Supplemental Material

NIH Stroke Scale: an alternative primary outcome measure for trials of acute treatment for ischemic stroke

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Table I. Sensitivity analysis: Application of the causal mediation model in MR CLEAN and IMS III, in which NIHSS scores of deceased patients were imputed by multiple imputation with regression.*

	Pathway c Effect of EVT on mRS (acOR)	Pathway a Effect of EVT on NIHSS (aβ)		Pathway b Correlation between NIHSS and mRS adjusted for EVT (acOR‡)		Pathway c' Effect of EVT on mRS adjusted for NIHSS (acOR)	
		NIHSS 24 hours	**NIHSS 5-7 days**	**NIHSS 24 hours**	**NIHSS 5-7 days**	**NIHSS 24 hours**	**NIHSS 5-7 days**
MR CLEAN	1.68 (1.22 to 2.32)	-19% (-28 to -9.2)†	-27% (-37 to -15)	0.80 (0.77 to 0.82)	0.78 (0.76 to 0.81)	1.30 (0.93 to 1.82)	1.16 (0.82 to 1.66)
IMS III	1.30 (0.97 to 1.75)	-1.3% (-15 to 14)	-6.1% (-21 to 11)	0.80 (0.78 to 0.82)	0.80 (0.78 to 0.83)	N/A	N/A

