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Ethnicity and other determinants of quality of functional outcome in acute ischemic stroke: the ENCHANTED trial

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Table 1; Figures 2

Abstract

Background and Purpose: Patient centered outcomes are important. We aimed to determine predictors of health-related quality of life (HRQoL) and develop utility-weighted modified Rankin scale (UW-mRS) scores in thrombolyzed acute ischemic stroke (AIS) patients from both arms of the Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED).

Methods: ENCHANTED was an international quasi-factorial clinical trial of different doses of intravenous alteplase and intensities of blood pressure control in AIS patients, with outcomes on the European quality of life scale (EQ-5D) and mRS assessed at 90 days post-randomization. Logistic regression models were used to identify baseline predictors of poor HRQoL (≤mean EQ-5D utility scores). Ordinary least squares regression derived UW-mRS scores.

Results: In 4016 AIS patients with complete EQ-5D and mRS data, independent predictors of poor HRQoL were older age (odds ratio 1.19, 95% confidence interval 1.12-1.27, per 10-year increase), non-Asian ethnicity (1.91, 1.61-2.27), greater stroke severity on the National Institutes of Health Stroke Scale (NIHSS) (1.11, 1.09-1.12), diabetes mellitus (1.41, 1.18-1.69), pre-morbid disability (mRS score 1 vs. 0; 1.62, 1.33-1.97), large vessel atheromatous etiology (1.32, 1.12-1.54) and proxy-respondent (2.35, 2.01-2.74). Sensitivity analyzes indicate the ethnicity influence on HRQoL was driven by the high proportion of Chinese (62.9% of Asian) participants with better HRQoL compared to 'non-Chinese' or 'other-Asian' groups. Derived utility values across mRS scores 0 to 5 were 0.977, 0.885, 0.748, 0.576, 0.194, and -0.174, respectively. Correlations between mRS and EQ-5D scores were stronger in Asians.

Conclusions: HRQoL is worse after thrombolyzed AIS in the elderly, non-Asians, with greater initial severity, diabetes mellitus, pre-morbid disability, due to large vessel atheroma,

and proxy assessment. The broader significance of better HRQoL in Asians is tempered by Chinese participants dominating analyzes. From UW-mRS scores indicating the greatest steps in mRS scores are between 5 and 3, treatments to avoid major disability provide the greatest benefits for patients.

Clinical Trial Registration-http://www.clinicaltrials.gov. Unique-identifier: NCT01422616

As stroke is the leading cause of adult disability and suffering,[1,2] it is important to quantify the health and wellbeing of survivors that extend beyond functional status according to the modified Rankin scale (mRS), the most popular stroke outcome measure used in practice and research. The mRS emphasizes the physical components of disability and inadequately captures the overall impact of stroke on one's 'healthy life' or health-related quality of life (HRQoL). A recent approach to address this deficiency is to produce utility-weighted mRS (UW-mRS) scores, which typically combine assessments on the 5-dimension European quality of life scale (EQ-5D) and mRS. This allows the steps between mRS scores to move from fixed to variable intervals in an effort to directly reflect patient and societal valuation of disability states in a range from 0 (death) to 1 (perfect health). We aimed to identify the clinical factors that determine 'poor HRQoL' and derive UW-mRS scores among all thrombolyzed patients with acute ischemic stroke (AIS) who participated in the international Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED).

Methods

Data sharing

Individual participant data used in these analyzes can be shared by request from any qualified investigator via the Research Office of The George Institute for Global Health, Australia.

