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Association of sleep apnea with clinically silent microvascular brain tissue changes in acute cerebral ischemia

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Abstract

The aim of this study was to determine the importance of sleep apnea in relation to clinically silent microvascular brain tissue changes in patients with acute cerebral ischemia. Patients with acute cerebral ischemia prospectively underwent nocturnal respiratory polygraphy within 5 days from symptom-onset. Sleep apnea was defined as apnea-hypopnea-index (AHI) ≥5/h. Experienced readers blinded to clinical and sleep-related data reviewed brain computed tomography and magnetic resonance imaging scans for leukoaraiosis and chronic lacunar infarctions. Ischemic lesions were considered clinically silent when patients did not recall associated stroke-like symptoms. Functional outcome was assessed with modified Rankin Scale at discharge, 6 and 12 months. Fifty-one of 56 (91 %) patients had sleep apnea of any degree. Patients with moderate-to-severe leukoaraiosis (Wahlund score ≥5) were found to have higher mean AHI than those with none or mild leukoaraiosis (34.4 vs. 12.8/h, $p < 0.001$). Moderate-to-severe sleep apnea (AHI >15/h) was found to be an independent predictor of moderate-to-severe leukoaraiosis (adjusted OR 6.03, 95 % CI 1.76-20.6, $p = 0.0042$) and of moderate-to-severe leukoaraiosis associated with clinically silent chronic lacunar infarctions (adjusted OR 10.5, 95 % CI 2.19-50.6, $p = 0.003$). The higher the Wahlund score and the AHI, the more likely unfavorable functional outcome resulted over time ($p = 0.0373$). In acute cerebral ischemia, sleep apnea is associated with clinically silent microvascular brain tissue changes and may negatively influence functional outcome. Routine sleep apnea screening and further investigation of possible long-term effects of non-invasive ventilatory treatment of sleep apnea appear warranted in this at-risk population.

Keywords

Acute stroke; Silent brain infarction; Sleep apnea; Leukoaraiosis

Introduction

Chronic microvascular brain tissue changes, comprising leukoaraiosis and lacunar infarctions, become more evident with improved resolution of brain imaging modalities thereby increasing their prevalence in the healthy elderly population [1, 2]. Their causal association with behavioural, neuropsychological and gait dysfunction as well as long-term

care dependency has been known for years [2-4]. In patients with acute cerebral ischemia, magnetic resonance imaging (MRI)-based investigations revealed a much higher frequency of chronic microvascular brain tissue changes affecting almost two in three patients, establishing such frequently clinically silent lesions as a risk factor for clinically apparent strokes [4–6]. Moreover, their prognostic relevance with regard to unfavorable functional outcome and increased recurrent stroke risk after a first-ever stroke has been well recognized [5–8].

Traditional modifiable vascular risk factors like arterial hypertension and diabetes mellitus are known to contribute decisively to the development of chronic microvascular brain tissue changes [2, 9]. However, acute stroke patients differ from the general population due to an accented vascular risk profile including untraditional risk factors like sleep apnea that itself has been associated with silent ischemic brain lesions in the general population [10–13]. Enhanced susceptibility of the deep white matter to hypoxic injury and hemodynamic alterations as a result of repetitive apneic episodes might be a potential pathophysiological link [14–16], yet it still remains a matter of debate whether the deleterious effects of sleep apnea are independent of other vascular comorbidities often existing in acute stroke patients. We sought to explore the relationship between sleep apnea and clinically silent chronic microvascular brain tissue changes in patients with acute cerebral ischemia.

Methods

Study population

This was a substudy of a prospective observational study on sleep apnea screening in consecutively enrolled patients (18–75 years old) with acute cerebral ischemia and transient ischemic attack (TIA) [17]. Exclusion criteria of the initial study included unfavorable premorbid functional condition defined by modified Rankin Scale (mRS) score > 3 points, known sleep apnea and clinically pre-diagnosed dementia. Enrollment period ranged from November 2009 to May 2011. The local institutional review board approved this study. Written informed consent was obtained from each patient prior to any study related procedures.