Abbreviations: aβ = adjusted regression coefficient beta. acOR = adjusted common odds ratio. CI = confidence interval. EVT = endovascular treatment. IMS III = Interventional Management of Stroke III trial. MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands. mRS = modified Rankin Scale. N/A = not applicable. NIHSS = National Institutes of Health Stroke Scale.
*All acORs and aβs are reported with their 95% confidence intervals. All pathways are adjusted for age, baseline NIHSS, collateral score, time from symptom onset to randomization. Pathway b and c' are additionally adjusted for sex, pre-stroke mRS, diabetes mellitus, hypertension, ischemic stroke, atrial fibrillation, ICA-T occlusion, IVT (in MR CLEAN only). Pathway c' was not tested in IMS III since no significant treatment effect was found on pathway c. †Interpretation of aβ: a patient with an NIHSS score of 15 at 24 hours after treatment with usual care alone, would have an NIHSS score of 12 at 24 hours when treated with EVT + usual care (15-15*0.19). ‡Expressed as an acOR for every 10% increase in the NIHSS.
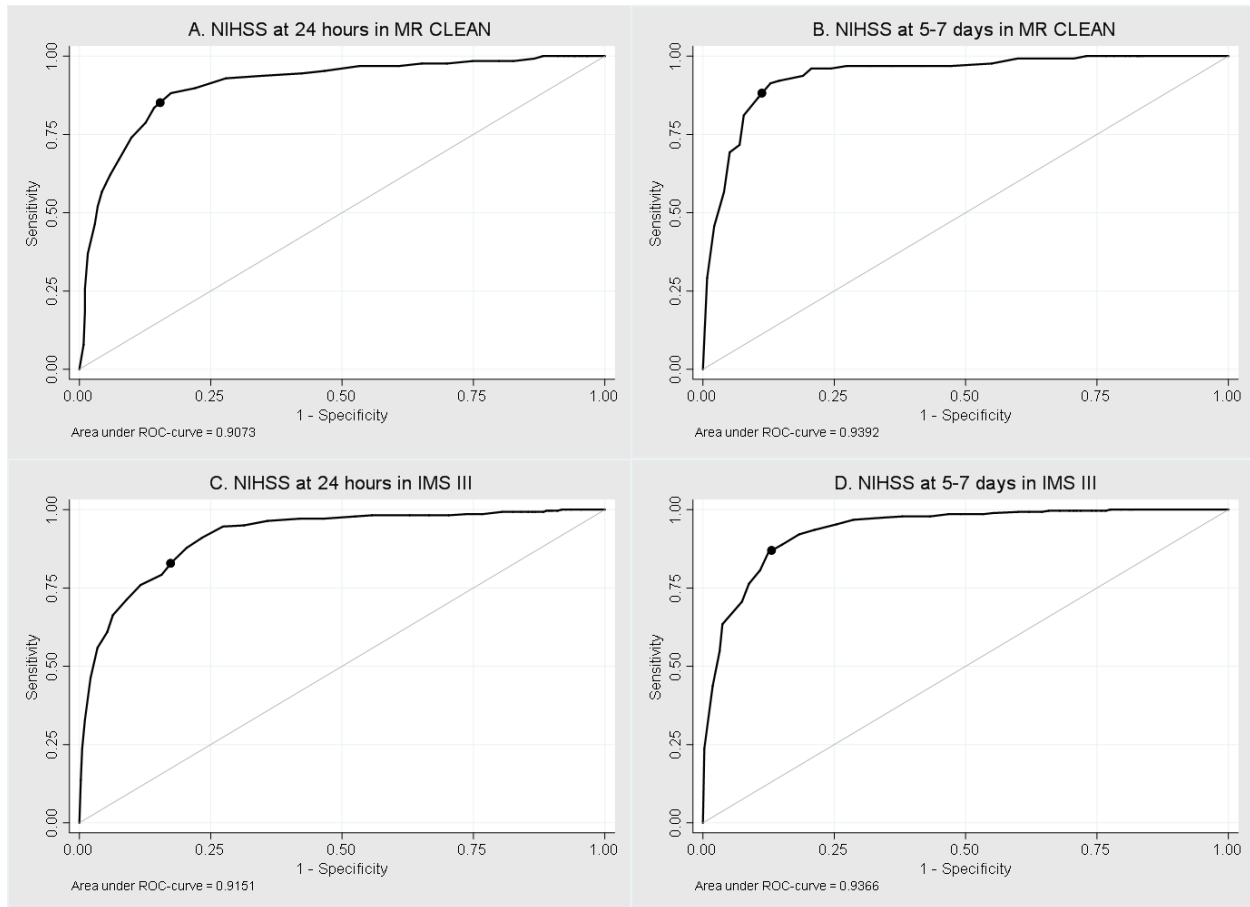
Table II. Unadjusted results of treatment effect on the mRS and NIHSS in MR CLEAN and IMS III.[*]

