ORIGINAL RESEARCH

Repeated Measures of Modified Rankin Scale Scores to Assess Functional Recovery From Stroke: AFFINITY Study Findings

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BACKGROUND: Function after acute stroke using the modified Rankin Scale (mRS) is usually assessed at a point in time. The analytical implications of serial mRS measurements to evaluate functional recovery over time is not completely understood. We compare repeated-measures and single-measure analyses of the mRS from a randomized clinical trial.

METHODS AND RESULTS: Serial mRS data from AFFINITY (Assessment of Fluoxetine in Stroke Recovery), a double-blind placebo randomized clinical trial of fluoxetine following stroke (n=1280) were analyzed to identify demographic and clinical associations with functional recovery (reduction in mRS) over 12 months. Associations were identified using single-measure (day 365) and repeated-measures (days 28, 90, 180, and 365) partial proportional odds logistic regression. Ninety-five percent of participants experienced a reduction in mRS after 12 months. Functional recovery was associated with age at stroke <70 years; no prestroke history of diabetes, coronary heart disease, or ischemic stroke; prestroke history of depression, a relationship partner, living with others, independence, or paid employment; no fluoxetine intervention; ischemic stroke (compared with hemorrhagic); stroke treatment in Vietnam (compared with Australia or New Zealand); longer time since current stroke; and lower baseline National Institutes of Health Stroke Scale & Patient Health Questionnaire-9 scores. Direction of associations was largely concordant between single-measure and repeated-measures models. Association strength and variance was generally smaller in the repeated-measures model compared with the single-measure model.

CONCLUSIONS: Repeated-measures may improve trial precision in identifying trial associations and effects. Further repeated-measures stroke analyses are required to prove methodological value.

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Key Words: cerebrovascular disease ■ functional outcomes ■ modified Rankin Scale ■ partial proportional odds ■ repeated measures ■ stroke

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CLINICAL PERSPECTIVE

What Is New?

- The modified Rankin Scale (mRS) literature has shifted from dichotomous to ordinal analyses of the mRS, improving statistical precision; however, such studies typically still analyze a single measurement of mRS following stroke (eg, day 90).
- Ordinal analyses of repeated measures of mRS over time may offer incremental improvements in statistical precision over ordinal single-measure analyses; however, this has not been investigated previously.
- Using a randomized control trial poststroke data set (n=1276) with 5 mRS measurements (days 1, 28, 90, 180, and 365) per individual, we compare associations from single-measure and repeated-measures models.

What Are the Clinical Implications?

- Single-measure and repeated-measures models identified demographic and clinical associations with functional recovery that can be validated in future predictive studies.
- The repeated-measures model generally had improved precision (reduced variance) compared with the single-measure model, which may be driven by increased use of available data; however, direction of associations was largely concordant between models.
- This article invites trial analysts to consider repeated-measures analysis of ordinal mRS to improve model precision and power, especially ex-post if repeated-measures data are already available.

Nonstandard Abbreviations and Acronyms

AFFINITY	Assessment of Fluoxetine in Stroke Recovery
mRS	modified Rankin Scale
NHMRC	National Health and Medical Research Council of Australia
NIHSS	National Institutes of Health Stroke Scale
PHQ-9	Patient Health Questionnaire 9

The modified Rankin Scale (mRS) is the most widely used primary outcome measure in stroke trials and is considered a valid tool for evaluating stroke interventions.[1,2] The mRS has 7 categories to measure functional status, ranging from independent and free of disability (0) to death (6). Historically, in analyses of variables associated with the mRS, mRS scores were dichotomously transformed rather than ordinally preserved, and statistical methods were single measure (usually 3 or 6 months after enrollment) rather than longitudinal.[3] Numerous trials and systematic reviews have found variance in the statistical significance of stroke interventions (as measured by treatment effect on mRS), depending on trial design, choice of outcome (including simplified and utility-weighted mRS) and statistical methods.[4–6] While ordinal mRS analyses have increased in number because of greater statistical power and association with long-term clinical outcomes and costs,[5,7] these are usually single mRS measurement analyses. A 2018 literature review found 2 studies using repeated measures of the mRS to analyze recovery over time; however, these did not analyze ordinal mRS.[8–10] Further to this, our literature searches have not revealed studies comparing single-measure and repeated-measures ordinal logistic mRS analyses to identify associations with functional recovery. If collected, usage of all serial follow-up data (rather than study end points) should strengthen validity of any identified associations with mRS by increasing statistical power[11] and is concordant with the Stroke Recovery and Rehabilitation Roundtable goals in applying repeated measures to understand the natural history of recovery and optimal timing of interventions.[12]

Previous repeated-measures analyses of the mRS have focused on either describing mRS over time or identifying treatment effect, rather than associations, and have not used ordinal logistic regression. A comparison of statistical methods[13] highlighted that multistate Markov models and partial proportional odds models were the most efficient in analyzing ordinal mRS, but noting that Markov models are designed for prediction of transitions between individual mRS categories[13,14] rather than identifying associations. A posttrial analysis of the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial further supports use of the partial proportional odds model for analyzing mRS, finding lower prediction error and better model fit when compared with the proportional odds model (with violation of the proportional odds assumption).[15] Another posttrial analysis of the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial used both repeated measures (baseline; day 7; months 3, 6, and 12) and single-measure methods to compare treatment effects of thrombolysis on dichotomized mRS (mRS <1).[16] At 90 days, repeated-measures analysis augmented treatment effect compared with single-measure analysis, with larger odds ratios and greater precision.[16] Another study used repeated-measures of mRS (baseline; months 1, 3, 6, 9, and 12) in generalized linear models to analyze thrombolysis and endovascular treatment effects on dichotomous and ordinal mRS but did not identify associations with functional recovery nor compare with single-measure analysis.[17]