Evaluation of vascular risk factors and clinical assessment

Anthropometric data including weight and height were self-reported by each patient and body mass index (BMI) was calculated. Patients were diagnosed as having arterial hypertension, if they had systolic ≥140 mmHg or diastolic blood pressure ≥90 mmHg during hospitalization or any antihypertensive medication before. Diabetes mellitus was defined by fasting serum glucose ≥7.0 mmol/l or serum glucose ≥ 11.1 mmol/l at 2 h following an oral glucose tolerance test, or prior use of antidiabetic therapy (oral or insulin). Hypercholesterolemia was defined as LDL cholesterol ≥2.6 mmol/l or total cholesterol ≥5.2 mmol/l, or prior use of lipid-lowering medication. Smoking status was defined as current use. Atrial fibrillation was based on at least one positive electrocardiogram before or during hospitalization. Coronary artery disease was based on self-reporting. We assessed National Institutes of Health Stroke Scale (NIHSS) scores at baseline and classified stroke etiology using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [18].

We followed patients prospectively for a period of 12 months with assessments of mRS at discharge, 6 and 12 months. Favorable functional outcome was defined as mRS 0-1. Recurrent cerebral ischemic events including TIA and acute ischemic stroke were assessed at 6 and 12 months.

Assessment of sleep apnea

All patients underwent nocturnal 6-channel portable respiratory polygraphy (SOMNOcheck effort®, Weinmann Medical Technology, Hamburg, Germany) within 3 ± 2 days from symptom-onset [17]. Each sleep polygram was analyzed manually according to the American Academy of Sleep guideline [19] by a sleep neurologist blinded to clinical and imaging data. The apnea-hypopnea-index (AHI) was calculated using the total number of respiratory events (apneas and hypopneas) per hour sleep, and categorized in any (AHI ≥5/h), mild (AHI 5–14/h), moderate (AHI 15–29/h) and severe (AHI ≥30/h) sleep apnea as previously reported [20]. Daytime sleepiness was assessed by Epworth Sleepiness Scale (ESS).

Imaging

Non-contrast computed tomography (CT) or multimodal MRI including fluid-attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) sequences were acquired shortly after admission as part of our institutional standard imaging protocol for acute stroke. Within 48 h from admission, either a repeat non-contrast CT or multimodal MRI scan was performed as part of routine diagnostic stroke work-up. The CT studies were acquired on a Somatom Sensation 64-slice scanner (Siemens Healthcare, Erlangen, Germany) and the MRI studies on a Siemens Sonata or Avanto 1.5 T scanner (Siemens Healthcare, Erlangen, Germany).

Two experienced investigators (J.G., V.P.) who met for consensus in case of disagreement reviewed all brain scans independently of any results of the clinical and sleep-related data. CT images were only favored when MRI was not obtained. Leukoaraiosis was assessed using the Wahl und score as previously described [21]. Briefly, leukoaraiosis was classified as ill-defined hypodensities ≥5 mm in diameter on non-contrast axial CT and ill-defined hyper-intensities ≥5 mm in diameter on axial T2-weighted or FLAIR MRI sequences, respectively (Fig. 1). Five different regions (frontal, parieto-occipital, temporal, basal ganglia, infratentorial) were scored with 0–3 points on both sides of the brain and the sum of all points added up to the final score. The extent of leukoaraiosis was stratified as no or mild (0–4), moderate (5–10) and severe (>10) leukoaraiosis [7].

In addition, all brain images were reviewed for chronic lacunar infarctions in any subcortical region of the penetrating arteries. On CT, any clear hypodensity <15 mm in diameter was considered a lacune. On MRI, lacunar infarction was defined as well-defined focal T2-weighted hyperintensity <15 mm in diameter that was clearly differentiated from acute DWI lesions. Chronic microvascular brain tissue changes were considered clinically silent when patients did not recall corresponding stroke-like symptoms.

Statistical analysis

Continuous and non-continuous variables are presented as mean ± standard deviation (SD), median (range) and percentages. Statistical comparisons were performed using Chi square test, Fisher's exact test, Student's *t* test and Wilcoxon rank sum, where appropriate. Pearson correlation coefficient was used to examine correlations between the AHI and leukoaraiosis. Univariate and multivariable analysis were conducted to evaluate the relationship between sleep apnea and clinically silent microvascular brain tissue changes controlling for age, gender and vascular risk factors. Crude and adjusted generalized estimating equations with a negative binomial distribution were used to evaluate functional outcomes over time with adjusted models controlling for age, baseline NIHSS and thrombolysis. Missing mRS outcome data were replaced by using the last-observation-carried-forward method. A p value of <0.05 was considered to be statistically significant.

