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ORIGINAL ARTICLE

Large disparities in 28-day case fatality by stroke subtype: data from a French stroke registry between 2008 and 2017

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Abstract

Background and purpose: The objectives of the present analysis were to assess 28-day stroke case fatality according to the stroke aetiology and to identify associated factors.

Methods: All stroke events in adults aged ≥ 35 years between 2008 and 2017 were collected in a population-based stroke registry in northern France.

Results: Out of a total of 2933 strokes, there were 479 (16%) haemorrhagic strokes and 2454 (84%) ischaemic strokes; the 28-day case fatality rates were 48% and 15%, respectively. Three-quarters of the 28-day case fatalities occurred within 6 days of the event for haemorrhagic strokes and within 16.5 days for ischaemic strokes. After an ischaemic stroke, the case fatality rate was higher for women (18%) than for men (12%, $p < 0.0001$); however, this difference disappeared after adjustment for age. Cardioembolic strokes (34%) and strokes of undetermined cause (33%) were the most common ischaemic subtypes, with case fatality rates of 16% and 18%, respectively. Large artery atherosclerosis (11%) and lacunar strokes (10%) were less common, and both types had a case fatality rate of 3%. Age at the time of the event and stroke severity were both significantly associated with case fatality. For some types of stroke, a history of cardiovascular events and residence in a nursing home were associated with a poor prognosis. Medical care in a neurology ward was inversely associated with case fatality, for all stroke subtypes.

Conclusions: In northern France, post-stroke case fatality remains high, especially for haemorrhagic stroke. Being treated in a neurology ward improved survival by around 80%.

KEYWORDS

case fatality, haemorrhagic stroke, ischaemic stroke, registry, TOAST

INTRODUCTION

Case fatality rates for acute stroke vary markedly from one study to another; these disparities might be directly related to the stroke's aetiology [1,2]. Furthermore, studies in Europe differ with regard to the enrolment criteria, design (hospital-based observational studies

vs. population-based registries), age range and stroke aetiology ascertainment. Geographical disparities might also be ascribable to differences in the population's socioeconomic status or in national medical care strategies [3–7].

Better knowledge of short-term post-stroke outcomes and case fatality as a function of the aetiology may help neurologists to give

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a more accurate prognosis. However, literature data on 28-day case fatalities for the various ischaemic stroke subtypes are scarce [8–11]. In France, stroke case fatality has been studied in the Dijon stroke registry [4,5,12] and in hospital-based administrative databases [13,14]. However, the latter do not include information on outpatient events and do not enable a detailed analysis by ischaemic stroke subtype.

In order to expand the data on stroke mortality in Europe, the objectives of the present study were (i) to assess and compare 28-day stroke case fatality rates as a function of the stroke aetiology and (ii) to identify factors possibly associated with case fatality in a region of France where the vascular risk is high. To this end, the exhaustive data recorded in a population-based stroke registry in the city of Lille (northern France) between 2008 and 2017 were analysed.

METHODS

The Lille Stroke Registry was created in 2008. All stroke events in adults aged 35 or over living in the city itself or the adjoining towns of Lomme and Hellemmes are recorded.

Each stroke event registered between 1 January 2008 and 31 December 2017 was included in the present analysis. According to the French national census in 2016, the area covered by this population-based registry contains a total of 232,737 inhabitants, of whom 94,331 were aged 35 or over. Cases of stroke were identified using several overlapping sources of case ascertainment in all the public- and private-sector hospitals, nursing homes, emergency departments and neurology departments in the area covered. The sources were cross-checked to ensure exhaustiveness, with notably a review of discharge letters, radiography department records, computerized lists covering the diagnosis upon discharge from hospital, emergency department case lists and death certificates. All incident (first-ever) and recurrent strokes were taken into account, regardless of whether or not the patient had been hospitalized. Cases of stroke were defined according to the World Health Organization's criteria as 'a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 h (or leading to death), and of presumed vascular origin' [15]. The cases were assessed on the basis of the patient's medical history (symptoms for more than 24 h), clinical examinations and radiological data. The patient's medical records and the registry database were screened for previous strokes.

Patients having experienced a transient ischaemic attack (i.e., an event whose cognitive and neurological symptoms disappeared within 24 h), brain tumour, multiple sclerosis, epilepsy, intracerebral haemorrhage or subdural haematoma related to traumatic brain injury were not included in the registry. In contrast, patients having recovered within 24 h of thrombolysis or thrombectomy were included. The stroke subtype was diagnosed on the basis of clinical signs and cerebral imaging. Radiographic data were used to define the stroke as an ischaemic stroke, a spontaneous intracerebral haemorrhage, a subarachnoid haemorrhage (excluded from this analysis)

or a stroke that could not be classified as ischaemic or haemorrhagic (also excluded from this analysis).

In 2017, the mean \pm standard deviation number of data sources per case was 3.8 ± 1.1 . Internal quality controls showed that only 1%–3% of cases are missing from the registry (cases occurring outside the area).

Aetiologies of ischaemic stroke

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria were used to define the five major pathophysiological subtypes of ischaemic stroke: cardioembolic stroke, large artery atherosclerosis, lacunar stroke, stroke of other determined causes (such as vasculitis or dissection) and stroke of undetermined cause [16].

