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Incidence of Aphasia in Ischemic Stroke

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Keywords
Aphasia · Incidence · Ischemic stroke · Risk factors

Abstract
Introduction: A decrease in ischemic stroke (IS) incidence has been observed in high income countries during the last decades. Whether this has influenced the occurrence of aphasia in IS is uncertain. We therefore examined the incidence rate and potentially related determinants of aphasia in IS. ***Methods:*** We prospectively examined consecutive patients admitted to hospital with first-ever acute IS between March 1, 2017, and February 28, 2018, as part of the Lund Stroke Register (LSR) Study, comprising patients from the uptake area of Skåne University Hospital, Lund, Sweden. Patients were assessed with National Institutes of Health Stroke Scale (NIHSS) at stroke onset. Presence of aphasia was evaluated with NIHSS item 9 (language). We registered IS subtypes and risk factors. To investigate possible temporal changes in aphasia incidence, we made comparisons with corresponding LSR data from 2005 to 2006. Incidence rates were calculated and adjusted to the European Standard Population (ESP) and to the Swedish population. ***Results:*** Among 308 included IS patients, 30% presented with aphasia (n = 91; 95% CI: 25–35), a proportion of aphasia in IS that was similar to 2005–2006. The incidence rate of aphasia was 31 per 100,000 person-years adjusted to the ESP (95% CI: 25–38 per 100,000 person-years) corresponding to a significant decrease of 30% between 2005–2006 and 2017–2018. The decrease was significantly more pronounced in men. The initial severity of aphasia remained unchanged, with the majority of patients having severe to global aphasia. No significant differences between vascular stroke risk factors were noted among stroke patients with or without aphasia. ***Conclusion:*** Even though the overall IS incidence rate has decreased during the first decades of the 21st century, the proportion of IS patients with aphasia at stroke onset remains stable at 30%. Aphasia continues to be an important symptom that needs to be considered in stroke care and rehabilitation.

Introduction

Effective preventive stroke treatments and reduction of stroke risk factors have led to a decrease in stroke incidence in high income countries during the last decades [1, 2]. Despite this, the number of patients living with stroke and the long-term effects of stroke are increasing due to an aging population and reduced stroke mortality [1, 3] and is projected to grow in the coming decades [4]. This indicates that the burden of stroke will continue to remain high in society.

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Aphasia after stroke poses a major disability for the patient and negatively impacts rehabilitation [5] and overall stroke outcome [6]. Moreover, aphasia is a condition that has one of the largest negative impacts on a person's health-related quality of life [7], with high risk of depression and lower likelihood of returning to work [8]. Accurate knowledge of symptoms and factors associated with aphasia are essential to provide optimal care of patients with this language disorder.

Recent changes in stroke incidence and advances in stroke care may also affect the epidemiology of aphasia in stroke [9]. Historically, the proportion of stroke patients with aphasia has been reported to be approximately 30%, although with a considerable range, varying between 19% and 62% among patients with ischemic stroke (IS) [10–13]. However, up-to-date data on the incidence of aphasia after IS in the past decade are scarce, and knowledge of current incidence and severity of aphasia is essential to facilitate planning of stroke rehabilitation, improve development of clinical guidelines for aphasia, and ultimately estimate health care cost. The aims of this study were to: (1) report the current incidence and severity of aphasia after first-ever IS; (2) identify pathogenetic mechanisms and risk factors associated with aphasia in IS; (3) investigate potential temporal changes of aphasia incidence after IS.

Methods

Data supporting the findings of this study are available from the corresponding author upon reasonable request. We consecutively included first-ever IS patients in the prospective study Lund Stroke Register (LSR), comprising the local uptake area of Skåne University Hospital Lund (SUHL), Sweden between March 1, 2017, and February 28, 2018. SUHL is the only hospital in this area designated for acute stroke care and stroke patients admitted to the hospital are identified for inclusion in LSR using "hot pursuit" methods as described below. The total population of the uptake area was 284,003 inhabitants (all ages) as of December 31, 2017 [14], with 8% ≥75 years and 50% females [14].

