Sex differences and hemoglobin levels in relation to stroke outcomes

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ABSTRACT

Objective: Women have worse outcomes after stroke compared to men. Since women have lower hemoglobin values, we examined whether hemoglobin levels may associate with worse stroke outcomes in women.

Methods: We retrospectively studied 274 patients enrolled in a prospective multicenter study. We explored the relationship of hemoglobin with clinical outcome at 6 months, as measured by the modified Rankin Scale (mRS). Ordinal logistic regression was used to evaluate the independent effect of hemoglobin on clinical outcome, and to explore the influence of sex on that association.

Results: Women had a lower mean hemoglobin level (11.7 ± 1.8 g/dL) compared to men (13.3 ± 1.7 g/dL). Low hemoglobin was associated with worse 6-month mRS outcomes in univariate analysis ($p < 0.001$). Lower hemoglobin remained independently associated with poor outcome after adjustment for comorbid disease, stroke severity, age, and sex. The inclusion of hemoglobin in the model attenuated the independent effect of sex on outcome.

Conclusions: Sex differences in stroke outcome are linked to lower hemoglobin level, which is more prevalent in women. Further examination of this potentially modifiable predictor is warranted. *Neurology*® 2013;80:719-724

GLOSSARY

CI = confidence interval; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **OR** = odds ratio; **SNP** = single nucleotide polymorphism; **STOPStroke** = Screening Technology and Outcome Project in Stroke; **YSS** = yield shear stress.

Women who have a stroke tend to recover less well than men,[1] resulting in greater dependency, institutionalization,[2–4] and poorer quality of life.[5] Several reasons for the disparity have been investigated, including sex differences in clinical presentation and resource use,[2,6] in acute stroke care,[2,7] and biological divergence related to sex steroid hormones.[1] Women with stroke are also older, which may account for some of the observed differences.[8,9] In the context of an expanding elderly population, it is expected that the proportion of women with stroke will further increase,[9] which amplifies the urgency of the problem.

Women also have a lower hemoglobin level than men, and previous data have shown that hemoglobin level correlates with worse neuroimaging surrogate outcomes.[10] This raises the possibility that a portion of the worse outcome may be mediated by hemoglobin level. The purpose of this study was to assess whether the difference in hemoglobin level between men and women was associated with neurologic outcome, and whether this might account for a proportion of the sex difference in stroke recovery previously observed.

METHODS **Study population.** We retrospectively analyzed the clinical data collected at a single center, as part of a prospective multicenter study evaluating the utility of new CT-based neuroimaging technology to improve prediction of stroke subtype and outcome (Screening Technology and Outcome Project in Stroke [STOPStroke] Study). The STOPStroke Study enrolled consecutive patients who were evaluated by multimodal CT (noncontrast CT, CT angiography, CT perfusion) within 24 hours of symptom onset for symptoms consistent with an acute ischemic stroke. Clinical outcome status was determined using the modified Rankin Scale (mRS)

obtained by telephone interview at 6 months. The study started in March 2003 and follow-up was completed in July 2006. For the present analysis, patients were eligible if they had a discharge diagnosis of stroke, had a 6-month mRS recorded, and were not treated with thrombolytic or investigational treatments. Patients with prestroke disability (mRS of >2) were excluded. All patients underwent a standardized evaluation of rehabilitation needs by the same team of physical, occupational, and speech therapists, and were given an individualized rehabilitation treatment plan before discharge.

