ORIGINAL RESEARCH

Impact of Hemoglobin Levels and Anemia on Mortality in Acute Stroke: Analysis of UK Regional Registry Data, Systematic Review, and Meta-Analysis

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***Background*—**The impact of hemoglobin levels and anemia on stroke mortality remains controversial. We aimed to systematically assess this association and quantify the evidence.

***Methods and Results*—**We analyzed data from a cohort of 8013 stroke patients (mean±SD, 77.81±11.83 years) consecutively admitted over 11 years (January 2003 to May 2015) using a UK Regional Stroke Register. The impact of hemoglobin levels and anemia on mortality was assessed by sex-specific values at different time points (7 and 14 days; 1, 3, and 6 months; 1 year) using multiple regression models controlling for confounders. Anemia was present in 24.5% of the cohort on admission and was associated with increased odds of mortality at most of the time points examined up to 1 year following stroke. The association was less consistent for men with hemorrhagic stroke. Elevated hemoglobin was also associated with increased mortality, mainly within the first month. We then conducted a systematic review using the Embase and Medline databases. Twenty studies met the inclusion criteria. When combined with the cohort from the current study, the pooled population had 29 943 patients with stroke. The evidence base was quantified in a meta-analysis. Anemia on admission was found to be associated with an increased risk of mortality in both ischemic stroke (8 studies; odds ratio 1.97 [95% CI 1.57–2.47]) and hemorrhagic stroke (4 studies; odds ratio 1.46 [95% CI 1.23–1.74]).

***Conclusions*—**Strong evidence suggests that patients with anemia have increased mortality with stroke. Targeted interventions in this patient population may improve outcomes and require further evaluation. **(*J Am Heart Assoc*. 2016;5:e003019 doi: 10.1161/JAHA.115.003019)**

Key Words: hemoglobin • mortality • prognosis • stroke

Anemia is common in patients presenting with acute stroke. Hospital-based studies have reported prevalence up to ≈30%.[1,2] Although anemia has been independently associated with increased mortality in a variety of conditions including chronic kidney disease,[3] heart failure,[4] and acute coronary syndromes,[5] observational studies investigating the association between anemia and mortality in stroke have shown conflicting results. Early studies found no association between anemia and stroke outcomes[6,7]; however, others have found both low and high hemoglobin levels to be associated with increased mortality,[8–10] suggesting a U-shaped relationship. Guidelines have been unable to specify the optimal treatment options for acute stroke patients with anemia.[11]

Previous studies were limited by small sample sizes, and a majority did not report outcomes by stroke subtype. In addition, no previous study stratified analysis by sex-specific hemoglobin levels. This is particularly important because of the natural variance in the normal hemoglobin ranges between sexes. The literature describes various plausible mechanisms that explain how anemia could directly contribute to poor outcomes.[12] There is a paucity of information, however, investigating the impact of an important clinical factor: whether stroke patients with anemia receive fewer preventative medications pertinent to stroke, such as antiplatelets and anticoagulants (antithrombotics). In addition,

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Table 1. Sex-Specific Sample Characteristics by Anemia Status

	Male			Female		
	Anemia	No Anemia	*P* Value	Anemia	No Anemia	*P* Value
Number	1017 (26.7)	2794 (73.3)		947 (22.5)	3255 (77.5)	
Age, y			<0.001			<0.001
≤60	46 (4.5)	424 (15.2)		29 (3.1)	208 (6.4)	
61–65	32 (3.1)	282 (10.1)		21 (2.2)	143 (4.4)	
66–70	50 (4.9)	340 (12.2)		33 (3.5)	231 (7.1)	
71–75	127 (12.5)	411 (14.7)		65 (6.9)	344 (10.6)	
76–80	187 (18.4)	470 (16.8)		137 (14.5)	522 (16.0)	
81–85	247 (24.3)	475 (17.0)		232 (24.5)	747 (22.9)	
86–90	234 (23.0)	279 (10.0)		253 (26.7)	635 (19.2)	
≥91	94 (9.2)	113 (4.0)		177 (18.7)	435 (13.4)	
Prestroke comorbidity						
Coronary heart disease	304 (29.9)	446 (16.0)	<0.001	230 (24.3)	475 (14.6)	<0.001
Previous stroke	287 (28.2)	607 (21.7)	<0.001	261 (27.6)	763 (23.4)	0.009
Congestive heart failure	143 (14.1)	154 (5.5)	<0.001	147 (15.5)	255 (7.8)	<0.001
Atrial fibrillation	217 (21.3)	307 (11.0)	<0.001	206 (21.8)	508 (15.6)	<0.001
Hypertension	422 (41.5)	650 (23.3)	<0.001	393 (41.5)	1044 (32.1)	<0.001
Hyperlipidemia	76 (7.5)	99 (3.5)	<0.001	42 (4.4)	135 (4.1)	0.698
Diabetes mellitus	183 (18.0)	231 (8.3)	<0.001	137 (14.5)	242 (7.4)	<0.001
Peripheral vascular disease	63 (6.2)	49 (1.8)	<0.001	28 (3.0)	61 (1.9)	0.042
GI bleeding and peptic ulcer	81 (8.0)	118 (4.2)	<0.001	62 (6.5)	142 (4.4)	0.006
COPD	90 (8.8)	113 (4.0)	<0.001	65 (6.9)	107 (3.3)	<0.001
Chronic kidney disease	93 (9.1)	37 (1.3)	<0.001	50 (5.3)	69 (2.1)	<0.001
Falls	161 (15.8)	160 (5.7)	<0.001	275 (29.0)	557 (17.1)	<0.001
Malignancy	240 (23.6)	274 (9.8)	<0.001	112 (11.8)	278 (8.5)	0.002
Dementia	47 (4.6)	43 (1.5)	<0.001	75 (7.9)	121 (3.7)	<0.001
Prior antithrombotic use			<0.001			0.286
No	447 (44.0)	1538 (55.0)		499 (52.7)	1779 (54.7)	
Yes	570 (56.0)	1256 (45.0)		448 (47.3)	1476 (45.3)	
Prestroke Rankin Scale score*			<0.001			<0.001
0	556 (54.7)	2119 (75.8)		388 (41.0)	1955 (60.1)	
1	155 (15.2)	286 (10.2)		135 (14.3)	399 (12.3)	
2	96 (9.4)	147 (5.3)		121 (12.8)	303 (9.3)	
3	131 (12.9)	142 (5.1)		160 (16.9)	354 (10.9)	
4	54 (5.3)	73 (2.6)		90 (9.5)	176 (5.4)	
5	25 (2.5)	27 (1.0)		53 (5.6)	68 (2.1)	
Stroke type			0.088			0.002
Hemorrhagic	121 (11.9)	392 (14.0)		95 (10.0)	454 (13.9)	
Ischemic	896 (88.1)	2402 (86.0)		852 (90.0)	2801 (86.1)	
OCSP classification			0.002			<0.001
TACS	215 (21.1)	500 (17.9)		248 (26.2)	699 (21.5)	
PACS	359 (35.3)	900 (32.2)		312 (32.9)	1084 (33.3)	