To identify first-ever IS patients for inclusion in the study during their hospital stay, research nurses during weekdays screened charts of patients admitted to SUHL for stroke symptoms. Stroke was defined according to the WHO criteria [15] and previous studies show that LSR includes approximately 94% of all patients with first-ever stroke [16]. We included patients who after information consented to participate in the study.

A physician performed assessment with the National Institutes of Health Stroke Scale (NIHSS) at stroke onset (hospital admission, median day 0). NIHSS was assessed before any potential administration of acute stroke recanalization treatment. When needed, we performed additional clinical assessments and also reviewed data from the patients' medical records. The diagnosis of aphasia was determined by NIHSS item 9 "best language," and we graded the severity of aphasia into 4 categories according to NIHSS item 9 (i.e., 0 = no aphasia, 1 = mild to moderate aphasia, 2 = severe aphasia, 3 = global aphasia). Stroke severity according to NIHSS was stratified into 3 groups: NIHSS score of 1–4 = mild stroke; 5–14 = moderate stroke; and ≥15 = severe stroke [17].

We collected additional patient data by interviewing the patients and/or their next of kin, and reviewing the patients' medical records concerning: whether care was provided at a dedicated stroke unit, length of stay, discharge location, in-hospital death, and traditional stroke risk factors: hypertension, diabetes mellitus, atrial fibrillation (AF), hypercholesterolemia, smoking, previous TIA, heart disease and ischemic heart disease, as defined previously [18, 19]. We also registered demographic characteristics: age, gender, and education.

The evaluations were performed primarily during the patients' hospital stay and missing data was subsequently complemented by contacting the patients and/or next of kin by telephone after their discharge from hospital. A research physician determined pathogenetic stroke mechanism according to the Trial of Org in Acute Stroke Treatment (TOAST) classification [20] and clinical stroke syndrome by using The Oxfordshire Community Stroke Project (OCSP) definitions [21]. Corresponding data from LSR between March 1, 2005, and February 28, 2006 (year 2005–2006), were used to investigate possible temporal changes in aphasia incidence (patient inclusion criteria were the same as described above). We also compared risk factors and demographic data between 2005–2006 and 2017–2018.

Data Analysis

Age- and sex-standardized incidence rates were calculated by using the direct method and per 100,000 person-years with 95% confidence intervals. Incidence rates were age and gender standardized to the Swedish population as of December 31, 2017 [14], and to the European Standard Population (ESP) from 2013 [22].

We assessed the occurrence of aphasia across age and gender. Categorical and binary variables were analyzed with the χ^2 test. We applied Mann-Whitney U test to detect differences between year 2005–2006 and year 2017–2018 in continuous variables (such as stroke severity according to NIHSS). Comparisons of categorical data with small sample size were examined using Fisher's exact test.

Patients were divided into two subgroups according to the presence or absence of aphasia. Associations between aphasia and age (unadjusted and adjusted for stroke severity), gender, education, and risk factors were examined using logistic regression analyses. Associations between aphasia and stroke severity were examined using the total NIHSS score excluding the NIHSS aphasia component (NIHSS item 9). Associations between aphasia and TOAST classification [20] were made including the 5 categories: (1) large-artery atherosclerosis (LAA), (2) cardioembolism (CE), (3) small-artery occlusion (SAO), (4) stroke of other determined etiology (OC), and (5) stroke of undetermined etiology (UND), and in addition, we performed calculations excluding SAO. The latter was done because a prerequisite for the TOAST category SAO is that the patient should not have evidence of cortical dysfunction such as aphasia.

Confidence intervals and comparisons of incidence rates between year 2005–2006 and year 2017–2018 were performed using Open Source Epidemiologic Statistics for Public Health [23]. All

