

Cognitive Predictors of Delirium on Long-Term Follow-Up after TIA and Stroke: Population-Based Cohort Study

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Keywords

Delirium · TIA and stroke · Cognitive impairment · Long-term follow-up

Abstract

Introduction: TIA and stroke cause cognitive impairment with a typical “vascular” pattern, including prominent frontal/executive deficits. Cognitive impairment is associated with increased delirium risk and the few available data suggest that executive dysfunction is important. We therefore determined the predictive value of both severity and pattern of cognitive deficits for delirium on long-term follow-up after TIA/stroke. **Methods:** Surviving TIA/stroke participants on October 1, 2013, in the Oxford Vascular Study (OXVASC) were assessed prospectively for delirium during all hospitalizations over the subsequent 6 months. Associations between OXVASC pre-admission mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores, and delirium during hospitalizations on follow-up were determined using logistic regression adjusted for covariates, including demographic factors, history of depres-

sion, baseline stroke severity, and admission illness severity. **Results:** Among 1,565 TIA/stroke survivors, 158 patients (mean/SD age = 79.2/11.5 years) had ≥ 1 admission and 59 (37%) had ≥ 1 delirium episode. Mean/SD time between baseline TIA/stroke and admission was 4.7/3.6 years and between most recent OXVASC cognitive testing and admission was 1.7/1.8 years. MMSE and MoCA scores were associated with delirium: odds ratio (OR) = 1.16 (95% CI 1.07–1.27, $p < 0.0001$ per point decrease in MMSE) and OR = 1.20 (1.11–1.30, $p < 0.0001$ MoCA) and associations were robust to adjustment for all covariates, including stroke severity: OR = 1.11 (1.01–1.22, $p = 0.03$, MMSE) and OR = 1.15 (1.05–1.25, $p = 0.003$, MoCA). All 10 subtests on the MoCA and 4/11 on the MMSE were significantly associated with delirium with highest predictive value for frontal/executive and recall domains. **Conclusions:** Cognitive impairment of increasing severity after TIA/stroke predisposed to delirium particularly deficits in frontal/executive domains and recall. Long-term risk of delirium should be considered as part of the overall cerebrovascular disease burden.

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Introduction

Pre-existing cognitive impairment predisposes to delirium [1, 2]. Stroke causes cognitive decline and dementia in proportion to its severity which may explain why a history of stroke is associated with increased delirium risk in general hospital cohorts [1–3]. The pattern of neurocognitive deficits may also be important: executive dysfunction has been postulated to increase delirium possibly through altered brain networks and reduced ability to integrate sensory inputs [4, 5]. Although stroke-associated cognitive impairment is heterogeneous depending on stroke location and the underlying neuropathology, a characteristic “vascular pattern” of deficits is seen, including relatively prominent frontal/executive dysfunction [6–8]. This cognitive impairment profile might therefore also increase the likelihood of delirium after stroke.

Delirium in the acute phase of stroke has shown to be associated with pre-existing cognitive impairment, as well as with stroke severity and infection [9], but there are few studies of delirium in the longer term after cerebrovascular events. In a population-based study, we determined associations between the severity and pattern of cognitive domain deficits occurring after TIA and stroke, and future delirium occurring during hospitalization on long-term follow-up.

Methods

Oxford Vascular Study

The patients in the current study were participants with TIA or stroke previously recruited since 1 April 2002 in the Oxford Vascular Study (OXVASC), an ongoing longitudinal population-based cohort study within a population of >92,700 covered by 9 primary care practices (~100 primary care practitioners) in Oxfordshire, UK [10]. The study was approved by the local research Ethics Committee. Informed written consent (or assent from relatives) was obtained for study interview and face-to-face and telephone follow-up as well as indirect follow-up using medical records.

TIA and stroke were defined clinically by WHO criteria and index cerebrovascular event severity was measured using the National Institutes of Health Stroke Scale (NIHSS) [10]. Patient data were collected by interview using a standardized form and from general practitioner records. Follow-up interviews were done by clinical fellows and trained research nurses at 1 and 6 months and 1, 5, and 10 years either in the out-patient clinic or by home visit. Cognitive testing was conducted at baseline and all follow-ups (Fig. 1) using one or more of mini-mental state examination (MMSE) [11] and Montreal Cognitive Assessment (MoCA) [12] validated for use in TIA/stroke [8].

