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Associations of Multimorbidity With Stroke Severity, Subtype, Premorbid Disability, and Early Mortality: Oxford Vascular Study

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Abstract

Background and Objectives: Patients with multimorbidity are under-represented in clinical trials. Inclusion in stroke trials is often limited by exclusion based on pre-morbid disability, concerns about worse post-stroke outcomes in acute treatment trials, and a possibly increased proportion of haemorrhagic vs ischaemic stroke in prevention trials. Multimorbidity is associated with increased mortality after stroke, but it is unclear whether this is driven by increased stroke severity, or is confounded by particular stroke subtypes or premorbid disability. We aimed to determine the independent association of multimorbidity with stroke severity taking account of these main potential confounders.

Methods: In a population-based incidence study (Oxford Vascular Study; 2002-2017), pre-stroke multimorbidity (Charlson Comorbidity Index-CCI; unweighted/weighted) in all first-in-study strokes was related to post-acute severity (≈24 hours; NIH Stroke Scale-NIHSS), stroke subtype (haemorrhagic vs ischaemic; Trial of Org 10172 in Acute Stroke Treatment-TOAST), and pre-morbid disability (modified Rankin score/mRS≥2) using age/sex-adjusted logistic and linear regression models, and to 90-day mortality using Cox proportional hazard models.

Results: Among 2492 patients (mean/SD age=74.5/13.9; 1216/48.8% male; 2160/86.7% ischaemic strokes; mean/SD NIHSS=5.7/7.1), 1402/56.2% had at least one CCI comorbidity, and 700/28.1% had multimorbidity. Although multimorbidity was strongly related to pre-

morbid mRS≥2 (aOR for per CCI comorbidity=1.42, 1.31-1.54, *p*<0.001) and comorbidity burden was crudely associated with increased severity of ischaemic stroke (OR per comorbidity: 1.12, 1.01-1.23 for NIHSS 5-9, *p*=0.027; 1.15, 1.06-1.26, for NIHSS≥10; *p*=0.001), no association with severity remained after stratification by TOAST subtype (aOR=1.02, 0.90-1.14, *p*=0.78 for NIHSS 5-9 vs 0-4: 0.99, 0.91-1.07, *p*=0.75 for NIHSS≥10vs0-4), or within any individual subtype. The proportion of intracerebral haemorrhage versus ischaemic stroke was lower in patients with multimorbidity (aOR per comorbidity=0.80, 0.70-0.92, *p*<0.001), and multimorbidity was only weakly associated with 90-day mortality after adjustment for age, sex, severity, and pre-morbid disability (aHR per comorbidity=1.09, 1.04-1.14, *p*<0.001). Results were unchanged using the weighted CCI.

Discussion: Multimorbidity is common in patients with stroke and is strongly related to pre-morbid disability, but is not independently associated with increased ischaemic stroke severity. Greater inclusion of patients with multimorbidity is unlikely therefore to undermine the effectiveness of interventions in clinical trials, but would increase external validity.

Introduction

Multimorbidity (often referred to as 'multiple long-term conditions') is common in older individuals,[1] particularly in patients with stroke,[2] and prevalence is predicted to rise further with continued population aging.[1, 3] Yet, patients with multimorbidity are generally underrepresented in randomised trials,[4] which may limit the generalizability of results,[5] and thereby exacerbate the existing tendency to under-treat in routine practice. Exclusion of patients with multimorbidity from acute stroke trials might be driven indirectly by increased pre-morbid disability, with a cut-off pre-morbid modified Rankin Scores (mRS) ≥2 excluding over a third of stroke patients older than 65 years and nearly two thirds older than 85,[6] but is also related to concerns about greater severity of stroke and increased early mortality in patients with multimorbidity. Such patients also tend to be excluded from trials of preventive treatments, such as antithrombotic treatment in secondary prevention of stroke,[7] partly due to a concern about an increased proportion of haemorrhagic vs ischaemic recurrent strokes.