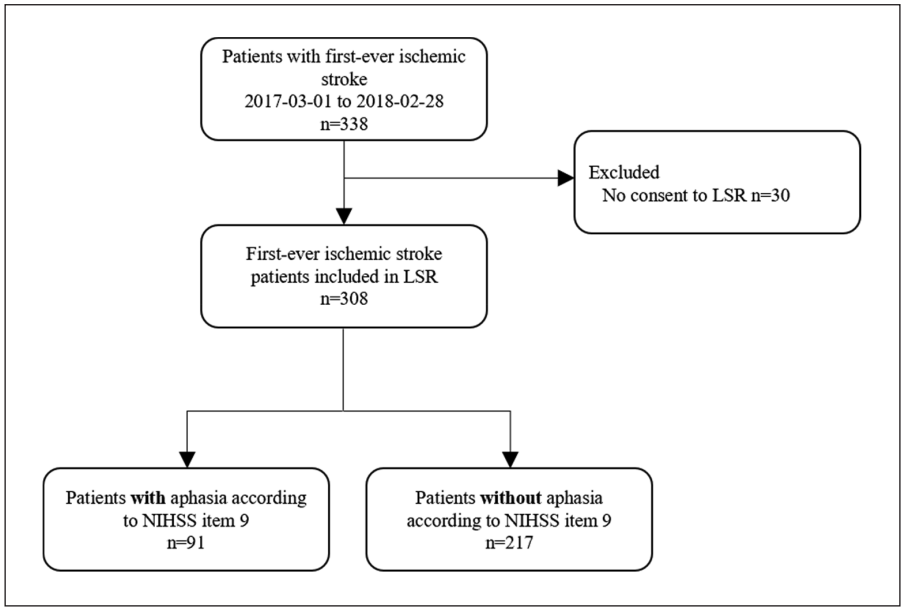

Fig. 1. Study flow diagram of the LSR cohort. LSR, Lund Stroke Register; NIHSS, National Institutes of Health Stroke Scale.

other statistical calculations were performed with the SPSS software package 25. Values of $p < 0.05$ were considered statistically significant. The study was approved by the Regional Ethical Review Authority in Lund (registration number 2016/179).

Results

In total, 338 patients were diagnosed with first-ever IS between March 1, 2017, and February 28, 2018. Among these, 308 patients were included in the study (Fig. 1). The median age of the included patients was 76 years (IQR 69–82 years) and 152 (49%) were female. Baseline characteristics are shown in Table 1.

The incidence rate of first-ever IS was 108 per 100,000 person-years (95% CI: 97–121 per 100,000 person-years) adjusted to the ESP. The overall proportion of IS patients with aphasia was 30% (95% CI: 25–35%) according to NIHSS item 9 ($n = 91$) in the acute phase of stroke onset. The overall crude incidence rate of first-ever IS aphasia amounted to 32 per 100,000 person-years (95% CI: 26–39 per 100,000 person-years). The age- and sex-standardized incidence rate adjusted to the Swedish population (of December 2017) was 35 per 100,000 person-years (95% CI: 33–49 per 100,000 person-years). Adjusted to the ESP, the overall incidence rate of aphasia after IS was 31 per 100,000 person-years (95% CI: 25–38 per 100,000 person-years). There was no significant difference between males and females in aphasia incidence rate adjusted to ESP year 2017–2018 ($p = 0.92$). Patients with aphasia had significantly more severe strokes, were older (Table 1), and had longer hospital stays in comparison to stroke patients without aphasia (median 8 days vs. 4 days; OR, 1.08; 95% CI: 1.04–1.12). These factors remained significantly associated with aphasia also after adjusting for NIHSS scores excluding the aphasia component (NIHSS item 9).

Patients with aphasia were more likely to be discharged to a short-term care facility (25% vs. 13%; $p = 0.01$), and the overall in-hospital mortality was higher for patients with aphasia (18%) in comparison to those without aphasia (2%, OR, 9.05; 95% CI: 3.20–25.54). However, when adjusting for stroke severity, the abovementioned factors were no longer significant among patients with or without aphasia. There were no significant differences regarding the prevalences of stroke risk factors (hypertension, diabetes mellitus, AF, hypercholesterolemia, smoking, ischemic heart disease, heart disease) between patients with or without aphasia. The proportion of stroke patients treated at a dedicated stroke unit was high (94%), and there was no difference between patients with or without aphasia (94% and 92%, respectively; OR, 1.01; 95% CI: 0.34–2.99).

