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Using measures of sarcopenia to predict recurrent cerebrovascular events in stroke and TIA patients

Frances A Kirkham, a Philip Rankin, a Eva Bunting, a Khalid Ali, a and Rajkumar Chakravarthi, a, b

Purpose: Sarcopenia is associated with poor outcomes, and evidence suggests an inverse relationship between skeletal muscle mass and cardiovascular risk. Sarcopenia has been studied after stroke, but its value as a risk factor for stroke has not been examined. This prospective cohort study measured sarcopenia in stroke/TIA patients at baseline to explore its role in predicting recurrent events.

Method: The Arterial Stiffness In Lacunar Stroke and TIA (ASIST) study included 96 patients with TIA/lacunar stroke, of which 82 patients (mean age 71.2 ± 10.8 years) had bioimpedance analysis to assess body composition. Skeletal Mass Index (SMI) was calculated and parameters of sarcopenia assessed using Davison (1) and Janssen (2) criteria. Recurrent cerebrovascular events were monitored over 5 years.

Results: Eighteen patients had recurrent events. On independent samples t test there were significantly more participants with sarcopenia in the recurrent events group (89% vs 56%, p < 0.001) using Davison (1) criteria, as well as lower mean SMI, significantly more participants with diabetes and higher arterial stiffness. On binary logistic regression, the only significant predictors of recurrent events were SMI (p = 0.036, hazard ratio = 0.414, 95% confidence interval 0.195-0.948) and diabetes (p = 0.004, hazard ratio = 9.06, 95% confidence interval 2.009-40.860) when corrected for age, sex and cardiovascular risk factors. Using Janssen (2) criteria in the regression, severe sarcopenia was a significant predictor of recurrent events (p = 0.028). There was a significant association between sarcopenia and recurrent events on Chi square based on Davison (p = 0.02) and Janssen (p = 0.034) definitions.

Conclusions: The presence of baseline sarcopenia in stroke and TIA patients is an independent predictor of recurrent events.

Keywords: Sarcopenia—Skeletal mass index—Stroke—Transient ischaemic attack

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“...now doth time waste me”

~ Richard II (Act 5 Scene 5), William Shakespeare

Introduction

Sarcopenia, understood as the progressive loss of skeletal muscle with age, has assumed greater importance in Comprehensive Geriatric Assessment (CGA) in recent years due to its association with chronic conditions and mortality. As a relatively recent concept, definitions and cohort-specific guidance on cut-offs for determining sarcopenia are still evolving and it was only recognised in the International Classification of Disease in 2016. In relation to stroke patients, sarcopenia is predominantly recognised after stroke, with a pooled prevalence of 42% in survivors. Both pre-stroke sarcopenia and the
development of sarcopenia in the early months following a stroke are associated with worse functional outcomes. However, the relationship of sarcopenia to recurrent stroke has yet to be explored.

The presence of sarcopenia is known to increase the risk of cardiovascular disease and mortality, independent of other known risk factors. One Japanese study found a link between sarcopenia (defined by questionnaire) and increased stroke severity, however, there is a paucity of evidence examining the relationship of sarcopenia to recurrent events. Indeed, where much research focuses on risk factors for initial stroke events, much less has centred on risk of recurrence and that which exists often centres on epidemiology and rates of recurrence, or the impact of specific interventions such as drugs. We were not able to find any studies which examined measures of body composition in relation to the risk of stroke recurrence. With approximately 30% of stroke survivors experiencing a recurrence, the ability to identify risk factors predictive of further events could be hugely beneficial to clinicians and patients. Targeting sarcopenia as a potentially modifiable risk factor could reduce the incidence of stroke.

This prospective cohort study recruited patients with lacunar stroke or TIA to look at whether the presence of sarcopenia at baseline increased the risk of recurrent stroke or TIA, independent of other risk factors.

Methods

Participants: The Arterial Stiffness in Lacunar Stroke and Transient Ischaemic Attack (ASIST) study (IRAS ID: 144157) recruited 96 patients with TIA/lacunar stroke from inpatient wards and TIA clinics in Brighton, East Sussex. Participants were over 40 years of age and had confirmed diagnosis of TIA or lacunar stroke. Participants attended a study visit where the below measures were taken within 14 days of stroke or TIA onset. Exclusion criteria: current treatment for malignancy or inability to give informed consent.