It is plausible that there may indeed be adverse impacts of multimorbidity on severity of stroke, either via effects on pathophysiology and progression of cerebral ischaemia, and/or on the effectiveness of treatments. Multimorbidity is consistently reported to be associated with increased mortality after stroke,[8-11] but it is uncertain whether this association is driven by increased severity of stroke, or is confounded by associations with particular stroke subtypes or with pre-morbid disability. Previous studies have largely focused on the impact of multimorbidity on overall all-cause mortality in large administrative or hospital datasets,[8-11]

but none have adjusted for pre-morbid disability or stratified by aetiological subtype. A better understanding of the association of multimorbidity with stroke severity, pre-morbid disability, and aetiological subtype is therefore required to understand apparent associations with post-stroke mortality. We aimed to determine these associations in a population-based stroke incidence study (Oxford Vascular Study-OXVASC).

Methods

OXVASC is a population-based study of all acute vascular events in a defined population of 94,973 persons registered with about 100 primary care physicians working in 9 general practices Oxfordshire, United Kingdom.[12-14] In the UK, almost all of the population is registered with a GP, who holds a life-long record of all medical consultations, investigations, and diagnoses made in either primary or secondary care. Further details on the underlying population have been published previously.[12-14] OXVASC has been approved by the local health research ethics committee (OREC A: 05/Q1604/70).

The present sample included all first-in-study strokes that were ascertained from April 1 2002 to March 31 2017. Case ascertainment was based on multiple sources, including a daily rapid access TIA/stroke clinic for patients with suspected TIA or stroke, daily searches of hospital admissions to relevant wards, emergency department attendances, and Bereavement Office records; and monthly searches of death certificates, coroner reports, GP diagnostic codes, and brain/vascular imaging referrals. Further details on the ascertainment methodology used in OXVASC are reported elsewhere.[12-14]

Patients were seen by study physicians as soon as possible following an index event. At initial assessment, data were collected on clinical and demographic variables, including pre-morbid disability (modified Rankin Scale),[15] and prior comorbidities, and cross-checked by review of GP records. All patients also had a detailed clinical examination including an assessment of their post-acute phase stroke severity (NIH Stroke Scale-NIHSS),[16] usually around 24 hours after onset. Data were also collected on brain and vascular imaging, 12-lead electrocardiograph, blood tests, echocardiography, and 5-day ECG monitoring.

If a patient died before a study assessment, information was obtained from records and eye witness accounts if possible. All cases were reviewed by the study's senior neurologist (PMR) and stroke defined using the World Health Organisation criteria[17] and ischaemic stroke subtype classified with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) system.[18]

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from patients, or assent was acquired from relatives if consent was not possible.

Data Availability

Requests for data will be considered by Rothwell (peter.rothwell@ndcn.ox.ac.uk).

Statistical Analyses

Patients with incomplete data (usually <2%) were excluded from analyses and no data were imputed. Continuous data were reported as either mean (standard deviation; SD) or median (interquartile range; IQR), as appropriate. Categorical data were presented as count (percentage). Differences between multimorbidity groups were explored using One-way ANOVA, Chi-Squared, or Kruskal-Wallis tests, as appropriate.

Pre-stroke multimorbidity was quantified using the both the weighted and unweighted versions of the Charlson Comorbidity Index (CCI).[19] For unweighted analyses, patients were classified as living with no comorbidity (CCI=0), one comorbidity (CCI=1), or multimorbidity (CCI≥2) and compared across groups, but regression analyses were also done across the full CCI score. Weighted analyses used CCI weights previously validated for stroke outcome studies (*eTable 1*).[10]

Associations between multimorbidity (using unweighted CCI) and stroke severity were analysed using crude and adjusted logistic regression models for NIHSS 5-9 and ≥10 versus 0-4. As the longer distribution of the weighted CCI allowed for linear regression analysis, a further set of analyses was also performed using linear regression with the weighted CCI and full ordinal NIHSS score. Analyses were performed including all patients, and also stratified by TOAST subtype, with subtype specific associations then pooled by fixed-effects meta-analysis. To explore possible associations between pre-stroke multimorbidity and subtype, crude and adjusted (age/sex) logistic regression models were used, with cryptogenic stroke was used as the reference group for TOAST subtypes. Additional analyses were also performed with stratification by age (<75/ ≥75 years) and sex.

Associations between multimorbidity and pre-morbid disability were analysed using crude and adjusted (age/sex) logistic regression models for mRS≥2 versus 0-1. Associations between multimorbidity and all-cause mortality within 90-days were assessed with Cox proportional hazard models (unadjusted, age/sex-adjusted, additionally adjusted for NIHSS and/or mRS, and stratified by TOAST subtype).

