant, antithrombin III, protein C and protein S deficiencies.⁹

We classified all ischaemic strokes based on the TOAST criteria as large vessel, cardioembolic, small vessel, cryptogenic and other determined etiology.¹⁰ Within the cryptogenic strokes, we sub-classified embolic stroke of undetermined source (ESUS), which denotes non-lacunar cryptogenic strokes in patients where embolism is the most likely stroke mechanism.¹¹

Statistical analysis

Comparison between the three age groups for various factors was performed using χ^2 test when the assumptions were met and Fisher's exact test otherwise. We derived Binomial Exact 95% confidence intervals for proportions of patients with at least one risk factor by age-group. Statistical analyses were conducted using Stata/SE 15.1 for Windows (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). Level of significance was $P < 0.05$.

Results

Prevalence

We identified 548 stroke and transient ischaemic attack patients over the three-year study period, 391 (71.4%) of whom were ischaemic strokes. Of the ischaemic stroke patients, 30 were aged 18 to 50 inclusive (7.7%), 40 were 51 to 60 inclusive (10.2%), and 321 patients (82.1%) were ≥ 61 . The majority were male, 223 overall (57%), and within each age group (Table 1).

Risk factors

Past or current cigarette smoking and hypertension were the most common risk factors regardless of age (Table 2). Whilst there is an increasing trend for hypertension with age, smoking is much less common in the ≥ 61 group compared to the youngest group. There were no patients with history of ischaemic heart disease or heart failure in the ≤ 50 age group (Figure 1). In total, of the six risk factors assessed, 86.7% of the patients had at least one risk factor in the 50 and under age group, compared

to 97.5% in the 51-60 inclusive age group and 97.2% in the ≥ 61 age group (Figure 2).

We found statistically significant differences between the youngest and oldest age groups for the presence of at least one of the six risk factors (86.7% versus 97.2%; $P= 0.018$), ischaemic heart disease (0% versus 30.6%; $P< 0.001$) and hypertension (36.7% versus 74.8%; $P< 0.001$), as well as a trend towards significance for diabetes ($P= 0.086$), dyslipidaemia ($P= 0.078$) and cigarette smoking ($P= 0.082$). Conversely, there were no significant differences between the 51-60 inclusive and ≥ 61 age group for the presence of at least one risk factor (97.5% versus 97.2%), heart failure (10% versus 9.8%), diabetes (30% versus 29.3%) and dyslipidaemia (35% versus 42%).

Mechanisms

Cryptogenic stroke was the most common mechanism in the youngest (46.7%) and intermediate (27.5%) age groups. The 51-60 inclusive age group also had an equally high proportion of cardioembolic strokes (27.5%), which was the main mechanism of stroke in the oldest age group (43.3%). The prevalence of other causes of stroke was low in all age groups (Table 3). Statistically significant differences were present between the

youngest and oldest age groups for cryptogenic (46.7% versus 18.1%; $P=0.001$), cardioembolic (23.3% versus 43.3%; $P=0.035$) and other causes (10% versus 1.9%; $P=0.033$), but absent for large (6.7% versus 18.7%) and small vessel disease (20% versus 18.07%). In contrast, there were no significant differences between the 51-60 inclusive and ≥ 61 age groups for all of the identified mechanisms.

One patient each in the 18-50 inclusive and 51-60 inclusive groups had carotid artery dissection. One patient in the youngest group had stroke attributed to thrombophilia. Apart from two cases of infective endocarditis and one case of patent foramen ovale (PFO) in the ≤ 50 population, the remaining cardioembolic strokes were from atrial fibrillation in patients ≤ 60 years (Table 4). Of the ischaemic strokes in the 18-50 inclusive group, only 13.3% were truly cryptogenic, with 20% having incomplete investigations and 13.3% qualifying the criteria for ESUS.

Table 1: Demographic data

Table 2: Traditional vascular risk factors of ischaemic stroke

Figure 1: Graphical representation of prevalence of risk factors by age

Figure 2: Prevalence of at least one risk factor for ischaemic stroke.

