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Cognitive Impairment, Vulnerability, and Mortality Post Ischemic Stroke: A Five-Year Follow-Up of the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) Cohort

Eva Gaynor
Royal College of Surgeons in Ireland, evagaynor@rcsi.ie

Daniela Rohde
Royal College of Surgeons in Ireland, danielamrohde@rcsi.ie

Margaret Large
Royal College of Surgeons in Ireland, margaretlarge@rcsi.ie

Lisa Mellon
Royal College of Surgeons in Ireland, lisamellon@rcsi.ie

Patricia Hall
Royal College of Surgeons in Ireland, patriciahall@rcsi.ie

See next page for additional authors

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Authors
Eva Gaynor, Daniela Rohde, Margaret Large, Lisa Mellon, Patricia Hall, Linda Brewer, Orla Conway, Anne Hickey, Kathleen Bennett, Eamon Dolan, Elizabeth Callaly, and David Williams

Cognitive impairment, vulnerability and mortality post-ischaemic stroke: A five-year follow-up of the ASPIRE-S cohort

Authors

Eva Gaynor[1]*, Daniela Rohde[2]*, Margaret Large[3], Lisa Mellon[2], Patricia Hall[3], Linda Brewer[4], Orla Conway[2], Anne Hickey[2], Kathleen Bennett[2], Eamon Dolan[5], Elizabeth Callaly[6], David Williams[4]

***denotes joint first authorship**

[1] Department of Medicine, Royal College of Surgeons in Ireland
[2] Division of Population Health Sciences, Royal College of Surgeons in Ireland
[3] Clinical Research Centre, Royal College of Surgeons in Ireland, Beaumont Hospital.
[4] Department of Geriatric and Stroke Medicine, Royal College of Surgeons in Ireland and Beaumont Hospital
[5] Department of Geriatric Medicine, Connolly Hospital Blanchardstown
[6] Department of Geriatric Medicine, Mater Misercordiae University Hospital, Dublin

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[$]Address for correspondence

Daniela Rohde, Division of Population Health Sciences, Royal College of Surgeons in Ireland, Beaux Lane House, Lower Mercer St., Dublin 2, Ireland. +353 86 6025805. danielamrohde@rcsi.ie

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Cerebrovascular disorders, stroke, mortality, secondary prevention, cognitive impairment, vulnerability

Abstract

Background: The aim of this study was to examine predictors of mortality in patients five years after ischaemic stroke, focusing on cognitive impairment, vulnerability and vascular risk factors assessed at six months post-stroke.

Materials and methods: Patients from the ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke) cohort were followed 5 years post-ischaemic stroke. Vascular risk factors, cognitive impairment and vulnerability were assessed at 6 months post-stroke. Cognitive impairment was assessed using a cut-off of <26 on the Montreal Cognitive Assessment. Vulnerability was defined as a score of ≥3 on the Vulnerable Elders Scale. Mortality and date of death were ascertained using hospital records, death notifications and contact with general practitioners. Predictors of mortality were explored using multivariate Cox proportional hazard models. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) are presented.

Results: Sixty-three of 256 patients (24.6%) assessed at six months post-stroke had died within 5 years. Cognitive impairment [HR (95% CI): 2.19 (1.42, 3.39)], vulnerability [HR (95% CI): 5.23 (2.92, 9.36)], atrial fibrillation [HR (95% CI): 2.31 (1.80, 2.96)] and dyslipidaemia [HR (95% CI): 1.90 (1.10, 3.27)] were associated with increased risk of 5-year mortality.

Discussion: Vulnerability, cognitive impairment, atrial fibrillation and dyslipidaemia at six months were associated with increased risks of mortality five years post-ischaemic stroke.

Conclusion: Identification and management of these risk factors should be emphasised in post-stroke care.