Study design

ENCHANTED was an international, multi-center, 2 x 2 quasi-factorial, prospective, randomized open-label blinded-endpoint (PROBE) trial that assessed the effects of low-dose versus standard-dose intravenous alteplase, and intensive versus guideline-recommended blood pressure (BP) lowering, in thrombolysis-eligible patients with AIS, the details of which are outlined elsewhere.[3-8] In brief, the ENCHANTED trial recruited an overall 4587 AIS patients, which included 3310 randomly assigned to low-dose (0.6mg/kg; 15% as bolus, 85%

as infusion over 1 hour) or standard-dose (0.9mg/kg; 10% as bolus, 90% as infusion over 1 hour) intravenous alteplase; and 2227 treated with alteplase randomly assigned to intensive BP lowering (target systolic BP 130-140 mm Hg) or guideline recommended BP lowering (target systolic BP <180 mm Hg). The study protocol was approved by the appropriate ethics committee at each participating center, and written informed consent was obtained from each patient or an appropriate surrogate. The study is registered with Clinicaltrials.gov (number NCT01422616).

Outcomes

Key patient demographic and clinical characteristics were recorded at the time of enrolment. Their final stroke diagnoses by presumed etiology, including large vessel occlusion/stenosis due to atheroma, were reported by clinician investigators at Day 7 (or immediately before discharge, if earlier). Neurological severity was measured using the National Institutes of Health Stroke Scale (NIHSS) at baseline, 24 hours, and Day 3 (or earlier on discharge from hospital). Clinical outcomes were assessed by telephone or in-person by trained independent researchers at Day 90 post-randomization; the primary outcome being functional status on the mRS. The secondary outcome was HRQoL on the EQ-5D-3L,[9] which defines general health status across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) according to three levels of severity (1 = no problems, 2 = some/moderate problems, and 3 = severe problems). Ratings on each subscale of the EQ-5D were synthesized into a single utility score using population-based preference weights obtained for the UK population.[10-12] Utility scores range from -0.594 to 1, with scores of 1 and 0 representing perfect health and death, respectively; negative scores represent health states considered worse than death.[10-12] For these analyzes, poor HRQoL was defined as scores of 2 or 3, defining problems reported within each dimension, or an overall health utility score ≤0.7 (rounded mean).

Statistical analysis

Binary logistic regression was used to define associations between patient characteristics and poor HRQoL. Sensitivity analyzes were performed to test associations of patient characteristics and poor HRQoL using different ethnicity analytic approaches, including non-Chinese vs. Chinese, non-Asian vs. Chinese, non-Asian vs. other-Asian, and other-Asian vs. Chinese. Association of NIHSS and EQ-5D utility scores (continuous variable) were assessed by linear regression. Boxplots were used to demonstrate relationships of Day 90 mRS scores and overall utility scores, while bar charts were used to describe relationships between mRS scores and individual dimensions on the EQ-5D. EQ-5D utility score trends across all mRS levels, between Asian and non-Asian patients, and between Chinese and non-Chinese, were tested using repeated measures analysis of variance. Independent sample t-test was used to assess differences of EQ-5D utility score between different levels of the mRS, and at each level of the mRS score according to Asian vs. non-Asian, and Chinese vs. non-Chinese. Associations between mRS and EQ-5D utility scores were assessed using Spearman's partial correlation analysis, adjusting for age and baseline NIHSS scores (≥14 vs. <14). The proportion of variance in EQ-5D utility scores that were explained by mRS scores, were obtained from calculating the multiple correlation coefficient (r^2) in regression models, adjusted for age and NIHSS scores (≥14 vs. <14). Correlation coefficients for mRS and EQ-5D utility scores were compared between Asians and non-Asians, and between Chinese and non-Chinese, using z test statistic with Fisher's r to z transformation.[13] Regression coefficients between Asians and non-Asians, and between Chinese and non-Chinese, were compared with an extensive t test.[13] Associations between proxy-respondents and mRS were assessed by Spearman's partial correlation analysis, and by logistic regression where mRS was considered as binary variable (0-1 vs. 2-5), adjusted for age, baseline NIHSS (≥14 vs. <14) and pre-stroke mRS (0 vs. 1). Associations between proxy-respondents and baseline

NIHSS (≥14 vs. <14) were tested using logistic regression adjusted for age. UW-mRS scores were derived from thrombolyzed participants in both the alteplase-dose and BP lowering intensity arms of the trial, using ordinary least squares (OLS) regression with mRS as a discrete ordinal explanatory dummy variable, and EQ-5D utility scores as a continuous response variable.[14] Independent sample t-test was used to assess differences in mean UW-mRS scores between the low-dose and standard-dose alteplase groups, and between intensive and guideline-recommended BP lowering groups. Consistency in the results using UK utility weights were tested with Chinese utility weights.[15, 16] Data are presented with odds ratios (OR) and 95% confidence intervals (CI), and a significance level was set at $P < 0.05$. All analyzes were undertaken using SAS enterprise (Version 7.1).