Results

We identified 56 patients who had complete and analyzable sleep polygrams among 61 patients with acute cerebral ischemia included in our previous study on sleep apnea screening [17]. Mean age was 64 ± 8 years, 46 % were men, 18 % had a TIA, median baseline NIHSS score was 1 (range 0–15) point, median ESS was 5 (0–13) points, mean AHI was 23.6 ± 19.3/h (median 20/h, range 0–79/h). Fifty-one of 56 (91 %) patients were found to have sleep apnea of any degree with obstructive the most common subtype (86 %), followed by mixed (10 %) and central (4 %) forms. With regards to TOAST [19], large-artery atherosclerosis (61 %) appeared to be the most frequent subtype for acute cerebral ischemia, followed by cardio embolism (18 %), small-vessel disease (12 %) and other cause (9 %). Baseline characteristics of the patients in this study are presented in Table 1.

Brain MRI scans were available in 42/56 (75 %), non-contrast CT scans were used in the remaining patients. Overall, 45/56 (80 %) patients were found to have leukoaraiosis of any degree (Wahlund score ≥1; mean 5.8 ± 5.7 points) with 17/56 (30 %) being moderate and 11/56 (20 %) severe. None of the patients with moderate-to-severe leukoaraiosis reported a history of stroke-like symptoms before the index stroke. Patients with moderate-to-severe leukoaraiosis (28/56, 50 %) were significantly older than those who had none or mild leukoaraiosis (67 ± 7 vs. 62 ± 8 years, $p = 0.027$). Chronic lacunar infarctions were present in 29/56 (52 %) patients, of which 28/56 (50 %) lacked clinically overt stroke-like symptoms. Of these, seven patients were found to have isolated clinically silent lacunar infarctions and 21 patients both moderate-to-severe leukoaraiosis and clinically silent lacunar infarctions. No significant differences in acute stroke TOAST subtypes were found between patients with no/mild and moderate/severe leukoaraiosis (±silent lacunar infarctions; $p = 0.076/0.266$). Patients with moderate-to-severe leukoaraiosis were found to have higher mean AHI than those with no or mild leukoaraiosis (34.4 vs. 12.8/h, $p <0.001$). Accordingly, severe sleep apnea was more frequently diagnosed in these patients (50 vs. 7 %, $p <0.001$). Further summary data are detailed in Table 2. The AHI and the extent of leukoaraiosis as indicated by the Wahlund score correlated moderately ($r = 0.4958$, $p = 0.0001$) even after adjustment for age and arterial hypertension ($r = 0.4470$, $p = 0.007$). Using logistic regression with adjustments for age, arterial hypertension, and diabetes

mellitus, AHI emerged as an independent predictor of moderate-to-severe leukoaraiosis (adjusted OR 1.06, 95 % CI 1.02–1.10, $p = 0.0009$). Similarly, moderate-to-severe sleep apnea (AHI ≥15/h) strongly predicted moderate-to-severe leukoaraiosis (adjusted OR 6.03, 95 % CI 1.76–20.6, $p = 0.0042$). With regard to clinically silent lacunar infarctions, neither the AHI nor moderate-to-severe sleep apnea appeared to be independent predictors (adjusted OR 1.03, 95 % CI 0.99–1.07, $p = 0.132$ and adjusted OR 2.7, 95 % CI 0.77–9.50, $p = 0.121$, respectively). However, when combining moderate-to-severe leukoaraiosis and clinically silent chronic lacunar infarctions, both the AHI and moderate-to-severe sleep apnea remained strong independent predictors (adjusted OR 1.12, 95 % CI 1.05–1.2, $p = 0.001$ and adjusted OR 10.5, 95 % CI 2.19–50.6, $p = 0.003$, respectively).

Using generalized estimating equations with a negative binomial distribution with AHI and mRS in their continuous form, AHI was highly associated with mRS over time ($p = 0.0018$). The Wahlund score was also highly associated with mRS over time ($p = 0.0011$). The higher the Wahlund score and the AHI, the more likely unfavorable functional outcome was achieved over time ($p = 0.0373$). Outcome data are summarized in Table 3.