Introduction

Stroke is one of the leading causes of death and disability worldwide (1). Patients with ischaemic stroke have a 2-3-fold increased risk of death compared to non-stroke patients (2, 3). While positive advances in acute stroke care have led to reduced mortality rates (4), approximately half of stroke patients die within five years post-stroke (5). Several vascular risk factors are associated with increased risk of mortality post-stroke (3, 6). In addition, cognitive impairment, which may be experienced by over half of patients six months post-stroke (7), is associated with increased mortality risk (8). Vulnerability in older people describes those at increased risk of functional decline or death, and is characterised by a loss of independence in activities of daily living (ADLs) and limitations in physical function, along with poor self-rated health (9). Vulnerability has been found to predict both morbidity and mortality in general older adult populations, with vulnerable patients having a 4-fold higher risk of mortality within 2 years (9), as well as an increased mortality risk over longer time periods (10). While vulnerability has been examined as a predictor of mortality in general older population cohorts, to our knowledge there has been no study to date that has explored vulnerability as a predictor of mortality in a post-stroke cohort. Additionally, previous studies of predictors of mortality post-stroke have included historical cohorts (e.g. (8)), which may not reflect modern acute and secondary stroke care and subsequent outcomes. Therefore, the aim of this study was to review predictors of mortality in patients five years post-ischaemic stroke, focusing on cognitive impairment and vulnerability in addition to vascular risk factors, and to provide an updated account of longer-term stroke outcomes.

Materials and methods

This analysis is based on data from a five-year follow-up of the ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke) cohort (7, 11, 12). ASPIRE-S recruited patients with acute ischaemic stroke from three Dublin hospitals in 2011-2012. 256 patients were assessed six months post-stroke, and followed-up at five years (2016-2017) (12).

Six-month assessment procedure

The six-month assessment was conducted by a member of the research team in either the participant's own home or a clinical research facility at one of the participating hospitals, according to participant preference (7). The assessment involved the collection of a venous

fasting blood sample, as well as blood pressure, height and weight measurements, and an assessment of cognitive function (7, 11). Demographic data at six months were collected using a self-completion questionnaire, which also included a section on vulnerability. Self-completion questionnaires were distributed by post to patients prior to the face-to-face assessments, and checked for completion by the research team at the time of interview. This procedure ensured that there were no partially completed questionnaires.

Outcomes

Mortality

The outcome was all-cause mortality within five years of the six-month follow-up assessment. All-cause mortality was determined using a website of death notifications (www.rip.ie), and consultation of hospital records and general practitioners. We recorded date of death during the follow-up period. The mean follow-up time was 4.93 years (SD 1.38) from the date of stroke and 4.38 years (SD 1.38) from the date of six-month assessment.

Predictors

Vascular risk factors

Prior to the present study, ASPIRE-S participants were last followed up at six months post-stroke (7, 11). A comprehensive assessment was completed, modelled on the EUROASPIRE protocol for the evaluation of adequacy of secondary prevention in post-discharge cardiac patients (13). Clinical measures included blood pressure, lipid profiles, fasting glucose levels, height, weight, smoking status, presence of atrial fibrillation (AF), and history of stroke or transient ischaemic attack (TIA) and ischaemic heart disease. We applied European secondary prevention targets (14) to classify participants with uncontrolled hypertension (BP ≥140/90mmHG), impaired glucose tolerance (fasting glucose level >6.0mmol/L), and overweight/obesity (BMI >25kg/M^2). In order to limit the number of cholesterol variables, dyslipidaemia was defined using the total cholesterol/high density lipoprotein cholesterol (TC/HDL-C) ratio, which has been utilised previously as a marker of cardiovascular risk (15, 16). At risk TC/HDL-C ratio was defined as ≥4.5 and ≥3.5 in men and women respectively.

Cognitive function

Cognitive function was assessed at six months post-stroke using the Montreal Cognitive Assessment (MoCA) (17), a rapid 30-point test that assesses several cognitive domains including visuospatial abilities, executive function, short-term memory and recall, attention,

language, concentration and orientation. This test is well documented for identifying cognitive impairment in post-stroke populations (18). We applied the recommended cut-off score of <26 to identify participants with cognitive impairment. The education adjustment was not applied in this study. We conducted sensitivity analyses using 1.) a more conservative cut-off of <24, and 2.) MoCA scores as a continuous variable, as it has been suggested that the original cut-off may yield low levels of specificity for cognitive impairment (19, 20).

