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ORIGINAL RESEARCH

Anemia Increases All-Cause Mortality Risk in Stroke Survivors on Antiplatelet Therapy: A Retrospective Cohort Study

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ABSTRACT

***Introduction*:** Approximately 20% of patients with stroke are anemic, and previous studies have identified a U-shaped relationship between hemoglobin levels and all-cause mortality in stroke survivors. However, these studies have not specifically focused on patients with stroke taking antiplatelet agents. This study investigates the impact of anemia and hemoglobin (HGB) on mortality in this population.

***Methods*:** This study included 356 stroke survivors from the National Health and Nutrition Examination Survey 1999–2018 who were taking antiplatelet agents. It analyzed the impact of HGB levels and anemia on all-cause mortality using Cox regression, examined the nonlinear relationship between HGB and mortality through restricted cubic splines (RCS), and illustrated survival over time using Kaplan–Meier survival curves.

***Results*:** RCS analysis revealed no nonlinear relationship between HGB and all-cause mortality (P for overall < 0.01, P for nonlinear $= 0.36$), with lower HGB levels associated with an increased risk of all-cause mortality. Cox regression analysis showed that HGB was negatively associated with mortality risk across all models (Model 4: hazard ratio = 0.81, 95% confidence intervals 0.73–0.91, $P < 0.01$). Additionally, anemia significantly increased the risk of mortality in all models (Model 4: hazard ratio = 2.05, 95% confidence intervals 1.43–2.95, $P < 0.01$). Kaplan–Meier survival curves demonstrated that the survival rate in the anemic group was significantly lower than that of the non-anemic group ($P < 0.01$).

***Conclusion*:** In stroke survivors taking antiplatelet agents, anemia is associated with an increased risk of all-cause mortality, while HGB levels are negatively correlated with mortality risk.

Keywords: Anemia; All-cause mortality; Stroke survivors; Antiplatelet; NHANES

Tieshi Zhu and Yong He contributed equally to this work.

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Key Summary Points

Why carry out this study?

Anemia increases mortality risk in patients with stroke, but limited research exists on its impact in stroke survivors taking antiplatelet medications.

This study aimed to examine the effect of anemia on all-cause mortality in stroke survivors who are on antiplatelet therapy.

What was learned from the study?

Hemoglobin is negatively correlated with all-cause mortality, with each 1 g/dL increase in hemoglobin reducing mortality risk by approximately 19%.

Anemia significantly increases mortality risk, regardless of age or gender.

INTRODUCTION

Stroke is one of the leading causes of death and disability worldwide, placing a substantial burden on individuals, families, and society [1–3]. Secondary prevention is a critical therapeutic strategy for stroke, with a significant proportion of patients with stroke requiring long-term antiplatelet therapy [4]. However, this can increase the risk of bleeding events, including gastrointestinal bleeding, gingival bleeding, and subcutaneous hemorrhage [5]. On the other hand, the use of antiplatelet medications reduces the incidence of ischemic events and improves patient prognosis, although a proportion of patients may develop anemia as a result of bleeding complications [6, 7].

Anemia can impair the blood's ability to transport oxygen and nutrients, exacerbating cerebral hypoxia and ischemia [8]. Additionally, anemia is positively associated with an increased risk of stroke [9]. Given this, understanding the prognostic impact of anemia on stroke survivors is crucial. Previous studies have shown that the risk of death in patients with cerebral infarction is related to admission hemoglobin levels in a U-shaped curve; however, low hemoglobin (HGB) concentrations at admission (< 14 g/dL for men and < 12 g/dL for women) did not increase the risk of death within 7 or 30 days after cerebral infarction [10, 11]. These studies primarily focused on the general stroke population rather than those taking antiplatelet medications. As antiplatelet drugs can lead to complications such as abdominal discomfort and bleeding, some patients may struggle with medication adherence [12]. Furthermore, because antiplatelet drugs can increase the risk of anemia through bleeding, it is important to investigate the impact of anemia on mortality risk in this patient group. This study aims to analyze the association between hemoglobin levels, anemia, and all-cause mortality in stroke survivors taking antiplatelet agents, using the National Health and Nutrition Examination Survey (NHANES) 1999–2018 data.