Continued

Table 1. Continued

	Male			Female		
	Anemia	No Anemia	*P* Value	Anemia	No Anemia	*P* Value
POCS	169 (16.6)	548 (19.6)		118 (12.5)	521 (16.0)	
LACS	209 (20.6)	696 (24.9)		186 (19.6)	786 (24.1)	
Undefined	65 (6.4)	150 (5.4)		83 (8.8)	165 (5.1)	
Inpatient mortality			<0.001			<0.001
Living	731 (71.9)	2393 (85.6)		635 (67.1)	2546 (78.2)	
Deceased	286 (28.1)	401 (14.4)		709 (21.8)	312 (22.5)	

The data are presented as number (%) for categorical variables. COPD indicates chronic obstructive pulmonary disease; GI, gastrointestinal; LACS, lacunar stroke; OCSP, Oxfordshire Community Stroke Project; PACS, partial anterior circulation stroke; POCS, posterior circulation stroke; TACS, total anterior circulation stroke.
*0: no symptoms; 1: no significant disability despite symptoms, able to carry out all usual duties and activities; 2: slight disability, unable to perform all previous activities but able to look after own affairs without assistance; 3: moderate disability, requires some help but able to walk without assistance; 4: moderately severe disability, unable to walk without assistance and to attend to own bodily needs without assistance; 5: severe disability—bedridden, incontinent, and requiring constant nursing care and attention.

there is a lack of data regarding the comorbidity burden in anemic stroke patients and inadequate control for this in statistical analyses.

The current study aimed to clarify these important questions by assessing the impact of admission hemoglobin levels and anemia on stroke mortality at different time points up to 1-year follow-up. A systematic review and meta-analysis were also carried out to further quantify the impact of admission hemoglobin and anemia on stroke mortality outcomes.

Methods

Database Study

The study population consisted of 8013 patients with acute stroke who were admitted consecutively between January 2003 and May 2015 to Norfolk and Norwich University Hospital, a regional tertiary center in East Anglia, UK, with a catchment population of ≈750 000. Ethics approval was obtained from the Newcastle and Tyneside National Health Service Research Ethics Committee (12/NE/0170), and the study protocol was approved by the steering committee of the register used. Individual patients were not required to provide written informed consent because this source is a research database register that included all consecutive patients.

The data collection methods for this prospective hospital-based register have been reported previously.[13] Briefly, the data were obtained from paper and electronic records, reviewed, and then entered into the register database. This was done by the hospital stroke data team and vetted by clinical team members for accuracy. For each patient admitted, the prestroke modified Rankin Scale score (scores are defined in Table 1), as modified by UK-TIA investigators,[14] was ascertained from nursing and medical records by stroke specialist nurses. At discharge, deceased or living status was recorded to capture in-hospital mortality. Follow-up for mortality was obtained by electronic record linkage with the Office of National Statistics data through hospital episodes in May 2015. For the purposes of this study, the follow-up was truncated at 365 days for all patients.

The variables included were age, sex, stroke subtype (ischemic or hemorrhagic), prestroke disability depicted by modified Rankin Scale score (0–5), Oxfordshire Community Stroke Project (OCSP) classification (total anterior circulation stroke, partial anterior circulation stroke, posterior circulation stroke, lacunar stroke), hemoglobin levels at admission, comorbidities (coronary heart disease, congestive heart failure, atrial fibrillation, hypertension, hyperlipidemia, previous stroke, diabetes mellitus, peripheral vascular disease, gastrointestinal bleeding, peptic ulcers, chronic obstructive pulmonary disease, chronic kidney disease, falls, malignancy, dementia), and prior use of antithrombotics. Mortality was assessed at several different time points: inpatient; at 7 and 14 days; at 1, 3, and 6 months; and at 1 year. Results were displayed selectively in Tables 2 and 3, and data for the 7- and 14-day time points were not included because of the similarity in results and to ensure brevity. Only confirmed cases of stroke were included. Stroke was diagnosed using evidence from clinical features and neuroimaging (typically computed tomography and, in some cases, magnetic resonance imaging). Anemia was defined according to the World Health Organization criteria of hemoglobin <12.0 g/dL in women and <13.0 g/dL in men, and elevated hemoglobin was defined as >15.5 g/dL in women and >17.0 g/dL in men.[15]

The associations between hemoglobin levels and age, sex, prestroke modified Rankin Scale score, stroke type, OCSP classification, comorbidities, prior antithrombotic use, and inpatient mortality were assessed using the chi-square test. Logistic regression models were constructed to assess the impact of hemoglobin levels (by quintiles) and anemia on

odds of death. Univariate and multivariate models were used to calculate unadjusted and adjusted odds ratios (ORs). Sex- and stroke type–specific analyses were performed controlling for age, OCSP classification, prestroke modified Rankin Scale score, comorbidities, and prior antithrombotic usage.

To better understand the potential mediating factors for the observed associations, we examined the distribution of selected chronic comorbidities between patients with anemia and no anemia and assessed the differences in proportions of patients receiving antithrombotic medications by a vascular indication (defined as presence of previous stroke, coronary heart disease, diabetes mellitus, peripheral vascular disease, hypertension, and atrial fibrillation). The analysis was performed using the SPSS version 23.0 (IBM Corp).

Table 2. The Impact of Hemoglobin Levels on Mortality at Different Time Points (Logistic Regression)