Common associations in stroke functional recovery models include age, preadmission comorbidities, pre-stroke dependency, and neurologic deficit.[18–22] mRS score is commonly recorded before the trial and at 90 days (and recommended at 90 days),[23,24] and models typically predict a single measure in time (eg, day 90 mRS).[18–22,25] However, individualized understanding of functional recovery over time may be clinically important to assist personalized rehabilitation and discharge. Understanding an individual's ordinal mRS score may assist with this,[26] while acknowledging that mRS as a global measure of function will not fully characterize physical or cognitive abilities.[27] Recovery is often not linear nor the same for each person,[28] and thus mRS should be assessed several times to reflect potential fluctuations. Previous longitudinal stroke studies have found that older age, male sex, previous ischemic stroke, peripheral artery disease, and diabetes are associated with mRS scores that either stay constant or increase over time, although broadly mRS scores decrease with time.[8,9,29,30]

The AFFINITY (Assessment of Fluoxetine in Stroke Recovery) trial found no benefit from 6 months of daily treatment with 20 mg of oral fluoxetine in reducing disability (measured by mRS at 6 months). This article is a secondary post hoc cohort level analysis of the AFFINITY trial data with repeated measures of mRS at baseline (day 1) and days 28, 90, 180, and 365. Our aims are 2-fold: (1) to identify baseline demographic and clinical associations with functional recovery (reduction in mRS score) over 12 months after the index stroke and use the statistical power of multiple measurements to compare findings of repeated-measures and single-measure analysis; and (2) to descriptively analyze the functional recovery of participants over 12 months. While recovery mostly occurs in the first 3 months, the literature is limited in reporting 12-month follow-up, which should capture most long-term stroke-related disability.[31] Our results may provide stakeholders with prognostic information, guide future stroke trial analyses, and identify associations for validation in future studies to develop a clinical model for predicting stroke recovery.

METHODS

Data Availability

The data that support the study findings are available from the corresponding author upon reasonable request. One of the authors (A.C.) had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Reporting Checklist

The Strengthening the Reporting of Observational Studies in Epidemiology[32] guidelines were used.

Trial Registration

The AFFINITY trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000774921) and Institutional Review Board ethics approval was obtained from the Royal Perth Hospital Ethics Committee (approval number EC2011/131), with written informed consent obtained from participants.

Participants

AFFINITY was a randomized, double-blind control trial that investigated the efficacy of 6 months of daily treatment with 20 mg of oral fluoxetine in addition to usual care compared with placebo, with 6 months of follow-up without fluoxetine.[33] The trial was conducted in Australia, Vietnam, and New Zealand, recruiting 1280 participants from 2013 to 2019. Participants were aged ≥18 years with a clinical diagnosis of ischemic or hemorrhagic stroke within the past 2 to 15 days and persisting neurological deficit with mRS ≥1. For this analysis, participants with an incorrect diagnosis of stroke (n=4) were excluded, leaving 1276 participants. A modified Consolidated Standards of Reporting Trials flow diagram can be viewed in Figure S1. Further details on trial methods, recruitment, and design have been published previously.[33]

Outcomes

For single measure analysis, the outcome variable was mRS at day 365. For repeated-measures analysis, the outcome variable was mRS at day 28, 90, 180 or 365. mRS was ordinally preserved without transformation. Trained clinical staff used the validated simplified mRS questionnaire to measure mRS.[34] Ninety-eight percent of the trial population was followed up to day 365.

Statistical Analysis

Baseline cohort characteristics were summarized using mean and SD for age at stroke, median with interquartile range for stroke scores and counts with percentage for binary variables (Table 1). The distribution of mRS scores (by category) over 12 months is visualized in the Figure, with a Sankey diagram visualizing transitions in mRS over 12 months in Figure S2. Patterns of mRS change (Worsening, Improving, Constant) between follow-up intervals are summarized with counts (percentages), mean mRS change, and SD (Table 2). Associations between key baseline independent variables (demographic, clinical) and mRS scores were analyzed using partial proportional odds ordinal logistic regression, as recommended by the Optimizing Analysis of Stroke Trials Collaboration[35] and validated in previous studies,[13,15] identifying associations rather than treatment effect and transitions.[13]

With <5% (n=30) of participants missing baseline (day 1) characteristics or day 365 mRS data, complete case analysis without imputation was used.

Baseline variables were selected according to clinical input from the AFFINITY Steering Committee, and associations with functional outcomes after stroke in the literature.[36] Regressor variables included demographics (age >70 years, sex, country of treatment), prestroke comorbidities (diabetes, coronary heart disease, ischemic stroke, depression), prestroke function (relationship status [single compared with relationship partner], living status [home alone compared with living with other people], employment, independence [mRS ≤2]), and current stroke (fluoxetine intervention, ischemic or haemorrhagic classification, stroke severity [National Institutes of Health Stroke Scale (NIHSS)] and mental health [Patient Health Questionnaire 9 (PHQ-9)]).

Regression analysis sought to identify associations or the unadjusted relationship between 2 variables of interest, explored within strata of a few confounding variables.[37] Partial proportional odds models identified associations between baseline variables and a single measure of mRS at day 365 and between baseline variables and repeated measures of the mRS at days 28, 90, 180, and 365. The Brant test was used to determine whether the explanatory variables satisfied the proportional odds assumption, finding violations for age at stroke >70 years, the NIHSS, and time since stroke. For these variables, associations for cumulative logit models corresponding to different categories of the mRS (eg, mRS 0–1 versus 2–6) are presented. Unadjusted associations reflect conditional total effects and are provided for all variables. Adjusted estimates (with covariates age at stroke >70 and sex) were only provided for nonexogenous variables (excluding age at stroke >70 years, sex, country of treatment, fluoxetine intervention, and time since stroke). A directed acyclic graph informing our adjusted regression analysis can be found in Figure S3. Clustered standard errors by country were used for both single-measure and repeated-measures models. Results are reported with odds ratios (ORs) and CIs. An OR <1 indicates lower odds and vice versa. For interpreting the cumulative logit ORs, an OR >1 indicates higher odds of having an mRS greater than the lower bound (eg, for the cumulative logit mRS 0 versus 1–6, an OR >1 indicates higher odds of an mRS >0).