METHODS

Population

The data for this study were obtained from NHANES, a population-based, cross-sectional survey designed to assess the health and nutritional status of the US household population. NHANES annually surveys a nationally representative sample of approximately 5000 individuals across various counties in the United States. The survey consists of an interview component, which collects data on demographics, socioeconomic status, dietary habits, and health-related factors, as well as a physical examination component that includes physiological measurements and laboratory testing.

For this analysis, we included 503 individuals with a history of stroke who were receiving antiplatelet therapy, based on NHANES 1999 to 2018. Of these, 69 were excluded due to missing HGB values, leaving 434 participants. Among these, one participant had missing educational data, two lacked marital status information, 31 were missing data on the poverty-to-income ratio (PIR), and 50 had no

information on alcohol consumption, resulting in 356 participants being included in the final analysis (Fig. 1).

Outcome

The primary endpoints in this study were survival status and survival time, which were obtained from the National Death Index database (https://www.cdc.gov/nchs/data-linkage/mortality.htm). We utilized the "MORTSTAT" variable to determine mortality status and the "PERMTH_INT" variable to calculate follow-up duration. These variables were matched to participants using the unique sequence number identifier.

Anemia

Anemia was diagnosed based on HGB levels obtained from the NHANES routine blood data. An HGB level of less than 13 g/dL for men and less than 12 g/dL for women was used as the diagnostic threshold for anemia [13].

Covariates

The covariates included in this study were age, gender, race, PIR, education, marital status, smoking status, alcohol consumption, hypertension, and diabetes mellitus. Most of these data were directly obtained from the NHANES database. Diabetes mellitus was defined as meeting any of the following criteria: (1) a physician-diagnosed diabetes condition; (2) use of glucose-lowering medications or insulin therapy; (3) a random blood glucose level > 11.1 mmol/L;

