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Outcomes in Children With Hemorrhagic Stroke

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Abstract

Objectives—To determine if a specific intracerebral hemorrhage ratio predicts poor outcome; whether predictors of outcome in adults, specifically hemorrhage location, ventricular involvement, or initial Glasgow Coma Scale score, predict outcome in childhood hemorrhagic stroke; and whether the cause of hemorrhagic stroke predicts outcome.

Design—Retrospective case study.

Setting—A single tertiary care pediatric hospital.

Participants—Fifty-nine cases who had nontraumatic hemorrhages.

Main Outcome Measures—We examined whether hemorrhage volume, location, initial Glasgow Coma Scale score, or associated diagnoses predicted outcomes. We contacted survivors and parents and assessed outcomes using measures of neurological function, quality of life, and caregiver stress.

Results—Twenty died of the hemorrhage or associated illnesses, and we obtained follow-up on 19 survivors. Most survivors had mild to moderate neurological deficits, but many reported impaired school or physical functioning. Increasing hemorrhage volume predicted poorer neurological outcomes and poorer quality-of-life ratings among survivors. Subjects who had intracranial vascular anomalies had the best outcomes of the group. Associated diagnoses strongly predicted scores on the parent- and child-rated quality-of-life measures. In contrast to what has been reported in adult studies, initial Glasgow Coma Scale score, primary location of the hemorrhage, and ventricular hemorrhage did not significantly predict outcomes, although ventricular hemorrhage was associated with trends toward poorer outcomes.

Conclusions—The mortality of hemorrhagic stroke in children is lower than that in adults. Childhood survivors tend to have mild to moderate physical deficits, but they may have significant impairment in other domains such as school functioning.

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The number of pediatric ischemic stroke studies have dramatically increased in recent years, but few studies have examined hemorrhagic stroke. Although recent estimates suggest subarachnoid and intracerebral hemorrhage may account for up to 45% of all childhood stroke,[1–7] outcomes research of pediatric hemorrhagic stroke is lacking. Only 1 study evaluated outcomes in survivors beyond 1 year post-stroke.[8] There is a need for further information regarding the outcomes of pediatric hemorrhagic stroke.

Two recent studies determined that the volume of hemorrhage predicts early outcome in children. Jordan and colleagues[9] and Beslow and colleagues[10] used a hemorrhage to brain volume ratio because brain volume varies with age. While these studies differed in their definition of brain volume (inclusion or exclusion of ventricles), one reported that a ratio greater than 2% predicted poorer outcomes while the other reported that a ratio greater than 4% predicted poorer outcome.

In an earlier study,[11] we examined survival and short-term outcome in patients who had intracranial hemorrhages including subdural hemorrhages. In that study, there was no long-term outcome. That earlier work suggested that specific causes for the hemorrhage were more likely associated with survival (intracranial vascular anomalies) than other causes (congenital heart disease, malignancies, and systemic illness).

In the current study, our aims were to determine (1) if a specific intracerebral hemorrhage ratio predicts poor outcome; (2) whether predictors of outcome in adults, specifically hemorrhage location, ventricular involvement, or initial Glasgow Coma Scale (GCS) score,[12–14] predict outcome in childhood hemorrhagic stroke; and (3) whether the cause of hemorrhagic stroke predicts outcome.

METHODS

We examined a consecutive cohort of children admitted to the Nationwide Children's Hospital between January 1, 2000, and February 28, 2009, for symptomatic subarachnoid or intracerebral hemorrhage. We chose this interval because images were available for electronic review. We previously reported the causes of hemorrhage and immediate mortality in a consecutive series of children who were admitted to the Nationwide Children's Hospital for intracranial hemorrhage (including subdural hemorrhage) from 2000 to 2007.[11] We included 50 of those subjects in this study. We selected subjects who had intracerebral hemorrhage where the hemorrhage volume could be measured with image analysis. We chose to include those earlier cases because we had not collected any long-term follow-up data and had not analyzed predictors of outcome in those cases. To assure that we had identified all possible subjects, we searched medical records from 2000 to 2009 for cases with the *International Classification of Diseases*, *Ninth Revision* codes of 430 (subarachnoid hemorrhage) and 431 (intracerebral hemorrhage), and we reviewed brain computed tomography and magnetic resonance radiology reports for terms pertaining to subarachnoid hemorrhage or intracerebral hemorrhage.