Cognitive assessments were completed with 226 out of 256 patients at six months post-stroke. Cognitive assessments were not carried out with patients who were unable to complete the MoCA, due to either very severe cognitive impairment, a visual impairment that precluded the person from being able to see the test sheet, or a motor impairment that prevented the person from being able to use a pen. Patients without cognitive assessments available at six months were significantly older, more likely to have had a moderate to severe stroke, and were more likely to have moderate to severe disability at six months post-stroke, than those patients who completed cognitive assessments.

Vulnerability

Vulnerability was assessed using the Vulnerable Elders Scale (VES). The VES is a standardised, validated, 13-point self-completion tool that identifies vulnerable individuals at risk for health deterioration and death in both acute and ambulatory settings (9, 10). The VES considers age, limitations in physical function, difficulties with ADLs, and self-rated health. Scores range from 0 to 10, with a score ≥3 used to identify vulnerable individuals. The VES was completed by 218 of 256 patients at six months post-stroke. Non-completion of the VES was due either to severe impairment or non-return of the self-completion questionnaire. Patients without VES scores available at six months were significantly older, more likely to have had a moderate to severe stroke, and were more likely to have moderate to severe disability at six months post-stroke, than patients who completed the VES.

Covariates

Bamford and TOAST classifications of the index event were recorded as part of ASPIRE-S. Stroke severity was assessed using the Scandinavian Stroke Scale (21). Scores range from 0 to 58, with scores of 0-25, 26-42 and 43-58 considered severe, moderate and mild strokes, respectively (22). As only ten participants were categorised as having had a severe stroke, we

combined the moderate and severe categories. Demographic data (age, sex, marital status, living arrangements, insurance type) were collected as part of the six-month assessment. Cardiovascular medication use was recorded at the six-month assessment by reviewing the patient's most recent prescription, pillbox or medication containers.

Ethical approval

This study adhered to the principles of the Declaration of Helsinki. Ethical approval was granted by the Research Ethics Committees at Beaumont Hospital (ref. 16/26), Mater Misericordiae University Hospital (1/378/1855), Connolly Hospital Blanchardstown (28/11/2016), and the Royal College of Surgeons in Ireland (REC 1355).

Statistical analysis

The study period was defined as the time from six-month follow-up assessment to death or study end (31st October 2017). Univariate associations with mortality were examined with log rank tests and Kaplan Meier plots for categorical variables, and univariate Cox regression for continuous variables. Predictors that were significantly associated with each outcome in univariate analyses were included in multivariate models. Due to sample size limitations and to avoid overfitting, separate multivariate Cox proportional hazards models were used to investigate each predictor of interest. Multivariate models including cognitive impairment (model 1), vulnerability (model 2), previous stroke/TIA (model 3), and at-risk TC/HDL-C (model 4) controlled for age, sex, and stroke severity, while the model including atrial fibrillation (model 5) controlled for age, sex, and use of anticoagulant medications. A sixth model examined both vulnerability and cognitive impairment simultaneously. TOAST classification violated the assumption of proportional hazards, and was excluded from further analyses as it was not significantly associated with mortality following adjustment for age and stroke severity. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for each model are presented. Goodness of fit was assessed using Harrell's c statistic, with values between 0.7 and 0.8 considered acceptable discrimination (23). Collinearity between predictor variables was assessed using the *collin* command in Stata (24). An alpha level of $p<0.05$ was assumed to denote statistical significance. Data were analysed using Stata© version 13.