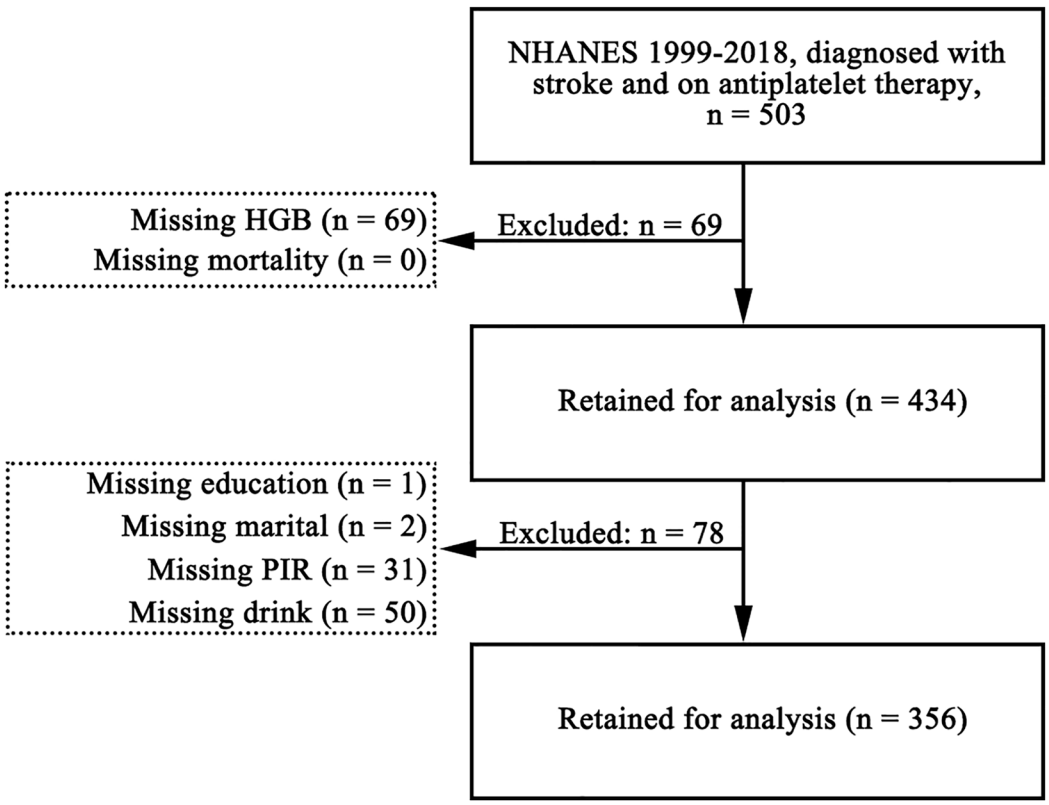

Fig. 1 Flowchart of participants included in this study. *NHANES* National Health and Nutrition Examination Survey, *PIR* poverty-to-income ratio, *HGB* hemoglobin

(4) a 2-hour blood glucose level > 11.1 mmol/L during an oral glucose tolerance test; or (5) a hemoglobin A1c level > 6.5% [14, 15]. Hypertension was defined as (1) a physician-diagnosed hypertension condition; (2) use of antihypertensive medications; or (3) an average blood pressure ≥ 140/90 mmHg [16]. Smoking status was categorized as "never" (fewer than 100 cigarettes smoked in a lifetime), "former" (smoked more than 100 cigarettes but had quit), and "current" (smoked more than 100 cigarettes and were currently smoking) [17]. Alcohol consumption was classified as "never" (fewer than 12 instances of alcohol consumption in a lifetime), "former" (more than 12 instances of lifetime alcohol consumption but none in the past year), and "current" (more than 12 instances of lifetime alcohol consumption, including within the past year) [18].

Statistics

Data processing was performed using R version 4.4.1. Continuous variables were analyzed using either the *t*-test or the Mann–Whitney *U* test, depending on the results of normality testing. Categorical variables were analyzed using either the chi-square test or Fisher's exact test, as appropriate. Cox regression was employed to assess the association between HGB levels or anemia and the risk of all-cause mortality. Kaplan–Meier survival curves were used to illustrate survival times in anemic versus non-anemic populations. The nonlinear association between HGB and all-cause mortality was evaluated using restricted cubic spline (RCS) analysis.

Four models were constructed for the Cox regression analysis, with the results reported as hazard ratios (HR) with 95% confidence intervals (CI) and *P* values: Model 1 was unadjusted; Model 2 adjusted for age, sex, and race; Model 3 further adjusted for education, marital and PIR; and Model 4 included additional adjustments for smoking status, alcohol consumption, hypertension, and diabetes. The variables included in the RCS model were identical to those in Model 4. For subgroup analyses, the same variables as Model 4 were used, excluding the subgroup variables. The RCS analysis incorporated the same covariates as Model 4. Statistical significance was defined as a two-tailed *P* value of < 0.05.

Ethical Approval

The project was authorized by the National Center for Health Statistics Research Ethics Review Board (Protocol #98-12, Protocol #2005-06, Protocol #2011-17, Protocol #2018-01). All participants signed a written informed consent form, and their privacy was protected. They were also informed of their right to contact NHANES for updates regarding the progress of the study.

RESULTS

Baseline Information and Survival Data for the Study Population

Table 1 presents the baseline characteristics and survival data of the study population, which consisted of 356 individuals with a median age of 72 years. Of these, 44.94% were female and 59.27% were white. During the follow-up period, 196 individuals died, with a median follow-up time of 79 months. A total of 78 individuals were diagnosed with anemia. No significant differences were observed between the anemic and non-anemic groups in terms of age, PIR, PLT, marital status, education, diabetes, or hypertension. However, the anemic group had a lower mean median level, lower median white blood cell count, shorter median survival time, a higher proportion of females, and a higher proportion of whites. Additionally, the anemic group had a higher proportion of smokers, a higher proportion of individuals who had never consumed alcohol, and higher all-cause mortality (Table 1).