Information collected: past medical history and information on recent stroke/TIA, clinical examination, blood pressure taken lying and standing, BMI, measures of arterial stiffness, blood test for inflammatory markers. Participants also undertook 24-hour ambulatory blood pressure measurement. Of the 96 recruited, 82 participants had measurements of body composition via bioimpedance analysis (TANITA BC-418) to assess sarcopenia. Patients were followed up over 5 years for recurrent events, defined as confirmed TIA or stroke diagnosed by a stroke physician or on brain imaging.

Measures of sarcopenia: Skeletal mass index (SMI) was calculated using the equation: SMI=Absolute skeletal mass/height in metres squared. Absolute SM (kg) = [0.401 \times (height²/resistance) + (3.825 \times gender) – (0.071 \times age) + 5.102] – height in cm; resistance in ohms; for sex, men=1, women=0; and age in years. Thresholds based on Janssen criteria were applied to divide participants into non-sarcopenic, moderate sarcopenia and severe sarcopenia groups.

SMI from appendicular free fat mass (FFM/height in metres squared) was calculated and criteria determined by Davison giving a binary categorisation of participants as sarcopenic or non-sarcopenic.

Statistical analysis

Data are presented as mean ± SD. Statistical analysis was performed using SPSS Version 26.0.0.0 with p value less than 0.05 considered statistically significant. Distribution of continuous variables was assessed for normality to determine appropriate statistical tests. Participants were divided into two groups based on whether or not they experienced a recurrent event. Independent samples t test was used to compare levels of cardiovascular risk factors and measures of sarcopenia between groups. Sarcopenic groups were compared using independent t test for binary categories (Davison criteria) or ANOVA for 3 categories (Janssen criteria). Binary logistic regression was used to calculate hazard ratios with 95% confidence intervals for having a recurrent event to assess measures of sarcopenia as predictors of recurrence alongside known cardiovascular risk factors. Cardiovascular risk factors included in the model were: age, sex, cardio-ankle vascular index, history of previous stroke or TIA, previous diagnosis of hypertension or diabetes, history of smoking, average resting systolic blood pressure. Pearson Chi square was used to assess the association between sarcopenic groups and groups who experienced recurrent events.

Results

Of the original 96 participants recruited, the 82 with measures of body composition were included in analysis, with mean age 71.2 (±10.8) years. During follow up over 5 years, 18 patients had recurrent events. One participant died in the follow up period after having two recurrent cerebrovascular events in that time. Follow up was completed by telephone, patient diary or electronic health records on all participants. The overall prevalence of sarcopenia in the cohort on Davison criteria was 53.8% among females and 71.4% among males. The prevalence of moderate sarcopenia on Janssen criteria was 42.3% among females and 42.8% among males, while the prevalence of severe sarcopenia was 30.7% among females and 44.6% among males (Fig. 1).

Independent samples t test was used to compare the group with further events to the group without further events (Table 1). The group with recurrent events had lower mean SMI (7.41 vs 8.12, p=0.087) but this did not quite reach statistical significance. The recurrent event group had significantly more participants with a history of diabetes, higher arterial stiffness on cardio-ankle.
Fig. 1. Comparison of levels of sarcopenia between males and females on Janssen and Davison criteria

Table 1. Comparison between participant groups on independent samples t test — groups determined by presence or absence of further events

<table>
<thead>
<tr>
<th>Variable</th>
<th>No further event</th>
<th>Further event</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.7</td>
<td>73.2</td>
<td>0.388</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>69:31</td>
<td>67:33</td>
<td>0.869</td>
</tr>
<tr>
<td>Cardio-ankle vascular index*</td>
<td>9.5</td>
<td>10.3</td>
<td>0.042*</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>17</td>
<td>28</td>
<td>0.323</td>
</tr>
<tr>
<td>Previous TIA (%)</td>
<td>20</td>
<td>28</td>
<td>0.505</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>48</td>
<td>44</td>
<td>0.768</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>14</td>
<td>50</td>
<td>0.011*</td>
</tr>
<tr>
<td>Average systolic blood pressure (mmHg)</td>
<td>145.3</td>
<td>145.9</td>
<td>0.924</td>
</tr>
<tr>
<td>Skeletal mass index</td>
<td>8.12</td>
<td>7.41</td>
<td>0.087</td>
</tr>
<tr>
<td>Sarcopenia (based on Davisson et al) (%)**</td>
<td>59</td>
<td>89</td>
<td>0.004***</td>
</tr>
</tbody>
</table>

