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ORIGINAL RESEARCH

Hemoglobin Concentration and Clinical Outcomes After Acute Ischemic Stroke or Transient Ischemic Attack

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BACKGROUND: Anemia or low hemoglobin can increase the risk of stroke. However, the association between hemoglobin and outcomes after stroke is uncertain. In this study, we aimed to investigate the association between hemoglobin and clinical outcomes, including mortality, poor functional outcome, stroke recurrence, and composite vascular events at 1 year.

METHODS AND RESULTS: We included the patients diagnosed with acute ischemic stroke or transient ischemic attack from the Third China National Stroke Registry. We used the Cox model for mortality, stroke recurrence, and composite vascular events and the logistic model for the poor functional outcome to examine the relationship between hemoglobin and clinical outcomes. In addition, we used the restricted cubic spline to evaluate the nonlinear relationship. This study included 14 159 patients with acute ischemic stroke or transient ischemic attack. After adjusted for potential cofounders, both anemia and high hemoglobin were associated with the higher risk of mortality (hazard ratio [HR], 1.73; 95% CI, 1.39–2.15; HR, 2.71; 95% CI, 1.95–3.76) and poor functional outcome (odds ratio [OR], 1.36; 95% CI, 1.18–1.57; OR, 1.42; 95% CI, 1.07–1.87). High hemoglobin, but not anemia, increased the risk of stroke recurrence (HR, 1.37; 95% CI, 1.05–1.79) and composite vascular events (HR, 1.41; 95% CI, 1.08–1.83). There was a U-shaped relationship between hemoglobin and mortality and poor functional outcome.

CONCLUSIONS: Abnormal hemoglobin was associated with a higher risk of all-cause mortality, poor functional outcome, stroke recurrence, and composite vascular events. More well-designed clinical studies are needed to confirm the relationship between hemoglobin and clinical outcomes after stroke.

Key Words: anemia ■ functional outcome ■ hemoglobin ■ mortality ■ recurrence ■ stroke

Stroke is a leading cause of death and disability worldwide, especially in low-income and middle-income countries. It was estimated that China had the highest age-standardized incidence of stroke (226 per 100 000) worldwide in 2017.[1] Although the age-standardized disability-adjusted life-years lost caused by stroke decreased by 33.1% from 1990 to 2017, the absolute number of all-age disability-adjusted life-years increased by 46.8% in China.[2,3] Identifying modifiable risk factors is of paramount importance to reduce stroke burden. Previous studies have indicated that abnormal hemoglobin concentration can increase the incidence of stroke.[4,5] In addition, low hemoglobin has an effect on enlarging the infarct volume and accelerating the velocity of infarct growth.[6] Anemia is common in patients with stroke, with a prevalence of 15% to 29%.[7] Whether hemoglobin concentration is associated with the outcomes in patients with stroke remains to be studied. A recent meta-analysis suggested that patients with anemia had a higher risk of mortality after stroke.[8] However, most of the studies are focused on the effect of low hemoglobin, and the influence of high hemoglobin on mortality after stroke is still controversial. Some studies found higher hemoglobin increased

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CLINICAL PERSPECTIVE

What Is New?

- The relationships between hemoglobin level and different outcomes are varied in patients with ischemic stroke or transient ischemic attack.
- Both anemia and high hemoglobin levels were associated with a high risk of 1-year all-cause mortality and poor functional outcome in patients with ischemic stroke or transient ischemic attack.
- A high hemoglobin level, but not anemia, was associated with an increased risk of stroke recurrence and combined vascular diseases.

What Are the Clinical Implications?

- Measurement of hemoglobin level might be helpful for identifying patients at high risk of poor outcomes.
- Future work is needed to confirm the relationship between hemoglobin and outcomes after ischemic stroke.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
NIHSS	National Institutes of Health Stroke Scale

the risk of mortality,[9,10] but others[8] reported null association. Moreover, the impact of hemoglobin concentration on functional outcome and recurrence after acute ischemic stroke (AIS) is not yet sufficiently elucidated.

In this study, we aimed to estimate the association between hemoglobin concentration and clinical outcomes after AIS or transient ischemic attack (TIA), including all-cause mortality, poor functional outcome, stroke recurrence, and composite vascular events at 1 year.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We retrospectively analyzed the data collected in the CNSR-III (Third China National Stroke Registry). The details of the CNSR-III have been published elsewhere.[11] Briefly, CNSR-III is a nationwide, prospective stroke registry in China. Patients aged ≥18 years who presented with AIS or TIA within 7 days of symptom onset were consecutively enrolled from 201 hospitals in China between August 2015 and March 2018. All patients with AIS were diagnosed according to the World Health Organization criteria[12] and confirmed by magnetic resonance imaging or brain computed tomography. TIA is defined as rapid onset of a focal neurological deficit attributed to focal brain or retinal ischemia lasting <24 hours, without evidence of associated acute focal infarction on imaging.[11] A total of 15 166 patients were enrolled in the registry. This study was approved by the ethics committee of Beijing Tiantan Hospital and participant hospitals. Informed consent was obtained from the patients or their legally authorized representatives. In this study, patients without baseline hemoglobin, with sickle cell disease, cancer (including active solid tumor, any history of cancer, and malignant hematological disorders), renal dysfunction, gastrointestinal ulcer or bleeding, and pregnancy or 6 weeks postpartum at baseline were excluded. In addition, patients who were lost to follow-up at 1 year were also excluded. Finally, a total of 14 159 patients were included.

Data Collection

In this study, all data were collected by trained research coordinators at admission or discharge. The demographic information, medical history, risk factors, prestroke modified Rankin Scale score, and clinical therapies (including tissue plasminogen activator, mechanical thrombectomy, and secondary stroke preventive medication) were collected through medical records or face-to-face interviews. The etiology of stroke was assessed according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria. The severity of stroke was estimated using the National Institutes of Health Stroke Scale (NIHSS), which was recorded by a face-to-face interview at admission.

Blood tests were routinely executed within 24 hours of admission, and the hemoglobin concentration was measured at admission. Patients were followed up by research coordinators at 3 months, 6 months, and 1 year after symptom onset and annually afterward. During the follow-up period, the events including mortality, cardiovascular events, and modified Rankin Scale scores were collected. In this study, the outcomes included all-cause mortality, poor functional outcome, stroke recurrence, and composite vascular events at 1 year. The death information was obtained from the relatives of the patients and was either confirmed by death certification from the attended hospital or the local citizen registry. The stroke survivors were queried about the cardiovascular events and then were confirmed by the treating hospital, and other suspected recurrent vascular events without hospitalization were judged by an independent end

point judgment committee. Poor functional outcome was defined as modified Rankin Scale scores ranging from 3 to 6 at 1 year. The stroke recurrence was defined as a new ischemic stroke or hemorrhagic stroke within 1 year after symptom onset. Composite vascular events included myocardial infarction, recurrent stroke, and vascular death. The definitions of the aforementioned outcomes were consistent with those previously described in the CNSR-III protocol.[11]

Statistical Analysis

We divided the participants into the following 3 groups according to World Health Organization criteria and previous studies: anemia (hemoglobin <12 g/dL for women, hemoglobin <13 g/dL for men), normal hemoglobin (hemoglobin 12–15.5 g/dL for women, hemoglobin 13–17 g/dL for men), and high hemoglobin (hemoglobin >15.5 g/dL for women, hemoglobin >17 g/dL for men).[8,13] Continuous variables were presented as median (interquartile range [IQR]) as a result of skewed distribution and were compared by nonparametric Wilcoxon or Kruskal–Wallis test. Categorical variables were presented numbers (percentages) and were compared by chi-square test or the Fisher exact test. We performed tests for linear trend to compare the baseline characteristics across the 3 groups.