Discussion

Our study showed that among patients with acute cerebral ischemia, sleep apnea appeared to be independently associated with leukoaraiosis, with the strongest association observed in those with higher degrees of both diseases. We found a risk factor association for clinically silent lacunar infarctions with moderate-to-severe sleep apnea only when combined with advanced leukoaraiosis.

Stroke clinicians have recognized sleep apnea as an independent risk factor for clinically apparent ischemic strokes [22–24]. It is unclear, however, whether sleep apnea contributes to the development of chronic microvascular brain tissue changes. While some investigations found no relevant association between sleep apnea and small vessel disease [25–27], our data confirm a recent cross-sectional investigation that found moderate-to-severe obstructive sleep apnea associated with a moderate degree of leukoaraiosis and silent lacunar infarctions in about 50 % of non-stroke patients [10]. Similarly, recent findings indicated that moderate-to-severe obstructive sleep apnea is an independent risk factor for leukoaraiosis in the general population [28]. Moreover, a substudy of the Sleep Heart Health Study revealed a higher portion and degree of confirmed central sleep disordered breathing patterns in patients who had progression of leukoaraiosis as compared with those who had no progression [11].

These findings originate solely from non-stroke populations, which underscores the clinical relevance of our findings indicating that such associations also extend to patients with acute cerebral ischemia. To our knowledge, only one study explored associations between sleep apnea and chronic microvascular brain tissue changes in a sample of acute stroke patients and found that higher degrees of sleep apnea were associated with increased leukoaraiosis [29]. However, it remains unclear whether these ischemic brain lesions had a history of clinically overt stroke-like symptoms. We have shown that moderate-to-severe sleep apnea increased the likelihood for having a coexistence of both an advanced degree of

leukoaraiosis and clinically silent chronic lacunar infarctions. This favors the earlier hypothesis that two different pathogenic mechanisms may account for lacunar infarctions: isolated lacunar infarctions may be linked to focal atherosclerotic steno-occlusive lesions at the origin of the penetrating arteries, whereas those with coexisting leukoaraiois may represent the end of a spectrum of a distinct diffuse small vessel disease (i.e. lipohyalinosis) [30, 31]. With our results, we may speculate that sleep apnea predominantly contributes to the latter pathology and promotes the development of lacunar infarctions that are conjugated with leukoaraiosis.

Nonetheless, our study design does not allow causal inferences about the role of sleep apnea as possible independent risk factor for chronic microvascular tissue changes.

Following stroke, untreated sleep apnea negatively affects short-term and long-term outcomes [32–35]. Thus, the cumulative risk of achieving an unfavorable functional outcome may grow notably in stroke patients who have both sleep apnea and chronic microvascular brain tissue changes as stroke patients with leukoaraiosis and chronic lacunar infarctions have worse functional outcomes themselves [6, 8]. Moreover, as chronic microvascular brain tissue changes have been proven nearly to triple the risk for a first-ever stroke in the general population [4], recent studies revealed that such lesions also increase the risk for a recurrent ischemic stroke independently by two- to sevenfold in cohorts of first-ever acute ischemic stroke patients [5, 6]. We found that both the degree of sleep apnea (as indicated by the AHI) and the extent of leukoaraiosis had an unfavorable impact on functional outcome emphasizing the importance of broad vascular risk factor screening as part of routine stroke work-up in this patient population. The challenge with sleep apnea identification in the acute setting of ischemic stroke has been a lack of clinical patient selection criteria for performing specific sleep studies [17, 35–37]. Chronic microvascular brain tissue changes could indirectly unmask stroke patients with a long-lasting history of sleep apnea requiring focused attention and define an at-risk population that could be tested in an acute or secondary prevention clinical trial for treatment of sleep apnea [38].

