**Online Supplementary Content**

**The association of follow-up infarct volume with functional outcome in acute ischemic stroke: a pooled analysis of seven randomized trials**

**Online supplementary table S1.** Baseline characteristics of all 1665 patients included in this study

**Online supplementary table S2.** Likelihood function test outputs and multivariable analyses for predictors of modified Rankin Scale score

**Online supplementary table S3a.** Follow-up infarct volume thresholds with high specificity for unfavorable outcome (modified Rankin Scale score of 3-6), CT only

**Online supplementary table S3b.** Follow-up infarct volume thresholds with high specificity for unfavorable outcome (modified Rankin Scale score of 3-6), MR only

**Online supplementary table S4.** Outcome table by imaging modality

**Online supplementary table S5.** Outcome table by follow-up acquisition time

**Online supplementary figure 1**

**Online supplementary figure 2**

**Online supplementary figure 3a**

**Online supplementary figure 3b**

**Online supplementary table S1.** Baseline characteristics of all 1665 patients included in this study

| **Characteristic** | **All** |
| --- | --- |
| Age, median [IQR] | 68 [57-76] |
| Female sex, n/N (%) | 781/1665 (46.9%) |
| Left hemisphere infarct, n/N (%) | 740/1649 (47.9%) |
| NIHSS score at baseline, median [IQR] | 17 [13-21] |
| Alteplase (tPA) delivered, n/N (%) | 1496/1665 (89.8%) |
| Randomized to endovascular therapy, n/N (%) | 844/1665 (50.7%) |
| Diabetes mellitus, n/N (%) | 270/1661 (16.3%) |
| Hypertension, n/N (%) | 936/1662 (56.3%) |
| Tobacco use, n/N (%) | 566/1519 (37.3%) |
| Onset to Alteplase (tPA) in min, median [IQR] | 117 [85-160] |
| Onset to randomization in min, median [IQR] | 182 [140-244] |
| Onset to reperfusion in min, median [IQR] | 291 [230-355] |
| ASPECTS at baseline, median [IQR] | 8 [7-9] |
| Occlusion location, n/N (%) | |
| Not available | 93/1665 (5.6%) |
| ICA | 422/1665 (25.3%) |
| M1 | 1024/1665 (61.5%) |
| M2 | 124/1665 (7.4%) |
| Other | 2/1665 (0.1%) |
| Collateral score, n/N (%) | |
| 0 | 13/1233 (1.1%) |
| 1 | 197/1233 (16.0%) |
| 2 | 530/1233 (43.0%) |
| 3 | 493/1233 (40.0%) |
| Abbreviations: FIV, follow-up infarct volume; NIHSS, National Institutes of Health and Stroke Scale score; ASPECTS, Alberta Stroke Program Early CT; ICA, internal carotid artery | |

**Online supplementary table S2**. Likelihood function test outputs and multivariable analyses for predictors of modified Rankin Scale score

