Effect of muscle alteration on long term survival in ischemic stroke patients

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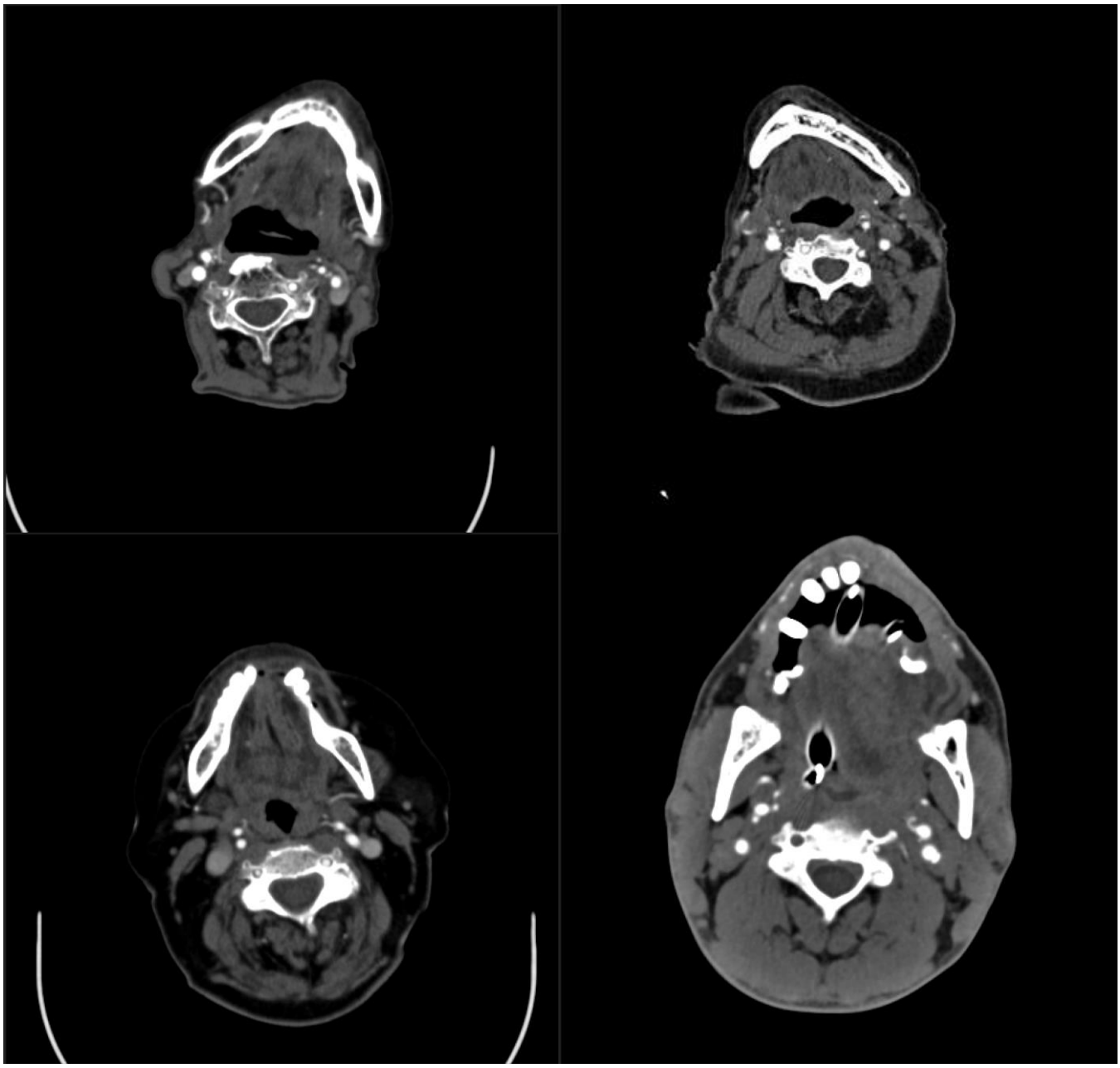
Bachelor thesis Medical Imaging and Radiation Therapy



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Preface

This research is written as a bachelor thesis of the study Medical Imaging and Radiation Therapy at Hanze University of Applied Sciences. The topic of the thesis is “Effect of muscle alteration on long term survival in ischemic stroke patients. The aim of the study is to uncover additional prognostic markers to improve and tailor treatment for ischemic stroke patients.

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Abstract

Patients who had an ischemic stroke have a poor life expectancy. To improve prognosis in ischemic stroke it is needed to discover additional prognostic biomarkers**.** This study investigated whether sarcopenia or myosteatosis affected long-term survival in ischemic stroke patients. The secondary aim was to investigate the neurological outcome of patients with and without myosteatosis.

This was a single-centre retrospective cohort study of 193 patients with a confirmed large vessel occlusion who had a computed-tomography scan. Skeletal muscle measurements were done at the third cervical vertebra. Optimal stratification was used to determine gender-specific cut-off points for sarcopenia and myosteatosis. Cox proportional hazards model was used to determine the effect of sarcopenia and myosteatosis on survival. Ordinal regression was used to determine neurological outcome using the modified Rankin Scale.

Myosteatosis was associated with age, INR level, thrombocyte count, creatinine level, CRP level, glucose level, myocardial infarction, peripheral artery disease, diabetes, hypertension, atrial fibrillation, hypercholesterolemia, and sarcopenia. Sarcopenia (HR 0.796, CI 0.455-1.393; *p*=0.424) did not display an effect on survival in the univariable analysis. Myosteatosis (HR 0.554, CI 0.335-0.916; *p*=0.021) had a significant influence on survival in the univariable analysis. When adjusted for other prognostic markers, myosteatosis (HR 0,598, CI 0.495-1.499; *p*=0.598) did not show effect on survival. No difference in neurological outcome was seen between having myosteatosis and not having myosteatosis in the ordinal regression.

Sarcopenia and myosteatosis are not associated with overall survival and neurological outcome in ischemic stroke patients.

Samenvatting

Patiënten die een ischemische beroerte hebben gehad, hebben vaak een slechte levensverwachting. Voor het bevorderen van de prognose na een ischemische beroerte is het nodig om prognostische biomarkers te onderzoeken. In deze studie werd onderzocht of sarcopenie en myosteatosis invloed hebben op de lange termijn overleving bij patiënten die een ischemische beroerte hebben gehad. De secundaire uitkomst van deze studie was het onderzoeken of myosteatosis invloed heeft op neurologische uitkomst.

Dit was een retrospectieve cohortstudie van 193 patiënten met een gediagnostiseerde occlusie in een grote craniale slagader, waarvan een computertomografie angiografie scan van de beroerte beschikbaar is. De skeletspier-metingen waren ter hoogte van de derde cervicale wervel uitgevoerd. Optimal stratification was gebruikt om genderspecifieke afkapwaarden voor sarcopenie en myosteatosis te bepalen. Het Cox proportional hazards model werd gebruikt om het effect van sarcopenie en myosteatosis op overleving te bepalen. Neurologische uitkomsten zijn onderzocht met ordinale regressie aan de hand van de modified Rankin Scale.