Variable	Hemoglobin quintile					Events
	1	2	3	4	5	
Male ischemic						
Number	635	675	667	644	677	
Inpatient	2.64 (1.83–3.81)	1.56 (1.08–2.25)	1.00	1.59 (1.06–2.38)	1.62 (1.08–2.42)	511
1 month	2.99 (2.06–4.34)	1.74 (1.19–2.53)	1.00	1.55 (1.03–2.34)	1.79 (1.19–2.68)	488
3 months	3.09 (2.24–4.25)	1.34 (0.96–1.85)	1.00	1.18 (0.82–1.69)	1.37 (0.96–1.95)	674
6 months	2.92 (2.16–3.94)	1.37 (1.01–1.85)	1.00	1.05 (0.75–1.46)	1.16 (0.83–1.63)	796
1 year	2.90 (2.18–3.86)	1.43 (1.08–1.90)	1.00	1.17 (0.86–1.59)	1.17 (0.86–1.60)	971
Male hemorrhagic						
Number	83	109	103	87	131	
Inpatient	1.23 (0.58–2.60)	0.83 (0.42–1.65)	1.00	0.86 (0.39–1.86)	1.05 (0.53–2.09)	176
1 month	1.22 (0.59–2.51)	0.92 (0.48–1.78)	1.00	0.81 (0.39–1.70)	0.93 (0.48–1.80)	173
3 months	1.16 (0.55–2.42)	0.67 (0.34–1.30)	1.00	0.76 (0.38–1.57)	0.68 (0.35–1.57)	200
6 months	1.65 (0.77–3.55)	0.81 (0.41–1.60)	1.00	0.78 (0.38–1.62)	0.73 (0.38–1.41)	221
1 year	1.97 (0.92–4.22)	0.81 (0.42–1.58)	1.00	0.73 (0.35–1.51)	0.79 (0.41–1.51)	229
Female ischemic						
Number	698	748	700	752	755	
Inpatient	1.47 (1.08–1.98)	1.05 (0.77–1.43)	1.00	1.39 (1.01–1.90)	1.20 (0.88–1.63)	792
1 month	1.48 (1.09–2.01)	1.16 (0.85–1.58)	1.00	1.23 (0.89–1.69)	1.26 (0.92–1.73)	733
3 months	1.70 (1.28–2.25)	1.16 (0.87–1.54)	1.00	1.34 (1.00–1.79)	1.19 (0.89–1.58)	1007
6 months	1.86 (1.42–2.44)	1.22 (0.93–1.60)	1.00	1.44 (1.09–1.89)	1.26 (0.96–1.67)	1159
1 year	1.86 (1.44–2.41)	1.23 (0.96–1.59)	1.00	1.29 (0.99–1.68)	1.13 (0.87–1.46)	1328
Female hemorrhagic						
Number	72	100	132	127	118	
Inpatient	2.56 (1.23–5.32)	0.80 (0.41–1.57)	1.00	0.80 (0.54–1.81)	1.35 (0.74–2.47)	229
1 month	2.61 (1.31–5.36)	0.80 (0.42–1.55)	1.00	1.12 (0.62–2.01)	1.46 (0.81–2.63)	226
3 months	2.26 (1.10–4.64)	0.88 (0.47–1.67)	1.00	0.94 (0.53–1.68)	1.22 (0.68–2.19)	256
6 months	2.02 (0.98–4.16)	0.97 (0.52–1.82)	1.00	0.80 (0.45–1.42)	1.22 (0.68–2.18)	278
1 year	2.59 (1.23–5.44)	1.20 (0.64–2.25)	1.00	0.95 (0.54–1.68)	1.35 (0.75–2.41)	292

The cutoff points for the quintiles are as follows: male: 12.4, 13.8, 14.6, and 15.6 g/dL; female: 11.7, 12.8, 13.6, and 14.5 g/dL. The variables adjusted for were age, Oxford Community Stroke Project classification, prestroke Rankin Scale score, prior antithrombotic use, coronary heart disease, previous stroke, congestive heart failure, atrial fibrillation, hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, falls, malignancy, dementia, gastrointestinal bleeding, and peptic ulcer. We also adjusted for International Normalized Ratio in patients with hemorrhagic stroke. The International Normalized Ratio was included as a dichotomous categorical variable: <1.40 versus ≥1.40. Data for the time points 7 and 14 days were removed for brevity. Mean ages for the male quintiles were 82.80, 80.48, 78.49, 78.09, and 78.38 years for quintiles 1–5, respectively. Mean ages for female quintiles were 83.04, 81.81, 80.45, 78.96, and 78.06 years for quintiles 1–5, respectively.

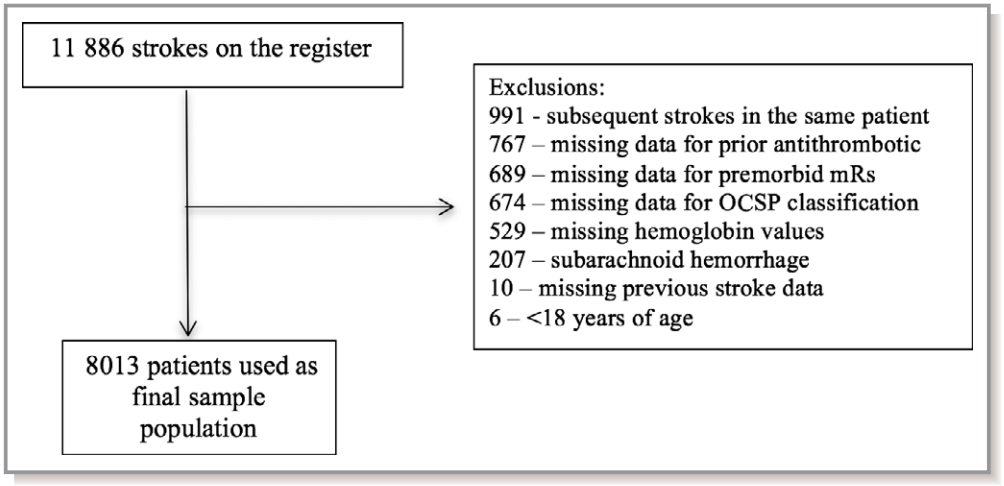

Figure 1. Patient inclusion chart. mRS indicates modified Rankin Scale score; OCSP, Oxfordshire Community Stroke Project.

Systematic Review and Meta-Analysis

We selected full journal articles reporting on studies that evaluated the association between baseline hemoglobin or anemia and subsequent mortality in patients diagnosed with stroke. PubMed and Embase were searched from inception until December 2014 using the following search terms with no language restriction: *stroke OR intracranial-hemorrhage OR intracerebral-hemorrhage AND haemoglobin OR hemoglobin OR anaemia OR anemia AND mortality OR fatal* OR survival OR death NOT rivaroxaban OR dabigatran OR apixaban OR sickle OR surgery OR glycated OR glycosylated OR HbA1C or erythropoie**. In addition, we checked the bibliographies of relevant articles for any studies that met our selection criteria.

Two reviewers (R.B. and K.H.) independently screened abstracts and titles. Potentially relevant studies were reviewed to confirm their eligibility. The selection and data extraction of included studies were performed by R.B. and K.H. and checked