Analyses were performed using Stata 16.1 (StataCorp, College Station, TX), using the gologit2 commands for partial proportional odds models.[38]

RESULTS

Table 1 summarizes baseline cohort characteristics for regression variables. Sixty-three percent of participants were men, with an average age of 64 years. Fifty-five percent of participants were recruited in Vietnam, 42% in Australia, and 3% in New Zealand. Before the stroke, 99% of participants were independent, 30% in full-time paid employment, and 53% retired. Most strokes were ischemic (85%). The median NIHSS score was 6 (moderate stroke severity); and the median PHQ-9 score was 4 (depressive disorder is unlikely).

The Figure presents the distribution of mRS scores over 12 months. Except for death (mRS 6), which increased over time, there was a general reduction in severity of mRS scores.

Table 2 presents patterns of recovery as measured by the mRS over 12 months. Most improvement in mRS scores occurred within 90 days, with a small number of participants (n=60) with worse mRS scores at day 365 compared with day 1 (77% attributable to

Table 1. Baseline Characteristics for Regression Variables of Interest (n=1276)

Factor	Values, n (%)
Male sex	801 (62.8)
Age at stroke, y, mean (SD)	64.0 (12.5)
Race	
Asian	727 (57.0)
White	518 (40.6)
Other race	31 (2.4)
Country treated in	
Australia	528 (40.4)
New Zealand	42 (3.3)
Vietnam	706 (55.3)
Paid employment	
Full-time	385 (30.2)
Part-time	144 (11.3)
Unemployed or disabled	37 (2.9)
Retired	677 (53.1)
Other employment	33 (2.6)
Functional status	
Independent prior*	1260 (98.7)
Previous medical history	
History of diabetes	289 (22.6)
History of coronary heart disease	114 (8.9)
History of ischemic stroke	161 (12.6)
History of intracranial hemorrhage	19 (1.5)
History of depression	49 (3.8)
Stroke diagnosis	
Intracerebral hemorrhage	185 (14.5)
Ischemic stroke	1091 (85.5)
NIHSS total score†, median (IQR)	6.0 (3.0–9.0)
PHQ-9 total score‡, median (IQR)	4.0 (1.0–7.0)

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; and PHQ-9, 9-item Patient Health.

*Independence was defined as estimated mRS ≤2 before stroke.

†Higher scores indicate greater neurological impairment.

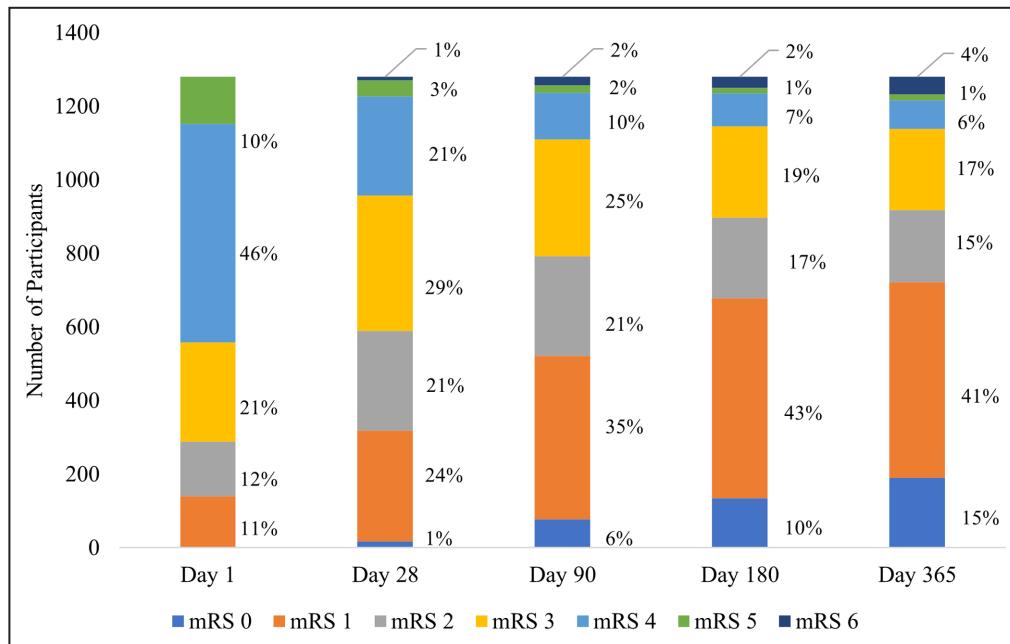‡Higher scores indicate more depressive symptoms.

Figure. Distribution of mRS scores at days 1, 28, 90, 180, and 365 (n=1276).
Visualization of the distribution of mRS scores by category at different follow-up points during the AFFINITY trial. AFFINITY indicates Assessment of Fluoxetine in Stroke Recovery; and mRS, modified Rankin Scale.

death). Differentiation between ischemic and hemorrhagic stroke can be seen in Tables S1 and S2. Participants with hemorrhagic strokes had more severe strokes (higher mean mRS at baseline) but had a slightly faster rate of recovery (as measured by change in mean mRS) than ischemic strokes.