Results

Out of 256 patients last followed up at six months, 63 (24.6%) had died during the follow-up period. Table 1 illustrates demographics, index event, vascular risk factor profiles, cognitive status and vulnerability for patients who survived and those who were deceased at follow-up. In univariate analyses, older age, cardioembolic stroke, history of AF, stroke/TIA prior to the index event, vulnerability and cognitive impairment were associated with all-cause mortality within five years (Table 1).

A number of separate cox proportional hazards models examined predictors of mortality, controlling for age, sex, and stroke severity (or use of anticoagulant medication in the model including history of atrial fibrillation) (Table 2). Both cognitive impairment [HR (95% CI): 2.19 (1.42, 3.39)] and vulnerability [HR (95% CI): 5.23 (2.92, 9.36)] were significantly associated with mortality at five years. While a history of AF [HR (95% CI): 2.31 (1.80, 2.96)] and at risk TC/HDL-C [HR (95% CI): 1.90 (1.10, 3.27)] also increased the risk of mortality, a history of stroke or TIA prior to the index event was not significantly associated with mortality [HR (95% CI): 1.26 (0.80, 1.99)]. When using the more conservative cut-off of <24 on the MoCA, cognitive impairment was significantly associated with mortality at five years, controlling for age, sex, and stroke severity [HR (95% CI): 1.82 (1.43, 2.31)]. Similarly, when modelling MoCA scores as a continuous variable, higher scores (indicating less impairment) were associated with decreased risk of mortality at five years, controlling for age, sex, and stroke severity [HR (95% CI): 0.92 (0.89, 0.96)]. Unadjusted Kaplan Meier plots for cognitive impairment (MoCA <26), vulnerability, history of AF, stroke/TIA prior to the index event and at-risk TC/HDL-C are shown in Figure 1.

A sixth model included both cognitive impairment and vulnerability simultaneously, controlling for age, sex, and stroke severity. Due to missing data, this model included 40 deceased patients. Both cognitive impairment [HR (95% CI): 2.16 (1.46, 3.18)] and vulnerability [HR (95% CI): 4.87 (2.69, 8.81)] were independently associated with a significantly increased risk of mortality within five years (Table 2).

Table 1. Univariate analysis of demographics, stroke event and cardiovascular risk factor profiles, cognitive status and vulnerability by survival status at 5 years.

		Survived five years post-stroke n (%)	**Deceased within five years n (%)**
Demographics	Age (Mean, SD)	66.2 (12.7)	77.7 (9.7)***
	Male	112 (58.0)	36 (57.1)
	Married (vs. not married)	122 (63.2)	38 (60.3)
	Living alone (vs. living with others)	50 (25.9)	16 (25.4)
	Private insurance (vs. public)	59 (30.6)	18 (28.5)
Bamford classification (25)	TACS (Total anterior circulation stroke)	11 (5.7)	4 (6.5)
	PACS (Partial anterior circulation stroke)	74 (38.3)	29 (46.0)
	POCS (Posterior circulation stroke)	59 (30.6)	11 (17.5)
	LACS (Lacunar stroke)	45 (23.3)	17 (27.0)
	Unclassifiable	4 (2.1)	2 (3.2)
TOAST classification (26)	Cardioembolism	69 (35.8)	31 (49.2)*
	Other	124 (64.2)	32 (50.8)
Vascular risk factors at six months	Hypertension (n=254)	138 (72.3)	42 (66.7)
	TC/HDL-C (n=221)	38 (21.8)	18 (38.3)*
	Impaired fasting glucose (n=231)	25 (14.0)	12 (23.1)
	Overweight/obese (n=250)	112 (59.0)	28 (46.7)
	Smoker	54 (28.0)	17 (27.0)
	History of alcohol abuse	28 (14.5)	9 (14.3)
	Stroke/TIA prior to index event	42 (21.8)	22 (34.9)*
	History of heart disease	53 (27.5)	22 (34.9)
	History of carotid stenosis	31 (16.1)	10 (15.9)
	History of AF	62 (32.1)	36 (57.51***
Stroke severity (n=253)	Moderate or severe	38 (19.7)	17 (28.3)
Cognitive impairment (n=226)	MoCA <26	90 (50.6)	38 (79.2)***
Vulnerability (n=218)	VES ≥3	65 (37.8)	37 (80.4)***