Anemia Increases the Risk of All-Cause Mortality

When HGB was analyzed as a continuous variable, the results indicated that HGB was negatively associated with the risk of all-cause mortality across all models (Model 1: HR = 0.86, 95% CI 0.79–0.94, *P* < 0.01; Model 2: HR = 0.82, 95%

Table 1 Baseline characteristics and survival data of study participants

	Total ($n = 356$)	Anemia ($n = 78$)	No ($n = 278$)	*P*
Age (years)	72.00 (64.00, 79.00)	75.00 (65.50, 80.00)	71.00 (63.25, 78.00)	0.13
PIR	1.60 (1.03, 2.97)	1.85 (1.18, 2.89)	1.57 (1.03, 3.02)	0.56
HGB (g/dL)	13.60 (12.60, 14.60)	11.80 (11.22, 12.30)	13.90 (13.30, 14.80)	< 0.01
WBC (10^9/L)	6.80 (5.68, 8.43)	6.15 (5.12, 7.80)	7.00 (5.90, 8.60)	< 0.01
PLT (10^9/L)	228.50 (192.00, 273.00)	213.50 (182.00, 275.00)	232.00 (194.25, 271.75)	0.26
Female	160 (44.94)	134 (48.20)	26 (33.33)	0.02
Race				< 0.01
White	211 (59.27)	171 (61.51)	40 (51.28)	
Black	68 (19.10)	42 (15.11)	26 (33.33)	
Mexican American	34 (9.55)	28 (10.07)	6 (7.69)	
Other	43 (12.08)	37 (13.31)	6 (7.69)	
Marital				0.72
Married	189 (53.09)	145 (52.16)	44 (56.41)	
Never married	16 (4.49)	12 (4.32)	4 (5.13)	
Separated	151 (42.42)	121 (43.53)	30 (38.46)	
Education				0.78
< High school	133 (37.36)	102 (36.69)	31 (39.74)	
High school	97 (27.25)	75 (26.98)	22 (28.21)	
> High school	126 (35.39)	101 (36.33)	25 (32.05)	
Smoke				0.02
Never	129 (36.24)	100 (35.97)	29 (37.18)	
Former	168 (47.19)	124 (44.60)	44 (56.41)	
Current	59 (16.57)	54 (19.42)	5 (6.41)	
Drink				< 0.01
Never	69 (19.38)	64 (23.02)	5 (6.41)	
Former	142 (39.89)	102 (36.69)	40 (51.28)	
Current	145 (40.73)	112 (40.29)	33 (42.31)	
Hypertension	319 (89.61)	249 (89.57)	70 (89.74)	0.96
Diabetes	176 (49.44)	130 (46.76)	46 (58.97)	0.06
Deceased	196 (55.06)	145 (52.16)	51 (65.38)	0.04
Follow-up time (months)	79.00 (41.75, 113.00)	56.00 (35.00, 81.25)	84.00 (46.00, 119.00)	< 0.01

Data are presented as median (Q1, Q3) or *n* (%)

Q1 first quartile, *Q3* third quartile, *PIR* poverty-to-income ratio, *HGB* hemoglobin, *WBC* white blood cells, *PLT* platelets

CI 0.74–0.92, $P<0.01$; Model 3: HR = 0.82, 95% CI 0.74–0.92, $P<0.01$; Model 4: HR = 0.81, 95% CI 0.73–0.91, $P<0.01$) (Fig. 2A). The RCS analysis revealed no nonlinear relationship between HGB and the risk of all-cause mortality (P for overall < 0.01, P for nonlinear = 0.36). The graph demonstrated a negatively correlated arc, with the risk of all-cause mortality decreasing as HGB levels increased (Fig. 2C).

When the analysis was stratified by the presence or absence of anemia, the results showed that anemia was positively associated with the risk of all-cause mortality across all models (Model 1: HR = 2.16, 95% CI 1.56–2.99, $P<0.01$; Model 2: HR = 1.89, 95% CI 1.35–2.65, $P<0.01$; Model 3: HR = 1.84, 95% CI 1.30–2.62, $P<0.01$; Model 4: HR = 2.05, 95% CI 1.43–2.95, $P<0.01$) (Fig. 2B). Kaplan–Meier survival analysis revealed that the survival time of the anemic group was shorter than that of the non-anemic group, with the two survival curves largely disjointed ($P<0.01$) (Fig. 2D).