Myosteatosis werd geassocieerd met leeftijd, INR-waarde, trombocyten aantal, creatine waarde, CRP-waarde, glucosewaarde, myocardinfarct, perifeer vaatlijden, diabetes, hypertensie, atriaal fibrilleren, hypercholesterolemie en sarcopenie. In het univariabele model had myosteatosis (HR 0.554, CI 0.335-0.916; *p*=0.021) significante invloed op overleving, maar sarcopenie (HR 0.796, CI 0.455-1.393; *p*=0.424) niet. Na het corrigeren voor andere prognostische biomarkers had myosteatosis (HR 0,598, CI 0.495-1.499; *p*=0.598) geen invloed op overleving. In de neurologische uitkomsten waren geen verschillen tussen patiënten met of zonder myosteatosis.

Sarcopenie en myosteatosis hadden geen impact op de lange termijn overleving en neurologische uitkomst bij ischemische beroerte patiënten.

Contents

Introduction

A cerebral vascular accident (CVA) is a sudden interruption of the blood flow to the brain or when a blood vessel ruptures in the brain and damages brain tissue. Approximately 42.000 patients suffer from a CVA in the Netherlands annually. Eighty-eight percent of these patients are older than 65 years. In 2017 there were 34.000 patients who suffered an ischemic stroke. One out of three patients who suffered an ischemic stroke, develop heart failure in the first years after the stroke. These patients have a poor life expectancy [1]. The prevalence of stroke is increasing because of higher blood pressure caused by an increase in obesity, lack of healthy nutrients and better survival for coronary heart disease [1]. Expected is that in the period of 2015-2040, prevalence will increase with fifty-four percent [1].

Loss of skeletal muscle mass, commonly referred to as sarcopenia, comes with ageing. As people get older they tend to become less active, hormone levels alter, protein requirements change and motor neurons decrease [2]. These factors all contribute to sarcopenia. Accumulation of intramuscular and intermuscular fat, i.e. myosteatosis, has been described as a strong prognostic marker in peripheral arterial disease, critical limb ischemia and abdominal aortic aneurysm [3][4][5]. Sarcopenia and myosteatosis are likely to co-exist [6].

Within the last four decades, there have been major improvements in outcome after a stroke [7]. With the introduction of aspirin, intensive neuro clinical care, intravenous thrombolysis and endovascular thrombectomy, mortality has decreased with sixty-nine percent for men and sixty-three percent for women [8]. There is however still need for additional biomarkers to predict outcome and tailoring treatment to the individual patient. To further improve outcome, more investigation is needed for different biomarkers. To date, no study has been conducted to determine the effects of sarcopenia and myosteatosis and mortality in stroke patients. If mortality can be predicted using sarcopenia and myosteatosis as markers, it can prove clinically useful by treating patients to counteract the effects of sarcopenia and myosteatosis.

The aim of this research is to determine whether sarcopenia and myosteatosis are predictors for long-term survival in ischemic stroke patients. Using diagnostic images from Computed Tomography scans of patients, sarcopenia and myosteatosis can be determined. The secondary aim is to determine whether patients with or without sarcopenia or myosteatosis have a worse neurological outcome. This will be done using the modified Rankin Scale (mRS).

Theoretical

Ischemic stroke

When an artery is occluded, the brain will not receive oxygen and as a result, neurological function decreases and eventually the cells start to die in 3-4 minutes [9]. When brain cells are without oxygen for more than 10 minutes the repercussions can have severe effects on the brain. The time between stroke and reperfusion determines the neurological outcome and prognosis, which differs per person. This is why fast treatment is important [10]. A large-vessel occlusion is a blockage of the proximal intracranial anterior and posterior circulation.

Diagnosis

Computer tomography (CT) is the primary method to diagnose stroke [10]. The diagnosis exists of neurological examination and three different CT scans, i.e. non-contrast CT (NCCT), CT perfusion (CTP) and CT Angiography (CTA). The NCCT is performed to rule out a haemorrhagic stroke. CTP defines the blood inflow and outflow characteristics of the brains. This is done with a high flow of contrast. Right after the injection, a one-minute scan follows to screen the physiological behaviour of the contrast. The image will get a colour from blue (normal time response) to red (low response). The colour depends on the time of the contrast in and outflow. Ischemic regions will be visible with the CTP. CTP is important for possible treatment, especially for IAT. CTA is the final scan of the brain in arterial phase. The CTA has a high sensitivity to diagnose and localize a thrombus or embolism.

Ischemic stroke has multiple treatment options, which depend on the stroke scale and the clinical status. First, possible treatment at a mild stroke is intravenous thrombolysis (IVT). IVT is a treatment using thrombolytic agents, which can dissolve the blood clot [11]. This can be administered when the NCCT is negative for a haemorrhagic stroke. If IVT was not effective or the stroke is intense, endovascular thrombectomy (EVT), also called Intra Arterial Trombectomia (IAT) is the next step. This usually happens within 6 hours, but still has effect within 24 hours of onset of the stroke. CTP is a good imaging method to define the ischemic brain area that is unable to be treated and recover, called the core. The treatable area is called the penumbra. During IAT, intervention radiologists remove the clot endovascular. This is minimally invasive and the most effective treatment for ischemic stroke for large vessel occlusions in the sphenoidal (M1) and the Sylvian (M2) segment [10].

Neurological outcome

The neurological status will be determined by a neurological disability scale: the modified Rankin Scale (mRS). Neurological examinations happen at the moment of the stroke and after approximately 90 days. The mRS Scale includes six stadia of the disability status of the patient caused by a neurological disease. Where 0 means normal functioning and 6 means death [12].

Myosteatosis

Usually, the muscle stores a small number of lipids into the muscle that is used for energy. Myosteatosis is pathologic fatty accumulation of the skeletal muscle, which consists of intramuscular and intermuscular fat [13]. The muscles store too much lipids, which causes a less dense muscle. When a muscle is less dense, the effectivity of the muscle decreases. Diabetes mellitus, insulin resistance, muscle atrophy and cancer are risk factors for myosteatosis.

Sarcopenia

Sarcopenia is the loss of skeletal muscle fibre and its function. This loss of skeletal muscle mass and function occurs with ageing and is further accelerated by malnutrition and in diseases where increased rates of sarcopenia negatively impact outcome; e.g. in cancer patients [14], liver transplant candidates, cardiovascular disease, and chronic kidney disease [15]. The differences between patients with/without sarcopenia and myosteatosis is shown in figure 1.