Note: *p<.05, **p<.01, ***p<.001

Table 2. Adjusted HR (95% CI) from Cox proportional hazards models for all-cause mortality based on cognitive impairment, vulnerability, atrial fibrillation, history of stroke/TIA, and TC/HDL-C

	Predictor	Adjusted Hazard Ratio (95% CI)*	*p*	Harrell's c
Model 1	Cognitive impairment[$] (n=225)	2.19 (1.42, 3.39)	<.001	.76
Model 2	Vulnerability[$] (n=216)	5.23 (2.92, 9.36)	<.001	.79
Model 3	History of stroke/TIA[$] (n=253)	1.26 (0.80, 1.99)	.315	.75
Model 4	TC/HDL-C[$] (n=219)	1.90 (1.10, 3.27)	.021	.75
Model 5	Atrial fibrillation[*] (n=256)	2.27 (1.71, 3.07)	<.001	.75
Model 6	**Cognitive impairment and vulnerability[$] (n=204)**	**Adjusted Hazard Ratio (95% CI)***	***p***	**Harrell's c**
	Cognitive impairment	2.16 (1.46, 3.18)	<.001	.81
	Vulnerability	4.87 (2.69, 8.81)	<.001	

$ adjusted for age, sex, and stroke severity

*adjusted for age, sex, and anticoagulant medication use

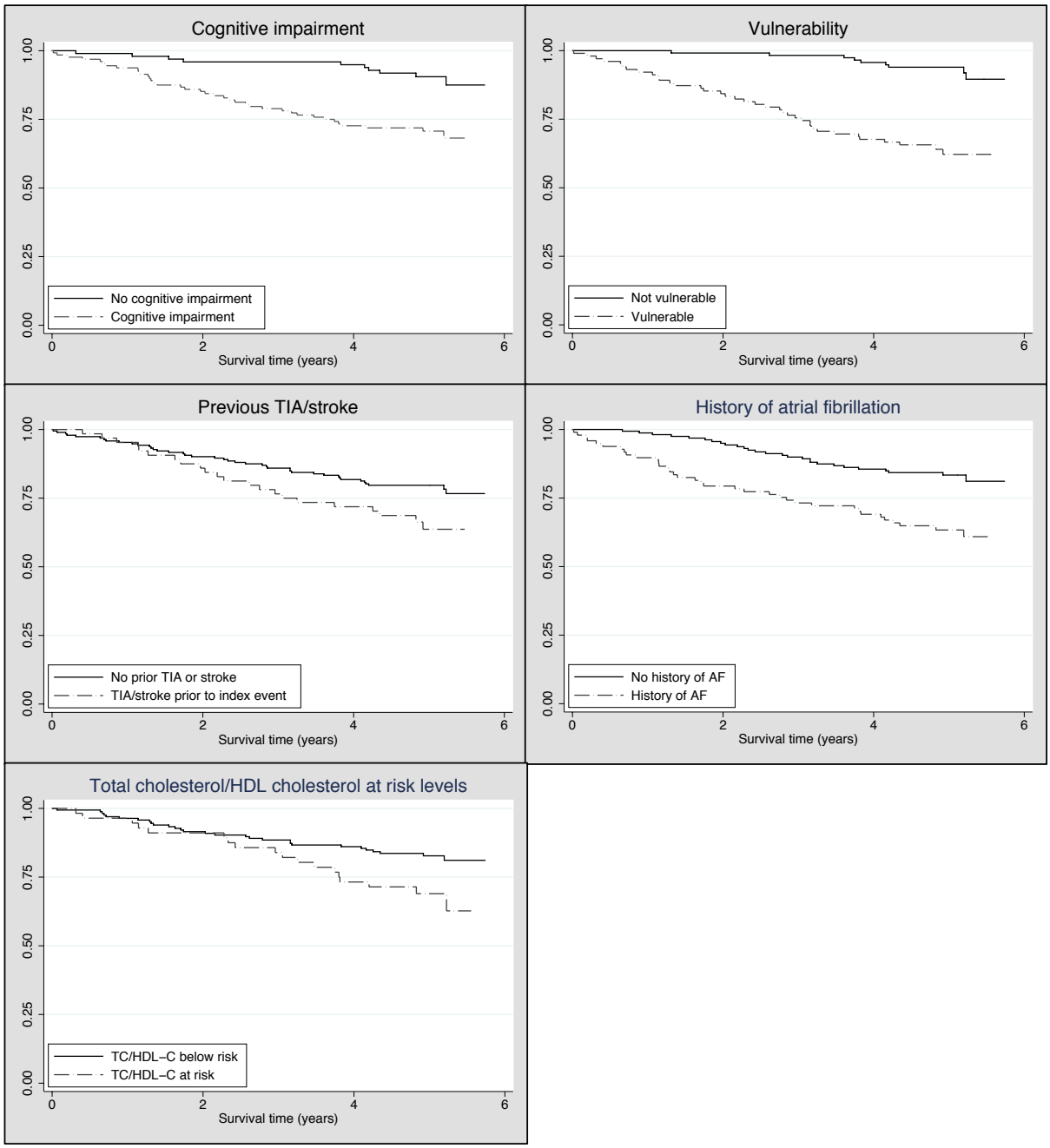

Figure 1. Kaplan Meier plots for vulnerability, CI, AF, previous stroke/TIA, TC/HDL-C at risk by survival time at 5 years

Discussion

We found that cognitive impairment, vulnerability, atrial fibrillation and at risk TC/HDL-C were associated with significantly increased risk of 5-year mortality post ischaemic stroke. Overall, we found that a quarter of 256 ischaemic stroke patients in our cohort had died within five years. This compares favourably with other long-term follow up studies. In a similar Irish population-based study, two-year mortality rates in post stroke patients have

been as high as 38.6% (27). However, the fact that patients who died prior to the six-month assessment were not included in our study may account for the lower mortality rate.

Vulnerability and cognitive impairment