After excluding the patients who were lost to follow-up, the patients with complete follow-up data were analyzed. We used the Kaplan–Meier method to evaluate the cumulative hazards of mortality, stroke recurrence, and composite vascular events within 1 year. The differences across hemoglobin levels were assessed by the log-rank test. We used the Cox proportional hazards model to estimate

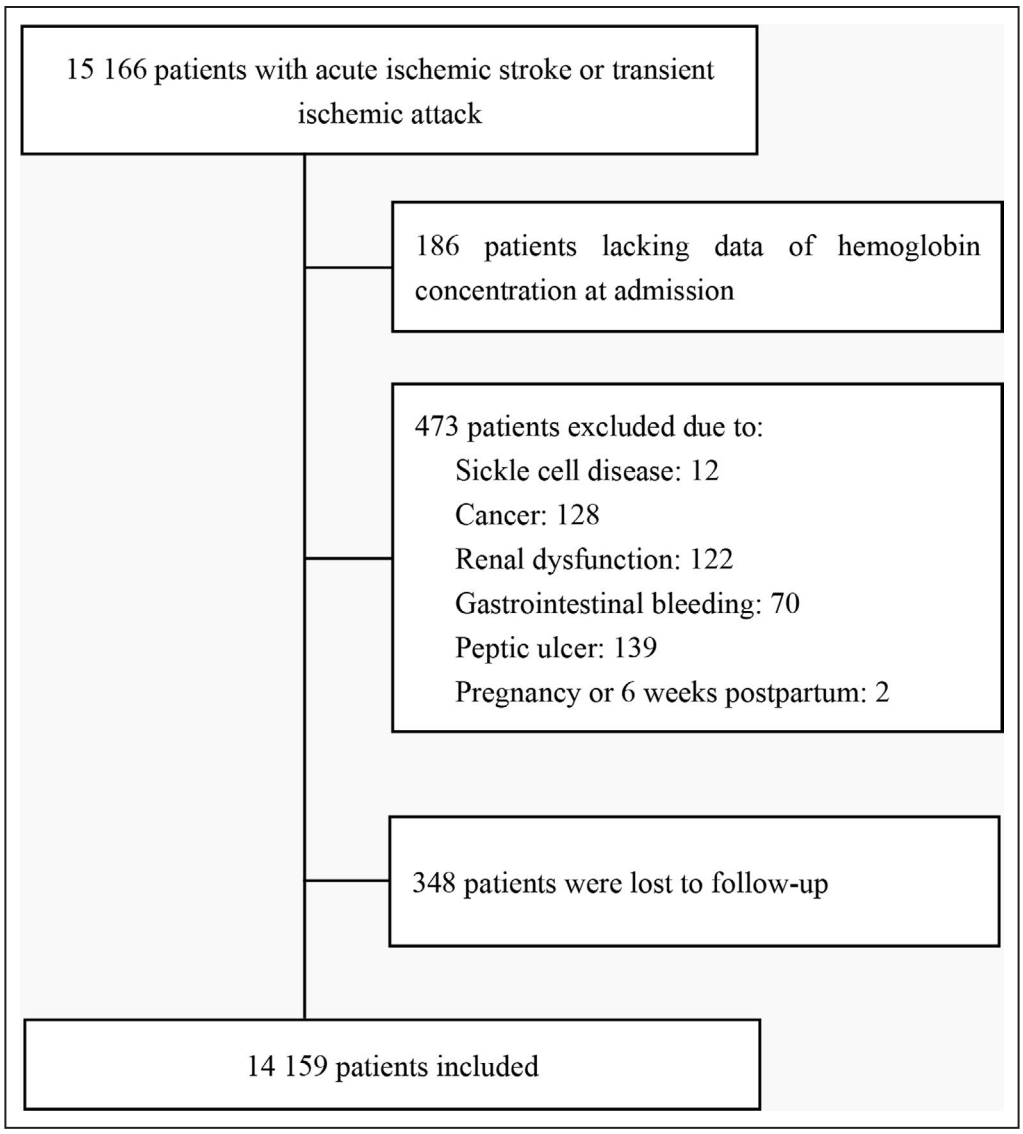

Figure 1. Flowchart of patient selection.

Table 1. Baseline Characteristics Between Included and Excluded Patients

Characteristics	Total (N=15 166)	Excluded (n=1007)	Included (n=14 159)	*P* value
Hemoglobin, g/dL	14.1 (13.0–15.2)	13.8 (12.7–15.1)	14.1 (13.0–15.2)	<0.001
Age, y	63.0 (54.0–70.0)	64.0 (56.0–72.0)	62.0 (54.0–70.0)	<0.001
Female sex	4802 (31.7)	292 (29.0)	4510 (31.9)	0.059
BMI, kg/m^2	24.5 (22.6–26.6)	24.2 (22.5–26.1)	24.5 (22.6–26.6)	0.001
Current smoker	4752 (31.3)	302 (30.0)	4450 (31.4)	0.342
Current drinking	2465 (16.3)	164 (16.3)	2301 (16.3)	0.977
Medical history				
Hypertension	9494 (62.6)	661 (65.6)	8833 (62.4)	0.039
Diabetes	3510 (23.1)	242 (24.0)	3268 (23.1)	0.489
Dyslipidemia	1191 (7.9)	97 (9.6)	1094 (7.7)	0.029
Stroke or TIA	3675 (24.2)	240 (23.8)	3435 (24.3)	0.759
Coronary heart disease	1608 (10.6)	123 (12.2)	1485 (10.5)	0.085
Atrial fibrillation	1019 (6.7)	91 (9.0)	928 (6.6)	0.002
Heart failure	94 (0.6)	16 (1.6)	78 (0.6)	<0.001
Peripheral vascular disease	118 (0.8)	16 (1.6)	102 (0.7)	0.002
Infection within 2 wk	450 (3.0)	40 (4.0)	410 (2.9)	0.052
Arthritis	329 (2.2)	31 (3.1)	298 (2.1)	0.040
Index event				0.015
Ischemic stroke	14 146 (93.3)	958 (95.1)	13 188 (93.1)	
TIA	1020 (6.7)	49 (4.9)	971 (6.9)	
Stroke etiology				0.003
Large-artery atherosclerosis	3856 (25.4)	287 (28.5)	3569 (25.2)	
Cardioembolism	917 (6.1)	81 (8.0)	836 (5.9)	
Small-vessel occlusion	3165 (20.9)	184 (18.3)	2981 (21.1)	
Other determined etiology	182 (1.2)	11 (1.1)	171 (1.2)	
Undetermined etiology	7046 (46.5)	444 (44.1)	6602 (46.6)	
Medication in hospital				
Cholesterol-lowering agents	14 506 (96.4)	944 (95.6)	13 562 (96.4)	0.154
Hypoglycemic agents	3792 (25.2)	248 (25.1)	3544 (25.2)	0.946
Antihypertensive agents	7000 (46.5)	491 (49.7)	6509 (46.3)	0.037
Antiplatelet agents				
No	440 (2.9)	52 (5.3)	388 (2.8)	<0.001
Mono antiplatelet	6445 (42.8)	486 (49.2)	5959 (42.4)	
Dual antiplatelet	8168 (54.3)	450 (45.6)	7718 (54.9)	
Anticoagulant agents	1546 (10.3)	124 (12.6)	1422 (10.1)	0.015
rt-PA intravenous thrombolytic	1266 (8.4)	91 (9.0)	1175 (8.3)	0.413
Mechanical thrombectomy	39 (0.3)	1 (0.1)	38 (0.3)	0.306
Recanalized through mechanical thrombectomy	35 (89.7)	1 (100.0)	34 (89.5)	0.732
Prestroke mRS scores 2–5	1344 (8.9)	108 (10.7)	1236 (8.7)	0.031
NIHSS score at admission	3 (1–6)	3 (2–6)	3 (1–6)	<0.001