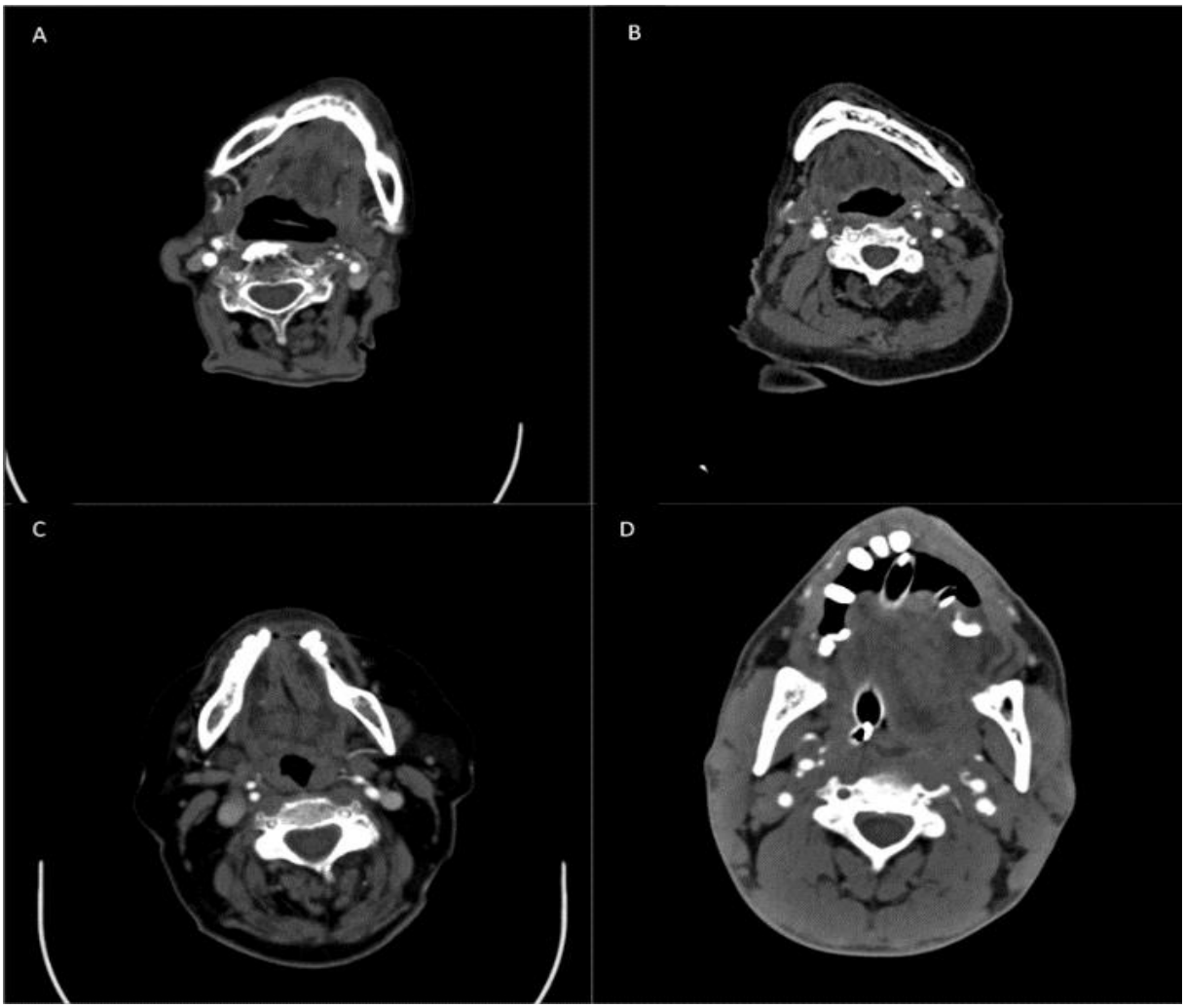

Figure 1: Difference between patients with/without sarcopenia or myosteatosis. A = sarcopenia (muscle area = 24.4 cm²), B = non-sarcopenia (muscle area = 59.8 cm²), C = myosteatosis (Hounsfield units = 22.7), D = non-myosteatosis (Hounsfield units = 70.7)

Prognostic markers

Hypertension is high blood pressure, which is pathologic. Hypertension is a big risk factor for stroke. Hypertension decreases vessel health. Glucose level is the amount of sugar in the blood. The normal value is 4-7.8 mmol/L. A value higher than 7.8 mmol/L can indicate diabetes [16]. C-reactive Protein (CRP) is a protein that binds on dead cells and bacteria, which can indicate inflammation [17]. Normal value is lower than 0.8mg/dL. A value higher than 0.8mg/dL can indicate inflammation. Creatinine levels can be used to determine the kidney-function. By measuring creatinine, the glomerular filtration rate can be determined. Normal value is between 88 mL/min and 137 mL/min [18]. International normalized ratio (INR) is a test that measures how fast blood can form a clot. Usually, a healthy person has an INR level

between 2 and 3 [19]. Hypercholesterolemia is a condition in which a person displays high levels of cholesterol in the blood. Thrombocyte count, also called platelets, are parts in the blood that causes coagulation with vessel injury by creating clots. The normal value is 150.000-400.000 platelets/uL [20]. Peripheral artery disease (PAD) is a disease where plaque, also called atherosclerosis, has built up inside the artery wall [21]. This can cause artery stenosis, therefore limiting the blood flow to body parts. Atrial fibrillation is an irregular heart rhythm as a result of a rapid heart rate [22]. This can be diagnosed with an ECG. Common causes are genetics, hypertension, a bad lifestyle, smoking and other pathologies.

Methods

This was a single-centre retrospective cohort study of patients with a confirmed large vessel occlusion who were treated at the University Medical Centre Groningen (UMCG), Groningen, The Netherlands, between June 2014 and December 2018. The UMCG is a regional comprehensive stroke centre in the Northern region of The Netherlands.

All patients are prospectively registered in a database for clinical follow-up [23]. Included were patients who had an ischemic stroke and diagnostic CT-imaging is available where at least the third cervical vertebra is visible. Patients were excluded if they were aged younger than 18 years or have a history of muscular disease. Patients were also excluded if they missed other prognostic biomarkers needed for the analysis which can be found in the patient demographics. Patient data were extracted from a prospective database that is maintained for quality control purposes. Additional data was gathered from patient electronic medical records. All patients were diagnosed with CT imaging. This exists of a NCCT, CTA, supplemented with CTP since September 2017. When a patient had multiple strokes, only the CT-scan from the first stroke was included and used for the analysis.

This study was approved by the Institutional Review Board of the University Medical Centre Groningen, The Netherlands (METc 2019/382). All the data were stored and analysed anonymously.

Patient demographics

The following patient data were extracted from the moment of the endovascular therapy: INR level, thrombocyte count, creatinine levels, CRP levels, glucose levels. In addition, these prognostic markers were also extracted: mRS, history of myocardial infarction, smoking, peripheral artery disease, diabetes, hypertension, atrial fibrillation and hypercholesterolemia.

Neurological Outcome

The secondary focus of this study was neurological outcome between patients who have myosteatosis and patients who did not display any signs of skeletal muscle deterioration. This was done using the modified Rankin Scale (mRS) determined at the follow-up. Follow-up was approximately 90 days after the stroke. Patients who had an initial mRS score higher than 2, were excluded.