Results

Among all 4587 ENCHANTED AIS participants, there were 4016 (mean age 66.1; 37.6% female; 67.0% Asian [62.9% Chinese]) with available Day 90 mRS and EQ-5D utility scores. Differences between included and excluded participants are outlined in Supplemental Table I.

The overall mean EQ-5D utility score of AIS patients was 0.72 (0.37). Variables significantly associated with poor EQ-5D utility score (≤0.7) were older age (OR 1.19, 95% CI 1.12-1.27, per 10-year increase), non-Asian ethnicity (1.91, 1.61-2.27), greater NIHSS score (1.11, 1.09-1.12), diabetes mellitus (1.41, 1.18-1.69), pre-morbid disability (mRS score 1 vs. 0; 1.62, 1.33-1.97), large vessel atheromatous etiology (1.32, 1.12-1.54) and use of proxy-respondent (2.35, 2.01-2.74) (Table 1). In sensitivity analyzes using different ethnicity analytical approaches, there was general consistency for the same variables to be selected when comparing non-Chinese to Chinese, non-Asian to Chinese (except large vessel atheromatous etiology was no longer significant), and other-Asian to Chinese; except ethnicity was no longer significant when non-Asian was compared to other-Asian (without

Chinese) (Supplemental Tables II to V). In particular, the general trend was for non-Asians to have poorer HRQoL compared to Asians (being predominantly Chinese).

EQ-5D utility scores decreased by 0.02 per 1-point increase in NIHSS scores, after adjusting for age, sex, diabetes mellitus, and proxy-respondent. Use of a proxy-respondent also had a significantly positive, albeit weak, correlation with mRS ($r=0.29$, $P<0.0001$; OR 1.16, 95% CI 1.09-1.22) after adjustment for age, baseline NIHSS and pre-stroke mRS. High baseline NIHSS (≥14) was significantly associated with use of proxy-respondents (OR 2.52, 95% CI 2.15-2.96, $P<0.0001$) for Day 90 outcome after adjustment for age. Amongst the baseline variables that were associated with the different dimensions of EQ-5D, the general trend was for most, including age, previous smoke, atrial fibrillation, diabetes mellitus, pre-stroke disability, and stroke etiology, to be correlated with the physical components - poor function/activity domains, for non-Asian ethnicity as well as using anti-platelet agents at admission to be correlated with the non-physical components - poor pain/discomfort and emotion (anxiety/depression), and for baseline NIHSS and proxy assessment to be associated with poor HRQoL in all dimensions (Supplemental Table VI).

Initial symptoms of unilateral weakness affecting the leg/foot and homonymous hemianopia, were significantly associated with poor EQ-5D utility score, after adjusting for age, sex, ethnicity, and stroke severity (Supplemental Table VII). However, those associations that remained significant were paresis of the leg/foot in patients with poor (mRS 2-6) and good (mRS 0-1) functional outcomes, dysphasia in patients with poor functional outcome, and paresis of the arm/hand in those with good functional outcome (Supplemental Tables VIII and IX). The general trend was for problems with the different EQ-5D dimensions to increase with progressive loss of function according to increasing mRS scores, with the largest step increases in problems to occur between scores 3 and 4, and 4 and 5 (Supplemental Figure I).