Prospective Ascertainment of Delirium

The Oxford University Hospitals NHS Foundation Trust (OUHFT) provides acute services for the population of approximately 660,000 in Oxfordshire, including all patients in the OXVASC study primary care practices. OXVASC patients requiring acute hospital care for any reason are admitted either to OUHFT or to Abingdon Emergency Medical Unit (EMU). To identify OXVASC participants admitted to hospital over the study period, we conducted daily searches of electronic (OUHFT) and paper records (EMU) for all new admissions excluding day case procedures, and cross-checked these against the register of OXVASC participants.

All TIA and stroke participants in OXVASC surviving on October 1, 2013, were included in the current study. Subsequent hospital admissions for any reason were prospectively identified from October 2013–April 2014 at the OUHFT and the Abingdon EMU. Patients were assessed as soon as possible after admission by members of the OXVASC study team. Delirium was ascertained using gold standard clinical diagnosis rather than retrospective hospital administrative diagnostic (ICD-10)-coded data since the latter are insensitive [13].

Delirium diagnosis was made according to the DSM-IV [14] criteria by STP after discussion with the OXVASC study team supplemented by review of the medical notes, including the OUHFT cognitive screen as described previously [2, 13] (see online suppl. methods; for all online suppl. material, see www.karger.com/doi/10.1159/000519900). The OUHFT cognitive screen is mandated on all patients admitted to the OUHFT or EMU who are aged ≥ 70 years or < 70 years with confusion/altered behaviour and includes the 10-point abbreviated mental test score (AMTS) [15] together with the Confusion Assessment Method (CAM) [16] for delirium. Illness severity was defined using the systemic inflammatory response syndrome (2 or more of heart rate > 90 beats per minute, temperature < 36 or $> 38^\circ\text{C}$, respiratory rate > 20 breaths per minute, white blood cell count $< 4 \times 10^9$ or $> 12 \times 10^9$ cells per litre) [17].

Statistical Analysis

Baseline characteristics of patients with any admission with delirium versus those without delirium were compared using *t* test and ANOVA for continuous variables and χ^2 for categorical variables. MMSE and MoCA cognitive test scores were obtained from the most recent OXVASC study follow-up performed prior to the hospital admission episode (Fig. 1). Cognitive test scores were dichotomized into mild (MMSE < 27 , MoCA < 26) and moderate/severe (MMSE < 24 , MoCA < 18) cognitive impairment using previously described cut-offs [8].

To determine the associations between pre-admission OXVASC cognitive impairment (MMSE and MoCA scores) and delirium occurring during hospitalization, we used data from all admissions to calculate odds ratios (ORs). We adjusted for demographic factors and then for key covariates known to be associated with delirium in general cohorts that were available in our dataset [1, 2]: age, sex, and education (model 1), age, sex, education, history of depression at baseline OXVASC assessment, and illness severity on admission (model 2), and then with the addition of baseline OXVASC stroke severity (model 3). Similarly, we examined associations between individual MMSE and MoCA subtest scores and delirium adjusted for age, sex, and education. We also performed the following sensitivity analyses:

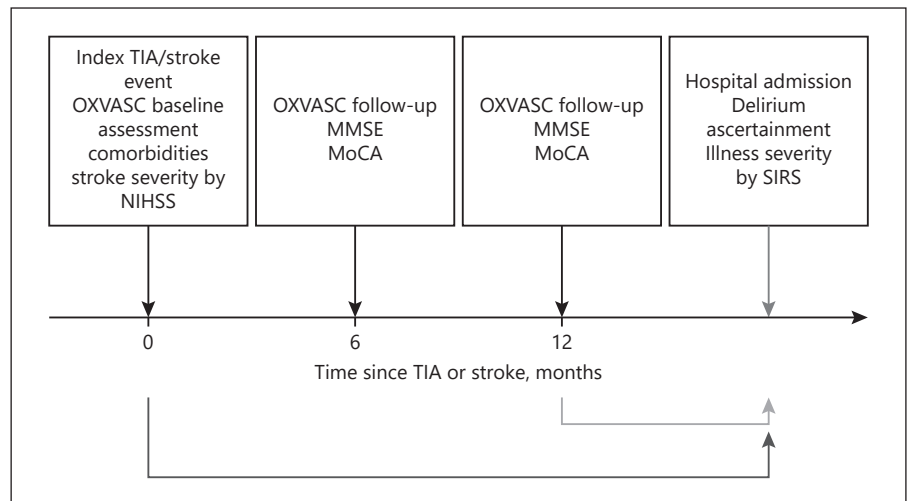


Fig. 1. Schematic diagram showing the design of the current study with the example of a patient who was hospitalized after their 12-month OXVASC follow-up and before their 5-year OXVASC follow-up. Time elapsed between OXVASC baseline TIA/stroke assessment to hospital admission is shown by the black curved arrow. NIHSS for stroke severity and comorbidities, including history of depression and vascular risk factors are acquired at baseline TIA/stroke assessment. Time between OXVASC follow-up MMSE

1. Substituting stroke severity in model 3 with the 1 month post-stroke modified Rankin score or baseline stroke subtype as defined by the TOAST classification.
2. Adjusting model 3 further for admission characteristics defined as elective versus unplanned admission and treatment speciality.
3. Using data restricted to the first admission only.

Results

Among TIA and stroke patients recruited since April 2002 (mean age/SD = 68.9/13.3 years, 676 TIA) 1,565 were still alive on October 12, 2013. Over the subsequent study period, there was a total of 194 admissions (100 to OUHFT and 94 to EMU) in 158 OXVASC participants (mean/SD age at admission = 79.5/11.2 years, range 47–100 years). The majority (170 [88%]) of admissions were unplanned: 122 (72%) to acute general (internal) medicine; 15 other medical services; 23 surgery; 10 trauma. Mean/SD time between baseline OXVASC TIA/stroke event and first hospital admission was 4.7/3.6 years and between most recent cognitive tests at OXVASC follow-up and first hospital admission was 1.7/1.8 years (Table 1).

Delirium occurred in 67/194 (34.5%) admissions and 59/158 (37%) patients had at least 1 admission compli-

and MoCA testing and hospital admission is shown by the grey curved arrow. During hospital admission, delirium diagnosis was ascertained together with illness severity as defined by the SIRS criteria. OXVASC, Oxford Vascular Study; NIHSS, National Institutes of Health Stroke Scale; MMSE, mini-mental-state-examination; MoCA, Montreal Cognitive Assessment; SIRS, systemic inflammatory syndrome.

cated by delirium (53 had 1 episode, 4 had 2 episodes, and 2 had 3 episodes). Patients with versus without delirium were older (mean/SD age = 84.9/8.9 vs. 76.7/11.2 years, $p < 0.0001$) with more depression at OXVASC baseline (21, 31.3% vs. 19, 15.0%, $p = 0.02$, adjusted for age) and worse pre-admission cognition (mean/SD MMSE = 23.1/5.1 vs. 26.0/3.8, $p = 0.002$ and mean/SD MoCA 18.8/6.1 vs. 23.9/4.5, $p < 0.0001$, adjusted for age) but were similar in terms of sex, education, and vascular risk factors (Table 1).

Associations between pre-admission cognitive impairment and delirium were stronger for the MoCA (OR = 1.20 95% CI 1.11–1.30, $p < 0.0001$ per point decrease) than the MMSE (OR = 1.16 1.07–1.27, $p < 0.0001$) and for more severe versus less severe impairment (Table 2). Associations were robust to adjustment for demographic factors (model 1) with OR = 1.14, 1.08–1.27 ($p = 0.005$) for MMSE and OR = 1.16, 1.06–1.25 ($p < 0.0001$) for MoCA and were largely unaffected by the addition of illness severity, depression history (model 2), and stroke severity (model 3, Table 2). Sensitivity analyses substituting post-stroke disability (modified Rankin score) or baseline stroke subtype for stroke severity in model 3 showed similar results as did further adjustment of model 3 for admission characteristics (elective vs. unplanned and treatment speciality, online suppl. Tables). Further