Table 3 summarizes associations between baseline characteristics and mRS scores using single-measure and repeated-measures methods. For single-measure analysis, lower mRS scores at day 365 were associated with male sex, age <70 at stroke, no history of diabetes, coronary heart disease, ischemic stroke, or depression; no fluoxetine intervention, ischemic stroke (compared with hemorrhagic), treatment in Vietnam (compared with Australia or New Zealand); lower baseline NIHSS or PHQ-9 scores; and prestroke independence, living alone, having a partner, and paid employment. Participants >70 years at stroke were associated with higher mRS categories. For the single-measure model, association of mRS with age at stroke >70 years increased in the cumulative logit models mRS 0 versus 1 to 6 to mRS 0 to 3 versus 4 to 6, before decreasing, whereas in the repeated-measures model, age at stroke >70 years had varying strengths of positive associations at different cumulative logit models. Participants with higher NIHSS scores were associated with higher mRS categories, with the association strength decreasing at higher mRS categories. This

Table 2. Patterns of Follow-Up Change in mRS Between Days 1, 28, 90, 180, and 365

	Day 1 (n=1276)	Day 28 (n=1263)	Day 90 (n=1253)	Day 180 (n=1249)	Day 365 (n=1246)
Worsening, n (%)	…	24 (2)	34 (3)	44 (4)	66 (5)
No change, n (%)	…	536 (42)	676 (54)	853 (68)	1002 (80)
Improving, n (%)	…	703 (56)	543 (43)	352 (28)	178 (15)
Incremental deaths, n (%)		9 (1)	12 (1)	7 (1)	18 (1)
mRS, mean (SD)	3.3 (0.0)	2.6 (0.0)	2.1 (0.0)	1.8 (0.0)	1.7 (0.0)
mRS, median (IQR)	4 (1)	3 (1)	2 (2)	1 (2)	1 (2)
mRS change, mean (SD)	…	−0.8 (0.9)	−0.5 (0.8)	−0.3 (0.6)	−0.1 (0.6)

Worsening, no change, and improving refer to the difference between the participant's mRS score at one assessment compared with the previous. For example, at day 90, 34 (3%) individuals had a worse (higher) mRS score than at day 28. Incremental deaths refer to new deaths between follow-ups. IQR indicates interquartile range; and mRS, modified Rankin Scale.

Table 3. Multivariable Partial Proportional Odds Regression of Day 365 mRS on Baseline Characteristics, Unadjusted and Adjusted Results of Single Measure (n=1276) and Repeated Measures Analysis (n=1246)

Factor	Univariable single measure model [OR, σ^2, (95% CI)]	Adjusted single measure model [OR, σ^2, (95% CI)]	Univariable repeated measures model [OR, σ^2, (95% CI)]	Adjusted repeated measures model [OR, σ^2, (95% CI)]
Demographics				
Male sex*	0.76†, 0.00, (0.70–0.81)	...	0.76†, 0.00, (0.75–0.77)	...
Age greater than 70y*	2.46†, 0.30, (1.59–3.79)‡ 2.62†, 0.04, (2.23–3.07)∥ 2.94†, 0.04, (2.56–3.38)¶ 3.44†, 0.11, (2.85–4.15)# 2.97†, 0.91, (1.58–5.58)** 2.52, 1.75, (0.90–7.04)††	...	2.12§, 0.29, (1.29–3.48)‡ 1.95†, 0.00, (1.89–2)∥ 2.3†, 0.05, (1.90–2.79)¶ 2.5†, 0.03, (2.16–2.89)# 3.17†, 0.32, (2.23–4.51)** 2.07, 1.02, (0.8–5.38)††	...
Before stroke				
Diabetes*	1.73†, 0.00, (1.61–1.87)	1.73†, 0.02, (1.45–2.06)	1.44†, 0.01, (1.28–1.61)	1.43†, 0.02, (1.18–1.74)
Coronary heart disease*	2.47†, 0.16, (1.79–3.4)	1.88†, 0.09, (1.37–2.57)	2.05†, 0.08, (1.56–2.69)	1.66†, 0.04, (1.30–2.12)
Ischemic stroke*	1.65†, 0.03, (1.32–2.06)	1.43§, 0.04, (1.11–1.85)	1.43§, 0.03, (1.13–1.8)	1.29, 0.03, (1.00–1.66)
Depression*	1.05, 0.03, (0.78–1.42)	0.92, 0.02, (0.70–1.22)	0.97, 0.01, (0.82–1.15)	0.88, 0.00, (0.76–1.00)
Independence*	0.09†, 0.00, (0.02–0.37)	0.15§, 0.01, (0.04–0.51)	0.12†, 0.00, (0.06–0.24)	0.18†, 0.00, (0.10–0.32)
Paid employment*	0.52‡, 0.02, (0.29–0.92)	0.75, 0.02, (0.52–1.09)	0.62, 0.03, (0.37–1.04)	0.86, 0.02, (0.60–1.22)
Partner*	0.71§, 0.00, (0.63–0.8)	0.87§, 0.00, (0.79–0.96)	0.77§, 0.00, (0.7–0.84)	0.92‡‡, 0.00, (0.85–1.00)
Living alone*	1.34§, 0.02, (1.11–1.61)	1.00, 0.00, (0.87–1.14)	1.23†, 0.00, (1.13–1.34)	0.97‡‡, 0.00, (0.95–0.99)
Current stroke (baseline)				
Fluoxetine intervention*	1.06, 0.00, (0.97–1.15)	...	1.02, 0.00, (0.93–1.12)	...
Haemorrhagic stroke*	1.3, 0.08, (0.86–1.97)	1.35‡‡, 0.03, (1.03–1.75)	1.48§, 0.04, (1.14–1.93)	1.52†, 0.01, (1.33–1.74)
Treated in Australia*	1.47†, 0.01, (1.25–1.73)	...	1.28†, 0.01, (1.12–1.46)	...
Treated in New Zealand‡‡	1.83†, 0.13, (1.25–2.68)	...	1.77§, 0.05, (1.38–2.26)	...
PHQ-9† Score	1.04§, 0.00, (1.02–1.06)	1.04†, 0.00, (1.01–1.07)	1.05§, 0.00, (1.03–1.06)	1.05§, 0.00, (1.03–1.07)
NIHSS Score	1.26†, 0.00, (1.24–1.28)‡ 1.26†, 0.00, (1.18–1.36)∥ 1.25†, 0.00, (1.18–1.33)¶ 1.24†, 0.00, (1.23–1.24)# 1.15†, 0.00, (1.10–1.19)** 1.13†, 0.00, (1.11–1.16)††	1.29†, 0.00, (1.24–1.33)‡ 1.3†, 0.00, (1.24–1.37)∥ 1.29†, 0.00, (1.24–1.35)¶ 1.25†, 0.00, (1.23–1.28)# 1.15†, 0.00, (1.12–1.19)** 1.13†, 0.00, (1.12–1.15)††	1.28†, 0.00, (1.26–1.3)‡ 1.28†, 0.00, (1.22–1.34)∥ 1.27†, 0.00, (1.20–1.35)¶ 1.29†, 0.00, (1.27–1.3)# 1.2†, 0.00, (1.20–1.21)** 1.16†, 0.00, (1.12–1.2)††	1.3†, 0.00, (1.26–1.34)‡ 1.3†, 0.00, (1.25–1.36)∥ 1.3†, 0.00, (1.25–1.36)¶ 1.3†, 0.00, (1.30–1.31)# 1.2†, 0.00, (1.19–1.22)** 1.15†, 0.00, (1.11–1.19)††
Time since stroke (reference: day 28)				
Day 90	...	...	0.21†, 0.00, (0.15–0.31)‡ 0.48†, 0.00, (0.46–0.5)∥ 0.52†, 0.00, (0.50–0.54)¶ 0.45†, 0.00, (0.43–0.46)# 0.78†, 0.00, (0.68–0.89)** 2.37, 2.30, (0.67–8.31)††	...