The inclusion criteria included symptomatic subarachnoid hemorrhage with extension into the parenchyma/ventricles or intracerebral hemorrhage occurring after 28 days of life until age 18 years in children admitted to the Nationwide Children's Hospital. We included subjects who had hemorrhage from a range of medical/surgical causes including cerebral and systemic malignancies. We included children with malignancies in part to be consistent with earlier studies of hemorrhagic stroke[8,9] and in part because these reflect cases that physicians see in pediatric stroke. Exclusion criteria included subdural hemorrhage, cases limited to subarachnoid hemorrhage without parenchymal/ventricular extension, neonatal intraventricular hemorrhage, hemorrhagic conversion of an ischemic stroke or a venous

infarct identified by the study neuroradiologist, asymptomatic hemorrhage, and hemorrhage resulting from birth, trauma, or neurosurgical intervention.

We reviewed the records related to a hospital admission to identify the first recorded GCS score. Most GCS scores were documented by outside hospital or emergency medical personnel prior to transfer and typically reflected an initial assessment of an evolving clinical picture. The study neurologist and research assistant reviewed the computed tomography or magnetic resonance images to identify whether the hemorrhages were subarachnoid, lobar, deep/subcortical, or posterior fossa (ie, cerebellar or brainstem) in location. We distinguished whether a hemorrhage appeared to begin in a specific location (primary site) or extended to a location (secondary site) and whether hemorrhage extended to the ventricles. For example, an intracerebral hemorrhage that extended to the ventricles and subarachnoid space was labeled as a primary intracerebral hemorrhage with secondary extension to the other locations. Hematoma and brain volumes were measured with manual segmentation using ITK-SNAP version 1.8 (http://www.itksnap.org/pmwiki/pmwiki.php). This image analysis method was the same as used by Beslow et al[10]; however, we chose to include ventricles while Beslow et al excluded them from their measure of cerebral volume. We used computed tomography scans for most cases (43), but we used magnetic resonance imaging in the rest (16). In 20 cases, a scan was repeated within 1 to 2 days of the initial scan. In that circumstance, we chose the scan with the largest hemorrhage for image analysis. Briefly, Digital Imaging and Communications in Medicine format T2-weighted sequence slices of the brain were converted to ANALYZE format by the program ImageJ (http://rsbweb.nih.gov/ij/) then imported into ITK-SNAP. The margins of the intracerebral hemorrhage, brain, and ventricles were manually traced on each slice by a research assistant blind to the clinical details. The total slices were summed to yield the volume of the intracerebral hemorrhage and respective brain structures. Hemorrhage volume was expressed as a ratio relative to the cerebral volume (hemispheres, ventricles, brainstem, cerebellum, and hemorrhage) to allow for age-related changes in total brain volume.

We searched the medical records for coexisting medical/surgical disorders that likely contributed to the hemorrhagic stroke. Our earlier work[11] suggested that patients with intracranial vascular anomalies had a better survival rate than patients with hemorrhages from other causes. In that study, the associated disorders could be collected under the categories of congenital heart disease, brain or systemic malignancy, or miscellaneous medical disorders, so we used those categories for our data analysis.

We contacted families of survivors by telephone under an institutional review board–approved protocol. Parents and subjects were asked to answer 4 questionnaires. Stroke outcome was assessed using the Recovery and Recurrence Questionnaire (RRQ), a modified version of the Pediatric Stroke Outcome Measure,[15] which can be administered via telephone.[16] Briefly, the RRQ uses parental report to assess sensorimotor function, language production and comprehension, and cognition/behavior on an ordinal scale. Quality of life was assessed with the PedsQL generic scales,[17] which use 5-point Likert scales to assess quality of life in physical, emotional, social, and academic domains. The PedsQL has been validated for telephone survey.[18–20] As an exploratory measure, we assessed parental stress with the Caregiver Strain Questionnaire (CSQ).[21] The CSQ has been used to assess parent/caregiver stress in other chronic pediatric conditions[22] and provides 3 subtotals including objective stress, internalized subjective stress, and externalized subjective stress. The CSQ was modified to include 20 items that provided a continuous measure of caregiver stress. As a further exploratory measure, the King's Outcome Scale for Childhood Head Injury (KOSCHI)[23] was used to provide a global estimate of outcome. The KOSCHI was recently used as an outcome measure in a study of pediatric hemorrhagic stroke.[10]