Our study has certain limitations. First, this was a sub-study of a prospective study of sleep apnea in acute cerebral ischemia patients that had different primary objectives than our exploratory analysis. Consequently, very few patients had major strokes as these were considered not amenable to early sleep apnea screening in the primary study and, therefore, sampling bias is likely. The collection of both TIA and acute stroke patients may have added another bias to our results. However, larger observational studies suggest that sleep apnea precedes acute stroke events (establishing it as a risk factor as opposed to a clinical manifestation of acute brain damage) and only a minority of patients experience relevant improvement of their sleep pattern over time [22, 23, 35]. Second, patients with gait and urinary incontinence were not excluded diminishing the validity whether the radiological classified chronic microvascular brain tissue changes were ultimately “silent”. However, we excluded patients with a history suggestive of cognitive decline or known dementia, which is known to be a major clinical manifestation of leukoaraiosis and chronic lacunar infarcts [2, 39]. Also, the “silence” of chronic microvascular brain tissue changes may be due to various reasons: lesions in non-eloquent brain areas like the frontal lobes, small lesions causing minor symptoms not recognized as stroke symptoms, the sensitivity and memory of the

patient. Particularly the latter reason may have introduced a recall bias [40]. Third, as we reviewed both hemispheres (including the affected side) on brain imaging, acute ischemic lesions may have obscured chronic microvascular brain tissue changes potentially resulting in an underestimation of the extent of these lesions. Also, we used two different imaging methods to assess chronic microvascular brain tissue changes; however, with regard to leukoaraiosis the Wahlund score is valid and equally sensitive in both techniques [21] and chronic lacunar infarctions can be well detected in both modalities [1]. Fourth, outside this study, some patients were prescribed to non-invasive ventilatory treatment after discharge (a total of seven patients at 12 months) and this may have confounded our reported associations on outcomes. Lastly, our results are limited by a relatively small number of patients studied.

In conclusion, sleep apnea is associated with clinically silent chronic microvascular brain tissue changes in patients with acute cerebral ischemia and may negatively influence functional outcome. Sleep apnea screening and the evaluation of possible long-term effects of non-invasive ventilatory treatment appear warranted in this at-risk population.

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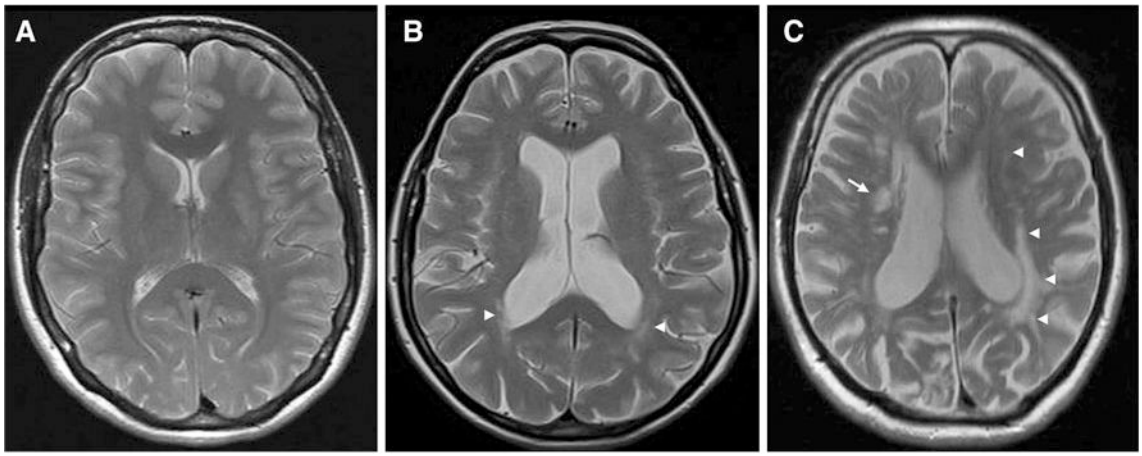

Fig. 1.

T2-weighted MRI scans depicting various grades of chronic microvascular brain tissue changes. No microvascular changes in a 45-year-old patient with an AHI of 3/h (**a**) Mild leukoaraiosis (Wahlund score of 3 points; *arrowheads*) in a 73-year-old patient with an AHI of 17/h (**b**); severe leukoaraiosis (Wahlund score of 22 points; *arrowheads*) and a small right-sided subcortical lacunar chronic infarction (*arrow*) in a 70-year-old patient with an AHI of 36/h (**c**)

Table 1

Baseline characteristics of the study population (n = 56)

