Associations of Multimorbidity With Stroke Severity, Subtype, Premorbid Disability, and Early Mortality

Oxford Vascular Study

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Study Question
Is the association of multimorbidity and early stroke mortality confounded by stroke severity, subtype, or premorbid disability?

What Is Known and What This Paper Adds
Multimorbidity (often referred to as “multiple long-term conditions”) is common in older persons, including patients with stroke, and prevalence is predicted to rise further with continued population aging. Patients with multimorbidity tend to be underrepresented in randomized clinical trials in stroke, partly because multimorbidity has been shown to be associated with an increased poststroke mortality. However, the drivers of this association are unknown. The results of this study show that multimorbidity was associated with a lower proportion of intracerebral hemorrhage and strongly associated with etiologic subtype of ischemic stroke and prior disability. However, multimorbidity was not an independent predictor of stroke severity and was only weakly associated with 90-day mortality. Our findings do not support the exclusion of patients with multimorbidity from clinical trials in stroke. They also suggest that studies of the impact of multimorbidity on short-term and long-term outcomes after stroke should take into account the associations with premorbid disability and etiologic subtype.

Methods
We studied all patients who had a first in-study stroke between 2002 and 2017 in the Oxford Vascular Study, a prospective population-based study in Oxfordshire, United Kingdom, with near-complete ascertainment and follow-up. Patients were assessed by study physicians as soon as possible after a stroke, typically within 1–2 days after the onset of symptoms. This assessment included a full clinical history along with data obtained on demographic variables, stroke severity (the NIH Stroke Scale), premorbid disability (modified Rankin scale), and all prior comorbidities, which were supplemented with access to electronic primary care records. All cases were reviewed by the senior neurologist of this study, and ischemic stroke subtypes were determined using the Trial of Org 10172 in Acute Stroke Treatment classification. Multimorbidity was quantified using both the weighted and unweighted Charlson Comorbidity Index (CCI). Associations between multimorbidity and premorbid disability, stroke severity, or etiologic subtype were obtained using logistic regression, and associations with all-cause mortality within 90 days were obtained using Cox proportional hazard models.

Results and Study Limitations
Of 2,492 patients included in the final analysis, 56.2% had at least 1 CCI comorbidity, and 28.1% had multimorbidity (2 or more CCI comorbidities). The most common comorbidities were cancer (13.8%), myocardial infarction (11.5%), and diabetes without end-organ damage (11.4%). Multimorbidity was associated with greater odds of prior disability (age-adjusted/sex-adjusted odds ratio [OR] per comorbidity 1.42, 1.31–1.54, p < 0.001) and a lower proportion of intracerebral hemorrhage (adjusted OR/CCI comorbidity vs ischemic stroke 0.80, 0.70–0.92, p <0.001). Multimorbidity was crudely associated with greater severity of ischemic stroke, but this was simply because patients with multimorbidity were more likely to have etiologic subtypes of stroke that are associated with greater stroke severity (age-adjusted/sex-adjusted OR per CCI comorbidity—cardioembolic: 1.33, 95% CI 1.19–1.48; large artery disease: 1.20, 1.04–1.38; multiple etiologies: 1.32, 1.01–1.72; Figure), and there was no independent association with severity after stratification by etiologic subtype. Multimorbidity was also only modestly predictive of all-cause death 90 days poststroke after adjustment for age, sex, stroke severity, and prior disability (adjusted hazard ratio 1.09, 1.04–1.14, p < 0.001). Sensitivity analyses excluding patients who received thrombolysis/thrombectomy or with potential reasons to limit investigations (metastatic cancer, hematologic malignancy, dementia, or care home residence) yielded similar results, as did analyses using the weighted version of the CCI.

Our study has some limitations. First, there was a risk of ascertainment bias because patients with multimorbidity may be less likely to present for minor stroke and clinicians may attribute symptoms to existing comorbidities. However, our case ascertainment aimed to identify all patients who sought medical attention with symptoms irrespective of the presumptive diagnosis of the clinician who first assessed them.
Second, there was possible underascertainment of comorbidities, especially in patients with aphasia or dementia, which we attempted to minimize by also obtaining recorded prior comorbidities from hospital and primary care medical records. Third, possible withdrawal/withholding of care or advanced directives in patients with multimorbidity may bias associations with outcome. However, exclusion of patients most likely to have treatment withheld did not alter our findings. Fourth, our study population was predominantly Caucasian. Finally, the CCI does not include all possible comorbidities that may be associated with the severity of stroke.

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**Figure** Distribution of the Unweighted Charlson Comorbidity Index (Left) and NIHSS Score at 24 Hours (Right) Across Different Etiologic Subtypes of Ischemic Stroke Using TOAST Classification

(A) Distribution of unweighted CCI across etiological subtypes of ischemic stroke. (B) Distribution of NIHSS at 24 hours across etiological subtypes of ischemic stroke. CCI = Charlson Comorbidity Index; NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.