Recorded variables

Survival was evaluated at 28 days post-stroke. All deaths were checked with the patient's family physician, in the local office of vital records and in the French national death certificate database. From 2008 onwards, the presence or absence of the following risk factors was recorded: previous stroke, a history of cardiovascular disease, a history of atrial fibrillation (AF) and place of treatment. From 2012 onwards, neurological impairments were assessed using the National Institute of Health Stroke Scale (NIHSS) score [17] on admission. On the basis of the NIHSS score, stroke severity was categorized as minor/moderate (score <15) or severe (score ≥ 15). The place of medical care was coded as a neurology department (neurology or neurosurgery departments in private- or public-sector hospitals) or another type of department (other departments in private- or public-sector hospitals or in nursing homes or rehabilitation units). The other variables were categorized as being present or absent.

Statistical analyses

Qualitative variables were compared using a chi-squared test and Fisher's exact test. Quantitative variables were compared using Student's *t* test. The survival time was defined as the time interval between the date of stroke symptom onset and the date of death. The 28-day case fatality rates were compared using proportion tests. Survival was analysed using the Kaplan–Meier method and (when valid) the log-rank test. Lastly, for deceased patients, the time between stroke onset and death was depicted as a box plot for each stroke subtype and compared using the Kruskal–Wallis test. Age- and sex-adjusted Cox regression models were built to assess the relationships between case fatality and variables of interest. Possible interactions with sex were investigated by including an interaction term in the model. All statistical analyses were performed with R software (version 3.5) [18] and the threshold for statistical significance was set to $p < 0.05$.

Ethics

Implementation of the Lille Stroke Registry had been approved by the French National Registry Committee (Comité National des Registres reference 2015/04/07) and the French National Institute for Public Health (Santé Publique France). The present study was authorized by the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, Paris, France; reference 986001 V 3). All data were anonymized prior to analysis.

RESULTS

Between 2008 and 2017, 3131 strokes of all types were recorded. A total of 103 meningeal haemorrhages and 91 non-specified strokes were excluded. Four patients were lost to follow-up at 28 days. The analyses were therefore based on 2933 strokes, of which 2332 (80%) were incident (first-ever).

The 2933 cases comprised 479 haemorrhagic strokes (16%) and 2454 ischaemic strokes (84%). When considering the ischaemic strokes, 34% were cardioembolic, 33% were of undetermined cause, 11% were due to large artery atherosclerosis, 10% were lacunar and 5% had other causes. In addition to the TOAST subtypes, 5% of the cases were 'probable' cerebral infarctions and 2% were cerebral infarctions with two or more causes (data not shown).

The proportion of women was higher for ischaemic strokes (and especially cardioembolic strokes: 64%, $p < 0.01$), whereas the proportion of men was slightly higher for large artery atherosclerosis (60%, $p < 0.01$) (Table 1). Depending on the type of stroke, women patients were 4–9 years older than men patients. There were significant differences in the risk factor distribution from one ischaemic stroke subtype to another (Table 1). The proportion of patients with a history of cardiovascular disease was lower for haemorrhagic strokes than for ischaemic strokes (14% and 20%, respectively; $p < 0.01$). The mean NIHSS score on admission was 11.8 for haemorrhagic strokes and 7.2 for ischaemic strokes ($p < 0.0001$). The proportion of patients treated in a neurology ward was higher for ischaemic strokes than for haemorrhagic strokes (81% and 63%, respectively; $p < 0.0001$). With regard to the ischaemic stroke subtypes, patients with cardioembolic stroke were more likely to have a history of cardiovascular disease (26%) and AF (57%) than patients with other types. The highest NIHSS score (9.1) amongst ischaemic stroke subtypes was observed for cardioembolic strokes.

The 28-day survival rate was lower after a haemorrhagic stroke than after an ischaemic stroke ($p < 0.0001$) (Figure 1a); furthermore, three-quarters of the 28-day deaths occurred in the first 6 days for haemorrhagic strokes and the first 16.5 days for ischaemic strokes ($p < 0.0001$) (Figure 1b). The respective time intervals for men and for women did not differ significantly (data not shown).

The 28-day survival rate was higher for large artery or lacunar strokes than for other ischaemic stroke aetiologies ($p < 0.0001$) (Figure 2a). The time interval between an ischaemic stroke and death

differed according to the aetiology ($p < 0.05$) (Figure 2b). Many of the 28-day deaths occurred in the third week for lacunar stroke, and half of the deaths occurred in the first week for the other aetiologies.

Table 2 gives the 28-day case fatality rates by sex, age and stroke aetiology. The case fatality rate was higher after a haemorrhagic stroke than an ischaemic stroke (48% vs. 15%, respectively; $p < 0.0001$). There was no difference in the 28-day case fatality rate between men and women after a haemorrhagic stroke (46% and 51%, respectively; $p = 0.24$), whereas the rate was significantly higher in patients aged 75 and over than in patients under the age of 75 (54% and 41%, respectively; $p < 0.01$). After an ischaemic stroke, the case fatality was significantly higher in women than men (18% vs. 12%, respectively; $p < 0.0001$) and significantly higher in patients aged ≥ 75 than in patients < 75 (21% and 8%, respectively; $p < 0.0001$). A statistically significant interaction between sex and age ($p < 0.05$) was observed for case fatality after an ischaemic stroke: 9% and 7% respectively for men and women < 75 ($p = 0.34$), and 17% and 23% for men and women aged ≥ 75 ($p < 0.05$). However, sex was no longer associated with case fatality after adjustment for age.