	Pathway c Effect of EVT on mRS (cOR)	Pathway a Effect of EVT on NIHSS (β)	
		NIHSS 24 hours	NIHSS 5-7 days
MR CLEAN	1.66 (1.21 to 2.28)	-19% (-30 to -7.7)†	-1.9% (-13 to 19)
IMS III	1.14 (0.86 to 1.51)	-27% (-39 to -12)	-4.2% (-21 to 16)

Abbreviations: β = regression coefficient beta. cOR = common odds ratio. CI = confidence interval. EVT = endovascular treatment. IMS III = Interventional Management of Stroke III trial. MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands. mRS = modified Rankin Scale. NIHSS = National Institutes of Health Stroke Scale.

[*]All cORs and βs are reported with their 95% confidence intervals. †Interpretation of β: a patient with an NIHSS score of 15 at 24 hours after treatment with usual care alone, would have an NIHSS score of 12 at 24 hours when treated with EVT + usual care (15-15*0.19).
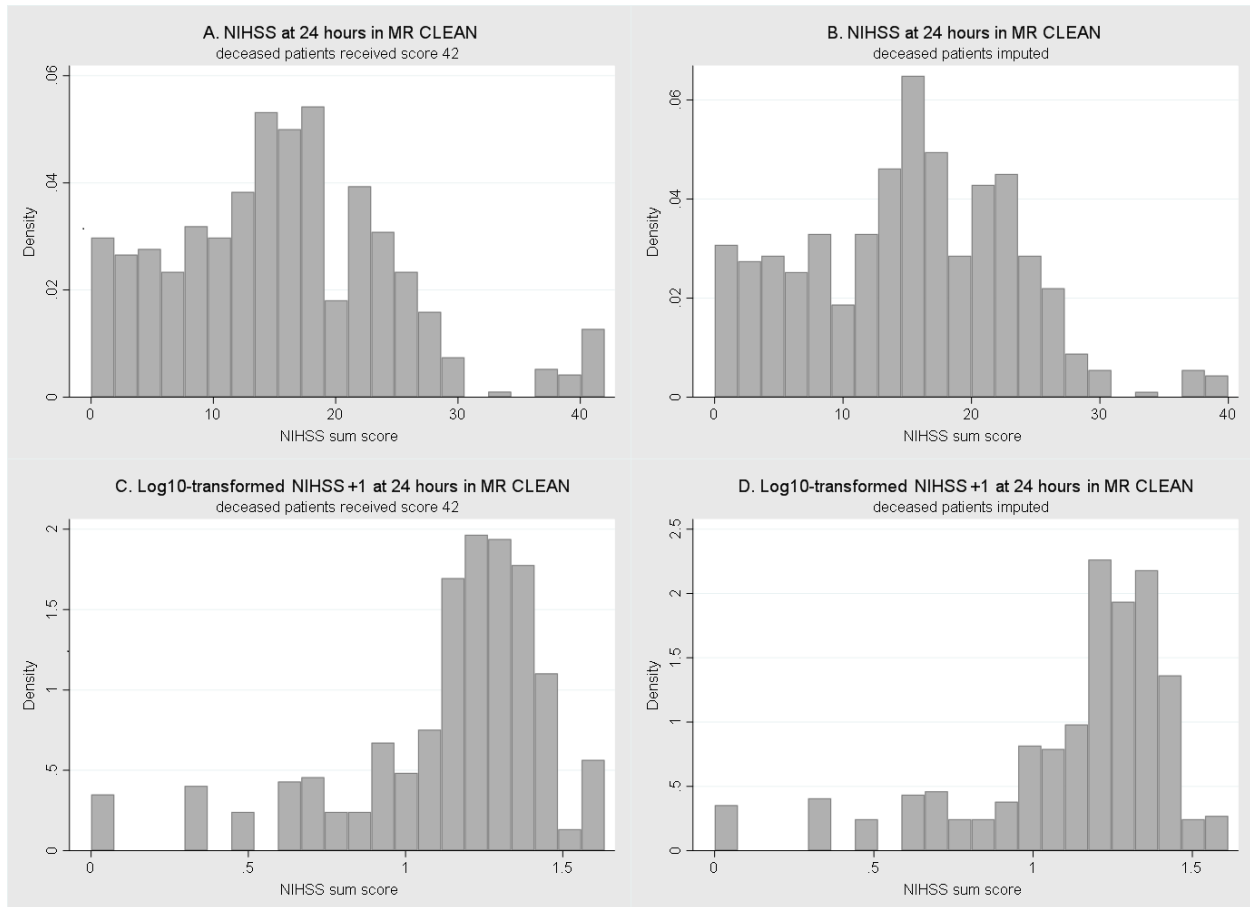
Figure I. ROC-curves (A-D) with their area under the curve for NIHSS at 24 hours and 5-7 days predicting mRS 0-2 in MR CLEAN and IMS III.*