We also performed three sensitivity analyses. First, a small number of patients had a stroke death in the community or died very shortly after arrival at hospital, and did not therefore have NIHSS assessed. To avoid potential bias due to exclusion of such cases, we did a set of analyses examining the within-subtype associations between multimorbidity and severity in which these cases were classified as NIHSS≥10 and allocated to either the intracerebral haemorrhage category or the TOAST Unknown ischaemic stroke subtype. Second, in attempt to minimise potential bias relating to delayed presentation or initial clinical assessment in patients with multimorbidity, we ran analyses excluding patients who received thrombolysis or thrombectomy. Third, to limit possible bias due to patient or physician decisions to limit investigation/treatment on the association of multimorbidity with 90-day mortality, we repeated analyses after excluding patients with metastatic cancer, haematological malignancy, dementia, or care home residence.

All analyses were performed using Stata (V16; College Station, USA). Significance was set at $p<0.05$.

Results

Of 2540 patients ascertained with probable or definite strokes between 2002 and 2017, 48 (1.9%) were excluded from the main analysis due to incomplete data on past medical history or NIHSS, mainly due to early death, non-hospitalisation, or limitations due to end-of-life care (*eFigure 1*). Of the 2492 (98.1%) remaining patients (mean/SD age=74.5/13.9 years; 1216 male; 2160 ischaemic strokes), 1402 (56.3%) had at least one prior CCI comorbidity and 700 (28.0%) had multimorbidity (≥2 CCI comorbidities; Table 1). The most common comorbidities were previous cancer (13.8%), myocardial infarction (11.5%), and diabetes without end-organ damage (11.4%; Table 2 and *eTables 1-3*).

Of patients with ≥2 CCI comorbidities, 375 (53.5%) had a pre-morbid mRS≥ 2 (Table 1). Multimorbidity was strongly associated with pre-morbid disability (age/sex adjusted OR per comorbidity=1.42, 1.31-1.54; aOR per weighted CCI point: 1.21, 1.14-1.28; both $p<0.001$).

The proportion of intracerebral haemorrhage (ICH) versus ischaemic stroke was lower in patients with multimorbidity (aOR/CCI comorbidity=0.80, 0.70-0.92, $p<0.001$; *eTable 4*), and remained so after excluding patients with known prior atrial fibrillation (0.83, 0.71-0.96, $p=0.016$).

CCI was crudely associated with increased NIHSS at 24 hours (OR per CCI comorbidity: 1.11 95%CI 1.01-1.23 for NIHSS 5-9 vs 0-4; 1.12, 1.03-1.21 for NIHSS≥10 vs 0-4; linear regression using weighted CCI & NIHSS: β=0.24, $p=0.005$; *eTables 5-7*) and in analyses

confined to ischaemic stroke (OR per CCI comorbidity: 1.12, 1.01-1.23 for NIHSS 5-9 vs 0-4, *p*=0.027; 1.15, 1.06-1.26, for NIHSS≥10 vs 0-4; *p*=0.001; β=0.30, *p*<0.001; *eFigure 2*). Associations were similar after exclusion of patients with known prior atrial fibrillation (*eTable 8*), after stratification by age and sex (*eTable 9*), and after excluding patients who received thrombolysis or thrombectomy (*eTable 10*).

However, CCI differed across TOAST subtypes of ischaemic stroke (*p*<0.001; Figure 1). Compared with patients who had cryptogenic events, comorbidity was greater in those with cardioembolic events (age/sex-adjusted OR per CCI comorbidity=1.33, 95%CI 1.19-1.48, *p*<0.001), large artery disease (aOR=1.20, 1.04-1.38, *p*<0.01), multiple aetiologies (aOR=1.32, 1.01-1.72, *p*<0.05), and incomplete investigation (TOAST Unknown classification; aOR=1.36, 1.19-1.56, *p*<0.001; Table 3 and *eTables 11-13*). On analysis of pre-stroke CCI versus NIHSS at 24 hours within individual TOAST subtypes, no significant associations remained for any subtype or on pooling of the within-subtype associations (Table 4 and e*Table 14*). Results were similar on linear regression of weighted CCI against NIHSS stratified by subtype (e*Tables 15-16*) and in sensitivity analyses designating the 30 patients without brain imaging who died in the community or shortly after arrival in hospital as having an NIHSS≥10 and having either an ICH or an ischaemic stroke of unknown TOAST aetiology (e*Table 17*).