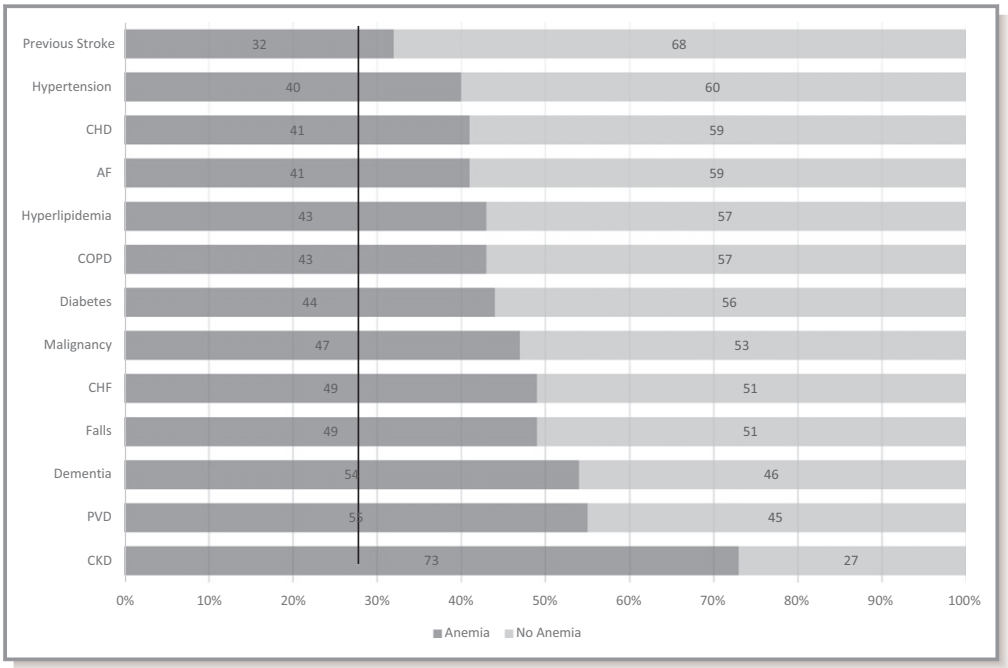

Figure 2. Prevalence of comorbidities by anemia status in men. The vertical line represents the expected proportion of comorbidity based on the proportion of stroke patients with anemia. Any dark bars to the right of the vertical line represent higher comorbidity burden in anemic patients compared with patients who were not anemic. AF indicates atrial fibrillation; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

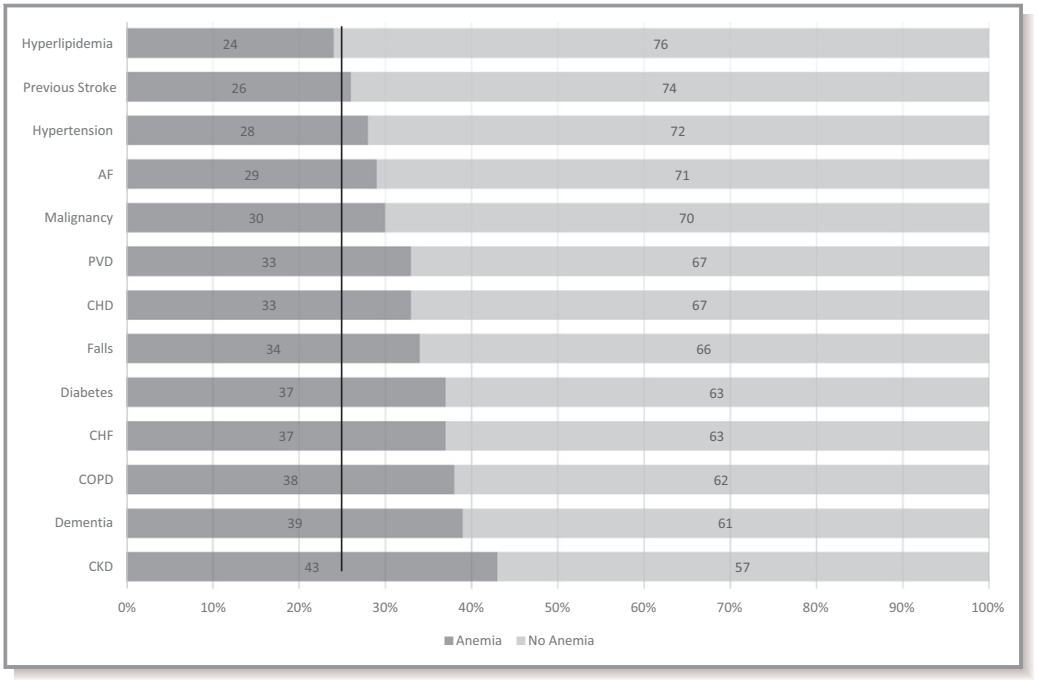

Figure 3. Prevalence of comorbidities by anemia status in women. The vertical line represents the expected proportion of comorbidity based on the proportion of stroke patients with anemia. Any dark bars to the right of the vertical line represent higher comorbidity burden in anemic patients compared with patients who were not anemic. AF indicates atrial fibrillation; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

by a senior reviewer (Y.K.L.). To assess study validity, included studies were assessed for the methods used for diagnosing stroke, determination of hemoglobin levels and anemia, ascertainment of mortality or outcome subsequent to the stroke, and the analytic procedures aimed at minimizing the risk of bias from confounders. We pooled the reported associations (adjusted OR if available) using the inverse variance method and random-effects model in RevMan 5.3 software (Nordic Cochrane Center). The comparisons of interest were for categories of anemia versus no anemia in patients with ischemic and hemorrhagic stroke versus the referent "normal" category. We evaluated heterogeneity by calculating the I^2 statistic, for which a value >50% was indicative of substantial heterogeneity. We also aimed to check for publication bias through a funnel plot if there were >10 eligible studies in our systematic review.

Results

Database Study

Of the 11 886 episodes recorded in the registry, 3873 were excluded for various reasons (Figure 1). Overall, 2659 of these episodes were excluded because of missing data, and 991 were excluded because they were related to secondary entry into the register due to subsequent stroke. The sample included in the current study consisted of 8013 patients with acute stroke admitted consecutively between January 2003 and May 2015. The mean age in the cohort was 77.81±11.83 years, 52.4% were women, and 86.7% had ischemic stroke. The most common OCSP stroke classification was partial anterior circulation stroke (33.1%), and the majority of patients (62.6%) had a prestroke modified Rankin Scale score of 0. Inpatient mortality was 21.3%, and 1 in 4 patients (24.5%) had anemia on admission.

Table 1 shows sex-specific sample characteristics by anemia status. Increasing age, higher prestroke disability, increased stroke severity, inpatient mortality, and all comorbidities (with the exception of hyperlipidemia in women) were associated with anemia (Figures 2 and 3). Prior antithrombotic use in men and ischemic stroke in women were also associated with anemia.

Table 2 depicts the impact of hemoglobin levels on stroke mortality by quintiles of sex-specific admission hemoglobin levels, presented separately for ischemic and hemorrhagic stroke. Quintile 1 contains those with the lowest values, and quintile 5 has the highest. The cutoff points were 12.40, 13.80, 14.64, and 15.60 g/dL for men and 11.70, 12.80, 13.60, and 14.50 g/dL for women. In men with ischemic stroke, low hemoglobin (quintile 1) was significantly associated with increased mortality at all time points measured compared with those with normal hemoglobin levels (quintile 3). High hemoglobin (quintile 5) was also associated with increased

odds of mortality at 4 time points; inpatient, 7 and 14 days, and 1 month. This suggested a U-shaped relationship between hemoglobin levels and short-term mortality in men with ischemic stroke. In women with ischemic stroke, low hemoglobin levels were significantly associated with mortality at 5 time points; inpatient; 1, 3, and 6 months; and 1 year. In women with hemorrhagic stroke, low hemoglobin levels were associated with increased mortality at all time points.