Subgroup analysis of HGB as a continuous variable showed that the HR was less than 1 in all subgroups except for the Mexican American subgroup. Significant results were observed in the subgroups of individuals aged ≥ 65, PIR 0–1, PIR > 3, male, white, no diabetes, and hypertension (Fig. 3). Subgroup analysis based on the presence or absence of anemia showed that HR was greater than 1 in all subgroups. Negative results were found in the PIR 1.1–3, Mexican American, other race, no diabetes, and no hypertension subgroups, while significant results were observed in the other subgroups (Fig. 4).

DISCUSSION

By analyzing data from NHANES 1999–2018 on stroke survivors taking antiplatelet agents, this study found that anemia significantly increased the risk of all-cause mortality. Additionally, HGB levels were negatively associated with the risk of all-cause mortality, with higher HGB levels corresponding to a lower risk of mortality.

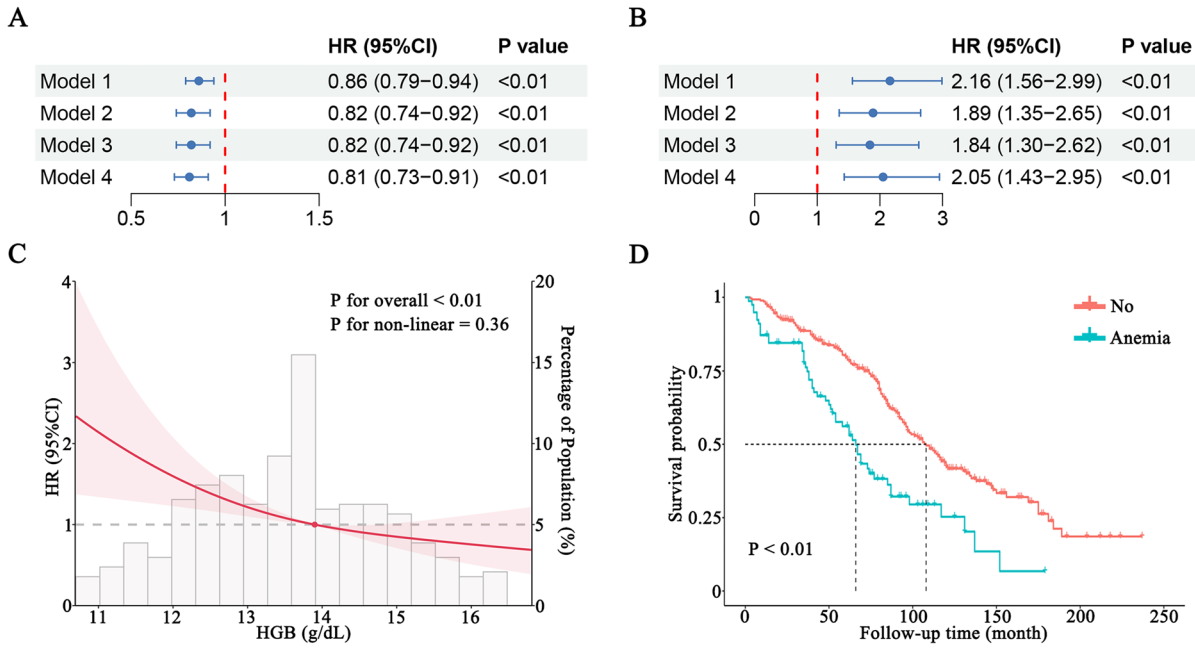

Fig. 2 Relationship between anemia and all-cause mortality risk. **A** Cox regression analysis of hemoglobin (HGB) and all-cause mortality risk. **B** Cox regression analysis of anemia and all-cause mortality risk. **C** Restricted cubic spline analysis of HGB and all-cause mortality risk. **D** Kaplan–Meier survival curves stratified by anemia status. *CI* confidence interval, *HGB* hemoglobin, *HR* hazard ratio