Table 1. Among 1,565 TIA/stroke survivors, demographic and clinical details for the 194 admissions over the study period with versus without delirium

	Total (N = 194)	Delirium (N = 67)	No delirium (N = 127)	p value	p value adjusted for age
Age at admission, years	79.5/11.2	84.9/8.9	76.7/11.2	<0.0001	<0.0001
Male sex	100 (55.5)	29 (43.3)	71 (55.9)	0.09	0.21
Education <12 years	73 (37.6)	26 (38.8)	47 (37.0)	0.40	0.80
Time from baseline TIA/stroke to admission, years	4.7/3.6	5.30/3.76	4.46/3.52	0.12	0.60
Time from cognitive testing at most recent OXVASC follow-up to admission, years	1.7/1.8	2.0/2.1	1.6/1.7	0.16	0.40
Baseline data obtained at time of TIA/stroke					
TIA	71 (36.6)	28 (41.8)	43 (33.9)	0.28	0.86
NIHSS	2.3/4.1	2.9/4.7	2.0/3.7	0.15	0.35
History of depression	40 (20.6)	21 (31.3)	19 (15.0)	0.007	0.02
Hypertension	127	49	78	0.10	0.17
Diabetes	45	17	28	0.60	0.24
Hyperlipidaemia	85	29	56	0.91	0.95
Myocardial infarction	30	14	16	0.13	0.24
Atrial fibrillation	57	25	32	0.08	0.16
Smoking, past or current	79	25	54	0.32	0.34
Peripheral vascular disease	30	14	16	0.13	0.24
Previous TIA	18	9	9	0.16	0.46
Previous stroke	16	6	10	0.82	0.61
Preadmission cognition from most recent OXVASC follow-up					
MMSE score	25.0/4.5	23.1/5.1	26.0/3.8	<0.0001	0.002
MoCA score	22.2/5.6	18.8/6.1	23.9/4.5	<0.0001	<0.0001

Numbers are N (%) or mean/SD. OXVASC, Oxford Vascular Study; NIHSS, National Institutes of Health Stroke Scale; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment.

Table 2. Associations between pre-admission cognitive impairment and delirium, unadjusted and adjusted for covariates, including demographic factors, history of depression, illness severity at the time of hospital admission, and stroke severity

	Unadjusted		Model 1 (age, sex, and education)		Model 2 (age, sex, education, depression, and illness severity)		Model 3 (age, sex, education, depression, illness severity, and stroke severity)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
MMSE/per point decrease	1.16 (1.07–1.27)	<0.0001	1.14 (1.08–1.27)	0.005	1.11 (1.02–1.22)	0.02	1.11 (1.01–1.22)	0.03
MoCA/per point decrease	1.20 (1.11–1.30)	<0.0001	1.16 (1.06–1.25)	<0.0001	1.15 (1.05–1.25)	0.001	1.15 (1.05–1.25)	0.003
MMSE <27	2.85 (1.50–5.43)		2.53 (1.15–5.56)		2.53 (1.13–5.67)		2.46 (1.08–5.62)	
MMSE <24	5.84 (3.05–11.18)		4.73 (2.13–10.5)		4.11 (1.82–9.28)		4.04 (1.79–9.15)	
MoCA <26	3.73 (1.94–7.16)		3.58 (1.60–8.00)		3.37 (1.48–7.66)		3.30 (1.43–7.57)	
MoCA <18	7.47 (3.73–14.94)		7.20 (3.00–17.26)		7.05 (2.89–17.21)		6.92 (2.83–16.95)	
MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; OR, odds ratio.								