Medical imaging and muscle measurements

CT imaging was performed on a Siemens SOMATOM Definition (AS, Edge, Flash) and Siemens SOMATOM (Force, Sensation) scanner (Siemens Medical, Erlangen, Germany). Slice thickness varied between 0.5mm and 6mm. All scans made with a slice thickness of 0.5mm were scanned in a different hospital. CTA scans were performed with intravenous contrast in the arterial phase. The CTA images were extracted from the Picture Archiving and Communication System (PACS). The measurements were obtained at the level of the third cervical vertebra (C3) on the axial slice where the vertebral foramen is uninterrupted [24]. The measurements consists of the m. sternocleidomastoid, the m. paravertebralis and the m. spinalis, as shown in figure 1. Measurement of these muscles is the most common method found in literature to compute the skeletal muscle index (SMI) using scans from the base of the neck and up [25][26][27]. In-house developed software (SarcoMeas 0.34; UMCG, Groningen, The Netherlands) was used to assess skeletal muscle mass [28]. This software allows for manual delineation of the area of interest with semi-automatic assessment of skeletal muscle area based on tissue attenuation, shown in figure 2. The range

used for defining skeletal muscle is from −29 Hounsfield units (HU) to +150 HU and for adipose tissue −190 HU to−30 HU [27]. Computed skeletal muscle area was normalized to patient height (cm²/cm) to calculate the SMI [29]. Men and women have a difference muscle composition, therefore they were separately analysed [30]. Skeletal muscle area was determined by two observers following training by an experienced musculoskeletal radiologist. After a week of segmenting, all the scans were reanalysed by the same two observers. All steps were also checked by an experienced interventional radiologist.

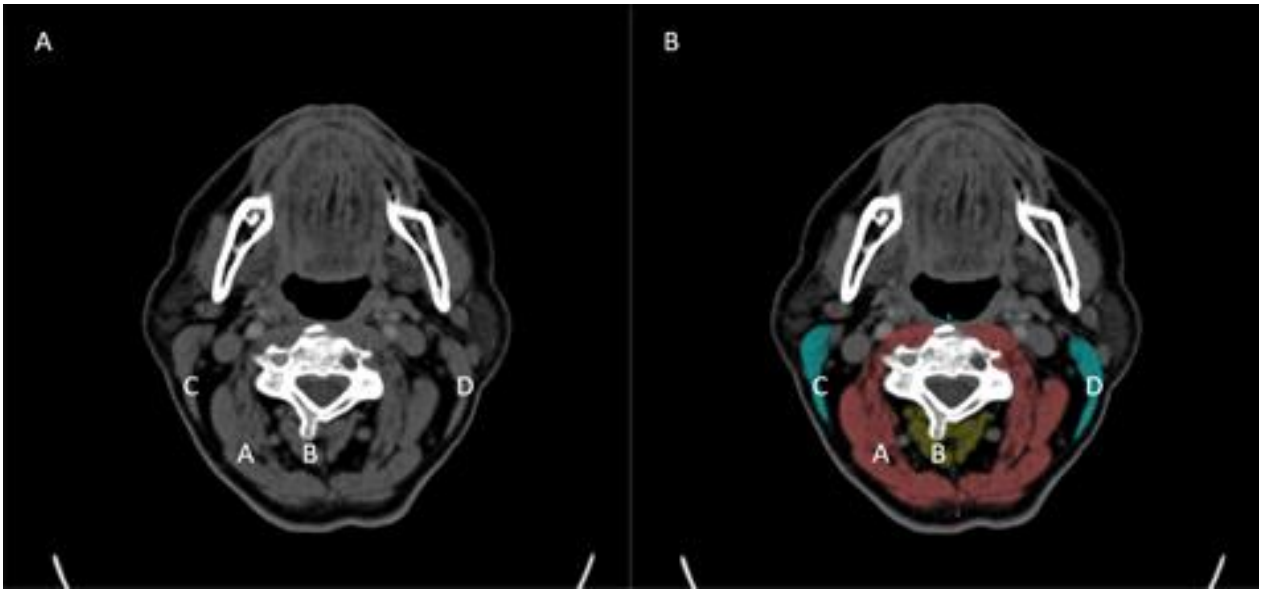

Figure 2: Example of the used delineation software. Image A: Exported CTA slice at the C3 level without delineation. Image B: Exported CTA slice at C3 level with delineation of all the muscles. Muscle A (red): Paravertebral muscle, muscle B (yellow): spinal muscles, muscle C (blue): right sternocleidomastoid muscle, muscle D (blue): left sternocleidomastoid muscle.

Statistics

The normality of the data was determined for all the continuous variables. Associations between the dependent and independent variables were determined using χ^2 test and Student's *t*-test depending on the measurement level. χ^2 test was used with gender, mortality, INR, thrombocyte count, creatinine levels, CRP levels, glucose levels, peripheral artery disease, diabetes, hypertension, atrial fibrillation and hypercholesterolemia. The Student's *t*-test was used with age and total days alive. Using optimal stratification, gender-specific cut-off values for sarcopenia and myosteatosis were determined. Optimal stratification is a method, used in previous literature, utilizing log-rank statistics to discover the most significant *p*-value in a time-to-event outcome [31]. Overall survival was determined using Kaplan-Meier method. Cox proportional-hazards model was used to make a survival model that describes the relationship of all the independent variables with the dependent variable. Ordinal regression was used to determine neurological outcomes using the mRS-scale. The analyses were conducted in IBM SPSS Statistics 23.0.0.3 software (IBM, Armonk, NY, USA). A *p*-value of <0.05 was considered to be statistically significant.

Results

Between June 2014 and May 2018, 373 ischemic stroke patients were treated in UMCG. After exclusion, a total of 193 patients were included. A flowchart of the inclusion/exclusion is included in Figure 5 in Appendix 1. The patient demographics are described in Table 1.

Gender-specific calculated cut-off values for myosteatosis were 36.43 HU for men and 39.08 HU for women. The gender-specific cut-off values calculated with SMI for sarcopenia were 12.93 cm^2/cm for men and 12.97 cm^2/cm for women. A total of 71 patients had myosteatosis and 47 patients had sarcopenia (Table 1). In total there were 20 patients with both sarcopenia and myosteatosis. Mean age of the patients with myosteatosis (75,76; ± 11,894) was higher in comparison for patients without myosteatosis (66,13 ± 13,537; $p < 0.001$). Gender has a significant relationship with myosteatosis, where females have a higher prevalence than males (70.42% vs 29.28%; p=<0.001). Lastly, more patients with myosteatosis showed hypertension from the measurement during the stroke (36.07% vs 57.75%; $p = 0.003$).