Data collection. Admission NIH Stroke Scale (NIHSS) score, prestroke disability, and clinical outcome at 6 months as defined by mRS were collected prospectively. Clinical characteristics including time of stroke onset (defined as last time the patient was known to be well) and demographic and medical information were ascertained for each patient through retrospective chart review. The hemoglobin level during hospitalization was abstracted retrospectively and the nadir used for analysis. Analysis was also performed using mean hemoglobin level and hemoglobin dichotomized into anemia, based on the WHO sex-specific definitions.[11] The Charlson comorbidity index was calculated[12] based on review of the medical record and then dichotomized around the median score. We classified stroke etiology using the Causative Classification of Stroke system.[13] For a subset of patients who had the requisite laboratory values available (n = 80), an estimate of whole blood viscosity was calculated based on fibrinogen and hematocrit, using the yield shear stress (YSS) formula, $YSS = 13.5 \ (10^{-6}) \ C_f^2 \ (Hct-6)^3$, where C_f is the fibrinogen concentration in gm/dL.[14,15]

Statistical analysis. Differences in clinical and laboratory variables according to sex were compared using Student t, Wilcoxon rank-sum, or Fisher exact test, as appropriate. Differences in clinical and laboratory variables according to mRS score were tested using one-way analysis of variance, Kruskal-Wallis, or χ^2 test, as appropriate. Because there were only 4 subjects with an mRS of 5, this group was combined with mRS 4 for all statistical analyses. Similar results were obtained in analyses when these subjects were combined with mRS of 6.

Ordinal logistic (ordered logit) regression analysis was performed with mRS as the dependent variable and the above clinical characteristics as independent variables. Models with and without hemoglobin were developed to determine whether there was attenuation of the effect of sex on outcome. The percent change in the β coefficient when hemoglobin was added was determined by $\log(OR_{unadjusted}) - \log(OR_{adjusted})/\log(OR_{unadjusted}) \times 100\%$. NIHSS score was log-transformed prior to addition into the model. All numeric variables were expressed as mean ± SD or median and interquartile range (IQR). A level of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using JMP 9.0 Pro and STATA statistical software (release 12, College Station, TX).

Standard protocol approvals, registrations, and patient consents. The local institutional review board approved all aspects of the study.

RESULTS The STOPStroke Study enrolled a total of 741 patients (580 patients at our institution) during the study period. We excluded patients who did not have a discharge diagnosis of stroke (136 patients) and those who were treated with intra-arterial thrombolysis (31), IV thrombolysis (70), or investigational treatments (8). Forty-one of the remaining subjects were lost to follow-up and 20 patients were excluded due to a prestroke mRS score >2. The remaining 274 patients comprised the final study population.

The clinical characteristics of the study cohort are presented in table 1, separated by sex. Compared to men, women were older by an average of 8 years ($p < 0.001$) and were significantly more likely to have a lower mean hemoglobin, by an average of 1.6 g/dL ($p < 0.001$). Women were also less like to have coronary artery disease ($p < 0.01$). At 6 months, women had worse median functional recovery ($p < 0.001$), which is consistent with previous reports.[2,3,8]

Table 2 shows the relationship of clinical characteristics to 6-month outcome, defined by the mRS score. Increased age was associated with more severe functional deficits ($p < 0.001$).[16–18] The NIHSS also predicted 6-month outcome ($p < 0.001$), as did lower hemoglobin level ($p < 0.001$). Dichotomization of hemoglobin into WHO-defined anemia[11] or mean hemoglobin yielded a similar relationship to outcome ($p < 0.001$ for both analyses). Women had a worse outcome compared to men ($p < 0.01$). Elevated blood glucose was associated with worse outcome ($p < 0.01$).[19–21] Viscosity, which is dependent upon hematocrit and fibrinogen, has been reported to be inversely associated with cerebral blood flow,[14,22]

Table 1	Clinical characteristics by sex		
	Male (n = 153)	Female (n = 121)	p
Age, y, mean ± SD	62 ± 14	70 ± 15	<0.001[a]
Nadir hemoglobin, mg/dL, mean ± SD	13.3 ± 1.7	11.7 ± 1.8	<0.001[a]
Acute NIHSS, median (IQR)	4 (2, 9)	5 (3, 12)	0.13
Blood glucose, mg/dL, median (IQR)	117 (106, 139)	126 (109, 151)	0.34
Yield shear stress, cP, mean ± SD	0.088 ± 0.069	0.075 ± 0.064	0.38
Comorbidities, n (%)			
Coronary artery disease	41 (27)	16 (13)	<0.01[a]
Diabetes mellitus	20 (13)	23 (19)	0.18
Hypertension	85 (56)	75 (62)	0.28
Atrial fibrillation	22 (14)	26 (21)	0.12
Smoking	52 (34)	37 (31)	0.55
Charlson comorbidity index, low, n (%)	68 (44)	53 (44)	0.92
Stroke subtype, n (%)			0.73
Small artery	15 (10)	16 (13)	
Large artery	30 (20)	17 (14)	
Cardioembolic	59 (39)	49 (41)	
Other	14 (9)	10 (8)	
Undetermined/unknown	35 (23)	28 (23)	
Median 6-month mRS (IQR)	1 (0, 2)	2 (1, 4)	<0.001[a]