The 28-day case fatality rates were lowest for large artery atherosclerosis or a lacunar stroke (3%; $p < 0.0001$ compared with the 28-day case fatality rate for cardioembolic stroke). For cardioembolic stroke, stroke of undetermined causes and stroke due to other causes, the case fatality rates were 16%, 18% and 19%, respectively (Table 2). The case fatality rates by stroke subtype including incident events only are presented in Table S1. The results were similar to those observed for stroke events as a whole.

Table 3 shows the adjusted hazard ratios (HRs) for 28-day case fatality and clinical characteristics, by stroke aetiology. Age > 75 was significantly associated with case fatality after a haemorrhagic stroke (HR 1.5), a cardioembolic stroke (HR 2.1) and a stroke of undetermined cause (HR 4.5). Having a previous stroke was a risk factor for cardioembolic stroke only (HR 1.8), whereas a history of cardiovascular disease or a history of AF were risk factors for strokes of undetermined cause only (HR 1.8 and 2.6, respectively). Living in a nursing home was a risk factor for case fatality after a cardioembolic stroke (HR 1.7) and a stroke of undetermined cause (HR 1.6). Treatment in a neurology department was inversely associated with case fatality for all stroke subtypes ($0.1 < HR < 0.4$). The risk factor with the largest effect size for case fatality for all stroke subtypes (except for lacunar stroke) was an NIHSS score of 15 or more. Indeed, a less severe haemorrhagic or ischaemic stroke was associated with better survival ($p < 0.0001$; Figure 3). Lastly, the very small number of deceased events after large artery atherosclerosis and lacunar stroke prevented us from assessing associations in these groups.

DISCUSSION

In the population-based Lille Stroke Registry, the 28-day case fatality after stroke remained high between 2008 and 2017, especially for haemorrhagic stroke. For ischaemic strokes, the case fatality ranged

TABLE 1 Baseline characteristics of patients by stroke subtype in the Lille Stroke Registry, 2008–2017

	Haemorrhagic stroke	Ischaemic stroke subtypes							
		Ischaemic stroke	p	Cardioembolic	Undetermined cause	Large artery atherosclerosis	Lacunar	Other cause	p
Number	479 (16)	2454 (84)		840 (34)	815 (33)	271 (11)	247 (10)	113 (5)	
Women	251 (52.4)	1365 (55.6)	0.19	541 (64.4)	447 (54.8)	109 (40.2)	120 (48.6)	54 (47.8)	<0.0001
Age, years	74 ± 14	74 ± 14	0.41	78 ± 13	73 ± 15	73 ± 12	73 ± 14	61 ± 16	<0.0001
Age (men), years	69 ± 14	70 ± 13	0.28	73 ± 12	69 ± 14	71 ± 12	69 ± 14	59 ± 13	<0.0001
Age (women), years	78 ± 14	77 ± 14	0.76	81 ± 12	76 ± 15	75 ± 12	76 ± 12	63 ± 19	<0.0001
Previous stroke	83 (17.6)	501 (20.5)	0.15	193 (23.1)	136 (16.7)	39 (14.4)	44 (17.9)	29 (25.9)	<0.001
Previous CV disease	66 (14.1)	488 (20.0)	<0.01	220 (26.3)	129 (15.9)	53 (19.6)	31 (12.6)	12 (10.7)	<0.0001
Previous atrial fibrillation	109 (23.2)	650 (26.6)	0.13	477 (56.9)	89 (10.9)	14 (5.2)	12 (4.9)	10 (8.9)	<0.0001
NIHSS score on admission ^a	11.84 ± 8.2	7.22 ± 7.2	<0.0001	9.12 ± 8.1	6.42 ± 6.5	7.54 ± 6.8	3.88 ± 3.1	5.91 ± 7.7	<0.0001
Residence in a nursing home	43 (11.6)	218 (11.1)	0.77	89 (12.5)	71 (11.1)	10 (4.9)	18 (9.0)	4 (4.2)	<0.01
Treated in a neurology ward	295 (62.8)	1957 (80.7)	<0.0001	706 (84.9)	619 (77.1)	239 (89.2)	221 (90.2)	80 (70.8)	<0.0001

Note: Values are quoted as n (%) or the mean ± standard deviation.

Abbreviations: CV, cardiovascular; NIHSS, National Institute of Health Stroke Scale.

^aRecorded in the registry since 2014 only.

p from a chi-squared test or Student's *t* test.