We modified 3 measures to facilitate analysis. The RRQ yields outcome scores ranging from 0 (normal) to 10 (severely impaired) but does not include a category for death. A number of subjects were deceased so we added a score of 11 (death) when analyzing potential predictors of the RRQ. The KOSCHI yields 5 outcome scores ranging from dead to normal (1=dead, 2=vegetative, 3=severe disability, 4=moderate disability, and 5=normal). The higher outcome levels 3, 4, and 5 are further subdivided to an "A" (poorer) and "B" (better) level, so we transformed the KOSCHI data to a 1 to 8 scale to account for the "A/B" subcategories. The quality-of-life measures do not account for deceased patients. The quality-of-life measures, which range from 0 to 100, were transformed by assigning a value of 0 to deceased subjects and increasing survivors' scores by 10 to a maximum of 110.

We used the cumulative logit model in logistic regression to test hemorrhage primary location, ventricular involvement, hemorrhage ratio, diagnosis, and initial GCS score as predictors of function as scored by the ordinal measures RRQ and KOSCHI. We examined ventricular involvement as a predictor of PedsQL scores with the Wilcoxon 2-sample test. We assessed GCS score, hemorrhage location, and associated diagnoses (intracranial vascular anomalies, malignancies, congenital heart disease, and other/miscellaneous) as predictors of PedsQL scores with the Wilcoxon rank sum and Kruskal-Wallis tests. We evaluated the hemorrhage ratio as a continuous predictor of the PedsQL scores with the Pearson correlation coefficient. We examined hemorrhage primary location, ventricular involvement, hemorrhage ratio, diagnosis, and initial GCS score as predictors of the CSQ scores with logistic regression and generalized linear models. We used logistic regression to test whether a hemorrhage to brain ratio of 2% or 4% predicted scores on each of the measures.

RESULTS

There were 59 subjects who met inclusion criteria; 28 were male and 31 were female. Fifty-four were white, 4 were African American, and 1 had ethnicity listed as "other." The hemorrhage locations were 37 lobar, 8 deep hemisphere, 2 primarily subarachnoid, and 10 brainstem/cerebellar. Ventricles were involved in 23 cases, of which 21 had a primary hemorrhage elsewhere. The hemorrhage ratios ranged from 0.07% to 13.36% of cerebral volume (eFigures 1A–C, https://sharedoc.nchri.org/Labs/RESLo/OCHS). Of the cases with associated conditions that increased the risk for hemorrhage, 28 had intracranial vascular anomalies ranging from arteriovenous malformations to cavernomas. Fourteen cases had malignancies, 11 brain and 3 systemic. Five cases had congenital heart disease, and these cases typically presented as catastrophic postoperative hemorrhages while the patients underwent anticoagulation. Eight cases had associated diagnoses that likely contributed to the hemorrhage: 2 had Moyamoya syndrome, 1 had renal disease, 1 had hemophilia, 1 had central nervous system vasculitis, 1 had von Willebrand disease, 1 had a brain abscess, and 1 had a fatty acid oxidation disorder. Four had no known disorder. Twenty subjects died of the hemorrhage or associated illnesses. We collected outcome data from 19 families but did not collect information from 20 families (15 could not be located and 5 declined to participate). Median age at the time of hemorrhage was 10.2 years (Table 1), and median age at outcome assessment was 16.8 years. Initial GCS score could be assessed in 36 cases and the median value was 14, although many subjects had a subsequent decline in the GCS score. The GCS score could not be assessed in the remaining cases because of paralysis or sedation.

Among the 19 survivors, the median RRQ score was 1, which translates to a mild to moderate degree of impairment.[15] The median KOSCHI score for the survivors was 5A, which indicates minimal impairment with daily function.[23] The parent- and patient-rated scores on the Ped-sQL were not normally distributed (Table 2), but when compared with published normative data,[24] parent- and patient-rated school quality of life was significantly

lower than normative means and patient-rated physical quality of life was significantly lower. Caregiver reports on the CSQ indicated slightly increased internalized stress.