Aphasia in Relation to Stroke Severity and Age

The prevalence of aphasia increased significantly with stroke severity, as measured by NIHSS (after excluding the aphasia component, NIHSS item 9, $p < 0.001$). Each 1-point increase on NIHSS (excluding item 9) increased the odds of aphasia by 19% (OR, 1.19; 95% CI: 1.13–1.26), after adjusting for age. The prevalence of aphasia in-

Table 1. Baseline characteristics of IS patients with and without aphasia year 2017–2018

Patients with first-ever ischemic stroke				
variable	patients without aphasia (*n* = 217)	patients with aphasia (*n* = 91)	all patients (*n* = 308)	OR (95% CI)*
Age, years, median (IQR)	74 (68–81)	78 (72–86)	76 (69–82)	1.04 (1.02–1.06)
Female gender, *n* (%)	101 (47)	51 (56)	152 (49)	1.46 (0.90–2.40)
NIHSS at baseline, median (IQR)	3 (1–5)	10 (4–19)	4 (2–7)	1.25 (1.18–1.32)
Stroke risk factors†				
Hypertension	172 (79)	70 (77)	242 (79)	0.87 (0.48–1.57)
Diabetes mellitus	72 (33)	28 (31)	100 (33)	0.90 (0.53–1.52)
AF	62 (29)	34 (37)	96 (31)	1.49 (0.90–2.50)
Hypercholesterolemia	123 (57)	47 (52)	170 (55)	0.82 (0.50–1.33)
Smoking	38 (18)	11 (12)	49 (16)	0.66 (0.32–1.35)
Previous TIA	43 (20)	14 (15)	57 (19)	0.74 (0.38–1.42)
Ischemic heart disease	50 (23)	24 (26)	74 (24)	1.20 (0.68–2.10)
Heart disease	97 (45)	48 (53)	145 (47)	1.38 (0.85–2.26)
Educational level, *n* (%)				
Low ≤9 years	107 (49)	49 (54)	156 (51)	Ref
Middle ≥10 ≤12 years	53 (24)	18 (20)	71 (23)	0.74 (0.39–1.40)
High ≥12 years	57 (26)	24 (26)	81 (26)	0.92 (0.51–1.66)
TOAST classification, *n* (%)				
CE	52 (24)	33 (36)	85 (28)	1.81 (1.06–3.06)
LAA	22 (10)	16 (18)	38 (12)	1.89 (0.94–3.80)
SAO	33 (15)	2 (2)	35 (11)	0.13 (0.03–0.53)
OC	6 (3)	0	6 (2)	–
UND	104 (48)	40 (44)	144 (47)	0.85 (0.52–1.39)
OCSP, *n* (%)				
LACI	55 (25)	4 (4)	59 (19)	0.14 (0.05–0.39)
PACI	93 (43)	44 (49)	137 (45)	1.25 (0.76–2.04)
POCI	52 (24)	10 (11)	62 (20)	0.39 (0.19–0.81)
TACI	17 (8)	33 (36)	50 (16)	6.69 (3.48–12.87)

AF, atrial fibrillation; TOAST, Trial of Org in Acute Stroke Treatment [20]; NIHSS, total score on National Institutes of Health Stroke Scale; IQR, interquartile range; OCSP, The Oxfordshire Community Stroke Project [21]; CE, cardioembolism; LAA, large-artery atherosclerosis; SAO, small-artery occlusion; OC, other determined etiology; UND, undetermined etiology; LACI, lacunar infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; TACI, total anterior circulation infarct. * Comparisons between patients without aphasia and patients with aphasia according to NIHSS item 9. † Definitions of stroke risk factors according to [18, 19].

creased by 4% per each year of age among the IS patients (OR, 1.04; 95% CI: 1.02–1.06). However, after adjusting for stroke severity, this increase was barely significant (OR, 1.03; 95% CI: 1.00–1.05).