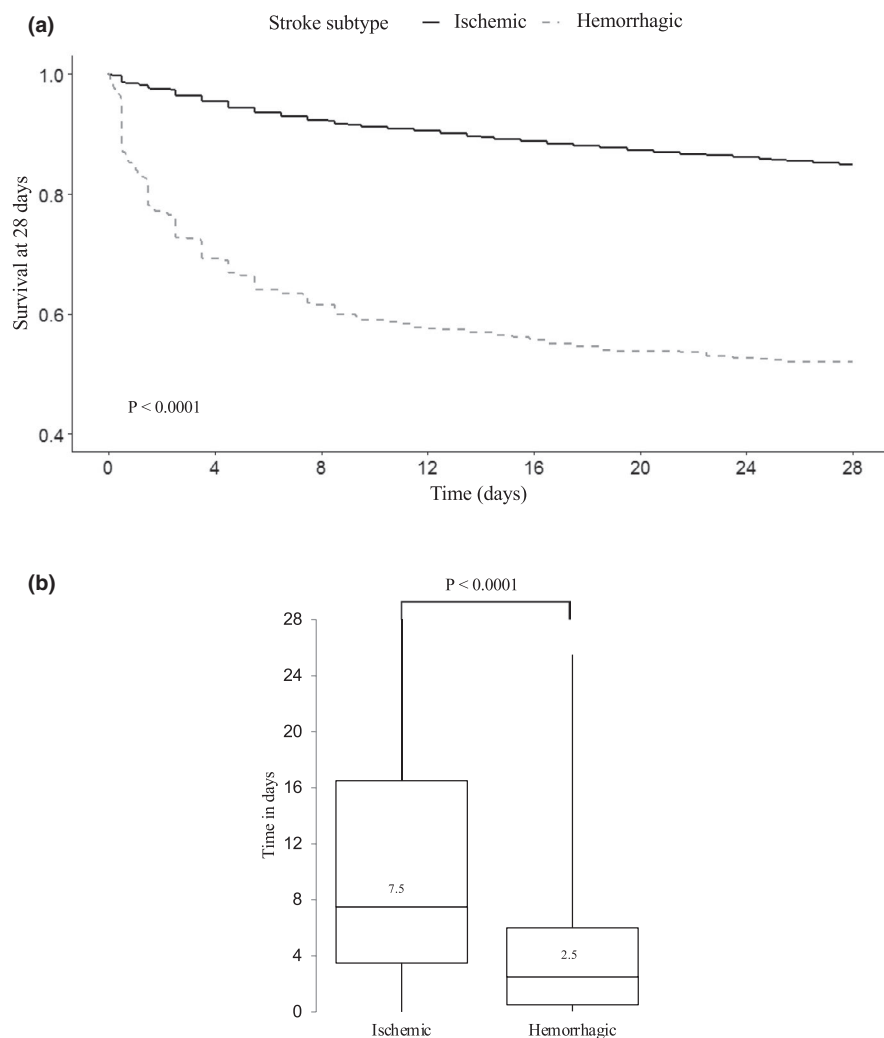


FIGURE 1 Survival and the time interval between the onset of stroke and death, by stroke subtype, Lille Stroke Registry, 2008–2017. (a) Survival curve at 28 days by stroke subtype. (b) Box plot of delay (in days) between the onset of stroke and death, by stroke subtype

widely according to the aetiology: from 3% in large artery and lacunar strokes to 15%–20% for the other ischaemic stroke subtypes. In addition to stroke aetiology, age and stroke severity were the main predictors of 28-day case fatality. Treatment in a neurology department was associated with improved survival for all stroke subtypes.

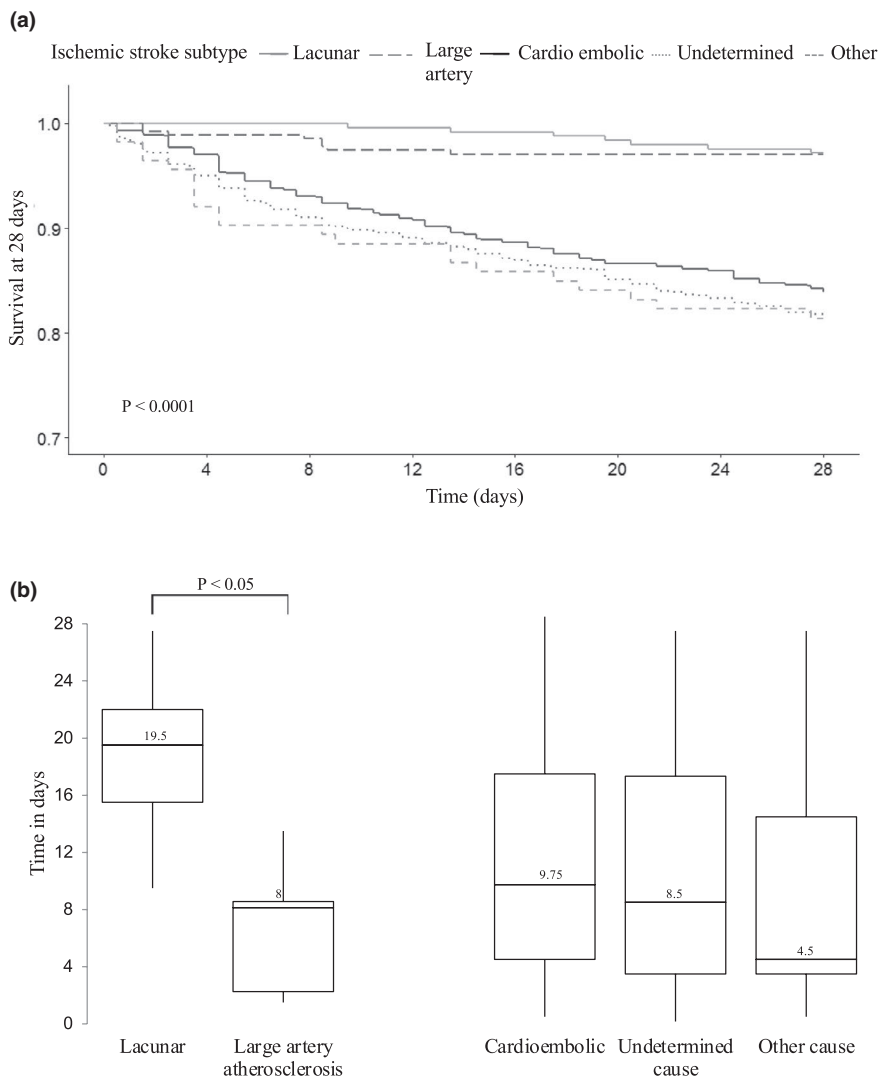
Haemorrhagic and ischaemic strokes accounted for 16% and 84% respectively of the stroke events in this population-based registry. The 28-day case fatality rate was three times higher for haemorrhagic stroke than for ischaemic stroke. Our findings confirm earlier observations in Europe and worldwide [3,7,19] and extend them to a European region in which the vascular risk is high [20,21]. Although haemorrhagic strokes were less frequent than ischaemic strokes, the prognosis for the former was far less favourable. For haemorrhagic strokes, 75% of the 28-day deaths occurred in the first week after the event, compared with 50% of the deaths for ischaemic strokes.