Data are provided as median (interquartile range) or number (percentage). BMI indicates body mass index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; and TIA, transient ischemic attack.

the association between hemoglobin concentration and clinical outcomes, including all-cause mortality, stroke recurrence, and composite vascular events at 1 year. The proportionality assumption was statistically assessed by scaled Schoenfeld residuals, and we found no violation of the assumptions. For the poor functional outcome at 1 year, the logistic regression model was used. The hazard ratio (HR) with 95% CI for the Cox regression model and odds ratio (OR) with 95% CI for the logistic regression model were calculated with the normal group as reference. Because patients in the current study were distributed

Table 2. Baseline Characteristics According to Hemoglobin Groups

Characteristics	Total (N=14 159)	Hemoglobin groups			*P* value for trend
		Anemia (n=2086)	Normal hemoglobin (n=11 538)	High hemoglobin (n=535)	
Age, y	62.0 (54.0–70.0)	68.0 (60.0–76.0)	62.0 (54.0–69.0)	57.0 (49.0–65.0)	<0.001
Female sex	4510 (31.9)	889 (42.6)	3515 (30.5)	106 (19.8)	<0.001
BMI, kg/m^2	24.5 (22.6–26.6)	23.7 (21.5–25.7)	24.6 (22.9–26.7)	25.2 (23.3–27.3)	<0.001
Current smoker	4450 (31.4)	441 (21.1)	3779 (32.8)	230 (43.0)	<0.001
Current alcohol drinking	2301 (16.3)	203 (9.7)	1966 (17.0)	132 (24.7)	<0.001
Medical history					
Hypertension	8833 (62.4)	1305 (62.6)	7160 (62.1)	368 (68.8)	0.202
Diabetes	3268 (23.1)	523 (25.1)	2648 (23.0)	97 (18.1)	0.001
Dyslipidemia	1094 (7.7)	152 (7.3)	901 (7.8)	41 (7.7)	0.504
Stroke or TIA	3435 (24.3)	564 (27.0)	2765 (24.0)	106 (19.8)	<0.001
Coronary heart disease	1485 (10.5)	275 (13.2)	1160 (10.1)	50 (9.4)	<0.001
Atrial fibrillation	928 (6.6)	188 (9.0)	703 (6.1)	37 (6.9)	<0.001
Heart failure	78 (0.6)	27 (1.3)	46 (0.4)	5 (0.9)	<0.001
Peripheral vascular disease	102 (0.7)	19 (0.9)	79 (0.7)	4 (0.8)	0.361
Infection within 2 wk	410 (2.9)	76 (3.6)	320 (2.8)	14 (2.6)	0.040
Arthritis	298 (2.1)	45 (2.2)	247 (2.1)	6 (1.1)	0.371
Index event					
Ischemic stroke	13 188 (93.1)	1945 (93.2)	10 729 (93.0)	514 (96.1)	0.276
TIA	971 (6.9)	141 (6.8)	809 (7.0)	21 (3.9)	
Stroke etiology					
Large-artery atherosclerosis	3569 (25.2)	529 (25.4)	2905 (25.2)	135 (25.2)	0.997
Cardioembolism	836 (5.9)	155 (7.4)	649 (5.6)	32 (6.0)	
Small-vessel occlusion	2981 (21.1)	371 (17.8)	2505 (21.7)	105 (19.6)	
Other determined etiology	171 (1.2)	47 (2.3)	113 (1.0)	11 (2.1)	
Undetermined etiology	6602 (46.6)	984 (47.2)	5366 (46.5)	252 (47.1)	
Medication in hospital					
Cholesterol-lowering agents	13 562 (96.4)	1987 (95.9)	11 059 (96.5)	516 (97.2)	0.084
Hypoglycemic agents	3544 (25.2)	500 (24.1)	2901 (25.3)	143 (26.9)	0.141
Antihypertensive agents	6509 (46.3)	904 (43.6)	5303 (46.3)	302 (56.9)	<0.001
Antiplatelet agents					
No	388 (2.8)	69 (3.3)	303 (2.6)	16 (3.0)	0.793
Mono antiplatelet	5959 (42.4)	902 (43.5)	4805 (41.9)	252 (47.5)	
Dual antiplatelet	7718 (54.9)	1102 (53.2)	6353 (55.4)	263 (49.5)	
Anticoagulant agents	1422 (10.1)	236 (11.4)	1124 (9.8)	62 (11.7)	0.224
rt-PA	1175 (8.3)	189 (9.1)	940 (8.2)	46 (8.6)	0.296
Mechanical thrombectomy	38 (0.3)	10 (0.5)	28 (0.2)	0 (0.0)	0.022
Recanalized through mechanical thrombectomy	34 (89.5)	7 (70.0)	27 (96.4)	…	0.019
Prestroke mRS scores 2–5	1236 (8.7)	207 (9.9)	975 (8.5)	54 (10.1)	0.208
NIHSS score at admission	3 (1–6)	3 (2–6)	3 (1–6)	3 (1–6)	<0.001

Data are provided as median (interquartile range) or number (percentage). BMI indicates body mass index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; and TIA, transient ischemic attack.

in 201 hospitals, the hospitals were added as clusters in the model, and the robust sandwich variance estimator was used to deal with the correlations. Variables were adjusted in the multivariable analyses if recognized as traditional predictors for stroke recurrence or associated with hemoglobin level in the