Stroke Classification

The most common TOAST category for all 308 IS patients, was undetermined (*n* = 144, 47%) followed by CE (*n* = 85, 28%). The pathogenetic mechanism for 36% of patients with aphasia (*n* = 33) was CE, which was significantly higher compared with stroke patients without aphasia (OR, 1.81; 95% CI: 1.06–3.06). However, after adjusting for stroke severity (i.e., NIHSS excluding item 9), the difference of TOAST categories between stroke patients with and without aphasia was no longer significant (OR, 1.18; 95% CI: 0.61–2.29). There was no change in association between stroke severity and aphasia also when excluding patients with SAO, a TOAST category that has a prerequisite of no cortical dysfunction such as symptoms of aphasia. Patients with aphasia more often presented with the OCSP syndrome total anterior circulation stroke (36% vs. 8%, $p < 0.001$) in comparison to stroke patients without aphasia.

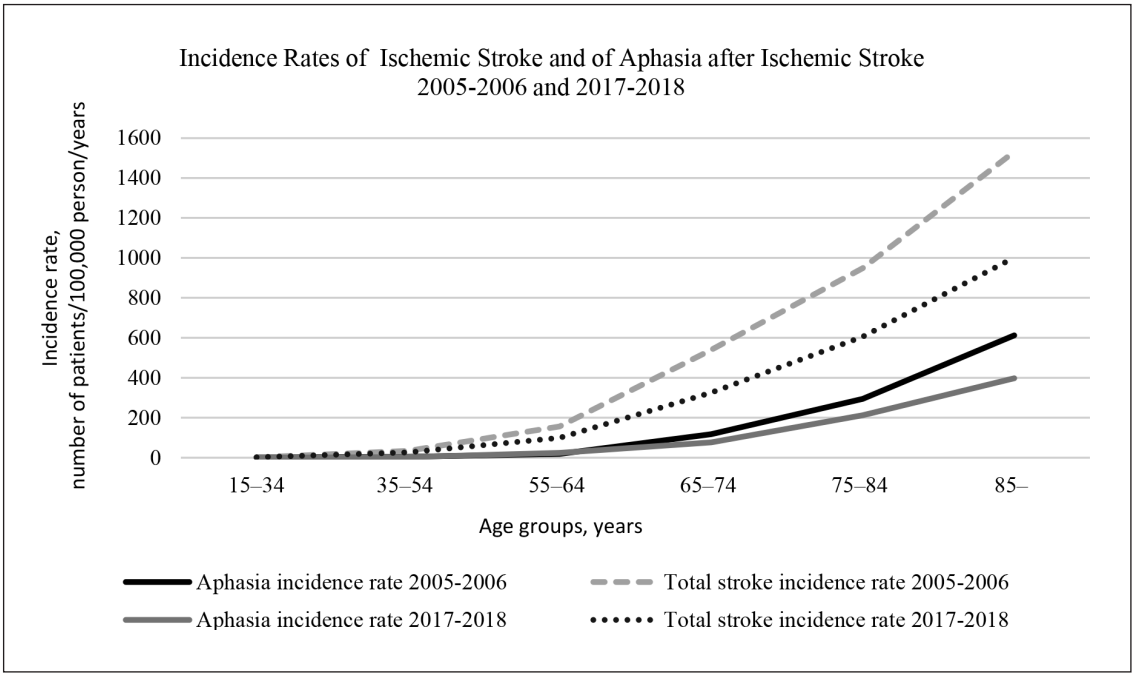

Fig. 2. Incidence rate of first-ever IS patients with and without aphasia across age groups year 2005–2006 and 2017–2018.

Temporal Changes – Incidence, Aphasia Severity, and Mortality between 2005–2006 and 2017–2018