In line with data from other population-based studies in Europe [10,22,23] large artery atherosclerosis and lacunar strokes accounted for 11% and 10% of all ischaemic strokes, respectively, whereas cardioembolic stroke and stroke of undetermined cause were more frequent (34% and 33%, respectively). Subtype-specific data on 28-day case fatalities are scarce. In the present study, the rate for large artery atherosclerosis (3%) was in the lower range of

values reported elsewhere (between 3% and 17%). This observation may be related to the recent improvements in stroke management in northern France—the use of mechanical thrombectomy for large artery occlusions, for example [24]. The favourable prognosis after lacunar stroke (3%) observed here was in line with the literature range (i.e., case fatality rates between 1% and 4%), and similar rates were found elsewhere for stroke of undetermined cause (between 13% and 26%) [5,12,25–30]. Lastly, the 28-day case fatality rate for cardioembolic stroke (16%) was slightly lower than the values reported in other studies (between 17% and 30%). This difference might have been due to better prophylaxis of cardioembolic stroke with new-generation anticoagulants (resulting in smaller strokes caused by subclinical AF) or the benefits of overall vascular risk factor management [31]. Of note, concerning reperfusion therapy, the proportion of patients treated after an ischaemic stroke during the study period was 15% (14% for intravenous recombinant tissue plasminogen activator between 2008 and 2017, and 6% for mechanical thrombectomy since 2014; data not shown).

Age has been consistently linked to case fatality after haemorrhagic and ischaemic strokes [28,29,32]. In the present study, the mean age was 4–9 years higher amongst women than amongst men for all stroke subtypes, suggesting that women are protected against

FIGURE 2 Survival and the time interval between stroke onset and death, by ischaemic stroke subtype, in the Lille Stroke Registry, 2008–2017. (a) Survival at 28 days by ischaemic stroke subtype. (b) Time interval (in days) between the onset of stroke and death, by ischaemic stroke subtype



cerebrovascular events at a younger age. With respect to stroke aetiology, there was no difference in the case fatality rate between men and women after a haemorrhagic stroke. In contrast, the case fatality after ischaemic stroke was higher in women over 75. However, this difference disappeared after adjustment for age, which indicates that

age contributed to the sex difference. Another confounding factor may possibly be stroke severity. As stroke severity from 2012 has been recorded in the registry, analyses using the 2012–2017 subsample were also performed and HRs of 28-day case fatality for stroke severity were further adjusted. The adjusted data confirmed that there

TABLE 2 Crude case fatality rate by stroke subtype, overall and by sex and age in the Lille Stroke Registry, 2008–2017

	Total	Men	Women	p	<75 years of age	≥75 years of age	p
Haemorrhagic stroke	48 [44; 53]	46 [39; 52]	51 [45; 57]	0.24	41 [35; 48]	54 [48; 60]	<0.01
Ischaemic stroke	15 [14; 17]	12 [10; 14]	18 [16; 20]	<0.0001	8 [7; 10]	21 [19; 23]	<0.0001
Cardioembolic	16 [14; 19]	12 [9; 17]	19 [16; 22]	<0.05	9 [6; 13]	20 [17; 24]	<0.0001
Undetermined cause	18 [16; 21]	16 [12; 20]	20 [17; 24]	0.09	7 [5; 10]	29 [25; 33]	<0.0001
Large artery atherosclerosis	3 [2; 6]	1 [0; 5]	6 [3; 11]	0.06	1 [0; 5]	5 [2; 10]	0.15
Lacunar	3 [1; 6]	2 [0; 6]	4 [2; 10]	0.27	2 [0; 6]	4 [2; 9]	0.45
Other cause	19 [12; 27]	17 [9; 28]	20 [12; 33]	0.64	17 [11; 26]	24 [11; 43]	0.43

Notes: Case fatality rates are reported as the percentage [95% confidence interval]. p from a chi-squared test.