Abbreviations: IQR = interquartile range; mRS = modified Rankin Scale score; NIHSS = NIH Stroke Scale.
[a] Significant.

Table 2

Table 2 Distribution of clinical characteristics according to outcome[a]

	mRS 0 (n = 60)	mRS 1 (n = 83)	mRS 2 (n = 35)	mRS 3 (n = 41)	mRS 4-5 (n = 28)	mRS 6 (n = 27)	Total (n = 274)	p
Age, y, mean ± SD	61 ± 14	63 ± 14	63 ± 14	67 ± 14	74 ± 13	75 ± 13	65 ± 14	<0.001[b]
Female, n (%)	16 (27)	34 (41)	13 (37)	25 (61)	17 (61)	16 (59)	121 (44)	<0.01[b]
Nadir hemoglobin, mg/dL, mean ± SD	13.3 ± 1.8	13.0 ± 1.5	12.5 ± 1.8	12.1 ± 2.1	11.6 ± 2.0	11.6 ± 1.7	12.6 ± 1.9	<0.001[b]
Mean hemoglobin, mg/dL, mean ± SD	14.1 ± 1.7	13.8 ± 1.4	13.3 ± 1.7	13.2 ± 1.6	12.7 ± 1.6	12.5 ± 1.6	13.5 ± 1.7	<0.001[b]
Anemia, WHO definition, n (%)	16 (27)	28 (34)	18 (51)	20 (49)	18 (65)	18 (67)	118 (43)	<0.001[b]
Acute NIHSS, median (IQR)	2 (1, 4)	4 (1, 6)	5 (2, 7)	7 (3, 11)	13 (5, 16)	15 (8, 20)	4 (2, 10)	<0.001[b]
Blood glucose, mg/dL, median (IQR)	116 (105, 138)	116 (103, 140)	116 (105, 137)	127 (114, 159)	137 (123, 170)	136 (107, 161)	121 (107, 145)	<0.01[b]
Yield shear stress, cP, mean ± SD	0.056 ± 0.025	0.100 ± 0.075	0.108 ± 0.072	0.072 ± 0.067	0.063 ± 0.029	0.109 ± 0.125	0.084 ± 0.067	0.33
Comorbidities, n (%)								
Coronary artery disease	13 (22)	11 (13)	7 (20)	12 (29)	7 (25)	7 (25)	57 (21)	0.35
Diabetes mellitus	4 (7)	12 (14)	8 (23)	10 (24)	3 (11)	6 (22)	43 (16)	0.10
Hypertension	34 (57)	40 (48)	22 (63)	25 (61)	18 (64)	21 (78)	160 (58)	0.13
Atrial fibrillation	6 (10)	12 (14)	4 (11)	9 (22)	8 (29)	9 (33)	48 (18)	0.04[b]
Tobacco use	27 (45)	28 (34)	16 (46)	7 (17)	4 (14)	7 (26)	89 (32)	<0.01[b]
Charlson comorbidity index, low, n (%)	32 (53)	42 (51)	13 (37)	16 (39)	12 (43)	6 (22)	121 (44)	0.08
Stroke subtype, n (%)								0.33
Large artery	8 (13)	14 (17)	9 (26)	7 (18)	7 (25)	2 (7)	47 (17)	
Cardioembolic	27 (45)	33 (40)	13 (37)	14 (35)	10 (36)	11 (41)	108 (40)	
Small artery	7 (12)	15 (18)	2 (6)	3 (8)	3 (11)	1 (4)	31 (11)	
Other	7 (12)	6 (7)	3 (9)	2 (5)	4 (14)	2 (7)	24 (9)	
Undetermined/unknown	11 (18)	15 (18)	8 (23)	14 (35)	4 (14)	11 (41)	63 (23)	