The hemorrhage to brain volume ratio (hemorrhage ratio) was an important predictor of outcome. Larger hemorrhage ratios predicted poorer outcomes, including death, on the RRQ and KOSCHI (Table 3) (eFigures 2A and B, https://sharedoc.nchri.org/Labs/RESLo/OCHS). In survivors, larger hemorrhage ratios predicted lower parent and patient ratings on the PedsQL, greater internalized care-giver stress on the CSQ, and a trend toward greater objective caregiver stress on the CSQ. The size of the hemorrhage ratio mattered. A hemorrhage ratio more than 2% did not predict RRQ or KOSCHI scores and was associated with a nonsignificant trend toward lower scores on the PedsQL (Table 4). A ratio more than 4% predicted significantly poorer outcomes on the RRQ and KOSCHI and poorer parent- and subject-rated PedsQL scores.

Initial GCS score did not predict outcomes on the RRQ or KOSCHI for deceased patients or survivors (eFigures 3A and B, https://sharedoc.nchri.org/Labs/RESLo/OCHS), and among survivors, GCS score did not predict parent or subject ratings on the PedsQL. There was a nonsignificant trend for GCS score to predict greater objective caregiver stress on the CSQ ($P = .07$, data not shown). The primary location of the hemorrhage (lobar, subcortical, subarachnoid hemorrhage, or posterior fossa) did not predict outcomes on the RRQ or KOSCHI for all patients (deceased and survivors) or the parent- or patient-rated scores on the PedsQL or CSQ among survivors. The presence of ventricular hemorrhage was associated with a trend toward poorer outcomes on the KOSCHI ($P = .10$) and multiple parent-rated PedsQL domains (physical, $P = .06$; social quality of life, $P = .08$; and school $P = .08$). Ventricular involvement did not predict outcomes on the RRQ, patient-rated PedsQL, or the CSQ.

The associated diagnoses significantly predicted the parent- and patient-related ratings on the PedsQL (Table 5) (eFigures 4A–D, https://sharedoc.nchri.org/Labs/RESLo/OCHS). Subjects with hemorrhage from an intracranial vascular anomaly had higher PedsQL scores than subjects who had hemorrhages from malignancies or congenital heart disease. Associated diagnoses did not predict outcomes on the RRQ and KOSCHI or increased caregiver stress.

COMMENT

Our aims were to determine whether hemorrhage volume predicted outcome, whether multiple adult predictors of outcome applied to children, and whether associated diagnoses predicted outcome in survivors. Hemorrhage size was an important predictor of death and impairment, poorer quality of life, and a trend toward greater caregiver stress. There was a threshold effect such that hemorrhages greater than 4% of the cerebral volume predicted poorer outcomes while smaller hemorrhages did not. In contrast with adult studies,[12] primary hemorrhage location, ventricular involvement, and initial GCS score did not predict outcome.

The associated diagnoses were important predictors of quality of life. Since we included patients with systemic or brain malignancies in our study, similar to the studies of Blom et al[8] and Jordan et al,[9] these diagnoses would be expected to be linked to a lower quality of life. While it is not surprising that subjects with intracranial vascular anomalies had better quality-of-life outcomes than those with malignancies or congenital heart disease, they also had better outcomes than subjects whose hemorrhages occurred in the setting of other medical disorders. The diagnosis categories were not associated with poorer outcomes on the RRQ and KOSCHI, possibly because the small sample size was underpowered to find differences in these ordinal variables.