Table 3. MMSE and MoCA subtest scores measured at the time of most recent pre-admission OXVASC follow-up for all admissions with and without delirium adjusted for demographic factors (age, sex, and education)

Test	Subtest details	Delirium (N = 67)	No delirium (N = 127)	p value adj
MMSE				
Orientation time/5	Orientation to time	3.67/1.48	4.49/0.79	0.02
Orientation place/5	Orientation to place	4.65/0/69	4.72/0.77	0.86
Registration/3	Repeat "apple, table, penny"	2.84/0.65	2.90/0.49	0.55
Calculation/5	Serial 7 subtraction/WORLD	2.86/1.90	3.77/1.67	0.008
Recall/3	Recall "apple, table, penny"	1.16/0.11	1.96/1.02	<0.0001
Naming/2	Naming (pen and watch)	1.88/0.45	1.97/0.23	0.20
Repetition/1	Repeat "no ifs, ands or buts"	0.47/0.51	0.69/0.47	0.11
Comprehension/3	Perform 3 step command	2.72/0.73	2.89/0.54	0.17
Reading/1	Obey "close your eyes"	0.91/0.29	0.95/0.23	0.32
Writing/1	Write a sentence	0.72/0.45	0.84/0.37	0.08
Drawing/1	Copy intersecting pentagons	0.44/0.50	0.75/0.44	0.03
MMSE duration/min	Time taken to perform the MMSE	6.19/2.48	5.92/6.44	0.54
MoCA				
Visuoexecutive/5	Trail B test, cube copy, and clock drawing	2.26/1.61	3.52/1.34	0.02
Naming/3	Confrontation naming (lion, hippo, and camel)	2.42/0.96	2.78/0.54	0.02
Digit span/2	Forward (5 digits) and backward (3 digits)	1.51/0.74	1.75/0.51	0.05
Attention/1	Tapping at the letter A in a list of letters	0.50/0.51	0.80/0.40	0.001
Calculation/3	Serial 7 subtractions	2.00/1.07	2.43/0.97	0.01
Repetition/2	Repetition of 2 complex sentences	1.19/0.82	1.53/0.75	0.05
Verbal fluency/1	≥11 words beginning with f in 1 min	0.27/0.45	0.57/0.50	0.001
Abstraction/2	Similarities e.g., train and bicycle = "transport"	1.09/0.84	1.47/0.62	0.01
Recall/5	Recall a list of 5 words	1.19/1.59	2.66/1.63	0.002
Orientation/6	Orientation to place and time	4.72/1.26	5.44/0.96	0.02
MoCA duration/min	Time taken to perform the MoCA	11.82/4.65	9.63/3.26	0.002
F words, number	Number of words given in 1 min	11.07/5.12	8.14/4.35	<0.0001

OXVASC, Oxford Vascular Study; MMSE, mini-mental-state-examination; MoCA, Montreal Cognitive Assessment. Bold values are significant.

sensitivity analyses using only the first admission only gave similar results (data not shown).

All 10 subtests on the MoCA and 4/11 on the MMSE were significantly associated with delirium (Table 3). Significant MMSE subtests were orientation to time ($p = 0.02$), calculation ($p = 0.008$), recall ($p < 0.0001$), and copying pentagons ($p = 0.03$, Table 3; Fig. 2). On the MoCA, the strongest associations were for sustained attention (tapping at the letter A, $p = 0.001$), verbal fluency ($p = 0.001$, total number of f words $p < 0.0001$), recall ($p = 0.002$), abstraction ($p = 0.01$), calculation ($p = 0.01$), visuo-executive function ($p = 0.02$), naming ($p = 0.02$), and orientation ($p = 0.02$, Table 3; Fig. 2). The time taken to perform the cognitive test was longer in those with versus without delirium for the MoCA (mean/SD = 11.8/4.7 vs. 9.6/3.3 min, $p = 0.002$) but not the MMSE (6.2/2.5 vs. 5.9/6.4 min, $p = 0.54$). Sensitivity analyses using only the first admission gave similar results (data not shown).

Discussion

In our study of TIA/stroke patients on long-term follow-up, rates of delirium associated with hospitalization were high and were broadly similar to those reported in general hospital cohorts of older patients [1, 2]. Pre-existing cognitive impairment of increasing severity, especially in frontal/executive and recall domains, predicted delirium in the long-term after TIA or stroke. Associations were robust to adjustment for other important factors including demographic characteristics, history of depression, and illness severity at the time of hospital admission and baseline stroke severity.