*p < 0.05
**p < 0.01
vascular index, and there was a significantly higher percentage with sarcopenia using Davison criteria (89% vs 56%, p=0.004). There was no significant difference in age between groups. Independent t test was used to compare the non-sarcopenic and sarcopenic groups on Davison criteria (Table 2). There were significant differences in age, arterial stiffness and number of recurrent events (30% of sarcopenic participants had a recurrent event compared to 7% of non-sarcopenic, p=0.006). Additionally, the sarcopenic group had a shorter mean time to event recurrence (mean days to recurrence 552.0 days compared to 797.5 days in the non-sarcopenic group) although this did not reach significance due to the relatively small number (n=18) of recurrent events. ANOVA was used to assess differences between sarcopenic groups (non-sarcopenic, moderate sarcopenia and severe sarcopenia on Janssen criteria). The only significant differences were age (p=0.03) and number of recurrent events (p=0.031) between sarcopenic groups.

Fig. 2 demonstrates the increase in recurrent events with increasing levels of sarcopenia on Janssen criteria. On binary logistic regression (Table 3), SMI (hazard ratio=0.414, 95% confidence interval 0.195-0.948, p=0.036) and the presence of diabetes (hazard ratio=9.06, 95% confidence interval 2.009-40.860, p=0.004) were the only significant factors in predicting recurrent events when corrected for age, sex and cardiovascular risk factors. When Janssen criteria for defining level of sarcopenia as normal, moderate or severe was included in the model, severe sarcopenia was a significant predictor of recurrent events (p=0.028). There was a significant association between the presence of sarcopenia and recurrent events.

Table 2. Comparison between sarcopenic groups on independent samples t test — groups determined as sarcopenic or non-sarcopenic using Davison criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-sarcopenic</th>
<th>Sarcopenic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>67.71</td>
<td>73.04</td>
<td>0.033*</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>57:43</td>
<td>74:26</td>
<td>0.139</td>
</tr>
<tr>
<td>Cardio-ankle vascular index**</td>
<td>9.00</td>
<td>10.03</td>
<td>0.004**</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>14</td>
<td>22</td>
<td>0.396</td>
</tr>
<tr>
<td>Previous TIA (%)</td>
<td>18</td>
<td>24</td>
<td>0.525</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>57</td>
<td>43</td>
<td>0.216</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>21</td>
<td>22</td>
<td>0.935</td>
</tr>
<tr>
<td>Average systolic blood pressure (mmHg)</td>
<td>149.5</td>
<td>143.5</td>
<td>0.201</td>
</tr>
<tr>
<td>High sensitivity CRP (µg/ml)</td>
<td>2.41</td>
<td>3.97</td>
<td>0.134</td>
</tr>
<tr>
<td>Recurrent event**</td>
<td>7</td>
<td>30</td>
<td>0.006**</td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.01

Fig. 2. Bar graph comparing number of participants with a further event between sarcopenic groups (based on Janssen criteria)
Discussion

This study found that the presence of sarcopenia on BIA body composition measurement in stroke and TIA patients at baseline was an independent predictor of event recurrence, regardless of which of the two sets of criteria for defining sarcopenia was used.

Risk factors for stroke recurrence

Reducing potentially modifiable risk factors is a vital component of secondary prevention in stroke and TIA patients. Previous studies have demonstrated that optimising risk factors can reduce stroke recurrence, including blood pressure management\(^{12}\). However, some factors associated with first stroke have not been established as specifically increasing the risk of stroke recurrence, for example age\(^{13}\), while there is doubt about the benefits of secondary prevention with some treatments such as statins in older patient groups\(^{14}\).