These conclusions were presented in summary form in a recent review, but the data behind the conclusions are now presented in this study. Our results are consistent with those of Blom et al,[8] who reported 56 children with non-traumatic hemorrhagic stroke. Thirty-one survivors were assessed at a median 11.4 years after hemorrhage. Fourteen had no physical deficit and 15 had mild to moderate physical deficits. The mean verbal and performance IQs were similar to published norms, but 15 children had impaired performance on 1 or more measures of cognitive function. Parents reported the children had impaired self-esteem and reduced family activities, and activities with friends were limited by emotional or behavioral problems. Parents endorsed feelings of anxiety and depression in their children, and parents experienced increased stress as caregivers. Our findings complement the work of Jordan et al,[9] who examined short-term outcomes of 28 children with nontraumatic intracerebral hemorrhage. Our range of initial GCS scores, hemorrhage ratios, and associated diagnoses were similar to those of Jordan et al.[9] Our finding regarding a hemorrhage ratio greater than 4% and poorer outcome was similar to that of Jordan et al, as well as our findings that GCS score and posterior fossa hemorrhage did not predict outcome. Our measurement of total cerebral volume was similar to that of Jordan et al[9] in that we included ventricular volume in the value for cerebral volume. Our results differed from those of Beslow et al,[10] who reported that hemorrhage more than 2% of brain volume and altered mental state on hospital admission predicted poorer outcomes. However, our study defined total cerebral volume as including ventricular volume while Beslow et al excluded the ventricles from cerebral volume. Also their study did not include subjects with brain tumors, isolated intraventricular hemorrhage, or subarachnoid hemorrhages.

Existing studies of pediatric hemorrhagic stroke are methodologically different; thus, the findings are difficult to generalize. However, taken together, the results indicate that the estimated mortality rate from childhood hemorrhagic stroke[9,11] is lower than the 39% to 53% 1-year mortality seen in adults.[25,26] Furthermore, childhood survivors appear to have higher levels of functioning compared with adult survivors.[12,27] Among childhood survivors, most have mild to moderate long-term physical disability,[15] but subjects and parents report significantly lower school function as well as impaired quality of life. The impact of hemorrhage also extends to the parents, as evidenced by an elevated level of caregiver internalized stress,[21] although it is lower than that reported with pediatric cancer patients.[22]

The current findings are tempered by a number of limitations. This study was performed at a single tertiary care children's hospital in North America; therefore, the results may not generalize to children in other settings or countries. Several adult predictors, such as GCS score and ventricular involvement, did not reach statistical significance, but we cannot exclude that our study was under-powered to detect small differences. We were unable to locate 25% of the potential participants, so mortality or survivor outcomes may have been different if they had been included. We used different outcome measures compared with previous studies, so our results are not easily compared or combined with those from previous reports. Finally, we relied on telephone interview to assess function, but detailed behavioral or cognitive assessments might have identified greater deficits than were reported.

Despite these limitations, this is one of the largest follow-up studies of pediatric hemorrhagic stroke and it is only 1 of 2 with follow-up that extends years after hemorrhage. Our results validate many findings of earlier studies and add new insights regarding the long-term outcome and quality of life following hemorrhagic stroke in children. As the long-term outcomes of hemorrhagic stroke become better characterized, physicians will be better able to recognize the range of sequelae that occur and identify the potential for long-term problems and thus be better able to help their patients.

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Table 1

Ages at Stroke Onset and Assessment, Time to Follow-up, Initial GCS Score, and RRQ and KOSCHI Scores at Follow-up

	Median (Range) [IQR]
Age at bleed, y (n = 59)	10.2 (0.1–18) [6.6–14.4]
Age at outcome assessment, survivors, y (n = 19)	16.8 (7.8–25.2) [11.3–19.9]
Time to follow-up, y	5.1 (1.2–8.0) [3.0–6.7]
Initial GCS score (n = 36)	14 (3–15) [10–15]
RRQ score, survivors (n = 19)	1 (0–6) [0–4]
KOSCHI score, survivors (n = 19)	5A (3–5B) [4B–5B]

Abbreviations: GCS, Glasgow Come Scale; IQR, interquartile range; KOSCHI, King's Outcome Scale for Childhood Head Injury; RRQ, Recovery and Recurrence Questionnaire.

Table 2

PedsQL Outcomes of Survivors, Published Normative PedsQL Scores, and CSQ Results

	Median (IQR)	Mean (SD)	Normative Mean (SD)[24]
Parent report			
Physical health (n = 19)	93.75 (43.75–100)	72.52 (34.05)	84.08 (19.70)
Emotional function (n = 19)	85 (60–100)	77.63 (25.95)	81.20 (16.40)
Social function (n = 19)	95 (50–100)	77.11 (29.64)	83.05 (19.66)
School function (n = 19)	65 (50–90)	67.50 (22.44)[a]	78.27 (19.64)
Subject report			
Physical health (n = 15)	90.63 (46.88–93.75)	73.96 (30.29)[a]	87.77 (13.12)
Emotional function (n = 15)	75 (65–85)	71.33 (25.46)	79.21 (18.02)
Social function (n = 15)	90 (80–100)	82.08 (25.74)	84.97 (16.71)
School function (n = 14)	75 (43.75–91.25)	67.86 (26.87)[a]	81.31 (16.09)
Caregiver stress (n = 18)			
Objective strain[b]	11 (10–30.25)		
Internalized strain[c]	10 (6–24.25)		
Externalized strain[d]	4 (4–5.25)		

Abbreviations: CSQ, Caregiver Strain Questionnaire; IQR, interquartile range.