(Continued)

Table 3. Continued

Factor	Univariable single measure model [OR, σ^2, (95% CI)]	Adjusted single measure model [OR, σ^2, (95% CI)]	Univariable repeated measures model [OR, σ^2, (95% CI)]	Adjusted repeated measures model [OR, σ^2, (95% CI)]
Day 180	…	…	0.12†, 0.00, (0.06–0.21)‡ 0.29†, 0.00, (0.26–0.32)‖ 0.35†, 0.00, (0.28–0.45)¶ 0.34†, 0.00, (0.33–0.35)# 0.78†, 0.00, (0.69–0.89)** 3.19, 6.21, (0.69–14.75)††	…
Day 365	…	…	0.07†, 0.00, (0.04–0.14)‡ 0.25†, 0.00, (0.21–0.29)‖ 0.32†, 0.00, (0.25–0.42)¶ 0.36†, 0.00, (0.31–0.42)# 1.22†, 0.00, (1.09–1.38)** 5.34‡‡, 17.75, (1.14–25.07)††	…

Results are presented to 2 decimal places. Adjusted estimates were not provided for exogenous variables (age at stroke greater than 70 years, sex, fluoxetine intervention, location of treatment and time since stroke). NIHSS indicates National Institutes of Health Research Stroke Scale (higher scores indicates greater neurological impairment). NIHSS indicates National Institutes of Health Research Stroke Scale (higher scores indicates greater neurological impairment); OR, odds ratio; and PHQ-9, 9-item Patient Health Questionnaire (higher scores indicates more depressive symptoms).

*Dummy Variable = 1 if true. Partner refers to participants who declared they were married or had a partner, relative to single participants. Living alone was relative to participants living in institutions or sharing a residence. Independence was defined as an estimated mRS score <2 before stroke. Haemorrhagic stroke was relative to ischemic strokes. Treatment in Australia and New Zealand was relative to Vietnam.

†*P*<0.001.

‡ mRS 0 vs 1 to 6: Odds ratio greater than 1 indicates higher odds of having an mRS greater than 0 (and vice-versa).

§ *P*<0.01.

‖ mRS 0 to 1 vs 2 to 6: Odds ratio greater than 1 indicates higher odds of having an mRS greater than 1 (and vice-versa).

¶ mRS 0 to 2 vs 3 to 6: Odds ratio greater than 1 indicates higher odds of having an mRS greater than 2 (and vice-versa).

mRS 0 to 3 vs 4 to 6: Odds ratio greater than 1 indicates higher odds of having an mRS greater than 3 (and vice-versa).

** mRS 0 to 4 vs 5 to 6: Odds ratio greater than 1 indicates higher odds of having an mRS greater than 4 (and vice-versa).

†† mRS 0 to 5 vs 6: Odds ratio greater than 1 indicates higher odds of having an mRS greater than 5 (and vice-versa).

‡‡ *P*<0.05.

was consistent across univariable and multivariable single-measure and repeated-measures regressions.

Repeated-measures analysis indicated that greater recovery time since stroke was generally associated with lower mRS scores. Greater time since stroke (at days 90, 180, and 365) was associated with lower mRS categories in all cumulative logit models, except for mRS 0 to 5 versus 6 (at days 90, 180, and 365) and mRS 0 to 4 versus 5 to 6 (day 365). The association of greater time since stroke with a lower mRS category increased in strength over time for all cumulative logit models from mRS 0 versus 1 to 6 to mRS 0 to 3 versus 4 to 6. Initially at days 90 and 180, greater time since stroke was associated with a lower mRS category for the cumulative logit model mRS 0 to 4 versus 5 to 6; however, this association changed direction at day 365. The association of greater time since stroke with a higher mRS category increased in strength over time for the cumulative logit model mRS 0 to 5 versus 6.

The direction of associations was largely concordant between single-measure and repeated-measures models except for a history of depression (positive OR in the univariable single-measure model, but negative OR in the univariable repeated-measures model and the multivariable single and repeated-measures model). However, the size of associations was generally reduced (ORs closer to unity) in the repeated-measures model, with lower variance (increased precision) and smaller CIs.