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictor** | **Odds ratio** | **95% confidence interval** | **P value** |
| **Model A: AIC=4842** | | | |
| Age (per 10 years) | 0.64 | 0.60-0.69 | <0.001 |
| Follow-up infarct volume (per 10 ml) | 0.88 | 0.87-0.89 | <0.001 |
| Baseline NIHSS score (per 5 point) | 0.78 | 0.71-0.85 | <0.001 |
| **Model B: AIC = 4781** | | | |
| Age (per 10 years) | 0.61 | 0.57-0.66 | <0.001 |
| Follow-up infarct volume (per 10 mL) | 0.91 | 0.90-0.93 | <0.001 |
| Baseline NIHSS score (per 5 point) | 0.82 | 0.74-0.91 | <0.001 |
| Symptom side left (vs right) | 0.92 | 0.75-1.12 | 0.41 |
| ASPECTS involvement | | | |
| Caudate | 1.06 | 0.83-1.36 | 0.62 |
| Lentiform | 0.81 | 0.60-1.11 | 0.19 |
| Internal Capsule | 0.44 | 0.34-0.56 | <0.001 |
| Insula | 0.75 | 0.58-0.96 | 0.025 |
| M1 | 0.94 | 0.73-1.21 | 0.62 |
| M2 | 0.82 | 0.64-1.05 | 0.11 |
| M3 | 1.00 | 0.76-1.32 | 0.98 |
| M4 | 0.82 | 0.63-1.08 | 0.15 |
| M5 | 0.77 | 0.60-0.99 | 0.041 |
| M6 | 0.78 | 0.59-1.03 | 0.082 |
| **Model C: AIC = 4825** | | | |
| Age (per 10 years) | 0.65 | 0.60-0.69 | <0.001 |
| Follow-up infarct volume (per 10 mL) | 0.88 | 0.87-0.90 | <0.001 |
| Baseline NIHSS score (per 5 point) | 0.77 | 0.70-0.85 | <0.001 |
| Hemorrhage |  |  |  |
| HI-1 | 0.84 | 0.64-1.10 | 0.20 |
| HI-2 | 0.61 | 0.46-0.82 | 0.001 |
| PH-1 | 0.72 | 0.50-1.04 | 0.077 |
| PH-2 | 0.66 | 0.43-1.00 | 0.049 |
| rPH (remote) | 1.86 | 0.87-3.98 | 0.11 |
| Interventricular hematoma | 0.30 | 0.13-0.67 | 0.004 |
| Subarachnoid Hemorrhage | 0.68 | 0.31-1.47 | 0.33 |
| Subdural hematoma | 0.23 | 0.01-4.35 | 0.33 |
| **Model D: AIC = 4775** | | | |
| Age (per 10 years) | 0.62 | 0.57-0.67 | <0.001 |
| Follow-up infarct volume (per 10 ml) | 0.92 | 0.90-0.94 | <0.001 |
| Baseline NIHSS score (per 5 point) | 0.82 | 0.74-0.90 | <0.001 |
| Hemorrhage | | | |
| HI-1 | 0.96 | 0.73-1.27 | 0.79 |
| HI-2 | 0.73 | 0.54-0.99 | 0.043 |
| PH-1 | 0.92 | 0.63-1.33 | 0.64 |
| PH-2 | 0.82 | 0.54-1.25 | 0.36 |
| rPH (remote) | 1.41 | 0.65-3.03 | 0.38 |
| Interventricular hematoma | 0.29 | 0.13-0.64 | 0.002 |
| Subarachnoid hemorrhage | 0.73 | 0.34-1.56 | 0.42 |
| Subdural hematoma | 0.17 | 0.01-3.28 | 0.24 |
| Symptom side left (vs right) | 0.91 | 0.75-1.11 | 0.36 |
| ASPECTS involvement | | | |
| Caudate | 1.09 | 0.85-1.40 | 0.49 |
| Lentiform | 0.81 | 0.60-1.11 | 0.20 |
| Internal Capsule | 0.45 | 0.35-0.58 | <0.001 |
| Insula | 0.78 | 0.60-1.01 | 0.057 |
| M1 | 0.93 | 0.72-1.20 | 0.57 |
| M2 | 0.82 | 0.64-1.06 | 0.13 |
| M3 | 0.98 | 0.74-1.29 | 0.88 |
| M4 | 0.82 | 0.63-1.08 | 0.15 |
| M5 | 0.77 | 0.60-0.99 | 0.042 |
| M6 | 0.77 | 0.58-1.02 | 0.066 |
| Odds ratios towards shift in better outcome on modified Rankin Scale  NIHSS = National Institutes of Health Stroke Scale; AIC = Akaike’s Information Criterion; HI = hemorrhagic infarct; PH = parenchymal hematoma; ASPECTS = Alberta Stroke Program Early CT score | | | |

**Online supplementary table S3a**. Follow-up infarct volume thresholds with high specificity for unfavorable outcome (mRS 3-6), CT only

|  |  |  |
| --- | --- | --- |
| Specificity | Follow-up infarct volume threshold in mL | 95% CI for unfavorable outcome |
| 95% | 122 | (92.4 to 97.1) |
| 90% | 80 | (87.2 to 92.5) |
| 80% | 31 | (77.7 to 83.2) |
| CI, confidence interval; mRS, modified Rankin Scale | | |

**Online supplementary table S3b**. Follow-up infarct volume thresholds with high specificity for unfavorable outcome (mRS 3-6), MR only

|  |  |  |
| --- | --- | --- |
| Specificity | Follow-up infarct volume threshold in mL | 95% CI for unfavorable outcome |
| 95% | 151 | (83.8 to 99.9) |
| 90% | 133 | (76.9 to 98.2) |
| 80% | 78 | (65.5 to 89.4) |
| CI, confidence interval; mRS, modified Rankin Scale | | |