We found that vulnerable patients were over 5-times more likely to be at risk of mortality compared to non-vulnerable individuals. Vulnerability as assessed by the VES has previously been reported to be associated with a 4.2 times increased risk of death or functional decline in community dwelling older adults (9), as well as being associated with increased use of healthcare services (28). Functional limitations are often overlooked or undetected by physicians in the community (29). The VES, which can be completed in under five minutes, might be a potentially useful screening tool to assess not only functional limitations, but also to identify patients at increased risk of mortality (9, 28), who may benefit from intensified monitoring or intervention.

Encouraging healthcare professionals to screen at-risk stroke patients could aid future care planning, including referral and involvement of multidisciplinary services. Rehabilitation programmes could help improve functional and physical abilities thereby reducing the risk of vulnerability in post-stroke patients. For example, exercise, balance and strength training programmes offered by physiotherapy can result in improved functional outcomes in stroke survivors (30). Comprehensive occupational therapy involvement aimed at improving functional performance and social participation may similarly improve stroke patients' abilities to perform activities of daily living (31). While further research is required, such interventions have shown potential to reduce mortality in vulnerable community dwelling older adults (32), and could be applied to vulnerable patients post-stroke. International guidelines have advised that a comprehensive rehabilitation programme should form part of routine post-stroke care and should be extended to community settings if required (33). Despite this, access to rehabilitation services in the community remain poor with studies showing up to 57% of stroke survivors not receiving the recommended therapy following discharge (34).