The overall IS incidence rate decreased with 36% adjusted to the ESP between 2005–2006 and 2017–2018, from 169 per 100,000 person-years in 2005–2006 (95% CI: 154–186 per 100,000 person-years) to 108 per 100,000 person-years in 2017–2018 (95% CI: 97–121 per 100,000 person-years; Fig. 2). The proportion of stroke patients with aphasia in the acute phase of stroke onset was 27% year 2005–2006 (95% CI: 23–32%) as compared to 30% year 2017–2018 (95% CI: 25–35%), indicating that there was no significant temporal change in aphasia incidence ($p = 0.45$). The total aphasia incidence rate adjusted to the ESP decreased with 30% ($p = 0.01$) from 44 per 100,000 person-years in 2005–2006 (95% CI: 37–54 per 100,000 person-years) to 31 per 100,000 person-years in 2017–2018 (95% CI: 25–38 per 100,000 person-years). The incidence rate for males was 59 per 100,000 person-years in 2005–2006 (95% CI: 46–74 per 100,000 person-years) and 32 per 100,000 person-years in 2017–2018 (95% CI: 23–42 per 100,000 person-years), indicating a significant decrease in incidence rate for men with aphasia ($p < 0.001$). The equivalent for women was 40 per 100,000 person-years in 2005–2006 (95% CI: 30–53 per 100,000 person-years) and 31 per 100,000 person-years in 2017–2018 (95% CI: 23–41 per 100,000 person-years) ($p = 0.22$). Though not significant ($p = 0.08$), there was a trend toward a higher proportion of women with aphasia in comparison to men (26% men vs. 34% women) in 2017–2018. In 2005–2006, there was no difference between men and women (27% vs. 27%) with aphasia. In 2017–2018, stroke severity (NIHSS) was higher for women in comparison to men ($p = 0.04$), whereas in 2005–2006 the stroke severity did not differ between men and women ($p = 0.19$). Comparing the total cohort of patients, stroke severity according to NIHSS (including item 9) remained stable between 2005 and 2006 (median NIHSS = 4) and 2017–2018 (median NIHSS = 4; $p = 0.44$). There was no difference between aphasia severity year 2005–2006 and year 2017–2018 ($p = 0.35$), likewise aphasia severity between genders was equivalent 2005–2006 ($p = 0.71$) and year 2017–2018 ($p = 0.69$). Among 91 patients with aphasia in 2017–2018, 36 had mild to moderate aphasia (39%; 95% CI: 30–50), 27 had severe aphasia (30%; 95% CI: 29–40), and 28 had global aphasia (31%; 95% CI: 22–41). The corresponding figures in 2005–2006 were 49 with mild to moderate aphasia (50%; 95% CI: 40–60%), 23 with severe aphasia (23%; 95% CI: 16–33%) and 26 with global aphasia (27%; 95% CI: 19–36%; Fig. 3). The proportion of all patients with acute IS who died at hospital during the acute phase