DISCUSSION

This article has presented poststroke recovery over 12 months for an international cohort of 1276 participants with acute stroke of mild to moderate severity. Most (81% of average 12-month mRS score improvement) recovery occurred in the first 3 months after stroke, in line with literature and recommended timing for functional assessment.[23,24,31] Nonetheless, small functional gains were made in the "late subacute" (4–6 months) and "chronic" phase (>6 months) as defined by the Stroke Recovery and Rehabilitation Roundtable.[12] This was reflected in the associations of time since stroke (at days 90, 180, and 365) with lower mRS categories in all cumulative logit models, except for mRS 0 to 5 versus 6 (at days 90, 180, and 365) and mRS 0 to 4 versus 5 to 6 (day 365). This can be explained by an increase in deaths over time compared with the day 28 reference category (sample total of 1% at day 28, 2% at day 90, 2% at day 180, and 4% at day 365) and an increase in mRS 5 and 6 (sample total of 5% at day 365) compared with day 28 (sample total of 4%), respectively. We note that the follow-up points are not evenly spaced in time, meaning that the strength

of the time associations are not directly comparable and are more heavily weighted toward early recovery (eg, from day 1 to day 28 compared with day 28 to day 90). In comparison with the National Institute of Neurological Disorders and Stroke control group at 12 months (mRS 0 [11%], mRS 1 [17%], mRS 2 [12%], mRS 3 [13%], mRS 4 [11%], mRS 5 [5%], and mRS 6 [29%]),[33] our 12-month results were more heavily weighted toward lower mRS scores, indicating greater recovery (mRS 0 [15%], mRS 1 [41%], mRS 2 [15%], mRS 3 [17%], mRS 4 [6%], mRS 5 [1%], and mRS 6 [4%]). This may reflect that AFFINITY enrolled less severe strokes compared with the National Institute of Neurological Disorders and Stroke.[33]

Identified associations with mRS align with a similar study, which found that younger age, lower baseline NIHSS, no prestroke health problems, previous stroke, diabetes, and coronary heart disease were associated with lower 6-month mRS scores.[39] Another study found younger age and lower baseline NIHSS was associated with improved recovery (measured by the Barthel Index).[29] The small association with male sex and improved recovery may be supported by literature suggesting female sex is associated with worse functional outcomes following stroke; however, this has not been fully explained.[40] Our finding that fluoxetine was associated with higher mRS scores may be related to the increased likelihood of adverse events (including seizures and falls) in AFFINITY.[33] With mixed literature comparing functional outcomes of ischemic and hemorrhagic stroke,[41–43] our results suggest hemorrhagic strokes are associated with higher mRS scores over 12 months.

While mRS scores have been used to predict poststroke depression at 6 months,[44] PHQ-9 at baseline had not been identified in the literature as an association with mRS or functional disability. A systematic review and meta-analysis of the impact of stroke on physical disability[45] concluded depression following stroke was associated with worse long-term disability. However, our repeated-measures results show that a history of depression was imprecisely associated with slightly lower mRS scores. This may be attributable to treatment of underlying (or poststroke) depression with fluoxetine (possibly reflected by the improved mood and emotional control in AFFINITY), although only 3% of participants had a prestroke diagnosis of depression, limiting analysis.[33] Our work also supports previous research suggesting independence (measured by prestroke mRS) is strongly associated with poststroke function,[46] which may explain why living alone was associated with improved function. However, 99% of participants were independent before the stroke. Having a marital partner has been linked to improved poststroke survival and recovery from disability,[47,48] aligning with our findings.

Repeated measures capture within-person and interperson variation, enabling research to be sensitive to

clinically important fluctuations in mRS scores during stroke recovery. Repeated measures of the same state improve precision. While this is limited by different measurements in time, this partially corrects single measures impacted by temporal confounders. Repeated measurements also improve precision by requiring fewer participants, as subjects act as their own "controls."[11] The direction of associations was concordant between single-measure and repeated-measures analysis except for a history of depression, which was associated with higher mRS scores in the univariable single-measure regression and a negative association in the repeated-measures regressions. However, precision of associations varied, with generally smaller associations, reduced variance (increased precision) and CIs in the repeated-measures model compared with the single-measure model.

Limitations

Our results may be less generalizable to more severe strokes, with a median baseline NIHSS of 6, and more participants (72%) recovering functional independence (mRS 0–2) at 6 months than estimated in original power calculations (42%).[33] While all mRS data were measured using the simplified mRS, variation in interrater and intrarater reliability may account for some change over time; however, data collector identity was unavailable. The simplified mRS is a patient-reported, not clinician-reported outcome, more closely reflecting patients' subjective experiences and perceptions but less objectively reflecting functional ability (eg, in disorders of neglect). Interobserver variability in mRS assessment across countries[49] may bias estimates for different locations and cultural groups. Additionally, as a secondary analysis of a randomized clinical trial, our results may not be generalizable to wider populations. Our model did not incorporate repeated measures of independent variables (eg, PHQ-9 at day 180), as these were measured later in the recovery period and were less complete than mRS data. Including repeated measures of independent variables may be an avenue of investigation for future stroke recovery modeling. We also note that the mRS curve is unlikely to be linear (with 1 study suggesting an S-shaped curve[50]); however, research in this area is still new, with optimal weightings yet to be decided.[4,50] Finally, we note that the adjusted OR is difficult to interpret because of its noncollapsible nature[51]; hence, we have provided both unadjusted and adjusted estimates to mitigate this.

CONCLUSIONS

Most participants improved or remained stable through follow-up over 12 months after stroke, with improved functional outcomes associated with various clinical and demographic variables. Repeated-measures analyses generally demonstrated improvement in association precisio. Additional repeated-measures analyses of stroke trials will improve understanding of its methodological value. Stroke trial analyses with repeated-measures data ex-post may wish to consider the potential of integrating follow-up assessments to improve precision, validity, and reliability of conclusions.

Affiliations

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SUPPLEMENTAL MATERIAL

Table S1. Patterns of follow up change in mRS between Day 1, 28, 90, 180 and 365 for haemorrhagic stroke.