In terms of body composition, studies have demonstrated a reduced risk of stroke recurrence for obese patients\(^{15}\). Although obesity and sarcopenia can co-exist, the inverse relationship between body mass and stroke recurrence aligns with our findings that sarcopenic patients have increased rates of recurrent stroke compared to non-sarcopenic patients and consolidates the evidence suggesting that body composition is an important predictor of future stroke events in this patient group. Potential mechanisms for this association have been purported, including oxidative stress, declining sex hormones and insulin resistance\(^{16-18}\). Our study did find a marginal increase in high sensitivity CRP in sarcopenic participants, possibly complementing the notion that inflammation plays a key role in the pathogenesis of both sarcopenia and cerebrovascular disease. However, the clinical relevance of this small difference in biomarkers is uncertain. Intervention studies have shown limited benefits of a variety of possible treatments for sarcopenia, with some studies showing benefit from resistance training and amino acid supplementation\(^{19}\). More research is needed into potential treatments and their ability to improve outcomes such as cardiovascular events and stroke in sarcopenic groups.

Sarcopenia as a predictor of cerebro- and cardiovascular disease

Our study showed that the presence of sarcopenia at baseline was a significant predictor of stroke recurrence in a UK cohort of older stroke patients. This remained significant when corrected for age and other cardiovascular risk factors to reduce the risk that age or cardiovascular health were acting as confounders in the relationship between sarcopenia and stroke recurrence. Until now, few studies have specifically investigated the relationship of sarcopenia to stroke. Nozoe et al used the SARC-F questionnaire to identify sarcopenia, finding an association with increased stroke severity\(^{10}\). This would reinforce our suggestion that sarcopenia is an important factor in cerebrovascular risk for older people. However, they did not measure muscle mass and they defined stroke severity in binary categories as mild or moderate-severe based on NIHSS score rather than using continuous variables, thus limiting their analysis. Hanatani et al used measures of muscle function (hand-grip strength and calf circumference) to create a sarcopenia score that was able to predict cardiovascular events (including stroke) in patients with abdominal obesity\(^{20}\). Another Korean study showed that being underweight was associated with increased incidence of cardiovascular disease and mortality, although they did not measure body composition and therefore could not determine levels of sarcopenia\(^{21}\). Meanwhile, another cross-sectional Korean study of patients who had not had overt clinical stroke used BIA to divide participants into ‘higher’ and ‘lower’ skeletal muscle mass (SMM) groups, finding that the lower SMM group were more likely to have white matter changes and silent

on Chi square based on Davison (p=0.02) and Janssen (p=0.034) definitions.

### Table 3. Binary logistic regression with the presence or absence of a further event as the dependent factor

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.949</td>
<td>0.874 - 1.031</td>
<td>0.218</td>
</tr>
<tr>
<td>Sex</td>
<td>3.043</td>
<td>0.222 - 41.643</td>
<td>0.404</td>
</tr>
<tr>
<td>Cardio-ankle vascular index</td>
<td>1.577</td>
<td>0.813 - 3.060</td>
<td>0.178</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2.034</td>
<td>0.402 - 10.278</td>
<td>0.390</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>1.354</td>
<td>0.308 - 5.946</td>
<td>0.688</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.952</td>
<td>0.199 - 4.553</td>
<td>0.950</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>9.060</td>
<td>2.009 - 40.860</td>
<td>0.004*</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.255</td>
<td>0.308 - 5.107</td>
<td>0.751</td>
</tr>
<tr>
<td>Average systolic blood pressure</td>
<td>1.004</td>
<td>0.969 - 1.039</td>
<td>0.840</td>
</tr>
<tr>
<td>Skeletal mass index (SMI)</td>
<td>0.430</td>
<td>0.195 - 0.948</td>
<td>0.036*</td>
</tr>
</tbody>
</table>

\(^*p<0.05\)
infarcts on brain imaging. Similarly, intracranial arterial stiffness has been shown to be associated with reduced SMI as measured by BIA.

There may be some evidence to suggest a differential relationship between sarcopenia and cardiovascular disease in men compared to women, based on analysis of over 7000 participants from the Korean NHANES study. Due to the small sample, we were not able to perform subgroup analysis by sex in our cohort, but the inclusion of sex in the regression model did not suggest this was a significant factor. Further studies are warranted to elucidate the role of sex in mediating this relationship.