Abbreviations: IQR = interquartile range; mRS = modified Rankin Scale score; NIHSS = NIH Stroke Scale.
[a] All statistical analysis was performed with mRS 4 and 5 combined due to the few numbers of subjects with mRS 5 (n = 4).
[b] Significant.

although not with neurologic outcome. In the subset of subjects in whom fibrinogen level was available (n = 80), there was no association between calculated viscosity (YSS[15]) and neurologic outcome.

Figure Ranges of modified Rankin Scale are shown for each hemoglobin quintile (n = 55)

We also evaluated common comorbidities and the relationship to outcome (table 2), and found that higher rates of atrial fibrillation predicted worse recovery (p = 0.04). On the other hand, tobacco use was associated with better outcome (p < 0.01). Other individual comorbidities, a composite index of comorbidity (Charlson index), or stroke subtype were not associated with neurologic outcome.

The figure graphically shows the relationship between neurologic recovery and hemoglobin divided into quintiles. The quintile with the lowest hemoglobin (9.7 g/dL ± 1.0) had a median mRS of 3 (IQR 1, 4), whereas the highest hemoglobin quintile (15.0 g/dL ± 0.5) had a median mRS of 1 (IQR 0, 2) (p <0.001, n = 55 for each quintile). The figure reveals a stepwise, dose-dependent relationship between hemoglobin quintile and functional recovery (p < 0.001). Prior studies have reported a nonlinear U-shaped relationship between admission hematocrit and outcome,[23,24] whereas others did not.[25] We explored
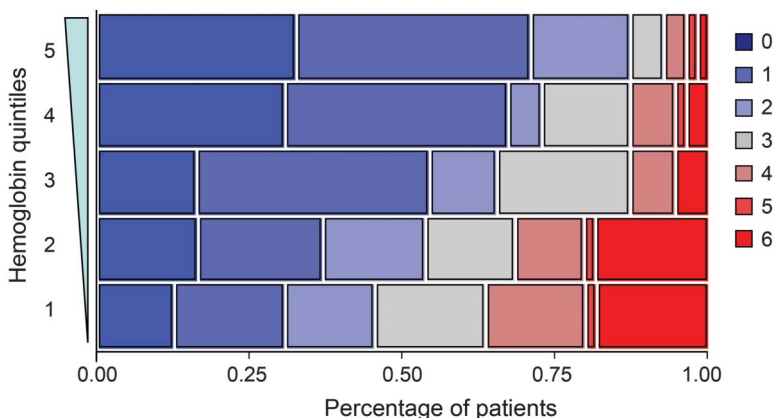
Table 3   Predictors of 6-month modified Rankin Scale score[a]