TABLE 3 Hazard ratios for 28-day case fatality by clinical characteristic and stroke subtype in the Lille Stroke Registry, 2008–2017

	Ischaemic stroke subtype													
	Haemorrhagic stroke	p	Ischaemic stroke	p	Cardioembolic	p	Undetermined cause	p	Large artery atherosclerosis	p	Lacunar	p	Other cause	p
N deceased/N total	232/479		380/2454		138/840		149/815		8/271		7/247		21/113	
Women vs. men ^a	1 [0.8; 1.3]	0.98	1.2 [0.9; 1.4]	0.2	1.1 [0.8; 1.7]	0.54	0.9 [0.6; 1.2]	0.35	4.0 [0.8; 20.2]	-	2.0 [0.4; 10.8]	-	1.1 [0.5; 2.7]	0.81
Age ≥75 years ^b	1.5 [1.1; 1.9]	<0.01	2.5 [2.0; 3.2]	<0.0001	2.1 [1.4; 3.4]	<0.0001	4.5 [3.0; 6.8]	<0.0001	3.1 [0.6; 15.7]	-	2.0 [0.4; 11.0]	-	1.3 [0.5; 3.6]	0.60
Previous stroke ^c	1.3 [0.9; 1.8]	0.11	1.5 [1.2; 1.9]	<0.001	1.8 [1.3; 2.6]	<0.001	0.8 [0.5; 1.3]	0.36	1.0 [0.1; 8.4]	-	0.9 [0.1; 7.8]	-	1.2 [0.5; 3.2]	0.70
History of cardiovascular disease ^c	1.3 [0.9; 1.9]	0.14	1.5 [1.2; 1.9]	<0.001	1.2 [0.8; 1.7]	0.44	1.8 [1.2; 2.6]	<0.01	0.6 [0.1; 4.9]	-	2.8 [0.5; 15.9]	-	1.3 [0.8; 6.9]	0.14
Previous atrial fibrillation ^c	1.2 [0.9; 1.6]	0.23	1.4 [1.2; 1.8]	<0.005	1.1 [0.8; 1.6]	0.51	2.6 [1.8; 3.8]	<0.0001	4.0 [0.7; 24.4]	-	NC	-	1.6 [0.4; 6.5]	0.50
NIHSS score ≥15 ^{c,d}	5.3 [2.5; 11.1]	<0.0001	6.9 [4.5; 10.6]	<0.0001	7.1 [3.8; 13.3]	<0.0001	5.9 [2.9; 12.3]	<0.0001	6.4 [0.5; 75.9]	-	NC	-	19.6 [2.0; 193.6]	<0.05
Residence in a nursing home ^c	1.1 [0.7; 1.7]	0.83	1.8 [1.4; 2.4]	<0.0001	1.7 [1.1; 2.7]	<0.05	1.6 [1.1; 2.5]	<0.05	NC	-	4.6 [0.8; 26.3]	-	NC	-
Treated in a neurology ward ^c	0.1 [0.1; 0.2]	<0.0001	0.22 [0.2; 0.3]	<0.0001	0.3 [0.2; 0.4]	<0.0001	0.4 [0.3; 0.5]	<0.0001	0.2 [0.1; 0.9]	-	0.1 [0; 0.5]	-	0.1 [0; 0.2]	<0.0001

Notes: Adjusted hazard ratios are quoted with their 95% confidence interval.

p values for large artery atherosclerosis and lacunar strokes were not calculated due to the small number of deceased patients.

On the basis of the NIHSS score, stroke severity was categorized as not severe (score <15) or severe (score ≥15).

Abbreviations: NC, not calculable, as there was at least one zero cell; NIHSS, National Institute of Health Stroke Scale.

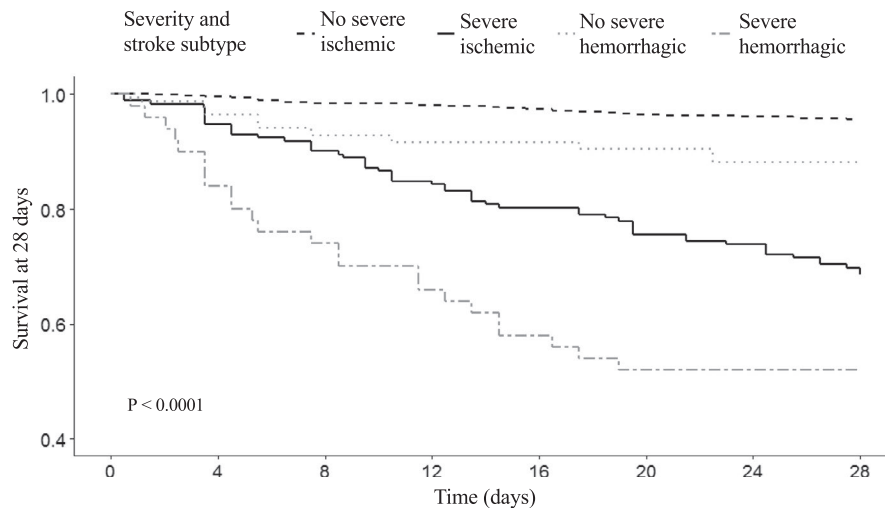
^aAdjusted for age.

^bAdjusted for sex.

^cAdjusted for age and sex.

^dRecorded in the registry since 2014 only.