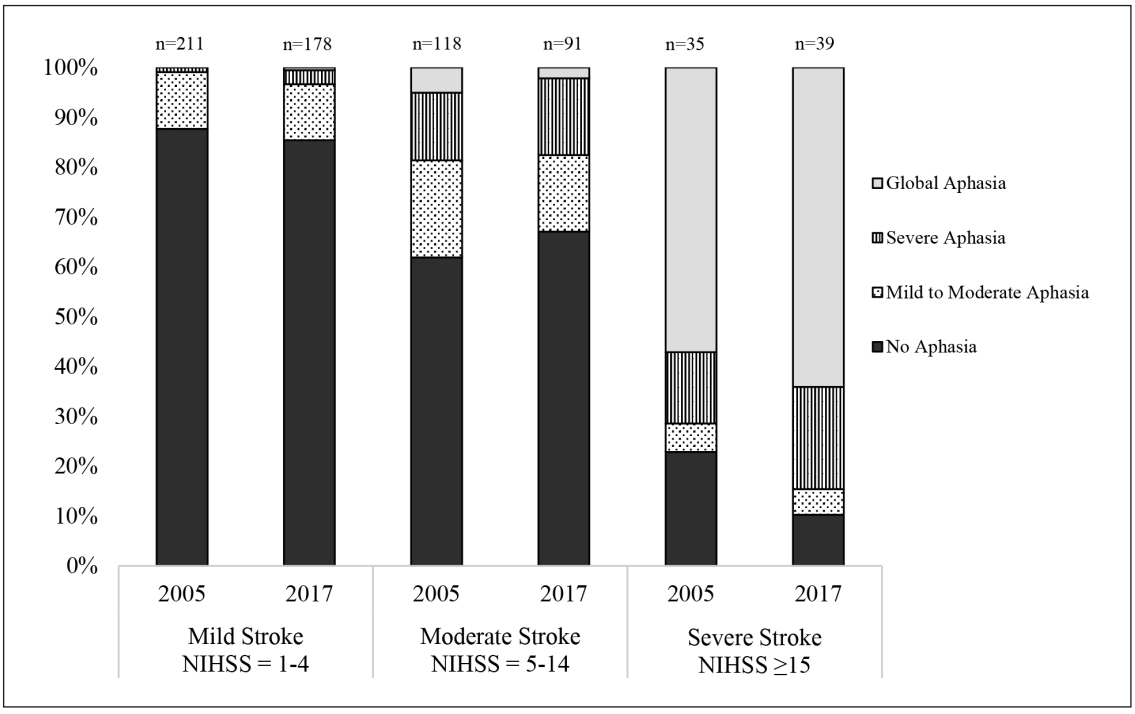

Fig. 3. Proportions of aphasia severity relative to stroke severity 2005–2006 and 2017–2018.

after stroke onset was 4% (n = 14) in 2005–2006 compared to 6% (n = 19) year 2017–2018 (no significant difference, p = 0.17). There was also no significant difference in mortality in the group of stroke patients with aphasia between year 2005–2006 and 2017–2018 (p = 0.08). However, patients with aphasia had significantly higher mortality in comparison to stroke patients without aphasia (p = 0.01), and this association remained between 2005–2006 and 2017–2018.

Discussion

The new data in this prospective study imply that despite a significant decrease in IS incidence rates during the past decade, the proportion of patients with aphasia in acute IS remains stable at approximately 30%. Aphasia was significantly associated with more severe strokes, an association that remained after removing the aphasia item from the total NIHSS score (p < 0.001). This was related to higher mortality and longer hospital stays of persons with aphasia and is in accordance with previous research [9].

A higher proportion of patients with aphasia presented with cardio-embolic stroke. This has also been reported in previous studies [12, 24], however, in our study, when adjusting for stroke severity (NIHSS excluding the aphasia item 9), cardioembolism as the underlying stroke mechanism according to TOAST was no longer significant. The probable risk of aphasia after stroke may therefore be more related to stroke severity rather than the underlying stroke mechanism. Patients with isolated subcortical infarcts may sometimes also have aphasia (e.g., if the lesion is in the thalamus), and this could be of interest to investigate in more detail in future studies.

The risk of aphasia in IS increases with age [24], and we can confirm that the odds of having aphasia increased by 4% per each year of age of stroke patients (OR, 1.04; 95% CI: 1.02–1.06). However, in contrast, when adjusting for stroke severity (NIHSS excluding the aphasia item), we found that the risk of aphasia is primarily associated with stroke severity (OR, 1.25; 95% CI: 1.18–1.32) rather than age. Nonetheless, aphasia is more frequent among older than younger stroke patients; only every seventh person with aphasia in our study was of working age (≤65), which is in line with data from previous studies [12]. The presence of vascular risk factors for stroke was equivalent between stroke patients with or without aphasia even though patients with aphasia had a tendency towards more often having AF. AF is a strong risk factor for severe strokes [25]

and may contribute to the stable initial stroke severity (NIHSS) of patients in our cohort between 2005–2006 and 2017–2018 and the steady aphasia incidence at 30%.

The incidence rate of aphasia in first-ever IS was 31 per 100,000 person-years after adjusting to the ESP [22]. The incidence rate of aphasia (ESP) decreased with 30% (i.e., from 44 to 31 per 100,000 person-years) between 2005–2006 and 2017–2018, which follows the decreasing stroke incidence rate reported in this study and in our region [16]. The decreased incidence rate of aphasia in IS was significantly more pronounced in men (decrease by 46%), while the observed trend towards decrease in women was nonsignificant (23%). This difference between men and women is of concern; however, the wide 95% CI urge for cautious interpretation and needs to be further investigated and confirmed in future studies. In contrast to previous epidemiological studies of aphasia [24, 26], we observed a trend toward a higher proportion of women having aphasia in year 2017–2018 as compared to 2005–2006. This may be explained by the change in demographics combined with the temporal change of stroke severity; where women had significantly more severe strokes in year 2017–2018 in comparison to men. Future studies investigating aphasia in relation to gender are warranted. The in-hospital mortality after stroke was similar 2005–2006 and 2017–2018 ($p = 0.17$), despite substantial changes in acute stroke treatment under the same time period. This may be related to the observed stable initial stroke severity as discussed above.