Figure 1 shows a strong negative relationship between increasing mRS and EQ-5D utility scores (r=-0.83; P<0.0001), using UK utility weights. The strength of this association was consistent using Chinese and UK utility weights for Chinese and non-Chinese participants, respectively (Supplemental Figure II). Figure 2 shows a stronger correlation between these two outcome measures in Asians compared with non-Asians, and for significantly fewer problems (i.e. higher EQ-5D utility scores) to be recorded in Asians. Similar results were seen when Chinese was compared with non-Chinese ethnicity (Supplemental Table X).

UW-mRS scores across mRS scores 0 to 5 were: 0.977, 0.885, 0.748, 0.576, 0.194, and -0.174, respectively (Supplemental Table XI). The closest mRS levels were 0 and 1, separated by only 0.092, whereas the widest separation of levels was between 3 and 4 (0.382), and 4 and 5 (0.368), respectively (all level differences, P <0.0001). Sensitivity analyzes using Chinese utility weights for Chinese participants showed similar results (Supplemental Table XII). Analysis of the separate arms of the ENCHANTED cohort using UW-mRS scores as the primary outcome measure showed no heterogeneity in the effects of low-dose (0.70±0.33) versus standard-dose (0.71±0.33) alteplase (P=0.418), and similarly no difference in the treatment effect of intensive BP lowering (0.74±0.32) versus guideline-recommended (0.72±0.32) BP lowering (P=0.379) in respective arms of the trial.

Discussion

These exploratory analyzes of the ENCHANTED trial outline the patterns and predictors of HRQoL following thrombolysis treatment for AIS. Specifically, the independent predictors of poor HRQoL were older age, non-Asian ethnicity, more severe neurological impairment, diabetes mellitus, higher pre-stroke mRS (1 vs. 0), large vessel atheromatous etiology, and use of proxy-respondents. Sensitivity analyzes showed the influence of ethnicity on HRQoL was driven by Chinese participants (62.9% of Asians) who had better HRQoL when

compared to either non-Chinese or other-Asian groups. Although there was a strong correlation between Day 90 mRS and HRQoL utility scores, which was more strongly correlated in Asians than non-Asians, and in Chinese than non-Chinese participants, the combined UW-mRS scores were consistently unequally spaced across all six mRS levels.

Our study confirms previous findings of age,[17-19] female sex,[17] diabetes mellitus,[18, 20] neurological severity,[18, 19] having a negative influence on HRQoL, and for proxy-respondents[17, 21-23] to provide lower assessment of HRQoL than patients. Moreover, the influence of diabetes mellitus appears to extend beyond physical functioning into memory and thinking.[24] Although proxies are necessary to obtain EQ-5D scores in patients with severe disability, cognitive impairment or communication difficulty, it is clear that these data require adjusted analyses to account for their more pessimistic view of health states than patients.[17, 21-23]

Ethnicity-specific differences in the perception of HRQoL have been noted by others. For example, a large population-based study of national-level US data showed that Asians had higher HRQoL than Whites across a range of similar health and disease conditions,[25] and was potentially explained by Asians having higher levels of perceived familial support than other groups.[26] Another study of Chinese-American patients also suggests this ethnic group may be distinguished from others in having better HRQoL due to well preserved social/family ties,[27] and strong relationships and support from friends.[28] Thus, Asian ethnic groups appear to have high levels of collectivism, in which individuals have close binds, connections and obligations to social/family norms and duties,[29] which may attenuate the adverse effects of illness, including stroke.

Compared to other studies , the ENCHANTED cohort produced lower UW-mRS scores despite exhibiting similar trends in steps between mRS scores[14] which may reflect differences between study populations and methods of deriving UW-mRS scores. Our study

included a much larger multi-ethnic population specifically in thrombolysis-eligible and treated AIS patients[20] than, for example, a UK study of 1283 patients with stroke or transient ischemic attack.[14] Another study by Hong et al.,[30] found even smaller HRQoL gaps between mRS scores 4 and 5, and 3 and 4, than in our study. However, the World Health Organization's person-tradeoff procedure was used whereby stroke clinician derived disability weights were constrained to scores between 0 and 1, and unabled to account for scores worse than death.