Table 3 shows the impact of anemia and elevated hemoglobin levels on mortality. In men with ischemic stroke, anemia was associated with higher odds of death at all time points assessed, and elevated hemoglobin was associated with increased odds of death at 3 time points; inpatient, 1 month, and 3 months. In men with hemorrhagic stroke, anemia was associated with increased mortality at 1 year, and elevated hemoglobin was associated with increased mortality at 4 time points; inpatient, 7 and 14 days, and 1 month. In women with ischemic stroke, anemia was associated with increased mortality at 1, 3, and 6 months and 1 year, whereas elevated hemoglobin was associated with increased mortality at 7 and 14 days and 1 month. In women with hemorrhagic stroke, anemia

Table 3. Effect of Anemia and Elevated Hemoglobin on Stroke Outcomes at Different Time Points (Logistic Regression)

	Anemia	Normal	Elevated Hemoglobin	Events
Male ischemic				
Number	896	2277	125	
Inpatient	1.75 (1.37–2.25)	1.00	1.85 (1.03–3.32)	511
1 month	1.86 (1.46–2.38)	1.00	1.79 (1.00–3.20)	488
3 months	2.18 (1.75–2.72)	1.00	1.86 (1.08–3.18)	674
6 months	2.25 (1.83–2.78)	1.00	1.46 (0.86–2.48)	796
1 year	2.25 (1.84–2.74)	1.00	1.50 (0.91–2.47)	971
Male hemorrhagic				
Number	121	367	25	
Inpatient	1.33 (0.77–2.31)	1.00	3.30 (1.19–9.17)	176
1 month	1.42 (0.83–2.42)	1.00	2.90 (1.08–7.75)	173
3 months	1.39 (0.81–2.39)	1.00	2.08 (0.75–5.78)	200
6 months	1.64 (0.94–2.85)	1.00	1.56 (0.56–4.40)	221
1 year	1.76 (1.01–3.04)	1.00	1.56 (0.56–4.35)	229
Female ischemic				
Number	852	2585	216	
Inpatient	1.20 (0.97–1.49)	1.00	1.30 (0.87–1.94)	792
1 month	1.29 (1.04–1.60)	1.00	1.49 (1.00–2.21)	733
3 months	1.39 (1.14–1.70)	1.00	1.19 (0.81–1.75)	1007
6 months	1.44 (1.18–1.75)	1.00	1.12 (0.78–1.62)	1159
1 year	1.48 (1.23–1.79)	1.00	1.04 (0.73–1.48)	1328
Female hemorrhagic				
Number	95	418	36	
Inpatient	1.90 (1.09–3.33)	1.00	2.76 (1.16–6.56)	229
1 month	1.82 (1.06–3.11)	1.00	2.11 (0.92–4.82)	226
3 months	1.80 (1.04–3.13)	1.00	2.08 (0.91–4.77)	256
6 months	2.05 (1.17–3.59)	1.00	2.99 (1.29–6.90)	278
1 year	2.11 (1.19–3.74)	1.00	2.63 (1.14–6.05)	292

The cutoff points were as follows: male: 13.0 and 17.0 g/dL; female: 12.0 and 15.5 g/dL. The variables adjusted for were age, Oxford Community Stroke Project classification, prestroke Rankin Scale score, prior antithrombotic use, coronary heart disease, previous stroke, congestive heart failure, atrial fibrillation, hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, falls, malignancy, dementia, gastrointestinal bleeding, and peptic ulcer. We also adjusted for International Normalized Ratio in patients with hemorrhagic stroke. The International Normalized Ratio was included as a dichotomous categorical variable: <1.40 vs ≥1.40. Data for the time points 7 and 14 days were removed for brevity.

Table 4. Use of Prior Antithrombotic by Anemia Status and Vascular Indication (Chi-Square Test)

	Vascular Indication Yes*			Vascular Indication No		
	Anemia	No Anemia	*P* Value	Anemia	No Anemia	*P* Value
Male			0.971			<0.001
No antithrombotic	237 (34.2)	456 (65.8)		210 (16.3)	1082 (83.7)	
Antithrombotic	447 (34.3)	857 (65.7)		123 (23.6)	399 (76.4)	
Female			0.032			0.334
No antithrombotic	270 (28.9)	665 (71.1)		229 (17.1)	1114 (82.9)	
Antithrombotic	350 (24.9)	1057 (75.1)		98 (19.0)	419 (81.0)	

*Indications considered were previous stroke, coronary heart disease, diabetes, hypertension, peripheral vascular disease, and atrial fibrillation.

was associated with increased mortality at all time points assessed, whereas elevated hemoglobin was associated with increased mortality at 3 time points; inpatient, 6 months, and 1 year.

Table 4 depicts prior antithrombotic use by anemia status and vascular indication. In women with a positive vascular indication, those with anemia were less likely to be on prior antithrombotics compared with those without anemia (P=0.032). Conversely, in men with a negative vascular indication, those with anemia were more likely to be on prior antithrombotics than those without anemia (P<0.001). In addition, anemia was associated with increased comorbidity burden in both sexes (Figures 2 and 3).

Systematic Review and Meta-Analysis

Our search identified 1424 citations. After detailed screening, 20 studies were included in our systematic review; the flow chart of study selection is shown in Figure 4, and Tables 5 and 6 show the key features of the selected studies. Overall, 10 studies assessed the impact of anemia on stroke[1,2,10,16–22] and 10 evaluated the association between stroke and hemoglobin