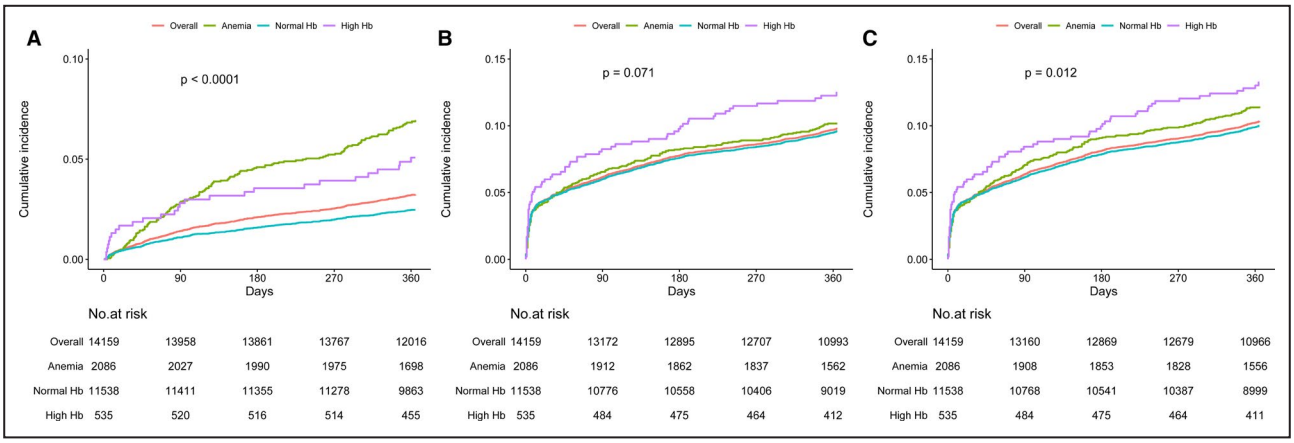

Figure 2. Kaplan–Meier curves for clinical outcomes.
A, Kaplan–Meier curve for all-cause mortality within 1-year. **B**, Kaplan–Meier curve for stroke recurrence within 1 year. **C**, Kaplan–Meier curve for composite vascular event within 1 year. Hb indicates hemoglobin.

univariate analysis with $P<0.2$. A total of 4 models were fitted. In model 1, no covariate was included. In model 2, age and sex were adjusted. In model 3, age, sex, disease history (diabetes, hypertension, stroke or TIA, coronary heart disease, heart failure, atrial fibrillation), prestroke dependency (modified Rankin Scale scores 2–5), smoking, drinking, body mass index, TOAST, index event, infection within 2 weeks

Table 3. Hazard Ratios or Odds Ratios (95% CIs) for Outcomes According to Hemoglobin Groups

Outcomes	Anemia	Normal hemoglobin	High hemoglobin
Death within 1 y			
n (%)	144 (6.9)	284 (2.5)	27 (5.1)
Model 1	2.86 (2.33–3.51)	Reference	2.08 (1.42–3.05)
Model 2	1.92 (1.55–2.38)	Reference	2.97 (2.02–4.36)
Model 3	1.71 (1.37–2.13)	Reference	2.79 (1.96–3.98)
Model 4	1.73 (1.39–2.15)	Reference	2.71 (1.95–3.76)
mRS scores 3–6 at 1 y*			
n (%)	421 (20.2)	1356 (11.8)	73 (13.6)
Model 1	1.90 (1.62–2.22)	Reference	1.19 (0.92–1.53)
Model 2	1.42 (1.23–1.65)	Reference	1.57 (1.23–2.00)
Model 3	1.35 (1.17–1.56)	Reference	1.44 (1.09–1.91)
Model 4	1.36 (1.18–1.57)	Reference	1.42 (1.07–1.87)
Stroke recurrence within 1 y			
n (%)	209 (10.0)	1097 (9.5)	66 (12.3)
Model 1	1.06 (0.91–1.25)	Reference	1.32 (0.99–1.78)
Model 2	0.98 (0.83–1.15)	Reference	1.44 (1.07–1.92)
Model 3	0.95 (0.81–1.13)	Reference	1.38 (1.05–1.81)
Model 4	0.94 (0.80–1.11)	Reference	1.37 (1.05–1.79)
Composite vascular events within 1 y			
n (%)	235 (11.3)	1144 (9.9)	70 (13.1)
Model 1	1.15 (0.98–1.34)	Reference	1.35 (1.00–1.81)
Model 2	1.05 (0.89–1.22)	Reference	1.47 (1.10–1.96)
Model 3	1.02 (0.88–1.20)	Reference	1.41 (1.07–1.85)
Model 4	1.01 (0.86–1.18)	Reference	1.41 (1.08–1.83)

Model 1: unadjusted model. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, disease history (diabetes, hypertension, stroke or TIA, coronary heart disease, heart failure, atrial fibrillation), prestroke dependency, smoking, drinking, body mass index, stroke etiology, index event, infection within 2 weeks before admission, and The National Institutes of Health Stroke Scale score at admission. Model 4: adjusted for variables in model 3, plus mechanical thrombectomy, antihypertensive agents, anticoagulant agents, and antiplatelet agents. mRS indicates modified Rankin Scale.
*Odds ratios were used for mRS scores 3–6.

before admission, and NIHSS score at admission were adjusted. In model 4, the covariates in model 3 and treatments including mechanical thrombectomy, antihypertensive agents, anticoagulant agents, and antiplatelet agents (no, mono antiplatelet, dual antiplatelet) were adjusted. Subgroup analysis was performed according to sex, age, NIHSS score, and etiology of stroke with an interaction test. Moreover, we used the restricted cubic splines with 5 knots at the 5th, 25th, 50th, 75th, and 95th centiles to evaluate the nonlinear relationship between hemoglobin concentration and clinical outcomes after adjusting all potential covariates. The nonlinearity of the dose response was tested by Wald statistics.

All analyses were performed using SAS version 9.4 software (SAS Institute, Inc., Cary, NC) and R version 3.5.1. All tests were 2 tailed, and $P<0.05$ was assumed to be of statistical significance.