Strengths of our analyzes include the use of a large dataset derived from an international multicenter study where data collection was standardized and near complete according to a rigorous protocol. Moreover, HRQoL measures were obtained from blinded assessors and sensitivity analyzes were undertaken according to Chinese and non-Chinese participants. Yet, as this was a selected clinical trial population with a restricted range of variables, there may be concerns over both the internal and external validity of the results. Moreover, the use of UK reference scores on the EQ-5D may not accurately reflect utility scores of AIS patients in other populations, although our results were confirmed in sensitivity analysis using Chinese utility weights.

In summary, the HRQoL of patients who survived thrombolyzed AIS was influenced by age, neurological severity, ethnicity, diabetes mellitus, pre-existing disability, large vessel atheromatous etiology and the use of proxy outcome assessment. Although caution may be warranted regarding the broader generalizability of the influence of Asian ethnicity due to the high proportion of Chinese participants, there was consistency in analyzes indicating Asians had a better HRQoL compared to others. In particular, there was a stronger correlation between mRS and EQ-5D scores in Asians (and Chinese) in the context of better overall HRQoL than non-Asians (and non-Chinese). As UW-mRS values showed the largest steps between mRS scores 5 to 4, and 4 to 3, effective therapies targeting reduction in moderate-

severe disability have the greatest potential to improve the health and wellbeing of those suffering AIS.

Author contributions

XC undertook analyzes and wrote the draft; CD, XW and CSA interpreted the data; all authors provided critical review and revisions, and approved submission of this article.

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Role of Sponsors

The funding bodies had no role in the design and conduct of the study; collection, management, analyzes, and interpretation of the data; and in preparation, review, or approval of the manuscript.

Conflicts of Interest Disclosures

CSA reports receiving research grants and lecture fees from Takeda fees, for serving on advisory boards for Amgen and Boehringer Ingelheim; RIL reports receiving fees for serving on a steering committee from Boehringer Ingelheim and lecture fees from Pfizer and Covidien; JC reports research grants and lecture fees from Servier for the ADVANCE trial and post-trial follow-up; PL reports grants and personal fees from The George Institute for Global Health, grants and non-financial support from Clinica Alemana de Santiago during the

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Table 1: Determinants of poor health-related quality of life in thrombolyzed patients with acute ischemic stroke

Variables	EQ-5D utility score*		Univariable		Multivariable	
	>0.7 (2860)	⩽0.7 (1156)	OR	P	OR	P
Age (years) †	64.6 (12.6)	69.6 (12.0)	1.39 (1.31-1.47)	<0.0001	1.19 (1.12-1.27)†	<0.0001
Female	1005/2860 (35.1)	503/1156 (43.5)	1.42 (1.24-1.63)	<0.0001		
Non-Asian	838/2860 (29.3)	483/1156 (41.8)	1.73 (1.50-2.00)	<0.0001	1.91 (1.61-2.27)	<0.0001
Clinical features						
Systolic BP (mmHg)	153.6 (18.5)	154.2 (18.8)	1.00 (1.00-1.01)	0.324		
NIHSS score	6 (4-10)	11 (6-16)	1.12 (1.11-1.14)	<0.0001	1.11 (1.09-1.12)	<0.0001
Medical History						
Hypertension	1799/2857 (63.0)	763/1155 (66.1)	1.15 (0.99-1.32)	0.065		
Previous stroke	487/2860 (17.0)	220/1156 (19.0)	1.15 (0.96-1.37)	0.905		
Coronary artery disease	347/2857(12.2)	184/1155 (15.9)	1.37 (1.13-1.66)	0.001		
Atrial fibrillation	381/2855 (13.4)	252/1155 (21.8)	1.81 (1.52-2.16)	<0.0001		
Diabetes mellitus	520/2857 (18.2)	277/1155 (24.0)	1.42 (1.20-1.67)	<0.0001	1.41 (1.18-1.69)	0.0002
Hypercholesterolemia	372/2857 (13.0)	234/1155 (20.3)	1.70 (1.42-2.03)	<0.0001		
Pre-stroke mRS=1	342/2857 (12.0)	277/1153 (24.0)	2.33 (1.95-2.77)	<0.0001	1.62 (1.33-1.97)	<0.0001
Medication at time of admission						
Antihypertensive agents	1207/2857 (42.3)	583/1155 (50.5)	1.39 (1.22-1.60)	<0.0001		
Warfarin anticoagulation	46/2856 (1.6)	30/1153 (2.6)	1.63 (1.03-2.60)	0.039		
Aspirin or other antiplatelet agents	524/2856 (18.4)	312/1153 (27.1)	1.65 (1.41-1.94)	<0.0001		
Glucose-lowering agents	322/2856 (11.3)	180/1153 (15.6)	1.46 (1.20-1.77)	0.0002		
Lipid-lowering agents	451/2855 (15.8)	271/1153 (23.5)	1.64 (1.38-1.94)	<0.0001		
Final diagnosis at time of hospital separation						
Large vessel atheromatous etiology	1125/2853 (39.4)	498/1154 (43.2)	1.17 (1.02-1.34)	0.030	1.32 (1.12-1.54)	0.0008