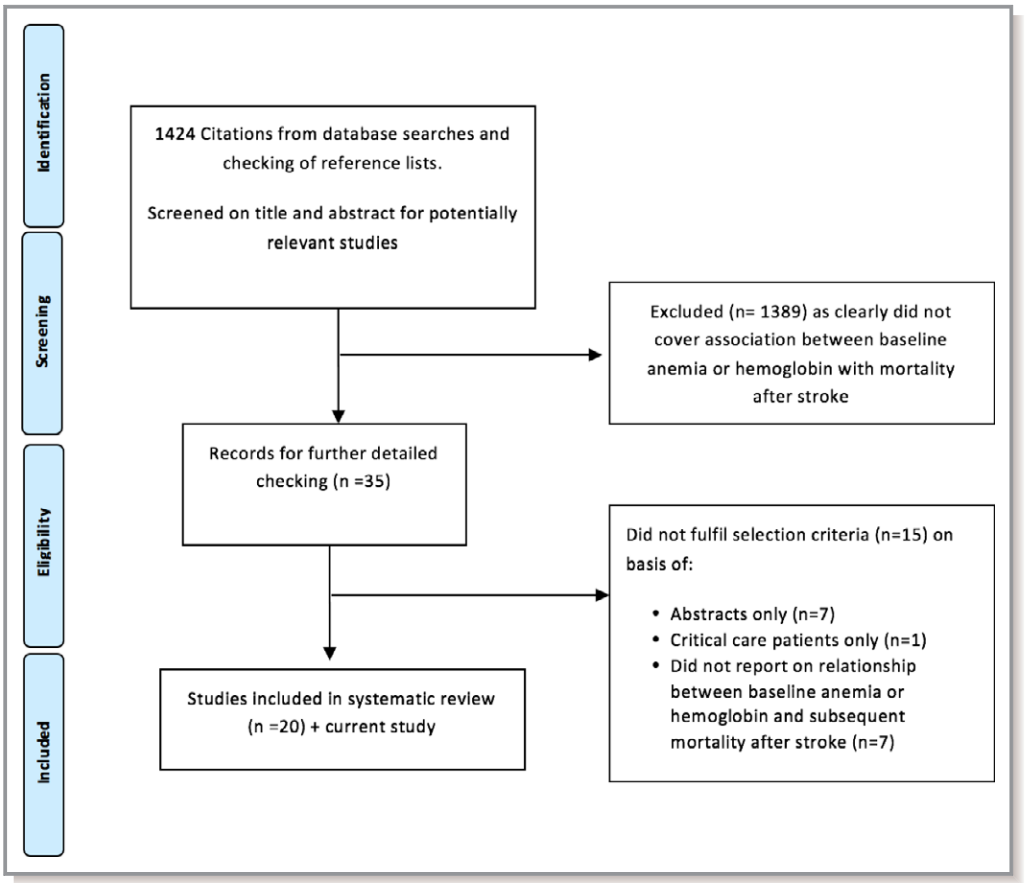

Figure 4. Flow diagram of study selection.

Table 5. Characteristics of Studies Examining the Relationship Between Anemia and Hemoglobin Levels and Stroke Outcomes

Author	Years Sampled	Study Design	n	Exposure	Outcomes	Main Result
Bhatia et al[6]	2000–2001	Prospective	116	Admission Hb	Mortality at 30 days	Hb not associated with outcome
Bussiere et al[23]	2003–2008	Prospective	2406	Admission Hb divided into quintiles—cutoffs: 100, 120, 140, 160 g/L	Mortality at 1 year, mRS at discharge	Hb predicted mortality at 1 year (aOR 1.39, 95% CI 1.01–1.91) in Hb <100 vs 141–160 g/L
Chang et al[24]	2008–2010	Prospective	106	Admission Hb, nadir Hb, and transfusion	In-hospital mortality, length of stay, and disability at discharge	Admission anemia did not predict outcomes
Czlonkowska et al[7]	1991–1992	Prospective	345	Admission Hb	Mortality at 30 days	Hb not associated with outcome
Diedler et al[25]	2004–2006	Prospective	196	Admission, mean and nadir Hb	mRS at discharge and 6 months	Admission Hb did not predict outcomes
Del Fabbro et al[16]	2001–2003	Retrospective	890	Anemia at admission	In-hospital mortality, survival at 1 year	Higher Hb predicted decreased mortality at 1 year: HR 0.98 (95% CI 0.97–1.00)
Gray et al[26]	1985–1986	—	122	Admission Hb	Mortality at 4 and 12 weeks	Hb not associated with outcome
Hao et al[2]	2002–2008	Prospective	1176	Anemia at admission	In-patient mortality, mortality, and disability (mRS >2) at 12 months	Anemia associated with inpatient mortality (aOR 1.66, 95% CI 1.08–2.56) and mortality at 12 months (aOR 1.56, 95% CI 1.05–2.31)
Huang et al[17]	2001–2003	Prospective	774	Anemia at admission	Inpatient mortality, mRS at discharge, stroke recurrence at 3 years	Anemia was associated with increased mortality at 3 years (aOR 2.22, 95% CI 1.13–4.39)
Kellert et al[8]	1998–2009	Prospective	217	Admission, mean and nadir Hb	Mortality and mRS at 3 months	Hb decrease was associated with increased mortality at 3 months (OR 1.34: 1.01–1.76) but admission Hb was not (OR not given)
Kumar et al[18]	1999–2005	Prospective	685	Anemia at admission	Mortality at 30 days, ICH volume	Anemia is not a predictor of mortality on multivariable analysis (OR 1.5, 95% CI 0.9–2.4)
Kuramatsu et al[19]	2006–2010	Prospective	435	Anemia at admission	mRS at 90 days and 1 year	Anemia was associated with poor long-term outcome (mRS 4–6 at 1 year; OR 7.5)
Milionis et al[20]	2003–2011	Retrospective	2439	Anemia at admission	Mortality and disability at 12 months	Anemia associated with mortality at 12 months (OR 2.70, 95% CI 2.12–3.43)
Nybo et al[21]	2003–2004	—	250	Anemia at admission	Mortality at 6 months	Anemia associated with greater risk of death at 6 months (OR 4.7, 95% CI 1.1–8.2)
Park et al[9]	2004–2009	Prospective	2681	Admission, nadir, time-averaged, and discharge Hb	Mortality and mRS at 3 months	Admission Hb predicted mortality 3 months (aOR: Q1 vs Q3 was 3.74 [95% CI 2.03–6.89] and Q5 vs Q3 was 1.99 [95% CI 1.02–3.91])

Continued

Table 5. Continued

Author	Years Sampled	Study Design	n	Exposure	Outcomes	Main Result
Sharma et al[27]	2003–2011	Post hoc analysis of RCT	3020	Admission Hb and Hb <13 g/dL	All-cause mortality	Hb <13 g/dL was a significant predictor of mortality (HR 1.60, 95% CI 1.22–2.10)
Sico et al[1]	1998–2003	Retrospective	1306	Anemia at admission	Inpatient mortality or discharge to hospice (combined end point)	Anemia was associated with outcome in patients with less severe stroke on subgroup analysis (aOR 4.17, 95% CI 1.47–11.90)
Tanne et al[10]	2001–2002	Prospective	859	Anemia at admission	Mortality at 1 month and 1 year, functional outcome using Barthel Index	aOR for mortality at 1 month was 1.90 (95% CI 1.05–3.43) and at 1 year was 1.72 (95% CI 1.00–2.93)
Wade et al[28]	1977–1982	Post hoc analysis of RCT	1377	Hb >15 vs ≥15 g/dL on study entry	Fatal and nonfatal strokes	No significant difference in Hb levels among those who died compared with survivors
Zeng et al[22]	2007–2008	Prospective	2513	Anemia on admission	Mortality and dependency (mRS >2) at 1, 3, 6, and 12 months	aOR for mortality in anemic versus nonanemic patients: 6 months 1.34 (95% CI 1.01–1.78), 1 year 1.33 (95% CI 1.00–1.75)

aOR indicates adjusted odds ratio; Hb, hemoglobin; HR, hazard ratio; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale score; OR, odds ratio; Q, quintile; RCT, randomized controlled trial.