Table 1: Patient characteristics with/without myosteatosis. Statistics used: a = χ^2 test, b = Student's t-test

Variables		Myosteatosis		
Total n=193		No (122)	Yes (71)	P-value
Age		66.13 (±13,537)	75.76 (±11,894)	< **0.001**[b]
Gender				< **0.001**[a]
	Male	82 (67.21%)	21 (29.58%)	
	Female	40 (32.79%)	50 (70.42%)	
Death		31 (25.41%)	30 (42.25%)	**<0.015**[a]
Days alive		893 (±568)	736 (±630)	0.770[b]
INR				0.741[a]
	< 1.9	112 (91.80%)	64 (90.14%)	
Normal value	2 - 3	6 (4.92%	3 (4.23%	
	> 3.1	1 (0.81%)	0	
Thrombocyte count				0.453[a]
	< 149	8 (6.56%	5 (7.04%)	
Normal value	150-400	108 (88.52%)	60 (84,51%)	
	> 401	5 (4.10%)	6 (8.54%)	
Creatinine level				0.720[a]
	< 87 mL/min	74 (60.66%)	42 (59.15%)	
Normal value	88 -137	42 (34.43%)	27 (38.03%)	
	> 138	6 (4.92%)	2 (2.82%)	
CRP level				0.846[a]
Normal value	< 0.8 mg/dL	13 (10.66%)	7 (9.86%)	
	> 0.9 mg/dL	108 (88.52%)	64 (90.14%	

Glucose level				0.646[a]
	< 3.9 mmol/L	1 (0.82%)	0	
Normal value	4 - 7.8 mmol/L	85 (69.67%)	46 (64.79%)	
	> 7.9 mmol/L	29 (23.77%)	19 (26.76%)	
Myocardial infarction		7 (5.73%)	8 (11.26%)	0.166[a]
Peripheral artery disease		10 (8.20%)	10 (14.08%	0.203[a]
Diabetes		18 (14.75%)	12 (16.90%)	0.691[a]
Hypertension		44 (36.07%)	41 (57.75%)	**0.003[a]**
Atrial fibrillation		25 (20.49%)	16 (22.54$)	0.738[a]
Hypercholesterolemia		24 (19.67%)	18 (25.35%)	0.409[a]
Sarcopenia		27 (22.13%)	20 (28.17%)	0.346[a]

In Figures 3 and 4, the neurological outcome is shown for men and women. There were 177 patients left after exclusion and 3 patients lacked follow-up mRS information. Figure 3 displays men with myosteatosis have a higher percentage of higher mRS scores. Figure 4 shows women with myosteatosis have lower percentage of low mRS scores, but higher percentage for high mRS scores. In men no significance was found in neurological outcomes between patients with myosteatosis and without myosteatosis. In women, only age (p=0.016) had a significant influence on a worse neurological outcome.

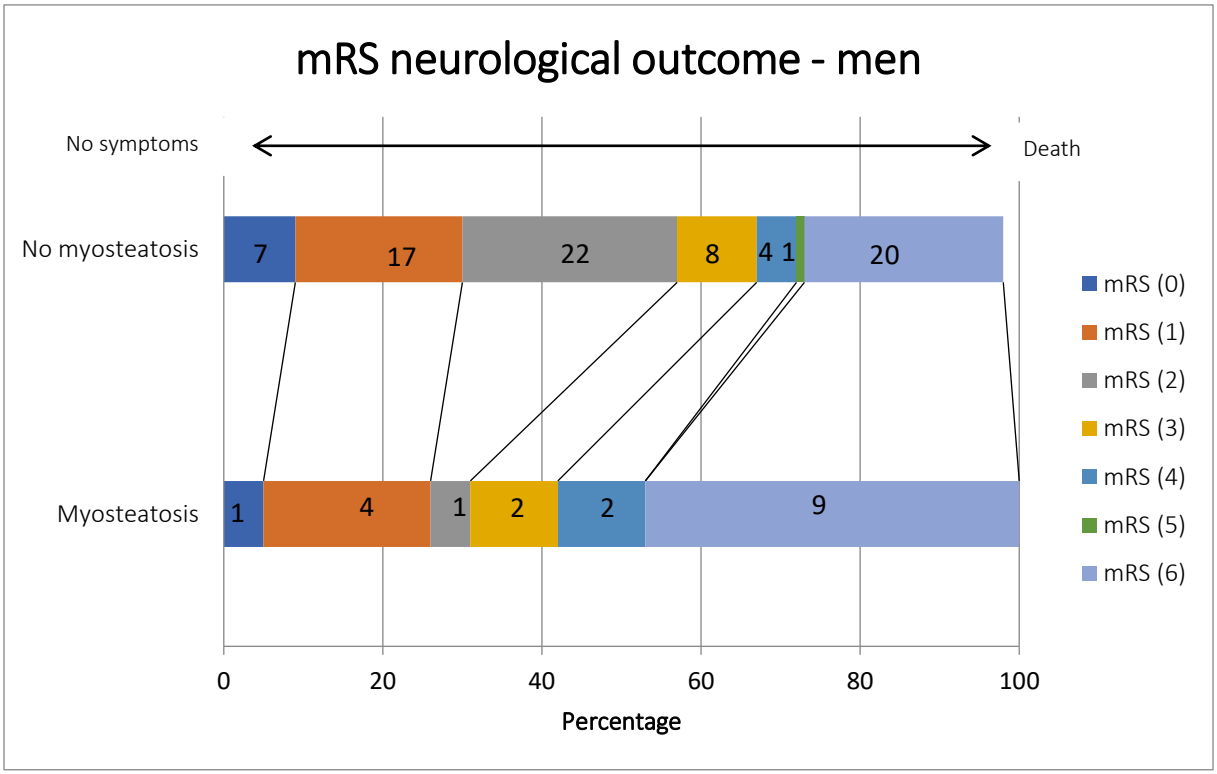

Figure 3: The figure shows the mRS-score with or without myosteatosis for men. In the bars the total number of patients with the corresponding mRS score is shown.