FIGURE 3 28-day survival by stroke severity and stroke subtype, Lille Stroke Registry, 2008–2017. On the basis of the NIHSS score, stroke severity was categorized as not severe (score <15) or severe (score ≥15)



was no difference in case fatality between men and women and that in fact the apparent sex difference was mainly due to age (Table S2). This hypothesis is consistent with a recent meta-analysis in which the higher case fatality observed in women versus men was mostly related to their older age [33]. Therefore, as seen for coronary heart disease, women appear to be protected from vascular complications until later in life. This sex advantage might disappear in the future, once the impact of smoking amongst women—a habit that increased significantly in the 1980s—becomes effective.

In the present study, a previous stroke, a history of cardiovascular disease and a history of AF were strongly associated with 28-day case fatality after an ischaemic stroke [34,35]. The association with a previous stroke was more pronounced for cardioembolic stroke, whereas the association with a history of cardiovascular disease was more pronounced for stroke of undetermined cause. AF is a mortality risk factor for ischaemic stroke [34–36]. In the present study, this relationship was particularly strong for strokes of undetermined cause; this association might be linked to the high proportion of cardioembolic events amongst cryptogenic strokes.

In agreement with earlier reports, stroke severity (as assessed by the NIHSS score) was strongly associated with case fatality after ischaemic stroke [28,29,32]; depending on the aetiological subtype, the risk was multiplied by as much as 20. Furthermore, the risk of death after a cardioembolic stroke or a stroke of undetermined cause was 1.7 times greater in nursing home residents than in people living at home; this might reflect increased frailty in elderly people [28,29,37,38]. Lastly, treatment in a neurology department was associated with 60%–90% lower case fatality rates for all stroke subtypes, showing the benefit of being treated in a specific department with expertise in neurological disorders and confirming the beneficial effects of the French national guidelines [39]. However, an inverse relationship in which (i) the most severe patients died very quickly at the emergency wards and therefore do not reach the neurological ward or (ii) people already hospitalized with severe comorbidities or elderly people in nursing homes are not transferred into the neurological ward, due to their associated pathologies or frailty, cannot be ruled out.

Our study had several limitations. First, the lack of baseline and post-stroke modified Rankin scale scores limited our knowledge of the prognosis. Secondly, the analyses were performed only on data from subjects aged 35 and over, since events in younger people were not recorded before January 2016 in the registry. Lastly, the numbers of cases for the rarest stroke aetiologies were relatively low, which limited the analyses' statistical power, especially for the analysis of trends in case fatality rates during the studied period. The study also had a number of strengths. The use of a population-based registry of in-hospital and out-of-hospital cases in a defined geographical area enabled us to exhaustively assess events and accurately analyse the case fatality data. Furthermore, there were very few missing data on 28-day vital status during the study period (2008–2017), since only four patients (0.13%) were lost to follow-up and the proportion of undetermined strokes, usually characterized by high early case fatality rates, was very low, contrary to what can be found in administrative economic databases [1,14]. Lastly, the present study was one of the largest yet to assess short-term survival as a function of the aetiology of ischaemic strokes; our findings might help neurologists to determine the patient's prognosis more reliably.

In conclusion, the present results (collected over a recent 10-year period) extended the literature data for Europe and provided a thorough description of short-term stroke case fatality rates at the population level. Our findings indicate that stroke aetiology is an important source of prognostic variability and that being treated in a neurology ward improved survival by around 80%.

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CONFLICT OF INTERESTS

The authors have no competing interests or conflicts of interest.