Studies in non-stroke cohorts have shown that delirium is more likely in patients with pre-existing cognitive impairment of increasing severity [1, 2]. Since stroke-associated cognitive impairment is linked in a stepwise fashion to the severity of the stroke [3], we might have

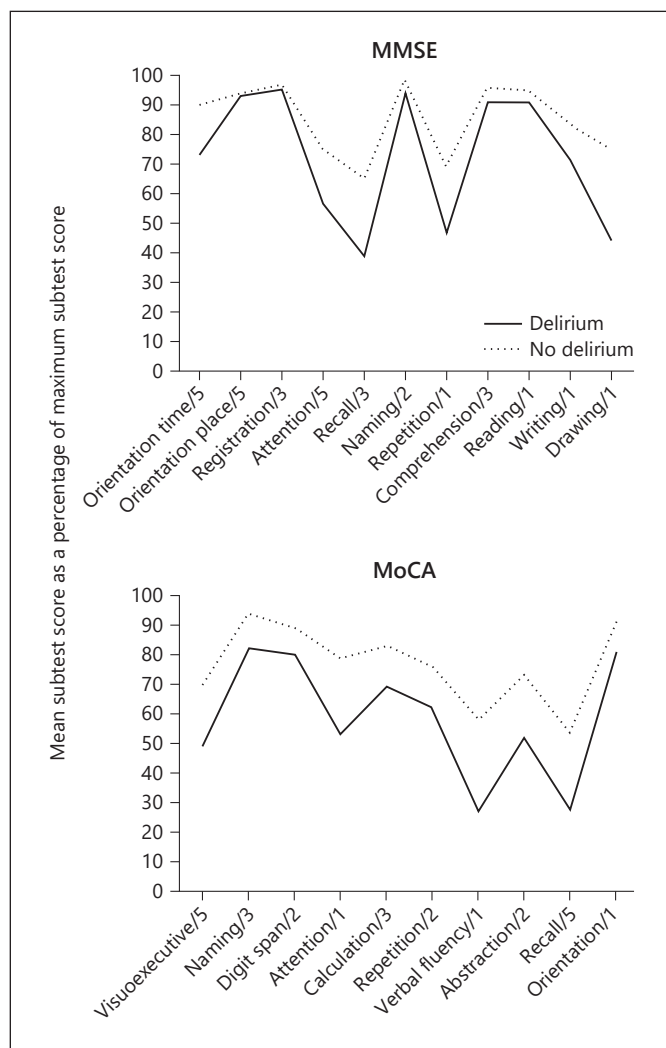


Fig. 2. Mean pre-admission MMSE (upper figure) and MoCA (lower figure) subtest scores shown as a percentage of the maximum subtest score, for patients with (dashed line) and without (solid line) delirium. MMSE, mini-mental-state-examination; MoCA, Montreal Cognitive Assessment.

expected less strong associations between preadmission cognition and delirium after adjustment for baseline stroke severity. In fact, this had little effect probably because the majority of survivors in our cohort had relatively minor strokes or TIA. Although the link between pre-existing cognitive impairment and delirium is well-established, there are few data on whether the underlying subtype of neuropathology is important. One small autopsy study failed to show a relationship between any specific neuropathological marker and delirium [18]. In contrast, patients with vascular versus Alzheimer's dementia

appear more likely to get delirium [19] and are over-represented in hospital cohorts [13]. In addition, neuroimaging studies suggest a stronger role for white matter disease than neurodegeneration in mediating delirium risk [20].

In our study, we saw strong associations between deficits in frontal/executive domains and memory and delirium risk. The MoCA has broader coverage of frontal and attentional cognitive domains than the MMSE and more difficult memory and language items. Consequently, impairment in nearly all the MoCA subtests predicted future delirium compared to only 4 of the MMSE subtests. The typical "vascular pattern" cognitive impairment profile after stroke with frontal/executive and recall deficits contrasts with that of early Alzheimer's disease in which short-term recall is most affected [6, 7]. Previous data on cognitive domain impairment profile and delirium risk are largely from highly selected elective surgical populations. Almost all studies are concerned with short-term delirium risk. Available data suggest associations with executive dysfunction: in 1 inclusive study of long-term (up to 1 year) prediction of delirium in older people living in residential care, strong associations with baseline Stroop test were found [21], although other studies have shown associations also with memory [22].