CCI was modestly predictive of all-cause death at 90-days following adjustment for age, sex and NIHSS (aHR=1.14, 1.09-1.19, *p*<0.001) and after further adjustment for pre-morbid mRS (aHR=1.09, 1.04-1.14, *p*<0.001; *eTable 18*) and stratification by TOAST subtype (pooled aHR/CCI comorbidity=1.09, 1.04-1.13; *p*<0.001). Results were similar after excluding patients with metastatic cancer, haematological malignancy, dementia, or care home residence (*eTable 19).*

Discussion

Multimorbidity has been widely reported to be associated with increased short and medium term mortality after stroke, which might provide some justification for exclusion of patients from randomised controlled trials of certain interventions. However, although some previous studies of the association of multimorbidity with outcome after stroke adjusted for stroke severity, none of the 22 studies included in recent reviews looked specifically at the association between multimorbidity and early stroke severity and none stratified analyses by aetiological subtype of ischaemic stroke.[2, 20] We showed that although multimorbidity was strongly associated with pre-morbid disability, consistent with studies in the general population,[21-23] there was no association with greater stroke severity after stratification by

aetiological subtype, and there was only a modest association with 90-day mortality after adjustment for severity and prior disability.

One previous study reported analyses of the prognostic value of multimorbidity in ischaemic stroke versus ICH,[24] but we are not aware of previous reports comparing multimorbidity rates between these subtypes or between TOAST subtypes of ischaemic stroke. The observed association in our study of multimorbidity with cardioembolic stroke might be expected due to inclusion of cardiac diseases in the CCI (myocardial infarction, congestive heart failure), and that with large artery disease aetiology likely reflects the inclusion of related comorbidities (myocardial infarction, peripheral vascular disease, diabetes) in the CCI. These associations would in turn explain the link between CCI and stroke due to multiple aetiologies. The tendency for patients with multimorbidity to receive incomplete investigation ('unknown' TOAST subtype) probably reflects the fact that some comorbidities contraindicate investigations (e.g. contrast-dependent arterial imaging, MRI-brain imaging) and investigations might be avoided for compassionate or pragmatic reasons in patients with comorbidities such dementia or metastatic cancer.

Our findings have implications for stroke researchers, clinicians and policy makers. Firstly, our results underscore the importance of adjusting for pre-morbid disability and stratifying by aetiological subtype in future research studies of multimorbidity and stroke. Secondly, given the aging population and predicted rises in rates of multimorbidity, our data suggest that the overall cost and burden of stroke will rise in parallel due to the association with stroke subtypes that tend to be more severe even though multimorbidity appears not be associated with greater severity of stroke within individual subtypes. Thirdly, this lack of a subtype-specific association of multimorbidity with stroke severity, and the weak association with early mortality after adjustment for confounders, suggests that the presence of multimorbidity *per se* should not discourage active treatment in routine clinical practice. Previous studies of the association of multimorbidity and post-stroke mortality have focussed mainly on longer-term mortality and reports of increased early mortality may have over-estimated the association by use of administrative data alone, without the potential to stratify by stroke subtype.[11, 24]

Our findings also have implications for the design, performance and interpretation of trials in patients with stroke. First, our finding that over a quarter of stroke patients has multiple prior comorbidities highlights the importance of being able to apply trial evidence in clinical decision making in this group. Second, our finding that multimorbidity was not independently related to stroke severity, and was only weakly associated with short-term mortality, suggests patients with multimorbidity should not be routinely excluded from trials unless

there is a specific reason to do so. Third, our finding that about half of stroke patients with multimorbidity have an mRS≥2 highlights one important mechanism for exclusion from trials and supports the use of primary outcomes based on ordinal rather than dichotomous analysis of the mRS.[6] Removal of this barrier to inclusion of patients with premorbid disability leaves little residual justification to exclude patients with multimorbidity either by strict inclusion criteria, or by investigators concerned about trial discipline or any adverse effects on power to detect treatment effects. Finally, our finding that multimorbidity is not associated with a greater proportion of ICH versus ischaemic stroke should encourage greater inclusion of patients with comorbidities in trials of antithrombotic treatment in prevention of stroke,[7] particularly if any increased risk of gastrointestinal bleeding can be mitigated.