RESULTS

After excluding the ineligible patients, 14 159 patients with AIS or TIA were included in this study. The detail of the inclusion of patients is shown in Figure 1. Patients included in the current study and those excluded were largely comparable (Table 1). Among the 14 159 patients included in the analysis, the median age was 62.0 years (IQR, 54.0–70.0 years), 31.8% were female patients, and 62.4% patients had hypertension at baseline. Table 2 shows the baseline characteristics of the patients by groups of hemoglobin concentrations. The mean hemoglobin concentration was 14.6±1.5 g/dL for men and 13.0±1.4 g/dL for women. The prevalence of anemia was 14.7% in the total population. Compared with men, the prevalence of anemia was higher in women (19.7% versus 12.4%; $P<0.001$). Compared with the high level of hemoglobin,

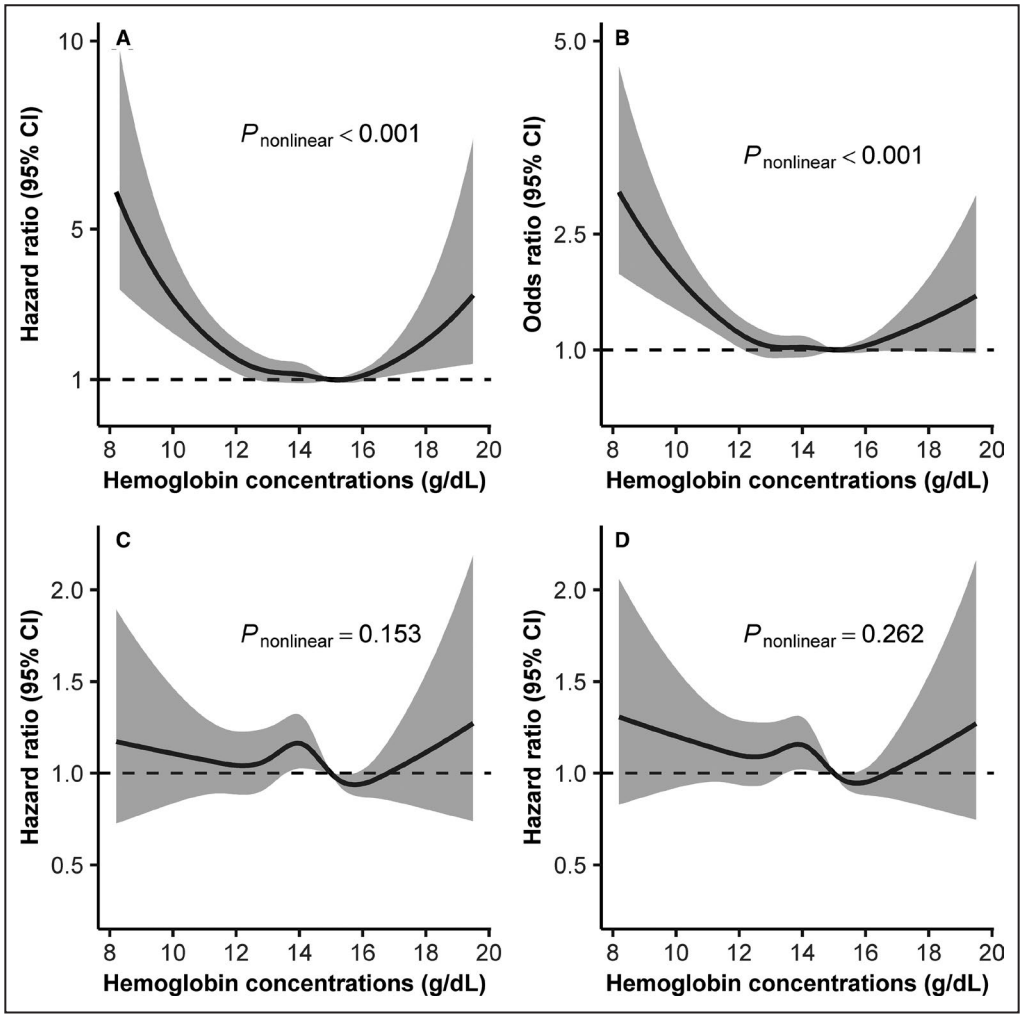

Figure 3. Association between hemoglobin and clinical outcomes.
A, Association between hemoglobin and all-cause mortality. **B**, Association between hemoglobin and poor functional outcome (modified Rankin Scale scores 3–6). **C**, Association between hemoglobin and stroke recurrence. **D**, Association between hemoglobin and composite vascular events.

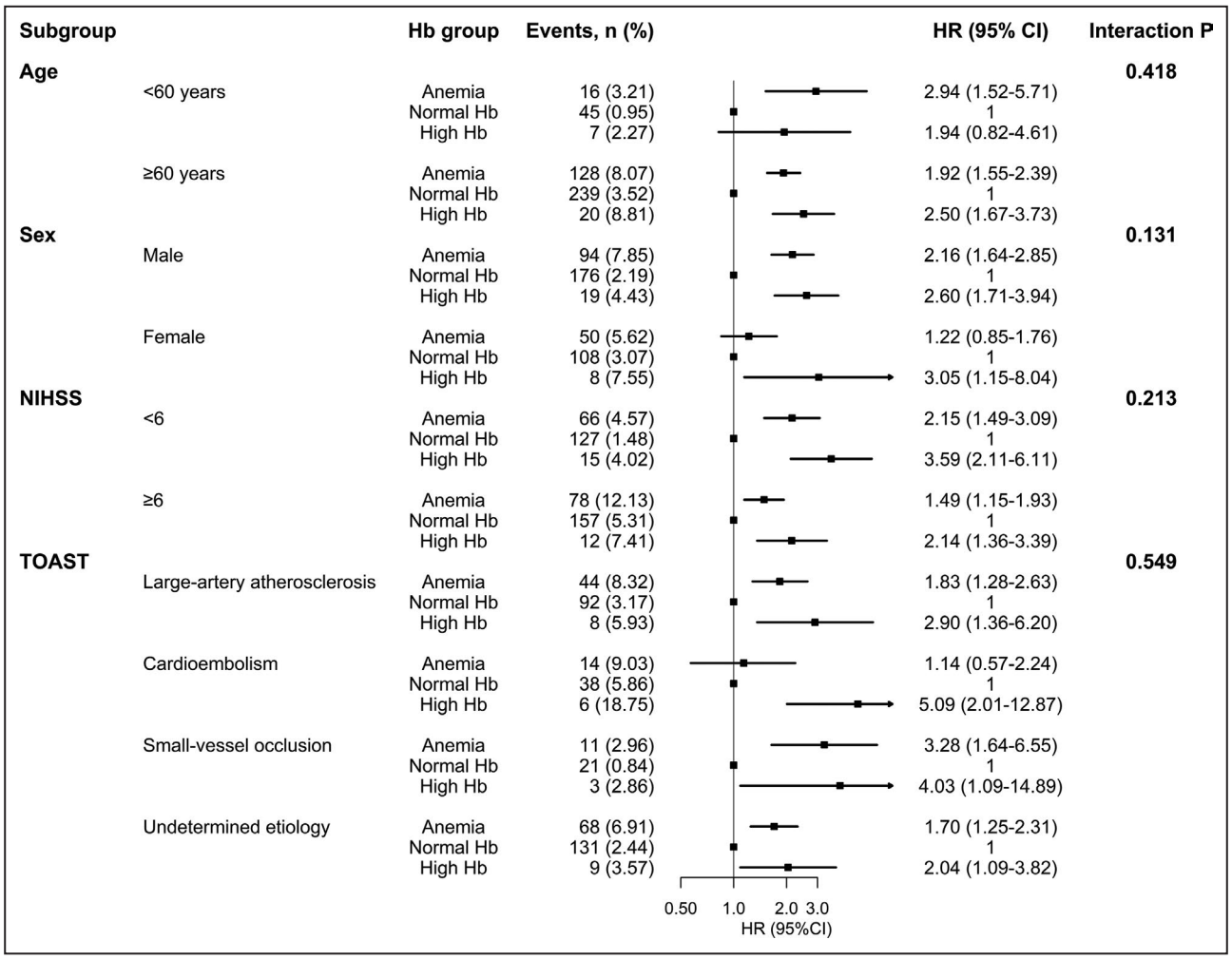

Figure 4. Subgroup analysis of association between hemoglobin groups and all-cause mortality.
Because the number of another determined etiology was small, the corresponding CI was extremely broad and the effects were not displayed. Hb indicates hemoglobin; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

the patients with anemia were more likely to be women and older, but less likely to be smokers or drinkers. Moreover, the prevalence of medical history was higher in the patients with anemia, such as diabetes, history of stroke or TIA, coronary heart disease, atrial fibrillation, and heart failure.