	Model A (with hemoglobin)		Model B (with hemoglobin)		Model C (without hemoglobin)	
Variable	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	1.04 (1.02–1.06)	<0.001[b]	1.04 (1.02–1.06)	<0.001[b]	1.04 (1.02–1.06)	<0.001[b]
Female sex	1.17 (0.90–1.52)	0.23	1.28 (0.73–2.26)	0.38	1.72 (1.05–2.82)	0.03[b]
Blood glucose	1.00 (1.00–1.01)	0.04[b]	1.00 (1.00–1.01)	0.61	1.00 (1.00–1.01)	0.65
NIHSS[c]	13.4 (7.03–26.3)	<0.001[b]	18.0 (8.95–36.2)	<0.001[b]	19.4 (9.67–38.9)	<0.001[b]
Atrial fibrillation	1.03 (0.77–1.40)	0.83	1.88 (0.93–3.79)	0.08	1.83 (0.91–3.68)	0.09
Tobacco use	0.76 (0.59–0.97)	0.03[b]	0.50 (0.30–0.85)	0.01[b]	0.47 (0.28–0.80)	<0.01[b]
Coronary artery disease			1.48 (0.80–2.75)	0.21	1.66 (0.90–3.06)	0.11
Hypertension			1.17 (0.69–1.98)	0.57	1.26 (0.74–2.12)	0.39
Diabetes mellitus			1.75 (0.85–3.61)	0.13	1.56 (0.76–3.19)	0.22
Stroke subtype						
Large vessel			0.65 (0.26–1.65)	0.36	0.81 (0.32–2.01)	0.65
Cardioembolic			0.42 (0.17–1.00)	0.05	10.48 (0.20–1.13)	0.09
Other			1.19 (0.37–3.87)	0.77	1.67 (0.54–5.12)	0.38
Undetermined			1.36 (0.56–3.30)	0.50	1.66 (0.70–3.98)	0.25
Hemoglobin[d]	0.83 (0.73–0.96)	<0.01[b]	0.85 (0.73–0.98)	0.03[b]	—	—

Abbreviations: CI = confidence interval; NIHSS = NIH Stroke Scale; OR = odds ratio.
[a] Model A includes only variables significant in univariate analysis. Models B and C include the additional variables listed.
[b] Significant.
[c] NIHSS was log transformed prior to the inclusion in the regression model.
[d] OR is for each g/dL increase in hemoglobin content.

this possibility in our cohort by assessing for a quadratic relationship between hemoglobin and outcome, but did not find one ($p = 0.45$).

The independent relationship between hemoglobin and outcome was explored in multivariable ordinal logistic regression (table 3). We first modeled outcome using predictors that were significant in univariate analysis (model A). There was an independent association of hemoglobin with functional recovery ($p < 0.01$), with an adjusted odds ratio (OR) of 0.83 (95% confidence interval [CI] 0.73–0.96) for mRS with each increase in hemoglobin of 1 g/dL. Other independent predictors included age, NIHSS score, blood glucose, and tobacco use. Female sex was not an independent predictor in this model. We obtained similar results when we substituted mean hemoglobin or anemia into the model, although mean hemoglobin exhibited a trend toward significance ($p = 0.06$).

Because hemoglobin might represent a surrogate for comorbid illness, we included all past medical history variables from table 2 and stroke subtype (model B, table 3). Addition of these variables did not alter the independent effect of hemoglobin on outcome ($p = 0.03$), nor the ORs. Similarly, the inclusion of the Charlson comorbidity index (rather than individual past medical history) had no difference in effect. In model B, female sex was not a predictor of outcome ($p = 0.38$).

However, when hemoglobin was withheld from the model (model C, table 3), female sex became a predictor of clinical outcome ($p = 0.03$) with an adjusted OR of 1.72 (95% CI 1.05–2.82). The relative change in the OR for sex after adjustment for hemoglobin was 55%, suggesting an effect of hemoglobin on the sex effect.[9] Age is also recognized as a confounder for the effect of sex on outcome.[8] For illustrative comparison, when age rather than hemoglobin was withheld from the model, female sex had an adjusted OR of 1.70 ($p = 0.051$, 95% CI 0.99–2.93), which corresponds to similar magnitude of change (54%).

In order to explore the effect of hemoglobin and sex in greater detail, we added the interaction term of hemoglobin × sex into the final model. This addition was not significant ($p = 0.30$), nor did it alter the ORs of either term individually. Next, we reasoned that males with low hemoglobin might also have worse outcome, even though this may represent a smaller subset of all subjects. Subgroup analysis of male subjects demonstrated a univariate association of low hemoglobin with worse outcome ($p < 0.01$), which remained so in the multivariable model ($p = 0.03$).

DISCUSSION The results from this study show that hemoglobin level is inversely associated with neurologic outcome after stroke. This association remains significant after adjusting for age, NIHSS score, blood

glucose, stroke subtype, and several common comorbidities. Most intriguingly, our data demonstrate that the well-described effect of female sex on outcome is significantly attenuated after incorporation of hemoglobin level in the model.