Change from previous period	Day 1 (n=185)	Day 28 (n=181)	Day 90 (n=178)	Day 180 (n=179)	Day 365 (n=179)
Worsening, n (%)	-	2 (1%)	3 (2%)	9 (5%)	11 (6%)
No change, n (%)	-	60 (33%)	90 (51%)	110 (61%)	134 (75%)
Improving, n (%)	-	119 (66%)	85 (48%)	60 (34%)	34 (19%)
Incremental deaths, n (%)		2 (1%)	3 (2%)	2 (1%)	2 (1%)
mRS, mean (SD)	3.8 (0.1)	2.9 (0.1)	2.4 (0.1)	2 (0.1)	1.9 (0.1)
mRS, median (IQR)	4 (0)	3 (2)	2 (2)	2 (2)	1 (2)
mRS change, mean (SD)	-	- 0.9 (0.9)	- 0.6 (0.9)	- 0.4 (0.8)	- 0.1 (0.6)

Worsening, No change and Improving refer to the difference between the participant's mRS score at one assessment compared to the previous. For example, at Day 90, 3 (2%) individuals had a worse mRS score than at Day 28.

Table S2. Patterns of follow up change in mRS between Day 1, 28, 90, 180 and 365 for ischemic stroke.

	Day 1 (n=1091)	Day 28 (n=1082)	Day 90 (n=1075)	Day 180 (n=1070)	Day 365 (n=1067)
Worsening, n (%)	-	22 (2%)	31 (3%)	35 (3%)	55 (5%)
No change, n (%)	-	476 (44%)	586 (55%)	743 (69%)	868 (81%)
Improving, n (%)	-	584 (54%)	458 (43%)	292 (27%)	144 (13%)
Incremental deaths, n (%)		7 (1%)	9 (1%)	5 (0%)	16 (1%)
mRS, mean (SD)	3.3 (0.0)	2.5 (0.0)	2.0 (0.0)	1.7 (0.0)	1.7 (0.0)
mRS, median (IQR)	4 (2)	3 (2)	2 (2)	2 (2)	1 (2)
mRS change, mean (SD)	-	- 0.7 (0.9)	- 0.5 (0.7)	- 0.3 (0.6)	- 0.1 (0.6)

Worsening, No change and Improving refer to the difference between the participant's mRS score at one assessment compared to the previous. For example, at Day 90, 31 (3%) individuals had a worse mRS score than at Day 28.