Our finding that cognitive impairment is associated with an increased risk of mortality post-stroke is also supported by previous studies, which have reported a 53% increased risk of mortality in those with cognitive impairment (8, 35). Many stroke patients develop delayed dementia (36); therefore, routine screening for cognitive impairment at regular intervals is

required to identify at-risk groups likely to require increased medical and social supports. Control of vascular risk factors has been shown to reduce both mortality as well as the rate of cognitive decline post stroke (37), suggesting that by controlling secondary risks, both the rate of cognitive decline and mortality rates post-stroke may be reduced.

Vascular risk factors

In addition to cognitive impairment and vulnerability, we found that atrial fibrillation was associated with an almost two-fold increased risk of mortality within five years. Previous studies have similarly reported that atrial fibrillation is associated with increased stroke severity and poorer outcomes, as well as increased mortality risk in long-term follow-up of stroke patients (38, 39). Adequate cardiac evaluation post-ischaemic stroke and appropriate initiation of anticoagulant therapy should thus be a priority in this group of patients.

TC/HDL ratio was associated with mortality in our cohort of ischaemic stroke patients. Hyperlipidaemia has been linked to increased cerebrovascular and cardiovascular risk (40), with high-dose statin therapy advised in secondary stroke prevention (41). However, its association with mortality post ischaemic stroke has been debated, with some long-term follow up studies suggesting a protective effect of hypercholesterolaemia on mortality (42). While recurrent stroke events tend to be related to higher rates of mortality in long-term follow-up studies (43), we did not find any association between previous stroke/TIA and mortality following adjustment for age and stroke severity.

Strengths and limitations

Our study has several strengths. Our assessment of patients six-months post ischaemic stroke was based on a robust standardised model based on the EUROASPIRE surveys (13). To our knowledge, this is the first study to examine the association between vulnerability as measured by the VES and mortality in a post-stroke population. Our findings highlight the potential utility of an easily performed screening tool to detect vulnerability post-stroke and identify at-risk patients in need of closer monitoring, with similar implications for screening patients with stroke for cognitive impairment, thus identifying at-risk patients who may benefit from intervention. Finally, our study provides a more up-to-date account of longer-term post-stroke outcomes, which may reflect recent improvements in acute stroke care and secondary prevention that are not captured by older studies.

There were some limitations, including a small sample size, potentially leading to a lack of statistical power. Although we controlled for age, sex, and stroke severity (or anticoagulant medication in atrial fibrillation) in multivariate models, we cannot rule out residual confounding. Due to some missing data on the MoCA and VES, not all deceased patients were included in multivariate analyses, which may have introduced bias. Non-completion was due mainly to the presence of more severe impairments, and patients without VES or MoCA scores available at six months were significantly older and more likely to have had a moderate to severe stroke than patients who completed these assessments. Therefore, it seems probable that the true associations between cognitive impairment or vulnerability and mortality may in fact be stronger than the associations observed in this study. This problem of missing data on cognitive assessments has also been reported by other studies (8). While assessments of vascular risk factors were based on objective measures, vulnerability was assessed through patient self-report, and may be subject to self-report bias (44). Finally, as only ten patients were classified as having had a severe stroke based on stroke severity scores, this study represents mainly mild to moderate strokes. Findings may not be generalisable to patient cohorts with more severe stroke.

Conclusion

We found that vulnerability, cognitive impairment, atrial fibrillation and TC/HDL ratio at six months were associated with an increased risk of mortality five years post-ischaemic stroke. This highlights the need for healthcare providers to closely monitor patients in these high-risk groups in long-term follow-up, and to employ risk reduction strategies.

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Author contributions

DR, EG, KB, AH and DW conceived and designed the study. EG, ML, PH, LM, LB, DR and OR collected the data. DR and EG analysed the data. EG and DR drafted the manuscript. All authors revised the manuscript and approved the final draft.

Conflicting interests

DW is an Advisory Board Member for Boehringer Ingelheim, Daiichi Sankyo, Bristol Myers Squibb, and Bayer and has received personal fees for this outside the submitted work. DW is Speaker Honorarium for Boehringer Ingelheim and has received personal fees for this outside the submitted work. All other authors have no conflicts of interest to declare.

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