Abbreviations: IMS III = Interventional Management of Stroke III trial. MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands. mRS = modified Rankin Scale. NIHSS = National Institutes of Health Stroke Scale. ROC = reveiver operating characteristic.
*ROC-curves A-D of set 1 of 5 imputed data sets are provided. The black markers in curves A-D show the optimal cut-off point of the sensitivity and specificity of the NIHSS for mRS 0-2, which are mentioned in the manuscript.
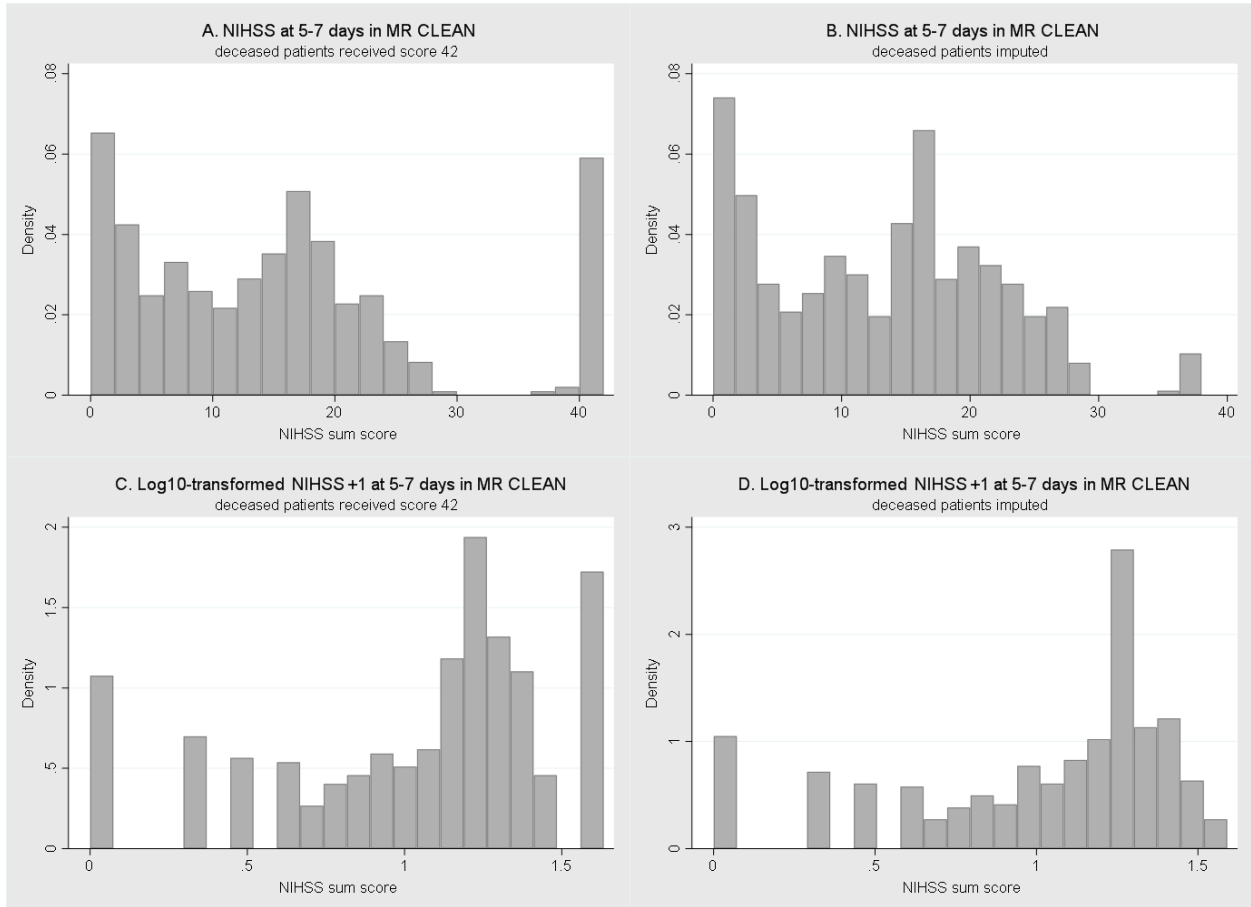
Figure II. Distribution of NIHSS (A,B) and log10-transformed NIHSS+1 (C,D) at 24 hours in MR CLEAN in the main analysis (A,C) and sensitivity analysis (B,D).*