Our study did, however, have several limitations. First, there is a risk of ascertainment bias whereby patients with multimorbidity may be less likely to present following minor stroke or clinicians may attribute symptoms of minor events to existing comorbidities. However, our case-ascertainment aimed to identify all patients who sought medical attention with TIA/stroke symptoms irrespective of the presumptive diagnosis of the clinician who first assessed them. Moreover, and residual under-ascertainment of patients with minor events would have increased the apparent association of multimorbidity with stroke severity. We also attempted to minimise any potential bias in relation to delayed presentation or delayed initial clinical assessment in patients with multimorbidity by assessing the NIHSS at a uniform time point after stroke onset (usually ~24 hours). Second, it is possible there was some under ascertainment of comorbidities, particularly in patients with aphasia or dementia. However, we also obtained recorded prior comorbidities from all hospital and primary care medical records. Third, our analyses stratified by aetiological subtype of ischaemic stroke were underpowered to exclude weak associations with outcome within subtypes. Fourth, potential withdrawal/withholding of care or advanced directives in patients with multimorbidity might bias associations with outcome. However, although we did not collect data on withdrawal/withholding of care or on advanced directives, exclusion of patients most likely to have treatment withheld did not alter our findings. Similarly, we did not measure the intensity of care in stroke patients with multimorbidity, which should be explored in future studies, but sensitivity analyses in relation to receipt of thrombolysis or thrombectomy did not alter our findings. Fifth, our findings should be interpreted in light of the fact that our study population is predominantly Caucasian. Finally, the CCI does not include all comorbidities that might be associated with severity of stroke. For example, we showed that prior atrial fibrillation was strongly predictive of increased severity. However, excluding patients with prior atrial fibrillation did not alter our findings.

In conclusion, multimorbidity was common in patients with stroke and was associated with pre-morbid disability, but it was not associated with increased severity of stroke independent of aetiological subtype, or with an increased proportion of ICH, and was only modestly associated with 90-day mortality after adjustment for pre-morbid disability and stroke severity.

Supplement Files - http://links.lww.com/WNL/C911

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Table 1. Baseline characteristics and subtype in 2492 first-in-study stroke patients, both in the overall cohort and stratified by pre-stroke multimorbidity level.

Clinical/Demographic Variables	CCI 0 (N=1090)	CCI 1 (N=702)	CCI ≥ 2 (N=700)	Full Cohort (N=2492)	*p*
Mean (SD) age	71.0 (15.7)	75.9 (12.7)	78.5 (10.5)	74.5 (13.9)	**<0.001**
Male Sex	543 (49.8%)	322 (45.9%)	351 (50.1%)	1216 (48.8%)	0.25
Pre-morbid mRS					**<0.001**
Median (IQR)	1 (0-1)	1 (0-3)	2 (1-3)	1 (0-2)	
≥2	246 (29.1%)	273 (38.9%)	375 (53.5%)	894 (35.9%)	
≥3	157 (14.4%)	179 (25.5%)	252 (36.0%)	588 (23.6%)	
Median (IQR) NIHSS at 24H	2 (1-7)	3 (1-9)	3 (1-9)	3 (1-8)	**<0.001**
Aetiological Subtype					**<0.001**
Intracerebral Haemorrhage	112 (64.7%)	70 (69.3%)	49 (84.5%)	231 (9.3%)	
Subarachnoid Haemorrhage	61 (35.3%)	31 (30.7%)	9 (15.5%)	101 (4.1%)	
Cardioembolic	228 (20.9%)	181 (25.8%)	246 (35.1%)	655 (26.3%)	
Large Artery Disease	93 (8.5%)	59 (8.4%)	63 (9.0%)	215 (8.6%)	
Small Vessel Disease	150 (13.8%)	79 (11.3%)	47 (6.7%)	276 (11.1%)	
Undetermined	280 (25.7%)	127 (18.1%)	115 (16.4%)	522 (20.9%)	
Unknown	107 (9.8%)	113 (16.1%)	122 (17.4%)	342 (13.7%)	
Multiple	31 (2.8%)	28 (4.0%)	36 (5.1%)	95 (3.8%)	
Other	28 (2.6%)	14 (2.0%)	13 (1.9%)	55 (2.2%)	

Using count of CCI comorbidities/unweighted.
CCI: Charlson Comorbidity Index, NIHSS: National Institutes of Health Stroke Scale

Table 2. Distribution of individual comorbidities across unweighted Charlson Comorbidity Index categories in 2492 patients with a first-in-study period stroke.