Variables	EQ-5D utility score*		Univariable		Multivariable	
	>0.7 (2860)	⩽0.7 (1156)	OR	P	OR	P
Small vessel disease	836/2853 (29.3)	189/1154 (16.4)	0.47 (0.40-0.56)	<0.0001		
Cardio-emboli	404/2853 (14.2)	252/1154 (21.8)	1.69 (1.42-2.02)	<0.0001		
Others	405/2853 (14.2)	195/1154 (16.9)	1.23 (1.02-1.48)	0.030		
Randomized to low-dose alteplase treatment	998/1994 (50.1)	451/869 (51.9)	0.93 (0.79-1.09)	0.363		
Randomized to intensive BP lowering treatment	732/1477 (49.6)	234/504 (46.4)	1.13 (0.93-1.39)	0.225		
Proxy-respondent	861/2859 (30.1)	641/1156 (55.5)	2.89 (2.51-3.33)	<0.0001	2.35 (2.01-2.74)	<0.0001

Data are n (%), mean (SD), median (IQR), or odds ratio (95% confidence interval). P values are based on Chi-square, T test, Wilcoxon signed-rank test, simple or multiple logistic regression.

BP denotes blood pressure, EQ-5D EuroQol 5-dimensional questionnaire, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, OR odds ratio