Abbreviations: MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands. NIHSS = National Institutes of Health Stroke Scale.
*Deceased patients were assigned the maximum NIHSS score of 42 in the main analysis; deceased patients were imputed by multiple imputation with regression in the sensitivity analysis.
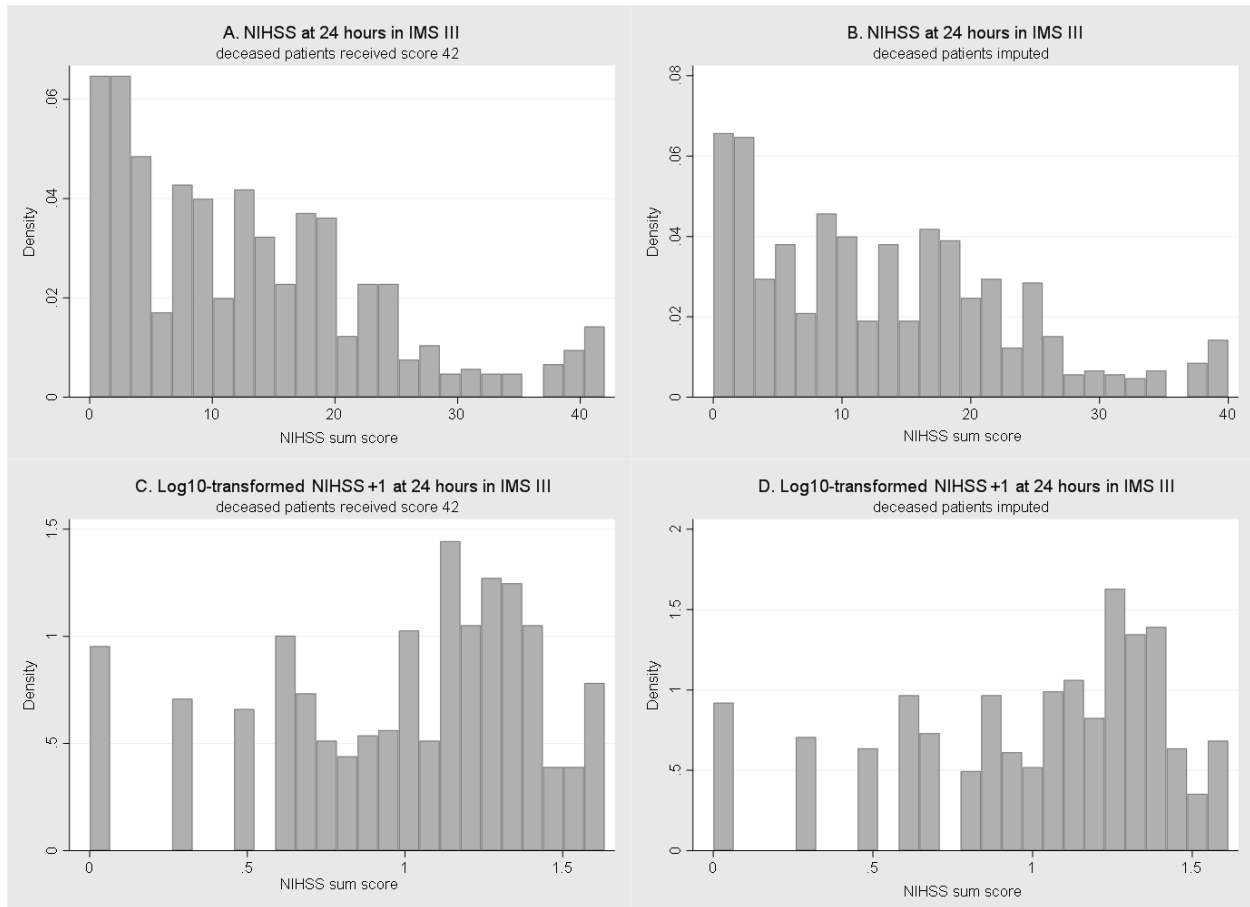
Figure III. Distribution of NIHSS (A,B) and log10-transformed NIHSS+1 (C,D) at 5-7 days in MR CLEAN in the main analysis (A,C) and sensitivity analysis (B,D.)*