	Comorbidity	N	CCI 0	CCI 1	CCI ≥ 2	*p*
CCI Comorbidities	Cancer (Metastatic)	27	0 (0)	4 (14.8)	23 (85.2)	**<0.001**
	Cancer (Solid)	343	0 (0)	143 (41.7)	200 (58.3)	**<0.001**
	Chronic Kidney Disease	227	0 (0)	55 (24.2)	172 (75.8)	**<0.001**
	Congestive Heart Failure	261	0 (0)	52 (19.9)	209 (80.1)	**<0.001**
	COPD	171	0 (0)	54 (31.6)	117 (68.4)	**<0.001**
	Connective Tissue Disease	121	0 (0)	19 (15.7)	102 (84.3)	**<0.001**
	Dementia	214	0 (0)	58 (27.1)	156 (72.9)	**<0.001**
	Diabetes (No End-Organ Damage)	285	0 (0)	118 (41.4)	167 (58.6)	**<0.001**
	Diabetes (W. End-Organ Damage)	77	0 (0)	5 (6.5)	72 (93.5)	**<0.001**
	HIV/AIDS	2	0 (0)	0	2 (100.0)	0.094
	Leukaemia	11	0 (0)	2 (18.2)	9 (81.8)	0.2
	Liver Disease	41	0 (0)	13 (31.7)	28 (68.3)	**<0.001**
	Lymphoma	21	0 (0)	6 (28.6)	15 (71.4)	**0.049**
	Myocardial Infarction	287	0 (0)	62 (23.0)	225 (78.4)	**<0.001**
	Peptic Ulcer Disease	201	0 (0)	56 (27.9)	145 (72.1)	**<0.001**
	Peripheral Vascular Disease	237	0 (0)	53 (22.4)	184 (77.6)	**<0.001**
Non-CCI	Hypertension	1494	559 (37.4)	438 (29.3)	497 (33.3)	**<0.001**
	Atrial Fibrillation	534	157 (29.4)	137 (25.6)	240 (44.9)	**<0.001**
	Hypercholesterolaemia	647	201 (31.1)	189 (29.2)	257 (39.7)	**<0.001**
	Full Cohort	2492	1090 (43.7)	702 (28.2)	700 (28.1)	N/A

Note: Expressed as count (percentage); p-value for the Chi-Squared test
CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome

Table 3. Age/sex-adjusted associations between pre-stroke multimorbidity and TOAST aetiological subtypes of ischaemic stroke.

Aetiological Subtype	N (%)	Age/Sex-Adjusted Odds Ratio (95%CI)
		Per CCI Comorbidity
Undetermined (Cryptogenic)	522 (30.0)	1.00
Small Vessel Disease	276 (11.1)	0.92 (0.79-1.07)
Cardioembolic	655 (39.6)	1.33 (1.19-1.48)***
Large Artery Disease	215 (26.3)	1.20 (1.04-1.38)**
Multiple	95 (3.8)	1.32 (1.01-1.72)*
Other	55 (2.2)	0.87 (0.67-1.12)
Unknown (Incomplete investigation)	342 (13.7)	1.36 (1.19-1.56)***
		Per point of weighted CCI
Undetermined (Cryptogenic)	522 (30.0)	1.00
Small Vessel Disease	276 (11.1)	1.00 (0.89-1.12)
Cardioembolic	655 (39.6)	1.23 (1.13-1.34)***
Large Artery Disease	215 (26.3)	1.16 (1.04-1.29)**
Multiple	95 (3.8)	1.28 (1.06-1.55)*
Other	55 (2.2)	0.96 (0.79-1.17)
Unknown (Incomplete investigation)	342 (13.7)	1.30 (1.18-1.44)***

*All subtypes vs. undetermined stroke; *p<0.05 **p<0.01 ***p<0.001*
CCI: Charlson Comorbidity Index