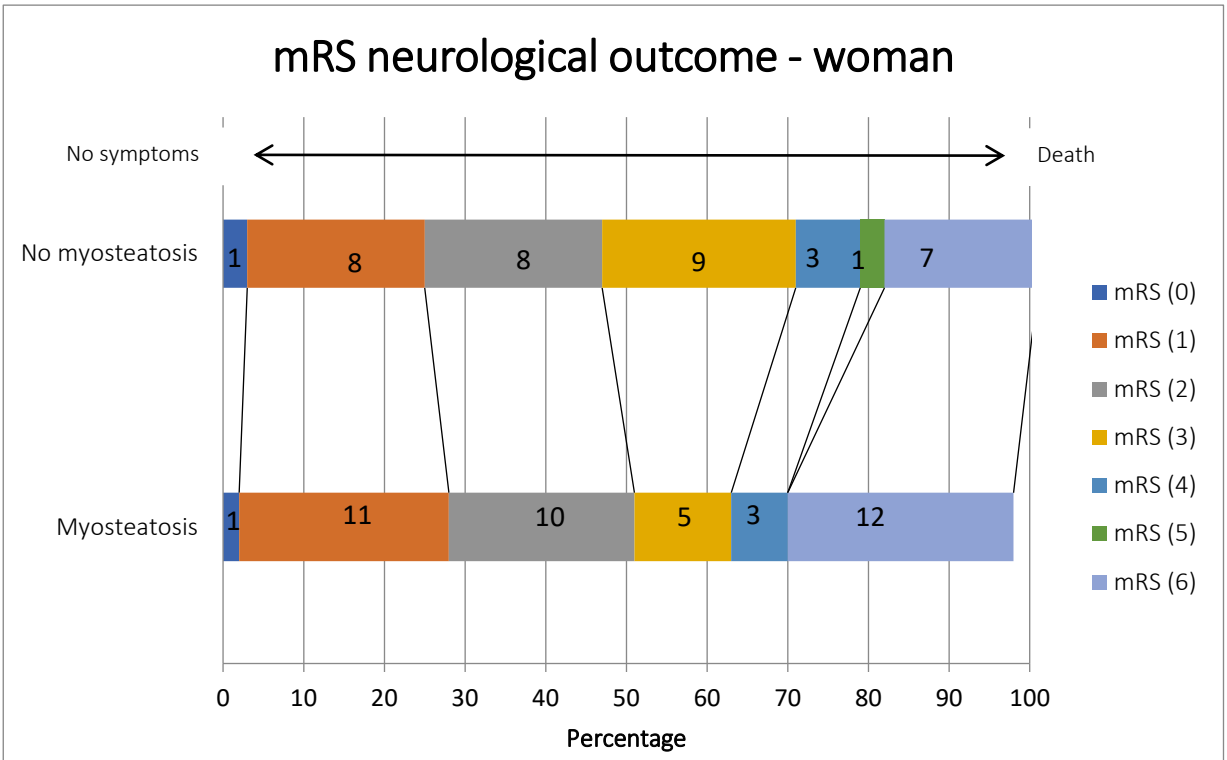

Figure 4: The figure shows the mRS-score with or without myosteatosis for women. In the bars the total number of patients with the corresponding mRS score is shown.

In Figure 6 in Appendix 2, a survival curve where the difference between patients with and without myosteatosis is displayed. Table 2 shows the Cox proportional-hazards model for the overall univariable and multivariable outcome. Median follow-up was 90 days. 58 patients were deceased at 90 days. In total 61 patients died. Overall mortality increased significantly for patients with myosteatosis (42.25%vs 25.41%; $p < 0.015$). In univariable analysis, myosteatosis was found to be a predictor of survival (HR 0.554, CI 0.335-0.916; p=0.021) whereas sarcopenia was not (HR 0.796, CI 0.455-1.393; p=0.424). Other prognostic factors included age, creatinine level, glucose level, peripheral artery disease, diabetes, hypertension and atrial fibrillation are significant in the univariable analysis. Age, myosteatosis, peripheral artery disease, diabetes, atrial fibrillation and hypercholesterolemia were included in the multivariable model. In multivariable analysis myosteatosis was found not to impact survival (HR 0,598, CI 0.495-1.499; p=0.598) was not significant anymore. Age (HR 1.037, CI 1.011-1.064; p=0.005) and atrial fibrillation (HR 0.509, CI 0.287-0.904; p=0.021) independently predicted survival in the current population.

Table 2: Univariable and multivariable Cox proportional-hazards model for overall survival in the whole population.

Variables - overall		Univariable			Multivariable		
		HR	95% CI	P-value	HR	95% CI	P-value
Age		1.052	1.019-1.086	**0.002**	1.037	1.011-1.064	**0.005**
Gender							
	Male	Ref					
	Female	1.213	0.730-2.016	0.455			
Myosteatosis		0.554	0.335-0.916	**0.021**	0.598	0.495-1.499	0.598

INR	< 1.9	0.332	0.037-2.989	0.326			
	2 - 3	Ref		0.212			
	> 3.1	0.208	0.028-1.518	0.121			
Thrombocyte count	< 149	2.053	0.501-8.413	0.318			
	150-400	Ref		0.436			
	> 401	1.236	0.207-7.399	0.816			
Creatinine level	< 87 mL/min	0.467	0.178-1.224	0.121			
	88 -137 mL/min	Ref		0.088			
	> 138 mL/min	0.356	0.138-0.915	**0.032**			
CRP level	< 0.8 mg/dL	Ref					
	> 0.9 mg/dL	0.983	0.423-2.282	0.967			
Glucose level	< 3.9 mmol/L	0.450	0.265-0.765	**0.030**			
	4 - 7.8 mmol/L	Ref		**0.013**			
	> 7.9 mmol/L	0	0-	0.967			
Myocardial infarction		0.747	0.322-1.736	0.498			
Peripheral artery disease		0.486	0.253-0.934	**0.030**	0.603	0.298-1.220	0.160
Diabetes		0.533	0.293-0.968	**0.039**	0.640	0.339-1.208	0.169
Hypertension		0.537	0.323-0.893	**0.016**			
Atrial fibrillation		0.360	0.215-0.603	**<0.001**	0.509	0.287-0.904	**0.021**
Hypercholesterolemia		0.578	0.335-0.996	**0.049**	0.634	0.362-1.111	0.112
Sarcopenia		0.796	0.455-1.393	0.424			

Men and women have a difference between skeletal muscle characteristics and adipose tissue, therefore it was separately analysed. Table 3 shows the univariate and multivariate analysis for men. Myosteatosis (HR 0.407, CI 0.202-0.819; *p*=0.012) shows significance in the univariable analysis. Age (HR 1.052, CI 1.019-1.086; *p*=0.002) shows the most significance paired with the highest hazard ratio. Peripheral artery disease, diabetes, hypertension and atrial fibrillation all show significant influence on survival in males. Sarcopenia does not show any significant influence on survival (HR 0.498, CI 0.255-1.003; *p*=0.149). In the multivariable analysis, age, myosteatosis and atrial fibrillation were used. None of these factors show any significance. Age has the highest hazard ratio, but no significance (HR 1.034, CI 0.998-1.070; *p*=0.064) and myosteatosis was also not significant (HR 0.523, CI 0.248-1.103; *p*=0.089).

Table 3: Univariable and multivariable Cox proportional-hazards model for overall survival in men.