Hemoglobin and Clinical Outcome

There were 1850 (13.1%) patients with poor functional outcome, of whom 455 (3.2%) died within 1 year. In addition, 1372 (9.7%) and 1449 (10.2%) patients experienced recurrent stroke and composite vascular events, respectively. Figure 2 depicts the cumulative hazards of mortality, recurrence, and composite vascular events by hemoglobin. The risk of mortality, recurrence, and composite vascular events was higher in patients with anemia and elevated hemoglobin, although it was not statistically significant for stroke recurrence (P=0.071).

Table 3 demonstrates the unadjusted and adjusted association between hemoglobin and clinical outcomes. The unadjusted regression models (model 1) suggested that both anemia (HR, 2.86; 95% CI, 2.33–3.51) and high hemoglobin (HR, 2.08; 95% CI, 1.42–3.05) were associated with a higher risk of 1-year mortality. The patients with anemia, but not elevated hemoglobin, had a higher risk of poor functional outcome compared with normal hemoglobin. When adjusted for potential covariates, patients with anemia and high hemoglobin were significantly associated with increased risk of mortality and poor functional outcome when compared with patients with normal hemoglobin. In the fully adjusted model (model 4), the adjusted HR for mortality was 1.73 (95% CI, 1.39–2.15) for anemia and 2.71 (95% CI, 1.95–3.76) for high hemoglobin; the adjusted OR for poor functional outcome was 1.36 (95% CI, 1.18–1.57) for anemia and 1.42 (95% CI, 1.07–1.87) for high hemoglobin.

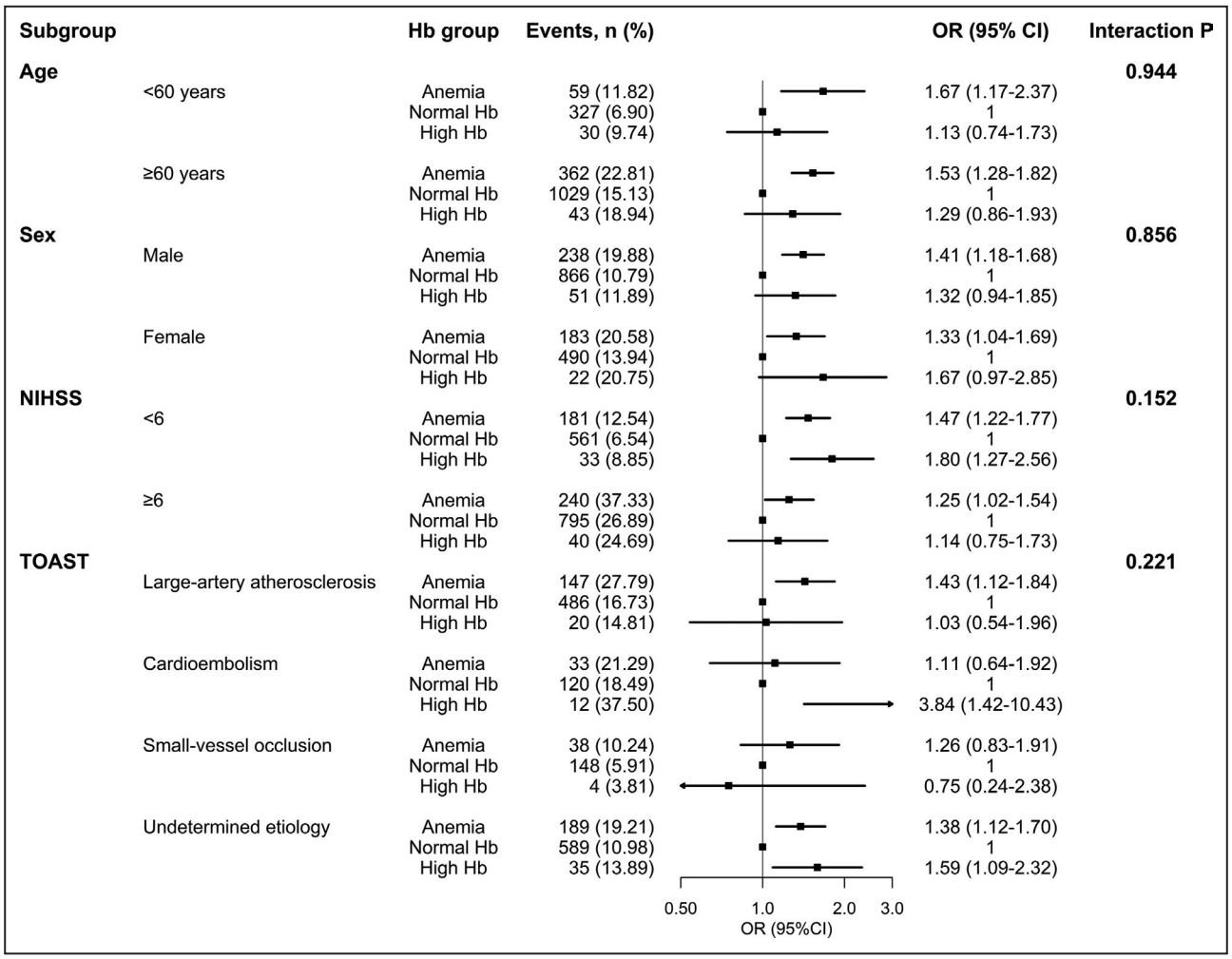

Figure 5. Subgroup analysis of association between hemoglobin groups and poor functional outcome (modified Rankin Scale scores 3–6).

Because the number of another determined etiology was small, the corresponding CI was extremely broad and the effects were not displayed. Hb indicates hemoglobin; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

As for the stroke recurrence and composite vascular events, the unadjusted models suggested no association with hemoglobin level. However, when adjusted for the potential covariates, the hazard of stroke recurrence was significantly higher in the group with elevated hemoglobin (HR, 1.37; 95% CI, 1.05–1.79), but not for anemia. Similarly, after adjusted for all covariates, the hazard of composite vascular events became significant for high hemoglobin (HR, 1.41; 95% CI, 1.08–1.83).