AUTHOR CONTRIBUTIONS

Victoria Gauthier: Formal analysis (lead); methodology (lead); writing original draft (lead). **Dominique Cottel:** Data curation (equal); methodology (equal); validation (equal); writing review and editing (equal). **Philippe Amouyel:** Funding acquisition (lead); methodology (equal); project administration (equal); resources (equal); writing review and editing (equal). **Jean Dallongeville:** Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); writing review and editing (equal). **Aline Meirhaeghe:** Conceptualization (equal); investigation (equal); methodology (equal); supervision (lead); validation (equal); writing review and editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Lecoffre C, De Peretti C, Gabet A, et al. National trends in patients hospitalized for stroke and stroke mortality in France, 2008 to 2014. *Stroke*. 2017;48:2939-2945.
- De Peretti C, Gabet A, Lecoffre C, Oberlin P, Olié V, Woimant F. Regional disparities in acute and post-acute care of stroke patients in France, 2015. *Rev Neurol*. 2018;174:555-563.
- Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. *Presse Med*. 2016;45:e391-e398.
- Béjot Y, Grelat M, Delpont B, et al. Temporal trends in early case-fatality rates in patients with intracerebral hemorrhage. *Neurology*. 2017;88:985-990.
- Bejot Y, Catteau A, Caillier M, et al. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. *Stroke*. 2008;39:1945-1951.
- Wolfe CDA. Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London Stroke Register. *J Neurol Neurosurg Psychiatry*. 2002;72:211-216.
- Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*. 2009;8:355-369.
- Saber H, Thrift AG, Kapral MK, et al. Incidence, recurrence, and long-term survival of ischemic stroke subtypes: a population-based study in the Middle East. *Int J Stroke*. 2017;12:835-843.
- Martinez-Majander N, Aarnio K, Pirinen J, et al. Embolic strokes of undetermined source in young adults: baseline characteristics and long-term outcome. *Eur J Neurol*. 2018;25:535-541.
- Kolominsky-Rabas PL, Weber M, Gefeller O, Neundorfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke*. 2001;32:2735-2740.
- Sacco S, Marini C, Totaro R, Russo T, Cerone D, Carolei A. A population-based study of the incidence and prognosis of lacunar stroke. *Neurology*. 2006;66:1335-1338.
- Bejot Y, Rouaud O, Durier J, et al. Decrease in the stroke case fatality rates in a French population-based twenty-year study. *Cerebrovasc Dis*. 2007;24:439-444.
- Lecoffre C, De Peretti C, Gabet A, et al. Mortalité par accident vasculaire cérébral en France en 2013 et évolutions 2008-2013. *BEH*. 2017;5:95-101.
- Gabet A, Grimaud O, de Peretti C, Béjot Y, Olié V. Determinants of case fatality after hospitalization for stroke in France 2010 to 2015. *Stroke*. 2019;50:305-312.
- World Health Organization. Noncommunicable Diseases and Mental Health Cluster. WHO STEPS stroke manual: the WHO STEPwise approach to stroke surveillance/Noncommunicable Diseases and Mental Health, World Health Organization: World Health Organization; 2005. <https://apps.who.int/iris/handle/10665/43420>
- Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35-41.
- Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864-870.
- R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019. <https://www.r-project.org/>
- Van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. 2010;9:167-176.
- Tuppin P, Ricci-Renaud P, de Peretti C, et al. Antihypertensive, antidiabetic and lipid-lowering treatment frequencies in France in 2010. *Arch Cardiovasc Dis*. 2013;106:274-286.
- Wagner A, Sadoun A, Dallongeville J, et al. High blood pressure prevalence and control in a middle-aged French population and their associated factors: the MONA LISA study. *J Hypertens*. 2011;29:43-50.
- Petty GW, Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke*. 1999;30:2513-2516.
- Schulz UGR, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. *Stroke*. 2003;34:2050-2059.
- Caparros F, Ferrigno M, Decourcelle A, et al. In-hospital ischaemic stroke treated with intravenous thrombolysis or mechanical thrombectomy. *J Neurol*. 2017;264:1804-1810.
- Tan Y, Zhan L, Chen X, Guo J, Qin C, Xu E. Risk factors, clinical features and prognosis for subtypes of ischemic stroke in a Chinese population. *Curr Med Sci*. 2018;38:296-303.
- Wafa HA, Wolfe CDA, Bhalla A, Wang Y. Long-term trends in death and dependence after ischaemic strokes: a retrospective cohort study using the South London Stroke Register (SLSR). *PLoS Med*. 2020;17:e1003048.
- Lavados PM, Sacks C, Prina L, et al. Incidence, case-fatality rate, and prognosis of ischaemic stroke subtypes in a predominantly Hispanic-Mestizo population in Iquique, Chile (PISCIS project): a community-based incidence study. *Lancet Neurol*. 2007;6:140-148.
- Abdo R, Abboud H, Salameh P, El Hajj T, Hosseini H. Mortality and predictors of death poststroke: data from a multicenter prospective cohort of Lebanese stroke patients. *J Stroke Cerebrovasc Dis*. 2019;28:859-868.
- Soriano-Tárraga C, Giralt-Steinhauer E, Mola-Caminal M, et al. Biological age is a predictor of mortality in ischemic stroke. *Sci Rep*. 2018;8:4148.
- Petty GW, Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. *Stroke*. 2000;31:1062-1068.

31. Kamel H, Healey JS. Cardioembolic stroke. *Circ Res.* 2017;120:514-526.
32. Wei W, Li S, San F, et al. Retrospective analysis of prognosis and risk factors of patients with stroke by TOAST. *Medicine.* 2018;97:e0412.
33. Phan HT, Blizzard CL, Reeves MJ, et al. Sex differences in long-term mortality after stroke in the INSTRUCT (INternational STROKE oUtcomes sTudy): a meta-analysis of individual participant data. *Circ Cardiovasc Qual Outcomes* 2017;10(2):e003436.
34. Rønning OM, Stavem K. Predictors of mortality following acute stroke: a cohort study with 12 years of follow-up. *J Stroke Cerebrovasc Dis.* 2012;21:369-372.
35. Carter AM, Catto AJ, Mansfield MW, Bamford JM, Grant PJ. Predictive variables for mortality after acute ischemic stroke. *Stroke.* 2007;38:1873-1880.
36. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke.* 2005;36:1115-1119.
37. Higuchi S, Kabeya Y, Matsushita K, et al. Barthel Index as a predictor of 1-year mortality in very elderly patients who underwent percutaneous coronary intervention for acute coronary syndrome: better activities of daily living, longer life: Barthel Index as ACS mortality predictor. *Clin Cardiol.* 2016;39:83-89.
38. Caldararo MD, Stein DE, Poggio JL. Nursing home status is an independent risk factor for adverse 30-day postoperative outcomes after common, nonemergent inpatient procedures. *Am J Surg.* 2016;212:202-208.
39. Schnitzler A. Indicateurs d'évaluation de la haute autorité de santé/ impact of the stroke plan on the management of acute ischemic stroke in France: trends of assessment indicators of the French National Authority for Health from 2011 to 2016. *BEH.* 2018;5:78-85.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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