Variables - Men		Univariable			Multivariable		
	Total n = 103	HR	95% CI	P-value			
Age		1.052	1.019-1.086	**0.002**	1.034	0.998-1.070	0.064
Myosteatosis		0.407	0.202-0.819	**0.012**	0.523	0.248-1.103	0.089
INR	< 1.9	0.301	0.031-2.929	0.301			
	2 - 3	Ref		0.275			
	> 3.1	0.208	0.028-1.563	0.127			
Creatinine level	< 87 mL/min	0.484	0.161-1.459	0.198			
	88 -137 mL/min	Ref		0.407			
	> 138 mL/min	0.498	0.166-1.489	0.212			
CRP level	< 0.8 mg/dL	Ref					
	> 7.9 mmol/L	0.524	0.260-1.054	0.070			
Myocardial infarction		0.523	0.217-1.260	0.148			
Peripheral artery disease		0.409	0.196-0.854	**0.017**			
Diabetes		0.424	0.207-0.868	**0.019**			
Hypertension		0.388	0.197-0.765	**0.006**			
Atrial fibrillation		0.427	0.217-0.842	**0.014**	0.568	0.270-1.190	0.136
Hypercholesterolemia		0.506	0.255-1.003	0.051			
Sarcopenia		0.498	0.193-1.285	0.149			

Table 4 shows the univariable and multivariable analysis for women, only age (HR 1.069, CI 1.031-1.107; *p*=<0.001 and atrial fibrillation (HR 0.299, CI 0.135-0.664; p=0.003) is significant in the univariable analysis. Myosteatosis shows no significant influence on survival in women (HR 0.530, CI 0.230-1.218; *p*=0.135). Sarcopenia did not show any significant influence (HR 1.161, CI 0.466-2.891; p=0.749). In the multivariable analysis age, myosteatosis and atrial fibrillation were included. Only age shows significance (HR 1.057, CI 1.018-1.098; *p*=0.004). Myosteatosis (HR 0.982, CI 0.406-2.370; *p*=0.967) shows almost no impact on survival with the multivariable analysis.

Table 4: Univariable and multivariable Cox proportional hazards model for overall survival in women.

Variables - Women		Univariable			Multivariable		
	Total n = 90	HR	95% CI	P-value	HR	95% CI	P-value
Age		1.069	1.031-1.107	**<0.001**	1.057	1.018-1.098	**0.004**
Myosteatosis		0.530	0.230-1.218	0.135	0.982	0.406-2.370	0.967
Thrombocyte count	< 149	0.133	0.315-0.5642	0.696			
	150-400	Ref		0.926			
	> 401	0		0.980			

Creatinine level	< 87 mL/min	0.267	0.033-2.167	0.217			
	88 -137 mL/min	Ref		0.074			
	> 138 mL/min	0.140	0.018-1.087	0.060			
CRP level	< 0.8 mg/dL	Ref					
	> 0.9 mg/dL	0.337	0.046-2.486	0.286			
Peripheral artery disease		1.187	01.161-8.759	0.867			
Diabetes		0.942	0.283-3.137	0.922			
Hypertension		0.793	0.367-1.715	0.555			
Atrial fibrillation		0.299	0.135-0.664	**0.003**	0.492	0.206-1.173	0.109
Hypercholesterolemia		0.780	0.294-2.069	0.618			
Sarcopenia		1.161	0.466-2.891	0.749			

Discussion

This study investigated the possible impact of sarcopenia and myosteatosis on the neurological outcome, short-term survival and long-term overall survival following endovascular therapy for large vessel occlusion stroke patients. To our knowledge, this is the first time this relationship has been described. For sarcopenia optimum stratification yielded no association with overall survival. Myosteatosis, on the other hand, was found to be associated with survival in univariable survival analysis as well as neurological outcome analysis. Despite this, the multivariable analysis could not confirm an independent association for either outcome variables. This implies no association exists between sarcopenia or myosteatosis and neurological outcome or overall survival following endovascular therapy for large vessel occlusion stroke patients. The univariable findings were deemed to be attributable to collinearity with age. Subgroup analysis for both genders revealed no gender-specific differences in the impact of sarcopenia or myosteatosis on outcome. In this patient cohort, history of atrial fibrillation, and as was expected, patient age, were found to be predictors for overall survival.

Over the past decade, particularly sarcopenia and to a lesser extent myosteatosis, have been thoroughly investigated for its impact in patients with e.g. cancer [32][33], liver transplant candidates [33], chronic heart failure [34], and chronic kidney disease [35][36] as well as geriatric populations in a broader sense [29][37]. Also, in patients with cardiovascular disease, worsened survival has been attributed to the presence of sarcopenia. Matsubara et al. found sarcopenia to be a prognostic factor for critical limb ischemia patients [4]. Moreover decreased psoas muscle mass was found to be associated with increased odds of major adverse cardiovascular and limb events in peripheral arterial disease [3]. In aneurysmal disease sarcopenia impacts overall survival following abdominal aortic aneurysm repair [5]. In one of these studies, the impact of myosteatosis was investigated along with sarcopenia and found the combination of myosteatosis and sarcopenia to be predictive of further deteriorated overall survival when compared to sarcopenia alone [38]. A recent study found a high prevalence of sarcopenia in patients treated for acute myocardial infarction [39], this study, however, did not investigate its impact on outcome. Furthermore, an association between stroke and sarcopenia has been described. In a Korean population-based study sarcopenia was found to be associated with an increased prevalence of cardiovascular diseases, especially stroke, in men over 50 years of age [40].

Comparable to the findings related to overall survival, neurological outcome in patients with and without myosteatosis measured using the mRS scale did not display any significant relationship when corrected for age. In women, age was directly related to a worse neurological outcome. In men, no significant relationship was found.

The used cut-off values of 12.93 cm^2/cm for men and 12.97 cm^2/cm for women were determined using optimal stratification. This resembles what Rebecca T. Karsten et al. [41] described and thus seems applicable. This study has several limitations. Due to the retrospective nature of this study, it is prone to missing data. The delineation software was unable to open CT-images with a different matrix than 512x512 and when the slice thickness was less than 1mm. There were 103 patients where prognostic biomarkers were missing, so we had to exclude 39% of the segmented data. Furthermore, many patient height measurements were missing. Only 139 of the 193 patients with prognostic variables were included for SMI measurement. Therefore, we could not include all patients in the sarcopenia analysis. Our dataset shows an unusual mortality rate, 58 patients died in 90 days and only 3 afterwards. 95% of the patients died in 90 days, whereas a study from Angel Ois et al. [42] reports a mortality rate of 15.2% in 90 days. Due to the large number of deaths in the first 90 days, it would be interesting to know the

causes and to analyse them. Unfortunately, it was not feasible to determine every cause and thus we were unable to analyse the data.

The results presented in this study suggest the detrimental effects of sarcopenia and myosteatosis do not impact mortality and neurological outcome following endovascular treatment for ischemic stroke. Considering the strong associated between sarcopenia and/or myosteatosis in other population-based studies, further research may be warranted to confirm this lack of association. Interpreting the results of this study with certitude, the prognostic outcome of stroke patients is unlikely to benefit the methods of care described in literature to treat sarcopenia and myosteatosis.

Conclusion

Sarcopenia and myosteatosis are not associated with overall survival and neurological outcome in ischemic stroke patients.