*Good (above) and poor (below) mean scores on the EQ-5D

†per 10-year increase

Figure legend

Figure 1 Relation of mRS and EQ-5D utility scores

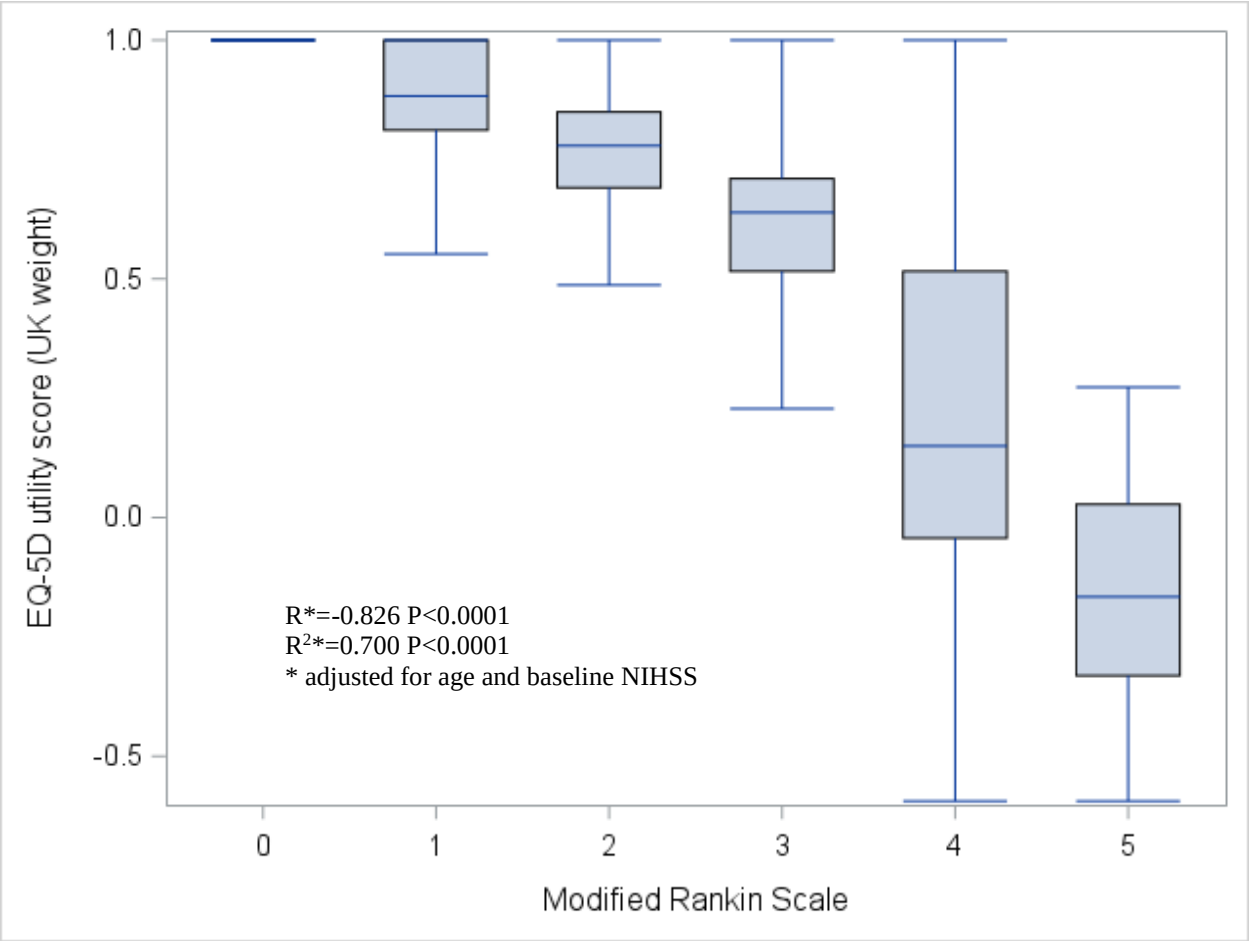
Footnote: EQ-5D denotes the 5-dimension European quality of life scale and mRS modified Rankin scale. R indicates Spearman's correlation coefficient and R^2 multiple regression coefficient

Figure 2 Relation of mRS and EQ-5D utility score by Asian versus non-Asian, and by Chinese versus non-Chinese, ethnicity of participants

Footnote: EQ-5D denotes the 5-dimension European quality of life scale and mRS modified Rankin scale. P for trend relates to comparison of EQ-5D utility scores across all mRS scores, between Asian and non-Asian patients, and between Chinese and non-Chinese, using repeated measures analysis of variance.