**Online supplementary table S4**. Outcome table by imaging modality

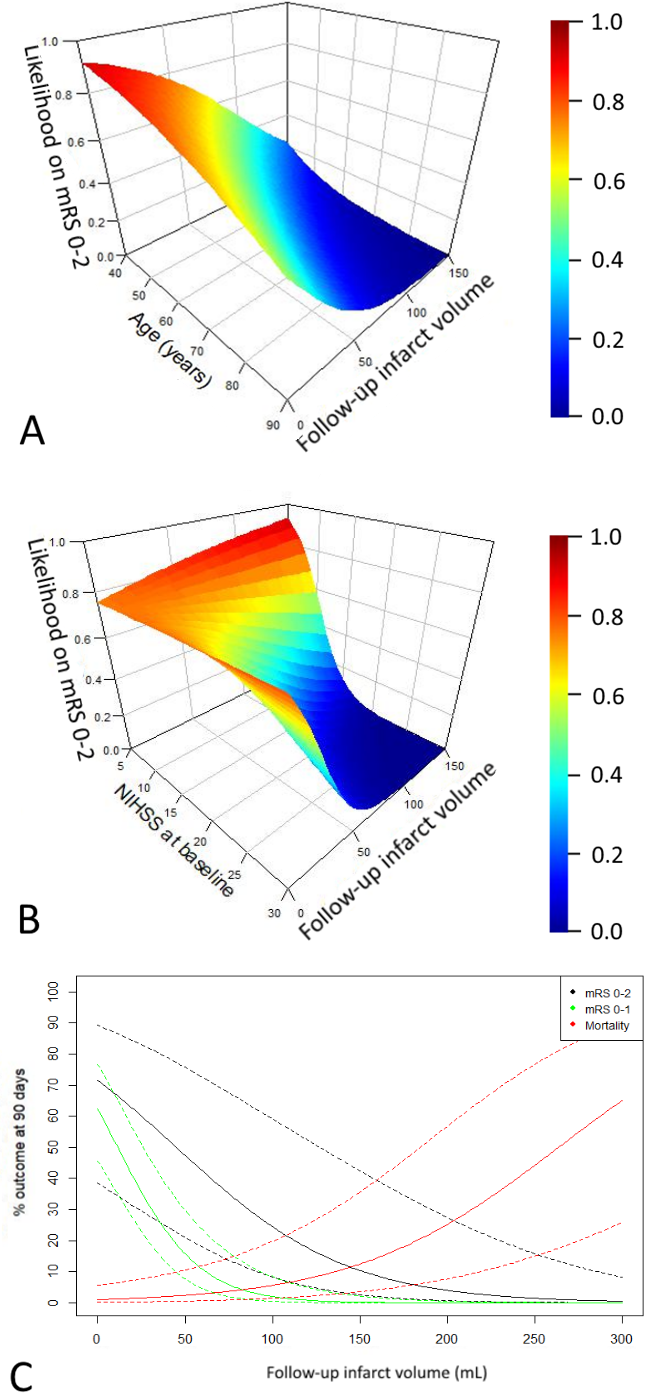
|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **MR imaging** | **CT imaging** | **P value** |
| Follow-up infarct volume in mL, median [IQR] | 22 [8 – 71] | 48 [15-131] | <0.001 |
| Modified Rankin Scale score at 90 days, median [IQR] | 2 [1-4] | 3 [2-5] | <0.001 |
| Onset to follow-up acquisition in hours, median [IQR] | 26 [23-148] | 35 [24-138] | <0.001 |
| Hemorrhage, n/N (%)a | | | |
| HI-1 | 72/282 (25.5) | 157/1383 (11.4) | <0.001 |
| HI-2 | 23/282 (8.2) | 172/1383 (12.4) | 0.042 |
| PH-1 | 15/282 (5.3) | 110/1383 (8.0) | 0.14 |
| PH-2 | 18/282 (6.4) | 100/1383 (7.2) | 0.70 |
| rPH (remote) | 12/282 (4.3) | 9/1383 (0.7) | <0.001 |
| Interventricular hematoma | 3/282 (1.1) | 40/1383 (2.9) | 0.097 |
| Subarachnoid hemorrhage | 2/282 (0.7) | 35/1383 (2.5) | 0.073 |
| Subdural hematoma | 0/282 (0.0) | 3/1383 (0.2) | 1.00 |
| TICI 2b/3, n/N (%)b | 107/125 (85.6) | 416/565 (73.6) | 0.004 |
| AOL 2/3, n/N (%)c | 119/125 (95.2) | 495/564 (87.8) | 0.016 |
| a Hemorrhages scored according to the anatomical description of the Heidelberg Classification.  b TICI 2b/3 indicates successful reperfusion  c AOL 2/3 indicates successful recanalization  TICI, thrombolysis in cerebral ischemia; AOL, arterial occlusive lesion | | | |