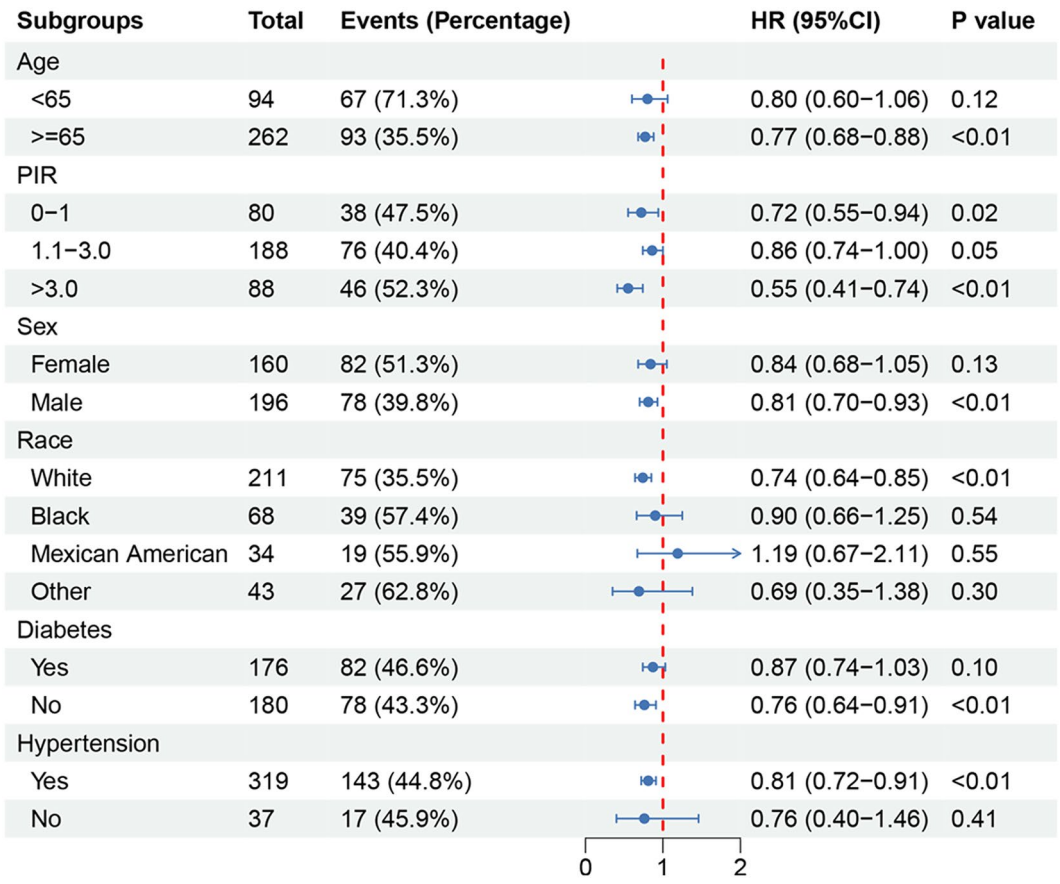

Fig. 3 Subgroup analysis of hemoglobin and all-cause mortality risk. *CI* confidence interval, *HR* hazard ratio, *PIR* poverty-to-income ratio

The relationship between anemia and stroke has been widely reported. HGB is associated with stroke in a U-shaped manner, where both high and low HGB levels increase the risk of stroke, thereby making anemia a risk factor compared with normal HGB levels [19]. In patients with acute ischemic stroke, anemia at admission has been identified as an independent predictor of all-cause mortality at discharge and at 12 months (OR = 1.66, 95% CI 1.08–2.56) [20]. Furthermore, anemia at admission was independently associated with prognosis in patients with a National Institutes of Health Stroke Scale score < 10 (HR = 4.17, 95% CI 1.47–11.90) but not in those with more severe strokes (HR = 0.82, 95% CI 0.30–2.22) [21]. A dynamic follow-up of HGB levels revealed that a greater decline in HGB during the follow-up period was associated with an increased risk of all-cause mortality [22]. Another study found that a decrease in HGB and hematocrit after admission was strongly correlated with poor prognosis and all-cause mortality following ischemic stroke [23]. In patients with intracerebral hemorrhage, anemia was an independent risk factor for all-cause mortality at 6 months and 1 year (OR = 1.338, 95% CI 1.01–1.78; OR = 1.326, 95% CI 1.00–1.75) [24]. Additionally, a negative association between HGB and poor functional prognosis at 3 months was observed in patients with nontraumatic cerebral hemorrhage (OR = 0.73, 95% CI 0.58–0.92, $P = 0.007$) [25]. Furthermore, mild anemia at admission (10.1–12 g/dL) did not increase the 1-year mortality risk in all patients with spontaneous hemorrhage, but it significantly increased the 1-year risk of all-cause mortality in patients with non-warfarin-associated spontaneous hemorrhage [26].