Figure S1. Modified CONSORT Flow Diagram for the AFFINITY trial secondary post-hoc cohort level analysis.
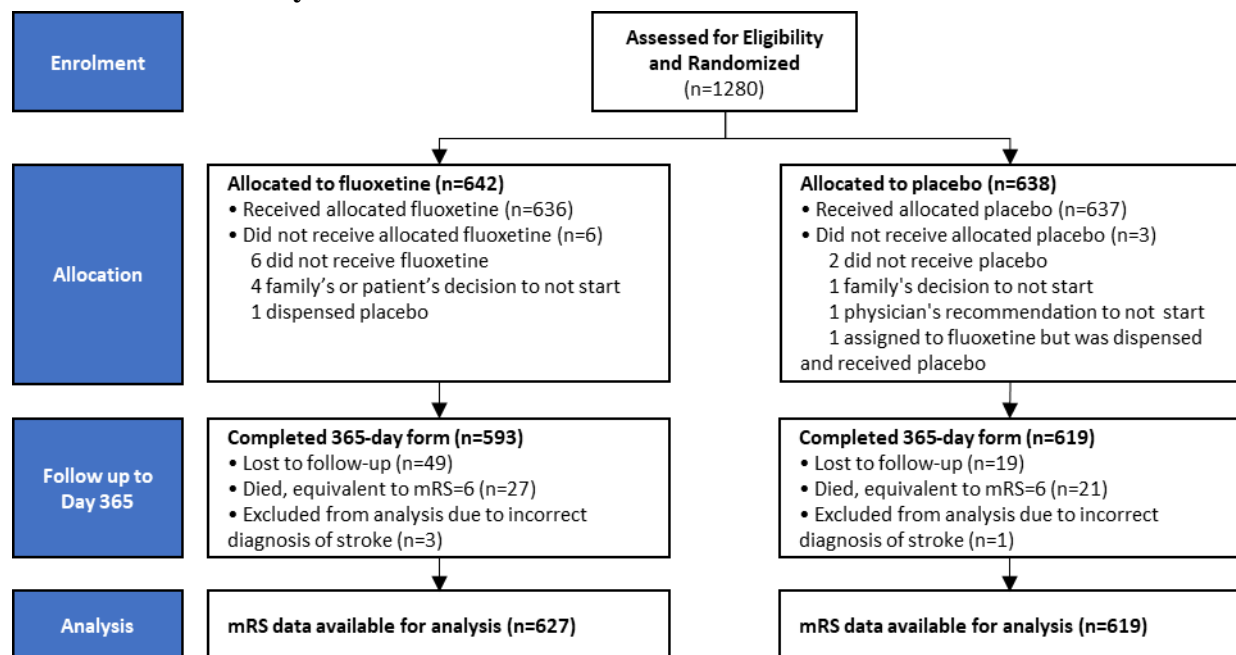
Figure S2. Sankey diagram of the mRS score over 1 year for AFFINITY study participants.
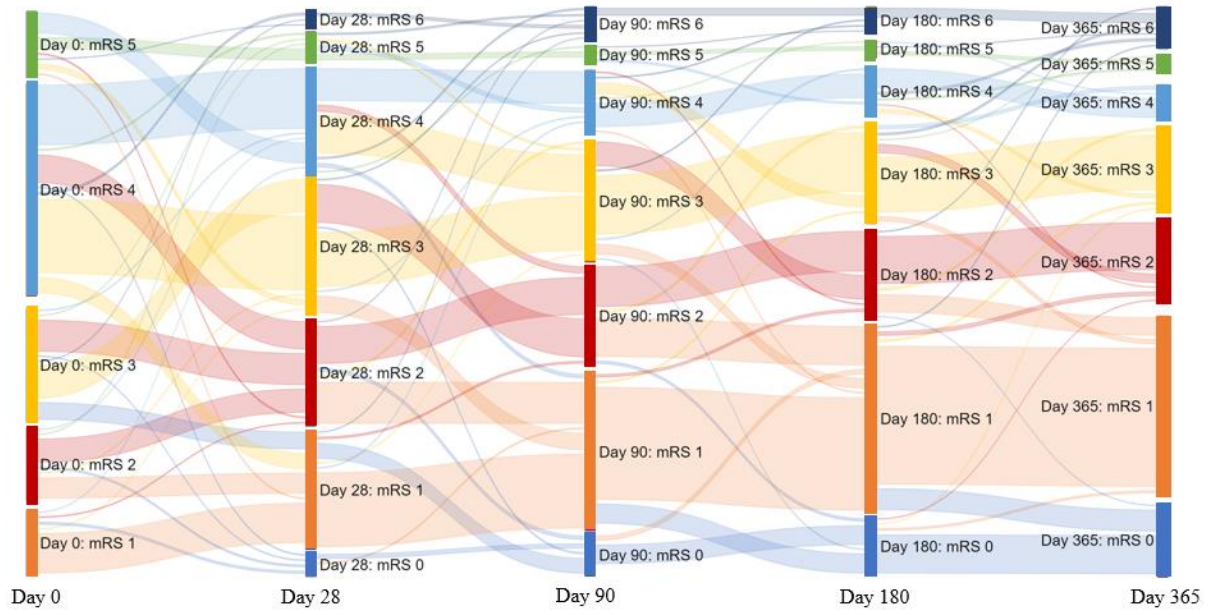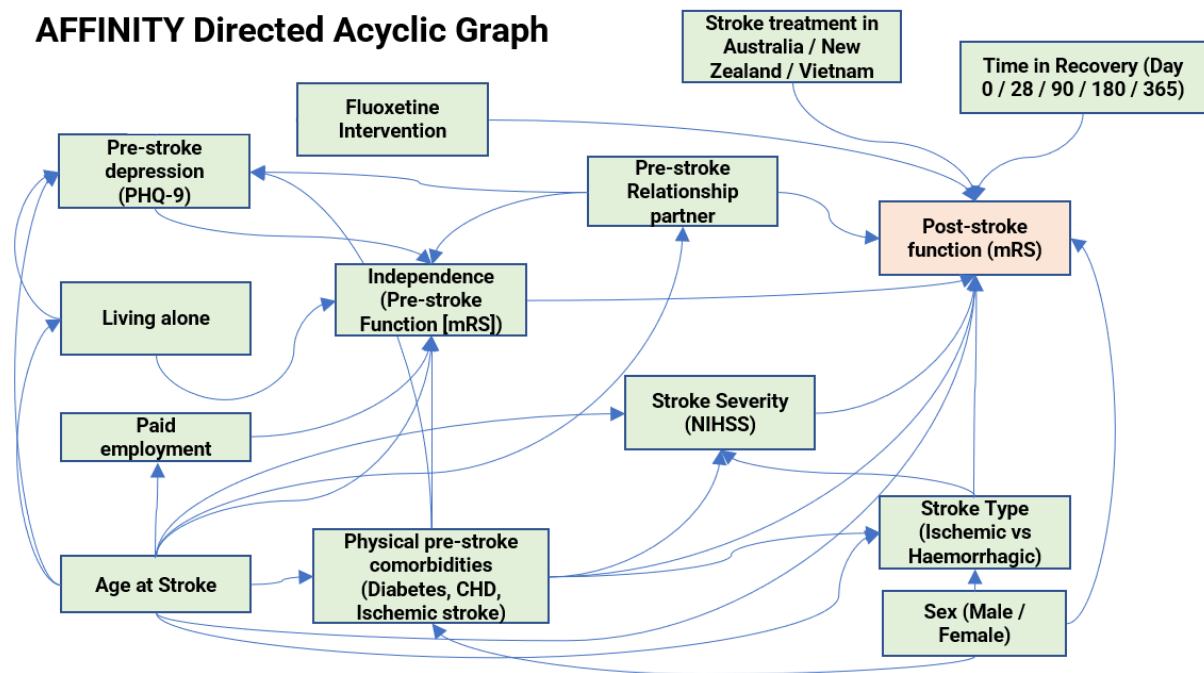
Figure S3 Directed Acyclic Graph for the AFFINITY trial secondary post-hoc cohort level analysis.

Arrows leading from one variable to another indicate the likely mediating effect of that variable.

Age at stroke and sex were deemed to be the only truly exogenous confounders for the explanatory variables; and were the only covariates used in adjusted regression.

Age at stroke, sex, fluoxetine intervention, country of treatment, and time since stroke were deemed to be exogenous variables not requiring adjustment.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

Guidelines Checklist

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	5
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	8-10
Objectives	#3	State specific objectives, including any prespecified hypotheses	10
Methods			
Study design	#4	Present key elements of study design early in the paper	11-12
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11

Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	11
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/a – not matched
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-13
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	n/a – referenced original AFFINITY trial methods.
Bias	#9	Describe any efforts to address potential sources of bias	11-13
Study size	#10	Explain how the study size was arrived at	11-12
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	11-13

Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	11-13
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a
Statistical methods	#12c	Explain how missing data were addressed	12
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	12
Statistical methods	#12e	Describe any sensitivity analyses	11-13 comparison of cross sectional and repeated measures
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	Full data in tables and Figure 1, Figure S1 and Figure S2. Refer to original AFFINITY study for

			original trial enrolment numbers.
Participants	#13b	Give reasons for non-participation at each stage	n/a – refer to original AFFINITY trial
Participants	#13c	Consider use of a flow diagram	n/a – refer to original AFFINITY trial
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	12
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	11-13
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information	Table 1, Table 2

		separately for exposed and unexposed groups if applicable.	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13 Table 3
Main results	#16b	Report category boundaries when continuous variables were categorized	Table 3, logit categories provided
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a – risk estimates not provided
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13 Table S1, Table S2
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13-17
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or	18

		imprecision. Discuss both direction and magnitude of any potential bias.	
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-18
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13-18
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19