**Online supplementary table S5.** Outcome table by follow-up acquisition time

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **≤48 hours** | **>48 hours** | **P value** |
| Follow-up infarct volume in mL, median [IQR] | 32 [9-104] | 56 [21-128] | 0.042 |
| Modified Rankin Scale score at 90 days, median [IQR] | 3 [2-5] | 3 [2-4] | 0.24 |
| Onset to follow-up acquisition in hours, median [IQR] | 24 [22-26] | 143 [114-165] | <0.001 |
| Hemorrhage, n/N (%)a |  |  |  |
| HI-1 | 110/878 (12.5) | 107/688 (15.6) | 0.090 |
| HI-2 | 74/878 (8.4) | 115/688 (16.7) | <0.001 |
| PH-1 | 58/878 (6.6) | 58/688 (8.4) | 0.18 |
| PH-2 | 69/878 (7.9) | 40/688 (5.8) | 0.13 |
| rPH (remote) | 13/878 (1.5) | 7/688 (1.0) | 0.50 |
| Interventricular hematoma | 28/878 (3.2) | 11/688 (1.6) | 0.050 |
| Subarachnoid hemorrhage | 25/878 (2.8) | 10/688 (1.5) | 0.084 |
| Subdural hematoma | 2/878 (0.2) | 0/688 (0.0) | 0.51 |
| TICI 2b/3, n/N (%)b | 306/391 (78.3) | 186/262 (71.0) | 0.041 |
| AOL 2/3, n/N (%)c | 355/390 (91.0) | 225/262 (85.9) | 0.042 |
| a Hemorrhages scored according to the anatomical description of the Heidelberg Classification.  b TICI 2b/3 indicates successful reperfusion  c AOL 2/3 indicates successful recanalization  TICI, thrombolysis in cerebral ischemia; AOL, arterial occlusive lesion | | | |

C:\Users\amboers\Google Drive\HERMES\Manuscript\submission Stroke\Figure2abc.tif

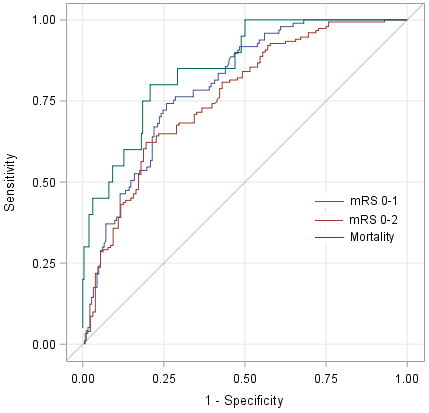
**Online supplementary figure 1.** A) Three-dimensional surface plots illustrating the relationship between follow-up infarct volume, adjusted probability of functional independence at 90 days (mRS 0-2) and age and B) baseline National Institutes of Health Stroke Scale (NIHSS) score. C) Estimated probability for excellent outcome (mRS 0-1), favorable outcome (mRS 0-2), and death (mRS of 6), adjusted for age and baseline NIHSS. Point estimates and 95% confidence interval.

****

**Online supplementary figure 2.** Analysis of patients with FIV assessed on MR imaging only. A) Three-dimensional surface plots illustrating the relationship between follow-up infarct volume, adjusted probability of functional independence at 90 days (mRS 0-2) and age and B) baseline National Institutes of Health Stroke Scale (NIHSS) score. C) Estimated probability for excellent outcome (mRS 0-1), favorable outcome (mRS 0-2), and death (mRS of 6), adjusted for age and baseline NIHSS. Point estimates and 95% confidence interval.

**C:\Users\amboers\Google Drive\Promotie Ending\Chapter 6\Figure4.tif**

**Online supplementary figure 3a**. Receiver operating characteristic (ROC) curves of follow-up infarct volume and dichotomized outcomes. Area under the receiver operating characteristic curves (AUC) were as follows: AUC of excellent outcome (mRS 0-1) = 0.80, functional independence (mRS 0-2) = 0.80, and death (mRS 6) = 0.79.

****

**Online supplementary figure 3b**. Receiver operating characteristic (ROC) curves of follow-up infarct volume and dichotomized outcomes for MR imaging only. Area under the receiver operating characteristic curves (AUC) were as follows: AUC of excellent outcome (mRS 0-1) = 0.80, functional independence (mRS 0-2) = 0.76, and death (mRS 6) = 0.86.