Variable	Summary data
Gender, male, *n* (%)	26 (46)
Age, mean ± SD (years)	64.3 ± 7.8
Vascular risk factors, *n* (%)	
Arterial hypertension	49 (88)
Diabetes mellitus	18 (32)
Hypercholesterolemia	33 (59)
Atrial fibrillation	8 (14)
Tobacco use	12 (21)
Coronary artery disease	4 (7)
Clinical data	
Acute ischemic stroke, n (%)	46 (82)
TIA, *n* (%)	10 (18)
IV thrombolysis, *n* (%)	11 (20)
NIHSS, median (range)	1 (0–15)
BMI, median (range)	27 (17–41)
ESS, median (range)	5 (0–13)
AHI, mean ± SD	23.6 ± 19.3
Sleep apnea, *n* (%)	51 (91)
Mild	18 (32)
Moderate	17 (30)
Severe	16 (29)

Table 2
Baseline characteristics according to extent of chronic microvascular brain tissue changes

Variable	No/mild leukoaraiosis (*n* = 28)	Moderate/severe leukoaraiosis	
		(*n* = 28)	+ clinically silentchronic lacunarinfarcts (*n* = 21)
Gender, male, *n* (%)	12 (43)	14 (50)	12 (57)
Age, mean ± SD (years)	62.1 ± 7.7	66.6 ± 7.3 *	65.4 ± 8
Vascular risk factors, *n* (%)			
Arterial hypertension	23 (82)	26 (93)	19 (90)
Diabetes mellitus	7 (25)	11 (39)	7 (33)
Hypercholesterolemia	18 (64)	15 (54)	12 (57)
Atrial fibrillation	3 (11)	5 (18)	2 (10)
Tobacco use	4 (14)	8 (29)	7 (33)
Coronary artery disease	0	4 (14)	4 (19) *
Clinical data			
Acute ischemic stroke, *n* (%)	20(71)	26 (93)	19 (90)
TIA, *n* (%)	8 (29)	2 (7)	2 (9)
IV thrombolysis, *n* (%)	6 (21)	3 (11)	31 (49)
NIHSS, median (range)	1 (0–15)	2 (0–7)	2 (0–7)
BMI, median (range)	26 (20–32)	27 (17–41)	26 (17–41)
ESS, median (range)	5 (0–11)	6 (0–13)	6 (3–13)
AHI, mean ± SD	12.8 ± 10.5	34.4 ± 19.8 *	32.7 ± 18.5 *
Sleep apnea, *n* (%)	23 (82)	28 (100) *	21 (100) *
Mild	13 (46)	5 (18) *	3 (14) *
Moderate	8 (29)	9 (32)	9 (43)
Severe	2 (7)	14 (50) *	9 (43) *

Comparisons were made between no/mild and moderate/severe leukoaraiosis groups *TIA* transient ischemic attack, *NIHSS* National Institutes of Health Stroke Scale, *BMI* body mass index, *ESS* Epworth sleepiness scale, *AHI* apnea-hypopnea index, *mRS* modified Rankin scale

* Indicates p value< 0.05

Table 3
Summary measures of clinical outcome along with 95 % confidence intervals

Variable	No/mild leukoaraiosis (*n* = 28)	Moderate/severe leukoaraiosis	
		(*n* = 28)	+ clinically silent chronic lacunar infarcts (*n* = 21)
Favorable outcome: 6 months, *n* (%, 95 % CI)	22 (79, 63–94)	16 (57, 38–76)	12 (57, 35–79)
Favorable outcome: 12 months, *n* (%, 95 % CI)	22 (79, 63–94)	19 (67, 50–86)	14 (67, 45–88)
mRS: d/c, median (range)	1 (0–5)	2 (0–4)	2 (0–4)
mRS: 6 months, median (range)	0.5 (0–5)	1 (0–6) *	1 (0–6) *
mRS: 12 months, median (range)	1 (0–5)	1 (0–6)	1 (0–6)
Ischemic event: 6 months, *n* (%)	0	1 (4)	1 (5)
Ischemic event: 12 months, *n* (%)	0	2 (7)	2 (10)
Death: 12 months, *n* (%)	0	1 (4)	1 (5)

Comparisons were made between no/mild and moderate/severe leukoaraiosis groups *mRS* modified Rankin scale, *d/c* discharge

* Indicates *p* value <0.05