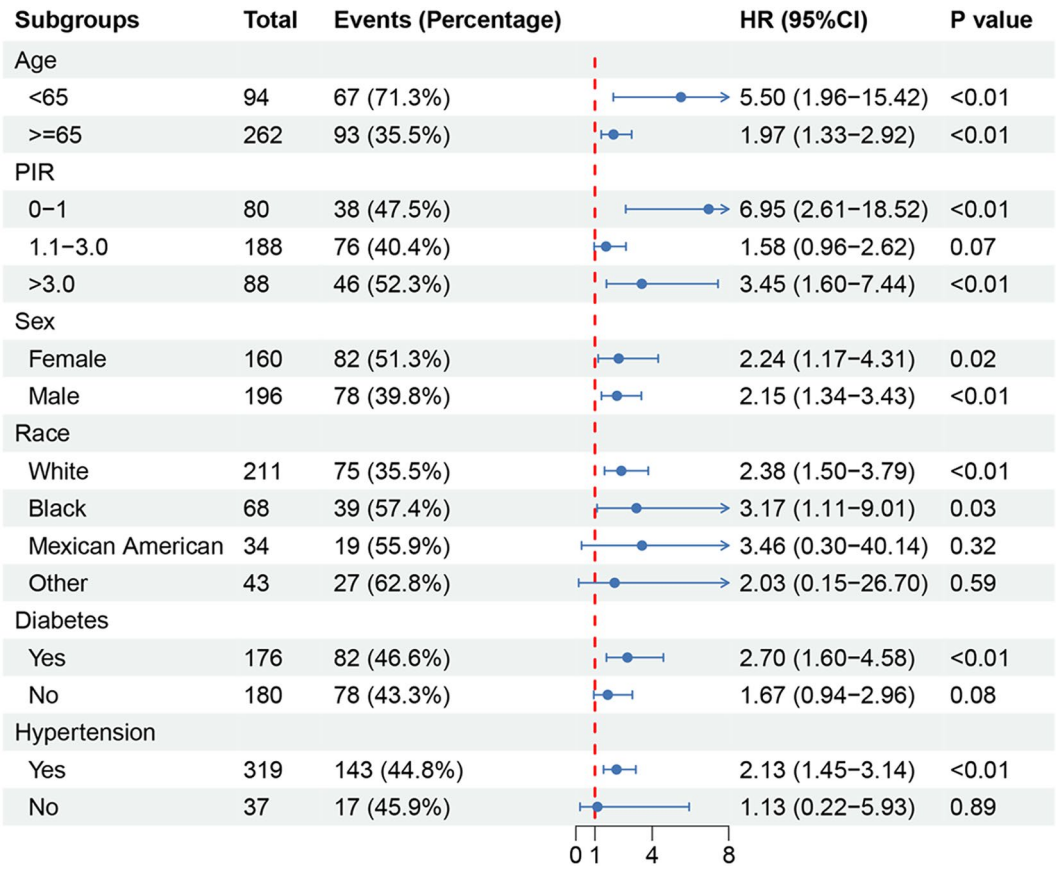

Fig. 4 Subgroup analysis of anemia and all-cause mortality risk. *CI* confidence interval, *HR* hazard ratio, *PIR* poverty-to-income ratio