Investigation into sex differences in stroke has identified a host of potential contributing factors.[1] Not only do women have a greater incidence of stroke, but they tend to be older at the time of presentation.[8] They also tend to have a higher prevalence of comorbid disease such as atrial fibrillation, and are less likely to receive acute treatment with alteplase.[1] While some of these observations may reflect the consequence of older age at presentation for women,[8] it is unlikely to account for the entirety of the difference.[9] For example, there is some evidence that underlying biological reasons may also play a role, including the differential effect of estrogen on cerebrovascular reactivity and its putative role as a neuroprotectant.[26,27] Our data herein raise another possible mechanism to account for sex differences in stroke outcome. As the major carrier of oxygen, variation in hemoglobin level may influence the degree of recovery in the injured ischemic brain. In turn, this may lead to reduced functional recovery. Intriguingly, in subgroup analysis only, we find hemoglobin is also associated with outcome in males, suggesting that the phenomenon is not limited to females but disproportionately affects them.

A potential confounder to the putative effect of hemoglobin is its association with comorbid disease, which may leverage an indirect penalty on neurologic recovery. We attempted to address this concern by including individual comorbidities and the Charlson comorbidity index into our model, and neither of these variables altered the independent effect of hemoglobin. Nevertheless, other unidentified comorbid factors may underlie the association that we observed with hemoglobin. On the other hand, the fact that sex-based variation itself correlates with outcome suggests that hemoglobin's effect may be independent of comorbid disease. Of course, our data do not address the question of a causative role for hemoglobin, which would require direct manipulation in a model system. Alternatively, Mendelian randomization analysis[28] of hemoglobin single nucleotide polymorphisms (SNPs) could potentially provide support for a direct influence on stroke outcome.

Prior studies evaluating red blood cell physiology in stroke have focused on high hematocrit level and its effect on hemorheology.[29] In patients, viscosity has been reported to be inversely associated with cerebral blood flow,[14,30] but it is less clear how that affects overall net cerebral oxygen delivery.[31] The role of viscosity is further clouded by negative trials of hemodilution.[32] We explored the effect of viscosity on neurologic outcome in a subset of subjects with available laboratory values; however, we did not find a significant association. Some studies have identified a U-shaped relationship between hematocrit and outcome[23]; others have not.[25] Our data did not identify a U-shaped relationship, although some of the differences may be due to differences in the timing of blood draw. On the other hand, we note that our cohort did not contain subjects with a highly elevated hematocrit (i.e., ~50%), which may be the population most susceptible to poor outcome. Further studies are necessary to sort out the pathophysiologic mechanism that may account for our findings.

There are limitations to our analysis. This study was prospective and required informed consent for participation, and therefore might be biased toward patients with less severe stroke (median NIHSS 5). The study also used 6-month outcome by phone, which may also bias toward less severe stroke, limiting the generalizability of our findings in severe stroke populations. Secondly, although we adjusted for potential confounding comorbidities, it remains possible that we could not account for unrecognized ones that may influence the effect of hemoglobin on outcome.

Our data demonstrate that lower hemoglobin is independently associated with worse neurologic outcome and hemoglobin attenuates the independent effect of female sex on outcome. As the key oxygen-carrying molecule in the body, hemoglobin may play a direct or indirect role in influencing brain recovery and neurologic function. The association between female sex and hemoglobin identifies a new dimension to understanding why women tend to experience worse outcome after stroke. Future studies that explore sex differences should include evaluation of the role of hemoglobin.

AUTHOR CONTRIBUTIONS

Dr. Kimberly: study concept and design, acquisition of data, analysis and interpretation, statistical analysis, drafting of the manuscript. Dr. Lima: acquisition of data, analysis and interpretation, critical revision of the manuscript. Ms. O'Connor: drafting and critical revision of the manuscript. Dr. Furie: analysis and interpretation of data, critical revision of the data, study supervision.

DISCLOSURE

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