The initial severity of aphasia remained unchanged between 2005–2006 and 2017–2018, with the majority of patients (50–60%) suffering severe or global aphasia (NIHSS score on item 9 ≥ 2). This is of concern because initial severity of aphasia strongly predicts outcome [27, 28] and aphasia represents one of the most devastating consequences after stroke with subsequent impact on quality of life [28], and has even been reported to be a marker for unfavorable outcome in patients with mild stroke [29].

Our study has limitations: it is hospital-based and not population-based which might infer a potential bias because aphasia may increase the probability of hospital admission after IS stroke onset [12]. However, population-based studies have reported similar incidence of aphasia in stroke [12], even though there may have been difficulties with evaluating the presence of aphasia in patients not being clinically examined at hospital. Exclusion of 30 patients may have affected our incidence; however, we tried to mitigate the potential risk of selection bias with consecutive inclusion of patients with a comprehensive range of stroke symptoms.

As strengths, we used "hot pursuit methods" to prospectively include patients from a well-defined population, during a defined time period. A high proportion of hospitalized IS patients was included in our study (91%). In addition, the local uptake area has only one hospital for acute stroke admissions and the rate of hospital admission for IS is high [16].

The use of NIHSS item 9 to identify aphasia can be discussed. However, we have previously validated NIHSS item 9 for this purpose and shown that NIHSS has acceptable diagnostic accuracy for detecting aphasia after acute stroke [30]. More comprehensive aphasia test batteries are often too demanding for the acute stroke patient and have long administration times, making them difficult to implement in the acute setting and leaving some patients not being evaluated regarding aphasia.

We did not include recurrent stroke patients and patients with aphasia caused by other mechanisms, consequently our findings may underestimate the total overall incidence rate of all patients with aphasia in the population. There have been temporal changes in acute stroke care in Sweden between 2005 and 2017 with an increase of recanalization treatment from 3% to 15% [31]. This may have reduced the long-term prevalence of aphasia after stroke, as well as affected stroke morbidity. We did not study possible changes of stroke morbidity in detail but the NIHSS in the acute phase was median 4 (IQR 2–8) in 2005–2006 and median 4 (IQR 2–7) in 2017–2018, indicating that acute stroke severity did not differ between the two periods. The Swedish Stroke Register (Riksstroke), however, reports that at 3 months after stroke onset, 22% were dependent in their activities of daily living (ADL) in 2005 compared to 17% year 2017 [31]. Even though not influencing the incidence of aphasia at stroke onset, current advanced acute stroke treatments may therefore have effect on the subsequent outcome of aphasia and studies examining this and how aphasia may be related to stroke morbidity and prognosis are warranted.

In recent years, the effects of aphasia therapy on recovery and the importance of intensive aphasia therapy on outcome have been highlighted [32, 33]. For the first time, intensive aphasia therapy and communication partner training was stressed in the stroke guidelines from Swedish National Board of Health and Welfare [34] in 2017–2018. Future research on improved aphasia treatment in relation to a potential reduced aphasia prevalence after stroke is needed.

In conclusion, the incidence rate of aphasia after IS has decreased, yet the proportion of IS patients with initial aphasia remains unchanged. The continued high inci-

dence of aphasia emphasizes the importance of consistent language screening of stroke patients in the acute phase to ensure optimal management. Future studies providing data on prevalence and recovery of aphasia after the acute phase are warranted to ascertain up-to-date knowledge on the long-term prognosis and burden of aphasia.

Acknowledgment

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Statement of Ethics

The study was approved by the Regional Ethical Review Authority in Lund (registration number 2016/179). Written consent was obtained from patients or from their next of kin to participate in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

All authors contributed to the study conception. Acquisition of data was performed by Angelina Grönberg and Martin Stenman, and analysis and interpretation of data was performed by all authors. Supervision was performed by Ingrid Henriksson and Arne G. Lindgren. An original draft was composed by Angelina Grönberg, and all authors revised previous versions of the manuscript and approved the final manuscript.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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