levels.[6–9,23–28] In terms of study design, 3 were retrospective cohort studies,[1,16,20] 13 were prospective cohort studies,[2,6–10,17–19,22–25] and 2 were secondary analyses of randomized control trials.[27,28] There were also 2 studies that did not state the design.[21,26] There was a high degree of diversity in geographic location, with cohorts from Germany,[8,19,25] Switzerland,[16,20] the United States,[18,24] the People's Republic of China,[2,22] Canada,[23,28] India,[6] Israel,[10] the Republic of Korea,[9] Denmark,[21] Taiwan,[17] the United Kingdom,[26] and Poland.[7] In addition, 2 studies were conducted across multiple countries.[1,27] Regarding stroke type, 9 studies assessed patients with ischemic stroke,[1,2,8,9,17,20,21,27,28] 6 assessed patients with hemorrhagic stroke,[9,18,22–25] and 5 evaluated both types of stroke.[6,7,10,16,26] The number of participants in the studies ranged from 106 to 3020. When combined with the participants from the current study, the total pooled study population included 29 943 participants of whom 24 816 were meta-analyzed. ORs included in the meta-analysis were from the mortality time point of 1 year or the closest time point available to 1 year.

Validity Assessment

Different methods were used for ascertainment of stroke diagnosis. Imaging (computed tomography, magnetic resonance imaging, or both) was used in 17 studies,[1,2,6–8,10,17–25,27,28] 1 study relied on clinical evaluation alone,[26] and 2 did not state the method used.[9,16] The methods used to ascertain mortality also varied. Attending doctors confirmed in-hospital mortality in 2 studies,[24,25] whereas death registry data were used in 4 studies.[10,20,21,23] Telephone interviews were used by 7 studies, typically in conjunction with other methods such as outpatient visit, home visit, mailed questionnaire, analysis of death registries, or review of medical records.[6,8,9,16,18,19,22] One study used outpatient visits only,[17] and the method used to establish mortality status was unclear in 6 studies.[1,2,7,26–28] Despite the variety of approaches taken to ascertain mortality, all seemed reliable.

Eleven studies used the World Health Organization definition of anemia as hemoglobin cutoffs,[2,8,10,16–22,24] 7 used prespecified values,[1,9,23,25–28] and 2 did not specify the values used.[6,7] By using prespecified thresholds in constructing categorical comparisons for anemia, it is possible that cut points have been drawn up that favor statistically significant findings. Eighteen studies adjusted for potential confounders[1,2,7–10,16–27]; however, there was great variation in terms of the variables adjusted for. These included age and National Institutes of Health Stroke Scale[1] as well as age, sex, insurance status, smoking, time to treatment, type of intervention, prestroke medication, body mass index, blood pressure, heart rate, Trial of Org 10172 Acute Stroke Treatment criteria classification, metabolic parameters, and comorbidities.[20] Consequently, many studies were liable to residual confounding (Table 6).

Table 6. Characteristics Determining Study Validity

Study	Method of Stroke Diagnosis	Time of Mortality Measurement	Method of Mortality Measurement	Confounders Adjusted for in Multivariate Logistic Regression	Hb Cutoffs Used	Stroke Types Considered
Bhatia et al[6]	Imaging	30 days	Telephone, outpatient, or home interview	—	—	Both considered together
Bussiere et al[23]	Imaging	30 days, 6 months, 1 year	Population registries	Age, sex, warfarin, INR, glucose, creatinine, blood pressure, IVH	Quintiles, cutoffs; 100, 120, 140, 160 g/L; anemia defined as <120 g/L	ICH only
Chang et al[24]	Imaging	In-hospital mortality	Attending physician	Age, nadir Hb, ICH score, intubation	Anemia (WHO definition)	ICH only
Czlonkowska et al[7]	Imaging or autopsy	30 days	—	Age, decreased consciousness, severity of weakness	—	Both considered together
Diedler et al[25]	Imaging	In-hospital mortality	Attending physician	Age, ICH volume, NIHSS, IVH, ICU stay, mechanical ventilation, RBC transfusion, mean Hb	Anemia definition: <12.1 g/L for women, <13.1 g/L for men	ICH only
Del Fabbro et al[16]	—	In-hospital, 1 year	Telephone interview, population registries	Age, GFR, comorbidities, functional status	Anemia (WHO definition)	Both considered together
Gray et al[26]	Clinical evaluation	4 and 12 weeks	—	Age, white cell count, hematocrit, Hb, urea	>16 g/dL defined as elevated	Both considered together
Hao et al[2]	Imaging	1 year	—	Age, sex, comorbidities, smoking, alcohol, NIHSS, eGFR	Anemia (WHO definition)	AIS only
Huang et al[17]	Imaging	3 years	Outpatient interview	Age, comorbidities	Anemia (WHO definition)	AIS only
Kellert et al[8]	Imaging	3 months	Telephone and outpatient interview	Age, NIHSS, blood glucose, microcytic and hypochromic RBCs, leukocytosis, creatinine, CRP	Anemia (WHO definition)	AIS only
Kumar et al[18]	Imaging	30 days	Telephone interview, medical records, population registry	Age, sex, warfarin, ICH volume, IVH, glucose, WBC	Anemia (WHO definition)	ICH only
Kuramatsu et al[19]	Imaging	90 days and 1 year	Telephone interview, mailed questionnaire	NIHSS, GCS, ICH score, ICH volume, IVH, Graeb score, midline shift, Hb, hematocrit, mechanical ventilation, pneumonia	Anemia (WHO definition)	ICH only
Milionis et al[20]	Imaging	7 days, 3 months, 12 months	Medical records, death certificate, population registry	Age, sex, smoking, insurance, time to treatment, type of intervention, comorbidities, prior medication, BMI, blood pressure, heart rate, TOAST classification, metabolic parameters	Anemia (WHO definition)	AIS only
Nybo et al[21]	Imaging	6 months	Population registry	Age, sex, comorbidities, Scandinavian stroke scale	Anemia (WHO definition)	AIS only
Park et al[9]	—	3 months	Telephone interview, chart review	Age, sex, blood pressure, prestroke mRS, NIHSS, comorbidities, blood glucose, thrombolysis	Prespecified quintiles	AIS only

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Table 6. Continued

Study	Method of Stroke Diagnosis	Time of Mortality Measurement	Method of Mortality Measurement	Confounders Adjusted for in Multivariate Logistic Regression	Hb Cutoffs Used	Stroke Types Considered
Sharma et al[27]	Imaging	—	—	Age, BMI, comorbidities, Hb, eGFR	Hb <13 g/dL	AIS only
Sico et al[1]	Imaging	In-hospital	—	Age, NIHSS	Hematocrit <31%	AIS only
Tanne et al[10]	Imaging	Mortality at 1 year	Population registry	Age, sex, stroke type, NIHSS, prior disability, comorbidities	Anemia (WHO definition)	Both considered separately
Wade et al[28]	Imaging	—	—	—	Cutoff at 15 g/dL	AIS only
Zeng et al[22]	Imaging	Discharge, 30 days, 3, 6, 12 months	Telephone interview	Age, sex, prestroke mRS, NIHSS, BMI, GCS, ICH volume, glucose, comorbidities, antithrombotic use, antihypoglycemic use, antihyperlipidemic use, family history, smoking, alcohol	Anemia (WHO definition)	ICH only

AIS indicates arterial ischemic stroke; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GCS, Glasgow Coma Scale; GFR, glomerular filtration rate; Hb, hemoglobin; ICH, intracerebral hemorrhage; ICU, intensive care unit; INR, International Normalized Ratio; IVH, intraventricular hematoma; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; RBC, red blood cell; WBC, white blood cell; WHO, World Health Organization.