Table 3: Causes/mechanisms of ischaemic stroke by age group

Table 4: Sub-analysis of ‘other’ and ‘cryptogenic strokes’ in those under 60

Discussion

The findings of our study suggest that 50 years is an appropriate upper age limit for defining young strokes. Our younger patients, aged 18-50 years inclusive, have significantly lower prevalence of traditional risk factors compared to the rest of the population, although these rates are still substantial. Furthermore, the youngest group differ significantly from the oldest group in terms of the mechanisms of stroke, whilst the intermediate and oldest groups are again similar. This suggests that in younger stroke patients 18-50 years inclusive, detailed investigation is required to identify less common risk factors and enable adequate secondary prevention. Conversely, in those aged 51-60 inclusive, the similarity to the ≥ 61 age group suggests that unnecessary and expensive investigations might not be required.

Whilst many studies recognise the lack of an agreed definition for young stroke, an aged based study is rare in the literature. Similarly, although it is known that the prevalence of ischaemic stroke is significantly higher in regional Australia compared to urban centers,¹² there is little published data on the prevalence and characteristics of ischaemic stroke in regional Australia. As a major regional health facility in Australia, our hospital affords us a snapshot of age distribution and risk factor profile of ischaemic stroke in non-metropolitan areas.

When young strokes are considered as 50 years and under, our prevalence is 7.7%; however, on extending the age limit to 60 years, our prevalence increases to 17.9%. Most studies of young ischaemic strokes describe similar variability, with a prevalence between 5-15%. The main reason for this is the variable definition of young stroke that is used.^{5,13,14} A clear definition of young stroke is therefore needed to guide epidemiological research, investigation and management. In keeping with other published data, we found that men tend to outnumber women in the ischaemic stroke population, regardless of age.^{5,14}

There were six major risk factors assessed amongst our patients: hypertension, past or present cigarette smoking, dyslipidaemia, diabetes, ischaemic heart disease and heart failure. The

high prevalence of these vascular risk factors in all age groups is an observation in our sample of patients but we are unable to comment on their attributable risks given the nature of the study. However, our findings are consistent with the INTERSTROKE study, which suggested that ten modifiable risk factors account for 90% of the population-attributable risk of all strokes independent of age, ethnicity, and region of the world. The risk factors assessed in the INTERSTROKE study were hypertension, smoking, diabetes mellitus, physical activity, psychosocial factors, abdominal obesity, alcohol, cardiac causes, and apolipoproteins.¹⁵

The most frequent risk factors in our ≤ 50 group were past or present cigarette smoking (60%), hypertension (36.7%), dyslipidaemia (23.3%) and diabetes (13.3%). This is similar to the Helsinki study that identified smoking (44%), hypertension (39%) and diabetes (10.3%) as common risk factors in their population of ischaemic stroke patients aged 18-49 years inclusive.¹⁶ The Fabry study also found that smoking (55%), hypertension (46.6%) and diabetes (10.3%) were the most common risk factors in their ischaemic stroke and transient ischaemic attack patients aged 18-55 years inclusive.¹⁷ Whilst diabetes was our fourth most common risk factor, our prevalence was higher than what was described in the Helsinki and Fabry studies.

The prevalence of risk factors in our study varied based on the age group. Whilst the intermediate and older age group demonstrated several similar risk factor profiles, there were several significant differences between the youngest and oldest groups. Other researchers have described similar findings, with smoking being most common in younger strokes, and hypertension, diabetes mellitus and ischaemic heart disease being more prevalent in the older population.^{6,18} The Helsinki study likewise demonstrated that risk factors in early midlife begin to resemble that seen in the elderly.¹⁶