**Prevalence and definitions of sarcopenia**

In this small cohort, we found a high prevalence of sarcopenia (between 53.8% and 87.4% depending on threshold criteria used), much higher than the 12.5% found in the BELFRAIL study of the oldest old in Belgium. However, their definition included both muscle mass and function, with much higher prevalence when broken down based on one of these measures alone. It is also clear that the threshold criteria used generates widely varying estimates of prevalence. As expected, there was a significant difference in age between sarcopenic and non-sarcopenic groups. However, there was no difference in age between the groups with and without recurrent events and our findings were corrected for age in regression analyses. However, given the small sample size, it must be recognised that the relationship between age and sarcopenia may interact with the increased risk of stroke with age, potentially providing a more refined way of measuring the impact of age on cerebrovascular disease.

We also found a higher prevalence of sarcopenia among men than women, although there are no specific studies assessing rates of sarcopenia across the sexes in stroke patients for comparison. Our findings would fit with the results of Park et al, suggesting the increased risk of stroke in sarcopenic males contrasted with females. Similarly, a Swedish study found some evidence that having mid-life cardiovascular disease amongst other factors was associated with reduced grip-strength in males in later life, but not in females. However, with our small cohort, the conclusions we can draw related to overall prevalence are limited. Ideally, large-scale national studies must be undertaken in both healthy and multimorbidity cohorts to generate reliable threshold criteria in order to enable comparison.

**Limitations**

This is a relatively small cohort study which may limit the generalisability of findings, however with a high recurrent event rate, we believe it is therefore comparable to many larger studies. The 2018 European Working Group paper on sarcopenia recommends using measures of muscle strength in the first instance when determining sarcopenia in clinical practice. We were only able to perform grip strength measurements on a small subgroup of our cohort which precluded using this data for analysis. However, multiple large international studies of sarcopenia have used muscle quantity and BIA is recommended by the EWGSOP in detecting reduced muscle mass. Meanwhile a study comparing all major diagnostic tools for defining sarcopenia showed they had similar value in predicting incident physical limitation and mortality. Newer methods for detecting sarcopenia are also being developed, including lower limb SMI and muscle ultrasound, which may offer further options in the future. Larger studies looking at both muscle mass and function are required to further explore the role of measures of sarcopenia in predicting stroke recurrence. Our patients were assessed between 1-14 days following acute stroke thus it is possible that their muscle mass may have begun to reduce since stroke onset thus absolute levels of muscle mass may not entirely reflect pre-stroke level. However, as all participants were similarly assessed, the comparison between the group experiencing further events and the group that did not experience further events should not have been affected as any difference would apply to both groups. This factor may partly explain the high prevalence of sarcopenia in the cohort. Additionally, further work in larger studies would be warranted to investigate the impact of sarcopenia on stroke and stroke recurrence in different age groups, as the small sample size limited our ability to perform subgroup analyses on the basis of age. Data on stroke severity was not collected with initial and recurrent events including both TIAs and lacunar strokes. In future work, it will be important to consider how the severity of initial event may impact development of sarcopenia and, therefore, potentially risk of recurrent events.

**Conclusion**

As a prospective cohort study, we were able to find an association between sarcopenia in TIA/stroke patients and recurrent cerebrovascular events independent of other cardiovascular risk factors. This demonstrates the importance of sarcopenia as a risk factor for cerebrovascular disease and enhances the growing body of evidence on the adverse outcomes associated with reduced skeletal muscle mass. More work is needed on sarcopenia, both in developing cohort-specific cut-offs for diagnosis and in estimating its impact on outcomes. However, our study suggests that non-invasive measurement of body composition may act as a potential tool in identifying stroke patients at high risk of recurrence. Further large-scale studies must look at the possibility of intervention in this group of patients to consider whether prevention or treatment of sarcopenia could reduce this risk.
Author's roles

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Declarations of Competing Interest

None

We certify that this work is A) novel. We believe this is the first study to investigate the relationship of baseline to sarcopenia to recurrent events in stroke and TIA patients.

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Supplementary materials


References