[a] Significantly less than published normative data, single-tailed t test, $P < .05$.

[b] No stress = 0; severe stress = 50.

[c] No stress = 0; severe stress = 30.

[d] No stress = 0; severe stress = 20.

Table 3

Total Range of Hemorrhage Ratios as Predictor of QOL and Caregiver Stress[a]

All Hemorrhages	Pearson Correlation Coefficient	*P* Value
Parent rating QOL		
Physical health	−0.44	<.01[b]
Emotional function	−0.32	.05
Social function	−0.36	.02
School function	−0.38	.02
Patient rating QOL		
Physical health	−0.38	.02[b]
Emotional function	−0.39	.02
Social function	−0.37	.03
School function	−0.35	.04
Caregiver stress		
Objective stress		.06[c]
Internalized stress		.04[c]
Externalized stress		.22[c]

Abbreviation: QOL, quality of life.

[a] As the hemorrhage ratio increases, it predicts poorer outcomes as measured by poorer QOL measures and increasing indications of caregiver stress.

[b] Logistic regression.

[c] Generalized linear model.

Table 4

Hemorrhage Ratios Were Dichotomized to 2% or Less and More Than 2% or 4% or Less and More Than 4% Then Analyzed as Predictors of RRQ Score, KOSCHI Score, and QOL[a]

	OR (95% Wald CI)	*P* Value
Hemorrhage >2% vs ≤2%		
RRQ score	1.70 (0.51–5.67)[b]	.39
KOSCHI score	0.43 (0.13–1.46)[b]	.18
Parent rating QOL		
Physical health		.05[c]
Emotional function		.14[c]
Social function		.10[c]
School function		.09[c]
Patient rating QOL		
Physical health		.06[c]
Emotional function		.10[c]
Social function		.10[c]
School function		.10[c]
Hemorrhage >4% vs ≤4%		
RRQ score	6.73 (1.68–27.01)[b]	.01
KOSCHI score	7.04 (1.74–28.57)[b]	.01
Parent rating QOL		
Physical health		<.01[c]
Emotional function		<.01[c]
Social function		<.01[c]
School function		<.01[c]
Patient rating QOL		
Physical health		<.01[c]
Emotional function		<.01[c]
Social function		.10[c]
School function		<.01[c]

Abbreviations: KOSCHI, King's Outcome Scale for Childhood Head Injury; OR, odds ratio; QOL, quality of life; RRQ, Recovery and Recurrence Questionnaire.

[a]This analysis demonstrated that hemorrhage ratios more than 4% of cerebral volume predicted poorer outcomes for all measures.

[b]Logistic regression.

[c]Wilcoxon 2-sample tests, 1-sided *t* test.

Table 5

Associated Diagnoses as a Predictor of Quality-of-Life Measures Reported by Parents and Subjects

	Diagnosis Ranking[a,b]	*P* Value[c]
Parent rating		
Physical health	IVCA>other>malignancy>CHD	.01
Emotional function	IVCA>other>malignancy>CHD	.02
Social function	IVCA>other>malignancy>CHD	.01
School function	IVCA>other=malignancy>CHD	.01
Patient rating		
Physical health	IVCA>other=malignancy>CHD	.02
Emotional function	IVCA>other=malignancy>CHD	.02
Social function	IVCA>other=malignancy>CHD	.01
School function	IVCA>other=malignancy>CHD	.01

Abbreviations: CHD, congenital heart disease; IVCA, intracranial vascular anomaly.

[a] Ranking determined by Wilcoxon rank sum test.

[b] Rank order of diagnostic criteria ranges from better outcomes on the left to poorer outcomes on the right.

[c] Kruskal-Wallis test.