Figure 3 shows the nonlinear relationship between baseline hemoglobin and clinical outcomes. The relationship between hemoglobin and mortality and poor functional outcome was U shaped. The relationship between hemoglobin and mortality and poor functional outcome was negative before 15 g/dL and became positive when hemoglobin was >15 g/dL. There existed a significantly nonlinear association between hemoglobin and mortality and poor functional outcome (both *P* for nonlinear <0.05). However, we did not find evidence of the nonlinear association between hemoglobin and recurrent stroke and composite vascular events (*P* values for nonlinear=0.153 and 0.262, respectively).

Subgroup Analysis

HRs for mortality, recurrent stroke, and composite vascular events and ORs for poor functional outcome by sex, age, NIHSS score, and etiology of stroke are shown in Figures 4 through 7. After adjusting for all potential confounding variables, the hazards or odds of mortality, poor functional outcome, recurrent stroke, and composite vascular events were not modified by sex, age, NIHSS score, and etiology of stroke (all *P* values for interaction >0.05).

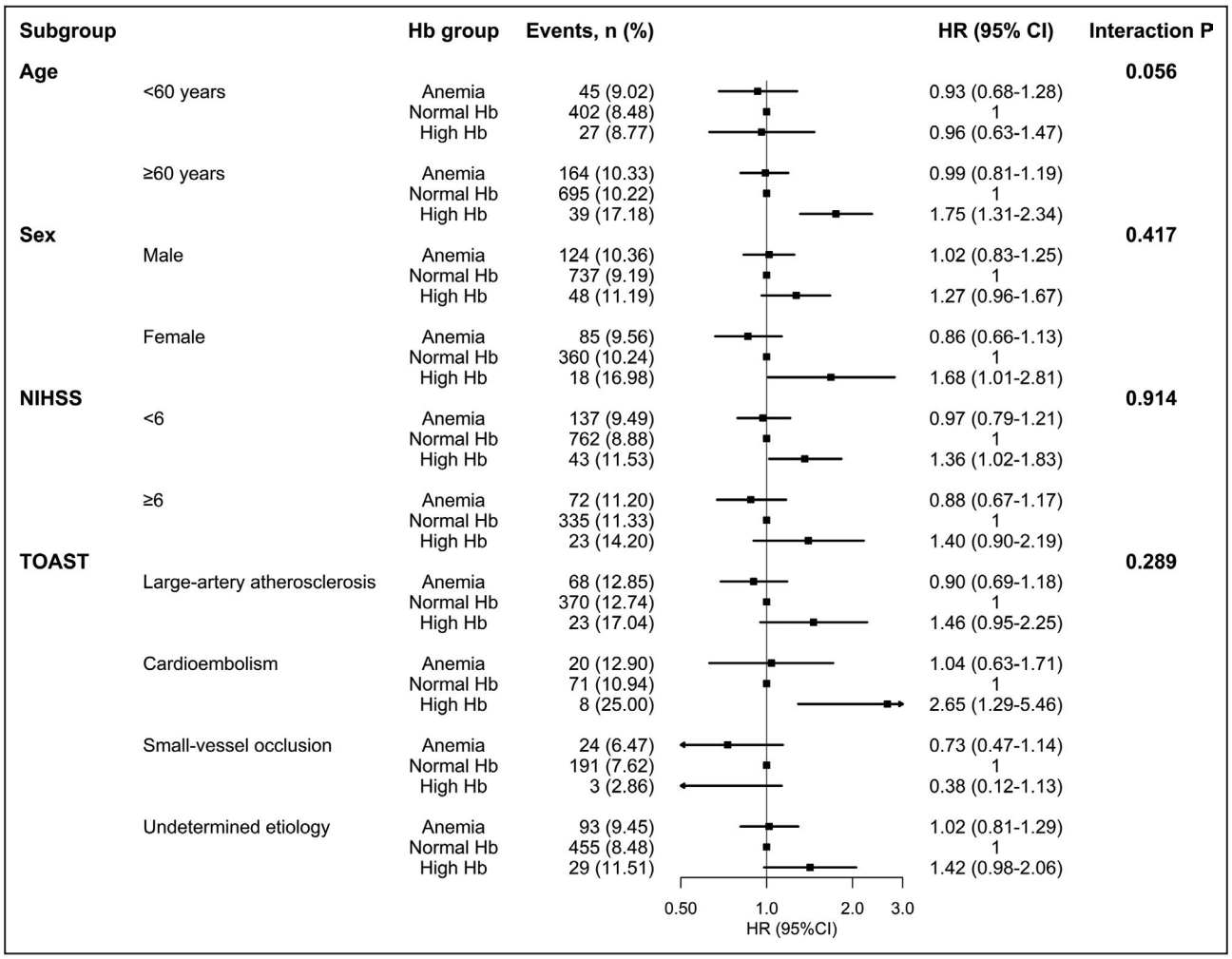

Figure 6. Subgroup analysis of association between hemoglobin groups and stroke recurrence.
Because the number of another determined etiology was small, the corresponding CI was extremely broad and the effects were not displayed. Hb indicates hemoglobin; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

DISCUSSION

In this large cohort of AIS and TIA, we found that compared with normal hemoglobin, both the lower hemoglobin and the higher hemoglobin had increased risk of all-cause mortality and poor functional outcome at 1 year. However, interesting, only the higher hemoglobin was associated with recurrent stroke and composite vascular events, and no evidence was found on the lower hemoglobin. The dose–response plots indicated that the association between hemoglobin and mortality and poor functional outcome at 1 year was U shaped.

Some studies have revealed that anemia at admission is related to mortality in patients with stroke. A recent meta-analysis, including 8 studies, suggested that anemia was associated with a higher risk of mortality in ischemic stroke (the pooled OR, 1.97; 95% CI, 1.57–2.47).[8] Our study was consistent with this result. However, the association between the high level of hemoglobin and mortality in ischemic stroke is contradictory. From a UK Regional Stroke Register, the patients with ischemic stroke were divided into 3 groups by hemoglobin concentration, including anemia, normal, and elevated hemoglobin groups, and no association was found between the elevated hemoglobin and higher mortality at 1 year both in men and women.[8] Tanne et al[9] studied of a cohort of 859 patients with stroke and reported that both lower and higher levels of hemoglobin were associated with higher mortality. Our study found the concordant result that both ends of hemoglobin concentrations were associated with higher mortality at 1 year.