All of the studies mentioned above had relatively short follow-up periods, with most reporting a 1-year risk of all-cause mortality. These findings consistently indicate that anemia increases the risk of all-cause mortality in both ischemic and hemorrhagic stroke, which aligns with the results of the present study. However, the follow-up period in the current study was longer, with a median follow-up of 79 months. Unlike previous studies, the present study did not observe a U-shaped relationship between HGB and risk of all-cause mortality. Instead, graphically, the risk of all-cause mortality was lowest in individuals with an HGB of 16 g/dL. In this study, 78 of the 356 participants were anemic, which is closer to the 23% anemia rate reported by Bussière et al. [26].

Several studies have proposed mechanisms linking anemia to poor stroke prognosis. In patients with ischemic stroke, decreased hemoglobin concentration reduces oxygen transport capacity, exacerbating the hypoxic conditions in the ischemic penumbra [27]. Additionally, increased blood flow in patients with anemia can generate vorticity, potentially dislodging thrombi that are adhered to the vessel wall [28]. High blood flow velocity also upregulates the expression of endothelial adhesion molecules, which may trigger an inflammatory response and subsequent thrombus formation [29]. Furthermore, anemia is associated with advanced age, inflammatory states, and underlying conditions such as chronic kidney disease, all of which increase the risk of cerebral infarction and contribute to poorer prognosis [30, 31]. In patients with cerebral hemorrhage, a metabolic penumbra surrounds the intracranial hemorrhagic focus, where reduced oxygen utilization

efficiency is compounded by anemia-induced hypoxia, further worsening pre-existing neurological damage [32, 33]. Additionally, anemia, potentially due to low red blood cell counts, increases the risk of volume expansion in intracranial hemorrhage, thereby heightening the risk of poor prognosis [34, 35].

In conclusion, anemia is associated with an increased risk of death in patients with stroke, regardless of whether they are taking antiplatelet agents. This risk is particularly elevated in patients with severe anemia or those experiencing progressive HGB decline. Clinicians should closely monitor HGB levels in patients with stroke and actively address the underlying causes of anemia. For patients with stroke receiving antiplatelet therapy, close monitoring of HGB levels is essential. The prevention and management of anemia are critical for optimizing prognosis. Even mild anemia has been associated with reduced survival and should not be overlooked in clinical practice. Early intervention, including timely consultation with a hematologist, may be warranted to mitigate its potential impact.

However, several limitations must be acknowledged. The diagnosis of stroke in this study relied on self-reporting by respondents, which may introduce error, and the severity of stroke was not assessed. Additionally, this study did not dynamically assess HGB levels or evaluate their cumulative effect over time. Although many confounding variables were adjusted for, it is possible that some important confounders were overlooked. The study also did not investigate the etiology of anemia, which may be beyond the scope of NHANES data, as these data do not provide sufficient detail to infer the causes of anemia. Finally, caution should be exercised when generalizing the findings of this study to other regions or populations.

CONCLUSION

In stroke survivors taking antiplatelet agents, anemia is associated with an increased risk of all-cause mortality, while HGB levels are negatively correlated with mortality risk, with lower HGB levels increasing the risk of all-cause mortality.

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Author Contributions. Tieshi Zhu contributed to data curation, formal analysis, software, and the writing of the original draft. Yong He was involved in data curation and formal analysis. Yuzhang Bei and Hui Mai were responsible for conceptualization, supervision, and the writing, review, and editing of the manuscript. All authors reviewed and approved the final manuscript.

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Data Availability. The data for this study were obtained from the NHANES database, publicly accessible at https://www.cdc.gov/nchs/nhanes/.

Declarations

Conflict of Interest. Tieshi Zhu, Yong He, Yuzhang Bei, and Hui Mai have nothing to disclose.

Ethical Approval. The project was authorized by the National Center for Health Statistics Research Ethics Review Board (Protocol #98-12, Protocol #2005-06, Protocol #2011-17, Protocol

#2018-01). All participants signed a written informed consent form, and their privacy was protected. They were also informed of their right to contact NHANES for updates regarding the progress of the study.

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