The mechanisms underlying the association between the cognitive domain impairment profile and delirium are unclear. Altered brain networks have been shown to underpin executive/attentional as well as memory deficits, and occur in stroke and neurodegenerative disease [5, 22]. These network changes may predispose to network disintegration and the delirium syndrome in the face of precipitants including acute illness or environmental changes [23, 24]. Alternatively, deficits in executive function and recall may associate with delirium because they are a clinical manifestation of the underlying cerebral pathology, including cerebrovascular disease burden, and associated blood-brain barrier permeability. Damage to the blood-brain barrier is thought to be an important mechanism in delirium through enabling inflammatory mediators to reach the brain [25].

Strengths of our study include the nesting within an on-going inclusive longitudinal population-based cohort study enriched for cerebrovascular disease with prospective patient evaluation for delirium. The study design allowed prospective assessment of pre-admission cognitive function using validated tests and robust adjustment for confounders often not considered in previous studies. Limitations include the use of cognitive screening tests rather than a comprehensive neuropsychological battery, although this enabled inclusion of older more impaired

patients at greater risk of delirium. In-depth neuropsychological assessment may have provided more detail on the pattern of cognitive deficits contributing to delirium vulnerability. In addition, we did not ascertain episodes of delirium occurring in non-hospitalized patients in the community. There are few existing data but community prevalence of <0.5% has been reported in older people without dementia [26]. Since delirium is a powerful driver of hospital admission even in those in long-term care [1, 26, 27], it is unlikely that there were large numbers of delirium cases in the community without admission. Also, we did not examine the precipitating factors for delirium in detail but the breakdown by admission type suggested that acute medical emergencies were important. Finally, we were only able to prospectively collect data on hospital admissions over a 6 month snapshot period rather than over the entire OXVASC study timeframe which would have enabled us to undertake a linear mixed-effects analysis increasing power and fully exploiting the longitudinal nature of OXVASC. The move to electronic patient records and better routine documentation of delirium may make this possible in future studies.

Conclusion

TIA/stroke-associated cognitive impairment increases the risk of future delirium with particular importance of deficits in frontal/executive function and recall. Further work is needed to establish the underlying mechanisms and whether inclusion of cognitive impairment profile improves the accuracy of delirium risk models [28]. Future large studies are required to enable mixed-effects modelling to determine the impact of delirium occurrence on future dementia risk. Long-term delirium risk and acute delirium at the time of stroke should be considered as part of the overall burden of TIA and stroke.

Acknowledgment

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The Oxford Vascular Study is approved by the local research Ethics Committee

(OxREC No. C02.043). Informed written consent (or assent from relatives) was obtained for study interview and face-to-face and telephone follow-up as well as indirect follow-up using medical records.

Conflict of Interest Statement

S.T.P. has received royalties from Oxford University Press and Cambridge University Press and Consultancy Fees from University of Michigan, USA and honoraria from the University of Trondheim Norway, La Trobe University, Melbourne, Australia, and the University of Sydney, Australia. R.J.T. and S.J.V.W. have nothing to declare. P.M.R. has received royalties from Oxford University Press and Cambridge University Press and honoraria for trial committee work from Bayer, Leverkusen, Germany and BMS.

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Author Contributions

S.T.P. designed this substudy, cleaned and assembled data, performed analyses, and wrote the manuscript. S.T.P. also developed, validated, and implemented the Oxford University Hospitals NHS Foundation Trust cognitive screen, as part of her role as Clinical Lead for Dementia and Delirium. R.J.T. and S.J.V.W. collected data. P.M.R. had set up and directed the Oxford Vascular Study and provided critical input to the analyses and manuscript.

Data Availability Statement

Applications for access to OXVASC study data will be considered by P.M.R. (peter.rothwell@ndcn.ox.ac.uk).

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

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