Similarly, we found that both anemia and high hemoglobin were also related to a higher risk of poor functional outcome. The association between hemoglobin and poor functional outcome has been reported in some studies.[14,15] However, the results were

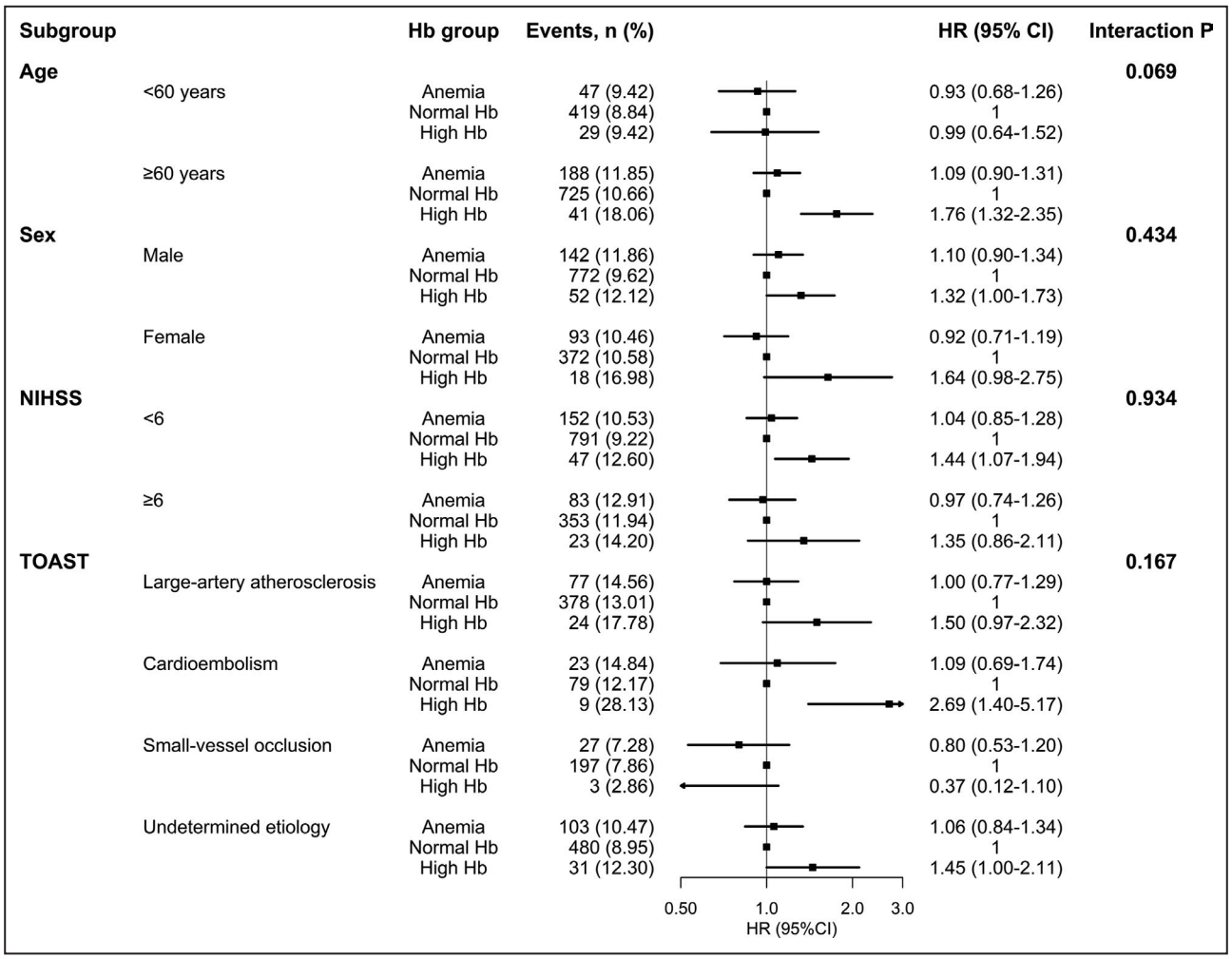

Figure 7. Subgroup analysis of association between hemoglobin groups and composite vascular events.
Because the number of another determined etiology was small, the corresponding CI was extremely broad and the effects were not displayed. Hb indicates hemoglobin; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

inconclusive. A study consisting of 536 patients with ischemic stroke did not find the predicted value of hemoglobin on functional outcome.[15] Another study of a prospective stroke registry from Korea indicated that lower hemoglobin, but not higher hemoglobin, was associated with an increased risk of poor functional outcome.[14] The different results may partly be attributed to the methods of study, and the previous 2 studies used 3-month functional outcomes. Interestingly, we found that among the minor stroke (NIHSS scores <6), but not severe stroke, both the anemia and high hemoglobin groups were associated with an increased risk of poor functional outcome compared with the normal hemoglobin group (Figure 5), which suggested that patients with minor stroke were more likely to be affected by hemoglobin level. More studies are needed to estimate the relationship between different levels of hemoglobin on functional outcomes.

In the current study, we found that the higher hemoglobin may increase the risk of stroke recurrence or composite vascular event. However, a recent study suggested that the higher hemoglobin was associated with a lower risk of stroke recurrence.[16] The contradictory results may be partly attributed to the difference in the categorization of hemoglobin. In the current study, we defined the high level of hemoglobin as >17 g/dL for men and >15.5 g/dL for women, and the number of patients with a high level of hemoglobin was small, and further studies with large sample size are needed to confirm our results. Considering all effects of high hemoglobin on other outcomes after stroke, the results were reasonable.

Although the specific mechanism of hemoglobin on clinical outcomes after stroke is not entirely clear, there are several potential mechanisms proposed. Low hemoglobin or anemia decreases the oxygen supply and energy to the brain.[17] Especially in patients with stroke,

low hemoglobin or anemia can reduce the oxygen carrying to the ischemic penumbral regions[18] and impair cerebral vascular regulation.[17] Furthermore, anemia of inflammation is another cause of anemia, which is mediated by inflammatory cytokines.[19,20] Inflammatory cytokines, such as interleukin 6 and tumor necrosis factor α, are associated with prognosis in patients with stroke.[21,22] High hemoglobin or hematocrit, which is associated with increased viscosity, can decrease cerebral blood flow. Consequently, patients with high hematocrit are at a higher risk of thrombotic events.[23] Hemodilution was expected to be used to improve survival or functional outcome for those with a high level of hemoglobin or hematocrit. However, no evidence was found on the effectiveness of hemodilution therapy in improving the outcomes in patients with ischemic stroke.[24]

There were several limitations in this study. First, this was a retrospective analysis and potential unmeasured confounders may exist. Although many covariates were adjusted in the study, some preexisting medical conditions that may affect hemoglobin level cannot be adjusted. We cannot conclude the casual relationship between hemoglobin and clinical outcomes. Second, we did not address the specific type of anemia, including anemia of iron deficiency, anemia of chronic disease, anemia of malnutrition, and so on, which may have different effects on the outcome after stroke. More studies designed to explore the relationship between a specific type of anemia and outcomes after stroke are needed in the future, and this may help to understand the mechanisms of hemoglobin on outcomes. Third, we cannot identify the patients with abnormal hemoglobin that emerged during hospitalization. Fourth, the number of patients with high hemoglobin was small in the study. The result should be explained with caution.

CONCLUSIONS

In summary, we found that both lower and higher hemoglobin were associated with a higher risk of mortality and poor functional outcome after AIS. Higher hemoglobin, but not lower hemoglobin, was associated with an increased risk of stroke recurrence and composite vascular events. More well-designed clinical studies are needed to confirm the relationship between hemoglobin and clinical outcomes after stroke.

ARTICLE INFORMATION

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Disclosures

None.

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