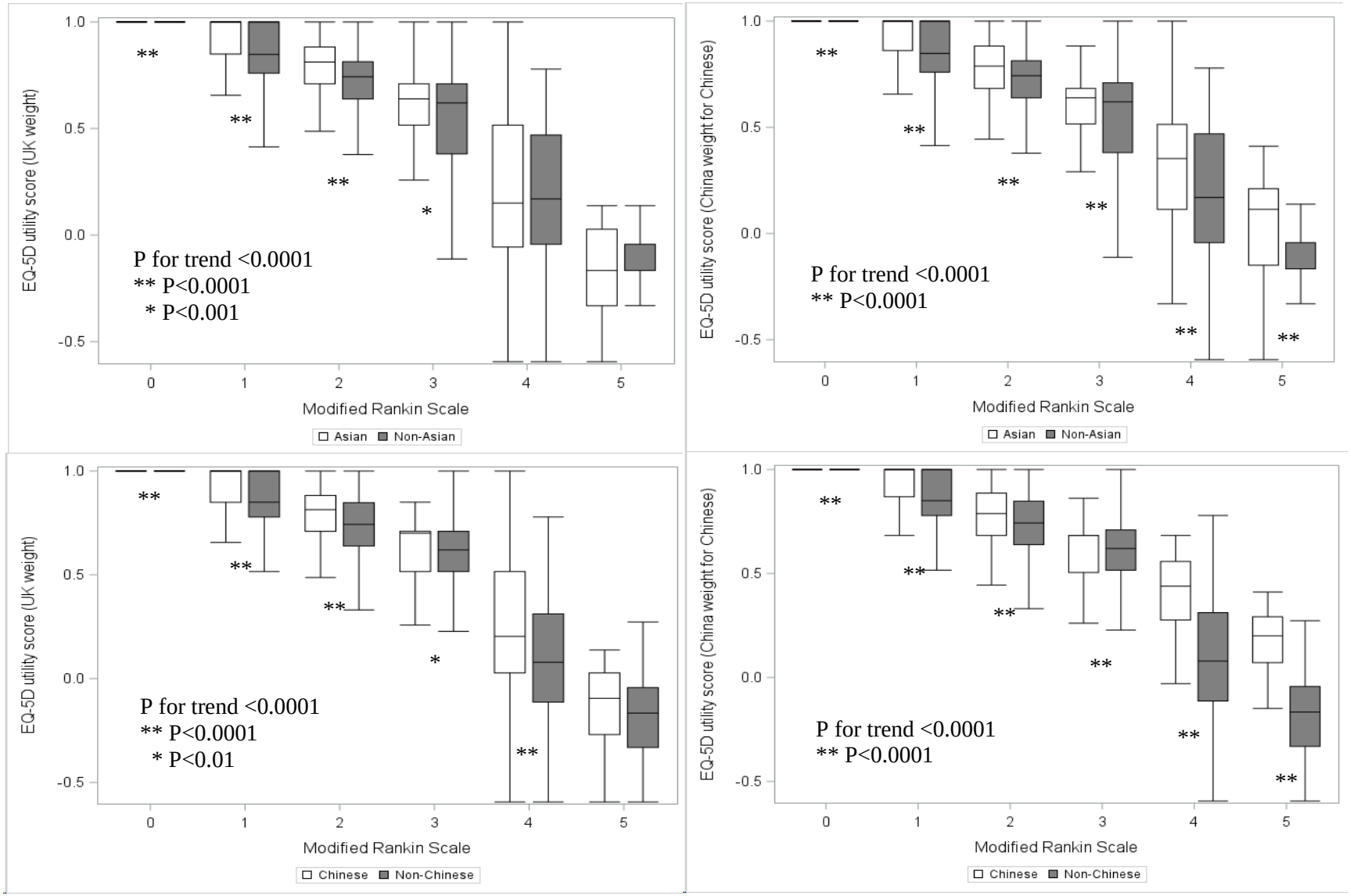
* and ** indicate significantly different EQ-5D utility scores on each mRS score between Asian and non-Asian, and between Chinese and non-Chinese, patients.

Figure 1.



n (%)	1148 (28.6)	1075 (26.8)	637 (15.9)	521 (13.0)	411 (10.2)	224 (5.6)
Mean (SD)	0.97 (0.08)	0.89 (0.15)	0.75 (0.16)	0.58 (0.21)	0.19 (0.33)	-0.17 (0.21)

Figure 2.


EQ-5D utility score (UK weight)
1.0
0.5
0.0
-0.5
0
1
2
3
4
5
Modified Rankin Scale
Asian
Non-Asian
P for trend <0.0001
** P<0.0001
* P<0.001
EQ-5D utility score (China weight for Chinese)
P for trend <0.0001
** P<0.0001
EQ-5D utility score (UK weight)
Chinese
Non-Chinese
P for trend <0.0001
** P<0.0001
* P<0.01
EQ-5D utility score (China weight for Chinese)
P for trend <0.0001
** P<0.0001