The general trend observed in studies of the mechanisms of ischaemic stroke between age groups was reflected in our study, with the youngest and oldest groups having significant differences, as well as non-significant differences between the middle and oldest age groups.^{19,20} Although vascular risk factors were highly prevalent in our youngest group, this did not reflect the frequencies of their associated stroke mechanisms in this group, with low numbers of small vessel and large artery disease. Most studies that included 50 as the cut-off for young stroke reported similar results.^{16,21} Some studies reported higher rates of small vessel disease and large-artery atherosclerosis, but they used 55 years as the upper limit for young stroke.²² These results are similar to the proportion reported in our 51-60 group. The dissociation between the vascular risk factors and

their associated stroke types in the young are likely due to the lack of time for these risk factors to accumulate and clinically manifest as a stroke. The implication of this is that the high prevalence of traditional vascular risk factors is not solely responsible for the stroke in the youngest group. However, the even higher prevalence of vascular risk factors in the oldest group who also have high frequencies of associated stroke mechanisms, suggest that they become more relevant with greater number of years exposed to the risk factors.^{19,20} Whilst the frequency of cryptogenic strokes in the youngest group in our population (46.7%) was higher than that reported in the literature, which ranges from 22-40%,^{16,21-23} true cryptogenic strokes only accounted for 13.3% of the ischaemic strokes, in that group, in our the study.

The most notable difference in the patients 50 years and under, compared to similar published studies, was the low prevalence of other causes of stroke. Important causes of stroke in the young frequently mentioned in the literature were rarely observed amongst our patients. These include thrombophilia, PFO and carotid artery dissection, observed in one patient each or 3.3% respectively in our youngest group. Carotid artery dissection, in particular, is often quoted as one of the commonest causes of young strokes in the developed world, with a prevalence varying from 9.9%-25%.^{5,6,16,21,22} The disparity is likely

explained by the small number of patients 50 years and under in our study. Although several studies have attributed varying proportion of their strokes to PFO and thrombophilia, their role in the development of stroke is not definitively established.^{24,25} The low numbers of PFO and thrombophilia in our population could therefore be due to either true low numbers or incomplete diagnostic workup.

Another marked difference in our population compared to other studies is the high prevalence of cardioembolic strokes in the older group, which accounted for 43.3% of all ischaemic strokes, and low prevalence of cryptogenic stroke (18.1%). Recent data estimate that cardioembolic strokes account for 20-30% and cryptogenic mechanisms are responsible for 30-40% of ischaemic strokes across all ages.²⁶ However, using extended cardiac monitoring, up to 9.2% of cryptogenic strokes can be re-classified as due to atrial fibrillation, a major cause of cardioembolism.²⁶⁻²⁹ We posit that the high number of cardioembolic strokes in our population is due to our routine practice of prolonged inpatient telemetry (72 hours or more) and outpatient Holter monitoring.

According to the 2016 census, the population of Ballarat had less weekly median income, lower educational attain-

ment and employment status compared to Victoria, and Australia in general.³⁰ Our region, which is part of Western Victoria, does have higher rates of risk factors such as obesity, smoking, physical inactivity and hypertension, compared to the Australian average.³¹ It would have been interesting to compare our data on the mechanisms and risk factors to a metropolitan cohort but there is paucity of published data.

Our study is the first to look at risk factors and mechanisms of stroke, stratified by age, in regional Australia. The data that we analyzed consisted of the information our hospital contributed to the Australian Stroke Registry. We assessed all patients using the same predefined criteria, reducing the variation that may have occurred particularly in the mechanisms of stroke, which are subjective.

There are several limitations. The small sample size affected the etiological stroke subtypes. This likely reduced the statistical power of our observations. Our dataset consistently included only six risk factors and the missing data might have provided a clearer picture of the risk factors in our population. The retrospective study design also has the inherent limitation of poorly recorded data, **inability to explore key demographic factors in regional centres such as socioeconomic status and**

ethnicity, as well as an inability to confidently assign causation. **Future prospective studies would benefit from analysing these demographic data, particularly regional centre data matched to metropolitan areas.**

Summary

In conclusion, the similarities in risk factor profiles and mechanisms of stroke between the intermediate and older groups and differences between the youngest and oldest groups' supports the consideration of 50 years as the cut-off for defining young strokes. However, further studies of larger patient numbers are required to establish this association. The present study also highlights the high prevalence of vascular risk factors in all age groups, and for that reason, we emphasize the need for strict risk factor control for the prevention of ischaemic strokes.

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