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Appendix 1: Flowchart

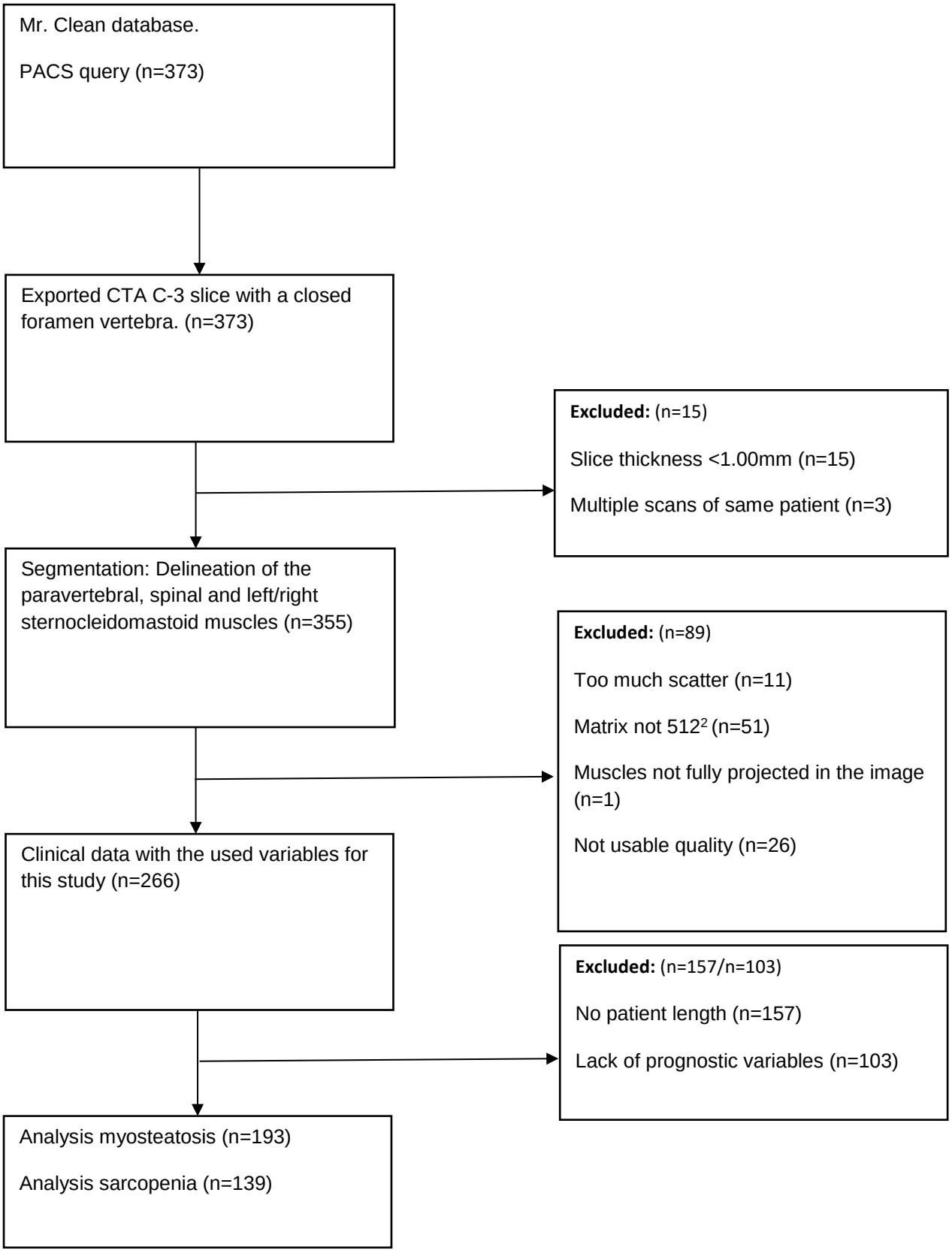

Figure 5: Flowchart of the inclusion criteria. Final number of patients used for myosteatosis analysis is n = 193 and for sarcopenia analysis is n = 139.

Appendix 2: Survival curve

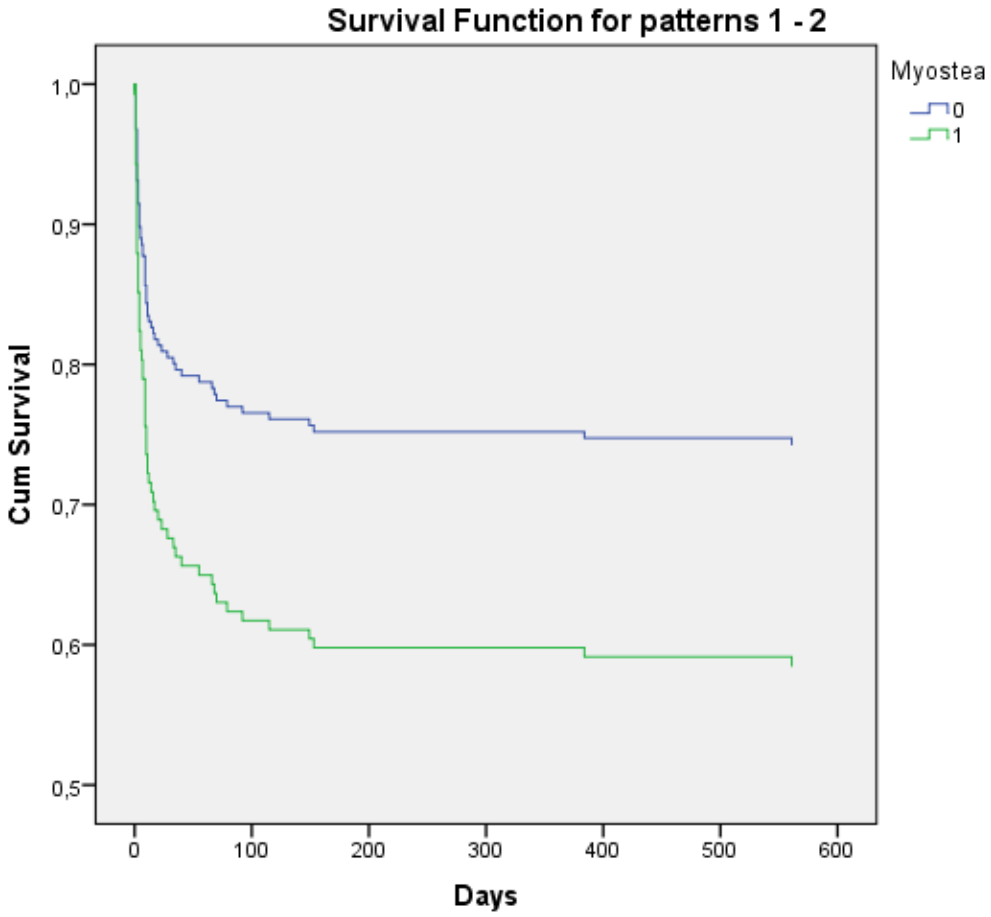

Figure 6: Survival curve of the overall survival. 0 = No myosteatosis, 1 = myosteatosis. The figure shows that patients with myosteatosis have a lesser survival than patients without myosteatosis.