Abbreviations: MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands. NIHSS = National Institutes of Health Stroke Scale.
*Deceased patients were assigned the maximum NIHSS score of 42 in the main analysis; deceased patients were imputed by multiple imputation with regression in the sensitivity analysis.
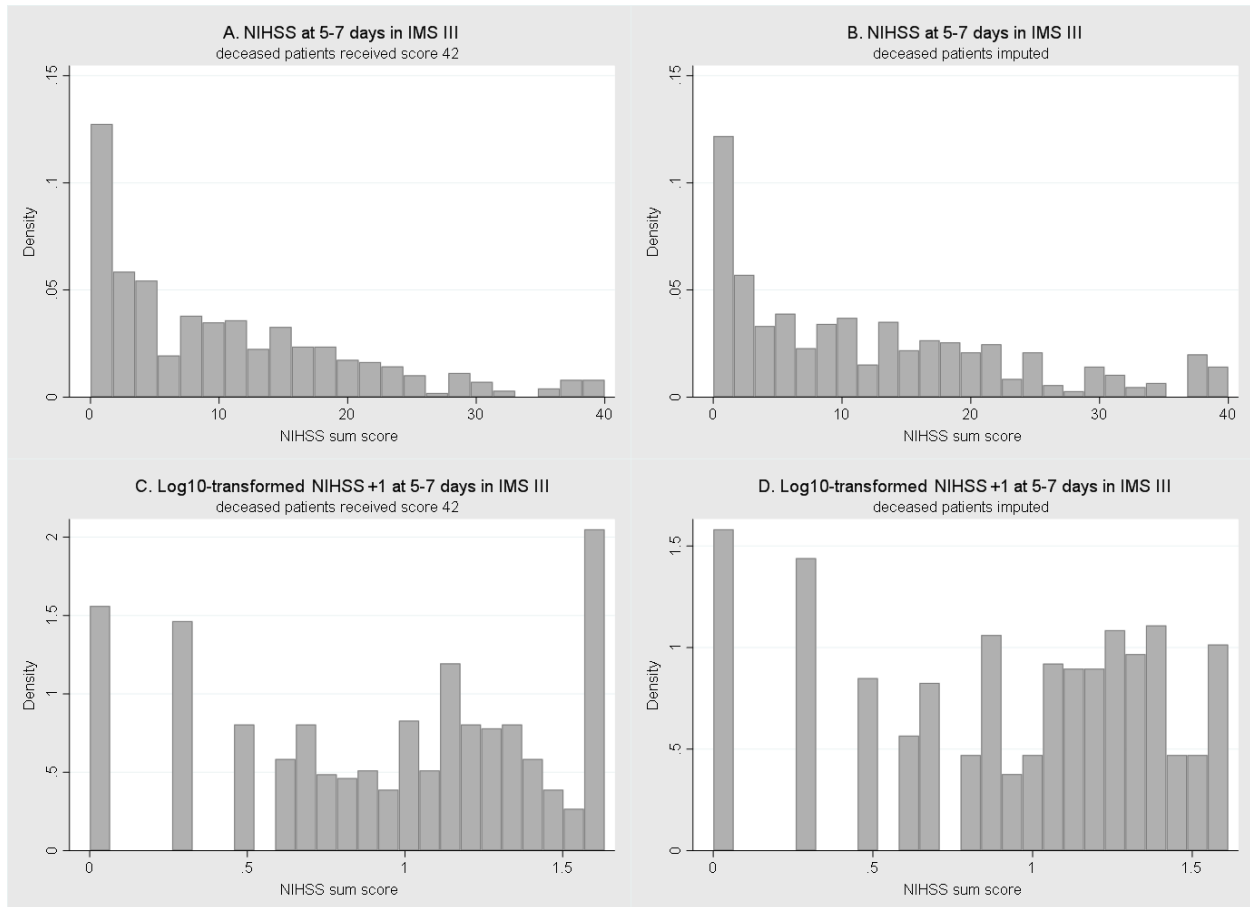
Figure IV. Distribution of NIHSS (A,B) and log10-transformed NIHSS+1 (C,D) at 24 hours in IMS III in the main analysis (A,C) and sensitivity analysis (B,D).*

Abbreviations: IMS III = Interventional Management of Stroke III trial. NIHSS = National Institutes of Health Stroke Scale.

*Deceased patients were assigned the maximum NIHSS score of 42 in the main analysis; deceased patients were imputed by multiple imputation with regression in the sensitivity analysis.

Figure V. Distribution of NIHSS (A,B) and log10-transformedNIHSS+1 (C,D) at 5-7 days in IMS III in the main analysis (A,C) and sensitivity analysis (B,D).*

Abbreviations: IMS III = Interventional Management of Stroke III trial. NIHSS = National Institutes of Health Stroke Scale.
*Deceased patients were assigned the maximum NIHSS score of 42 in the main analysis; deceased patients were imputed by multiple imputation with regression in the sensitivity analysis.