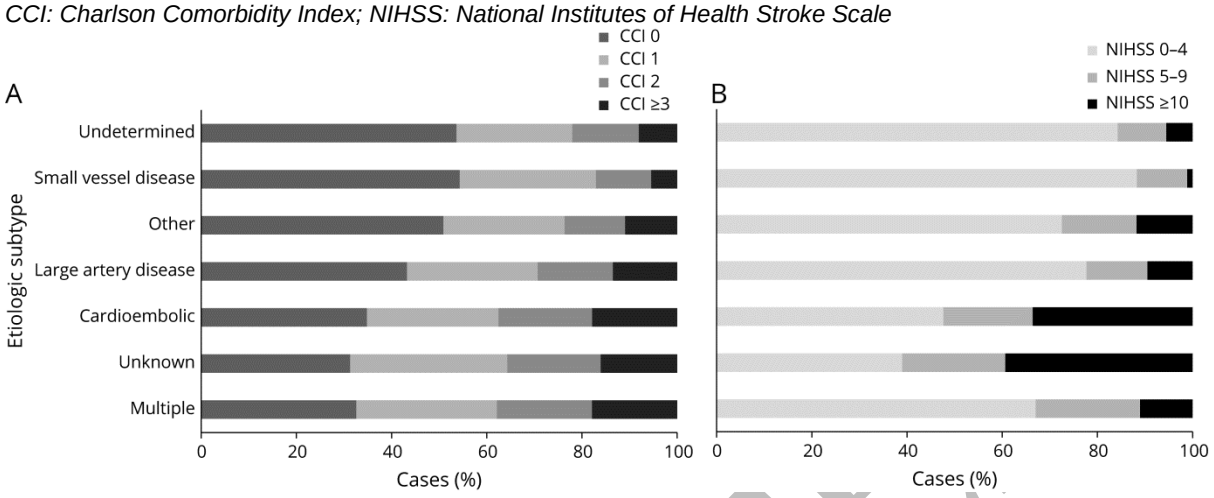
Table 4. Age/sex-adjusted associations between pre-stroke multimorbidity and stroke severity at 24 hours in ischaemic stroke patients, stratified by TOAST aetiological subtype, with pooled estimates obtained by meta-analysis of the subtype-specific results.

TOAST Category	*Crude OR Per CCI Comorbidity (95%CI)*			*Age/Sex-Adjusted OR Per CCI Comorbidity (95%CI)*		
	NIHSS 0-4	**NIHSS 5-9**	**NIHSS ≥ 10**	**NIHSS 0-4**	**NIHSS 5-9**	**NIHSS ≥ 10**
Cardioembolic	1.00	1.09 (0.93-1.27)	0.97 (0.85-1.11)	1.00	1.08 (0.91-1.29)	0.94 (0.82-1.08)
Large Artery Disease	1.00	0.89 (0.63-1.26)	1.13 (0.80-1.58)	1.00	0.91 (0.62-1.35)	1.12 (0.79-1.60)
Small Vessel Disease	1.00	0.79 (0.50-1.26)	1.29 (0.49-3.42)	1.00	0.71 (0.43-1.18)	0.97 (0.31-2.98)
Undetermined	1.00	0.96 (0.73-1.27)	0.69 (0.41-1.09)	1.00	0.93 (0.68-1.27)	0.66 (0.41-1.06)
Unknown	1.00	1.08 (0.85-1.38)	1.11 (0.91-1.36)	1.00	1.09 (0.84-1.43)	1.11 (0.91-1.36)
Multiple	1.00	0.79 (0.50-1.23)	1.09 (0.64-1.87)	1.00	0.81 (0.49-1.32)	1.11 (0.65-1.89)
Other	1.00	1.71 (0.93-3.16)	0.30 (0.05-1.87)	1.00	2.33 (0.94-5.76)	0.33 (0.05-2.15)
Pooled Estimate	1.00	1.03 (0.93-1.14)	1.01 (0.91-1.11)	1.00	1.02 (0.90-1.14)	0.98 (0.89-1.09)

Estimates obtained using the weighted version of the CCI are found in the Online-only Data Supplement.
**p<0.05, **p<0.01, ***p<0.001*
CCI: Charlson Comorbidity Index; NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio

Figure 1. Distribution of the unweighted Charlson Comorbidity Index (A) and NIH Stroke Scale score at 24 hours (B) across different aetiological subtypes of ischaemic stroke using TOAST classification.

Panel A: CCI (counts/unweighted); Panel B: NIHSS
CCI: Charlson Comorbidity Index; NIHSS: National Institutes of Health Stroke Scale



Associations of Multimorbidity With Stroke Severity, Subtype, Premorbid Disability, and Early Mortality: Oxford Vascular Study

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