Meta-analyses of pooled results showed that anemia is associated with an increased risk of mortality in ischemic stroke (pooled OR 1.97, 95% CI 1.57–2.47) (Figure 5).We also found a significant association for the evaluation of anemia and mortality in hemorrhagic stroke, albeit at a lower magnitude of association (OR 1.46, 95% 1.23–1.74) (Figure 6).The number of studies providing ORs for the relationship between elevated hemoglobin and stroke mortality was insufficient for a meta-analysis to be conducted. Although available data suggest that elevated hemoglobin predicts short-term mortality in ischemic stroke, findings are less consistent for hemorrhagic stroke (Table 7). The funnel plot depicting ORs for mortality in anemic ischemic stroke patients shows asymmetry (Figure 7), with an underrepresentation of studies on the left side that we would typically expect to consist of those reporting no significant harm in the relationship between anemia and stroke mortality. We encountered 5 such studies that reported no significant association in our systematic review that we could not incorporate into the meta-analysis because ORs were not given, causing asymmetry in the funnel plot.

Discussion

Our study examined the association between anemia and hemoglobin levels and mortality in acute stroke in a large unselected stroke patient population and sought to quantify this association using systematic review and meta-analysis. At 24.5%, prevalence of anemia was high in the cohort analyzed in the current study. Low hemoglobin levels were associated with older age, increased stroke severity, higher prestroke disability, and the increased comorbidity burden. This suggested that outcomes were mediated by the impact of confounders; however, we found anemia to be independently associated with mortality subsequent to making the appropriate adjustments. A systematic review and meta-analysis of the literature confirmed our findings. In addition, we found elevated hemoglobin to be associated with poorer outcomes in acute stroke, suggesting a U-shaped relationship between hemoglobin levels and stroke mortality.

The literature has described several pathological mechanisms that can plausibly explain the independent association between anemia and increased mortality risk in stroke. First, by lowering the oxygen-carrying capacity of blood, anemia may intensify ischemia and thus hypoxia within the penumbral lesions in patients with ischemic stroke.[29,30] Second, anemia can compromise cerebrovascular autoregulation, leading to fluctuations in cerebral perfusion; this alters the delivery of oxygen to the brain,[31,32] thereby exacerbating damage caused by ischemia or hemorrhage. Third, augmentation of cerebral blood flow can create turbulence, which can trigger the migration of an existing thrombus and lead to a

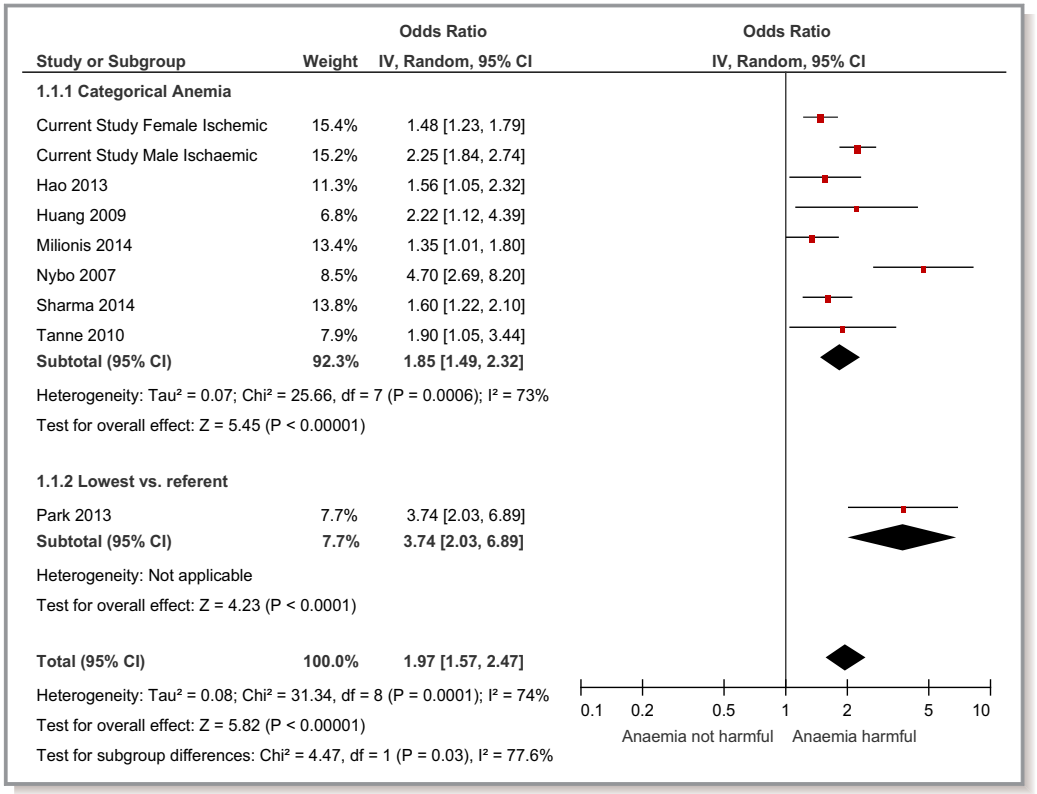

Figure 5. Meta-analysis of studies analyzing the impact of anemia at admission on mortality in ischemic stroke. IV indicates inverse variance.

thromboembolism.[33] Fourth, anemia may lead to hyperdynamic circulation, which has been shown to modulate the expression of adhesion molecules on vascular endothelial cells by upregulating their production. This may trigger an inflammatory response that leads to thrombus formation in a process similar to atherosclerosis.[34,35] Fifth, anemia may worsen outcomes in stroke because of its relationship with inflammatory mediators; it can upregulate the production of inducible nitric oxide synthase and CXC chemokine receptor 4,[36] both of which have been associated with brain damage during ischemia.[37,38]

In addition to the pathophysiological mechanisms described, there is also a plausible clinical explanation for the excess mortality risk in stroke patients with anemia. It may be the case that anemic patients were less likely to be prescribed antithrombotics because of the increased risk of bleeding. This was suggested by a finding shown in Table 4 in which fewer anemic women who had a positive vascular indication were on prior antithrombotics compared with those without anemia. This finding potentially supports the well-documented differential management of cardiovascular risk factors between sexes. The reverse trends were observed for

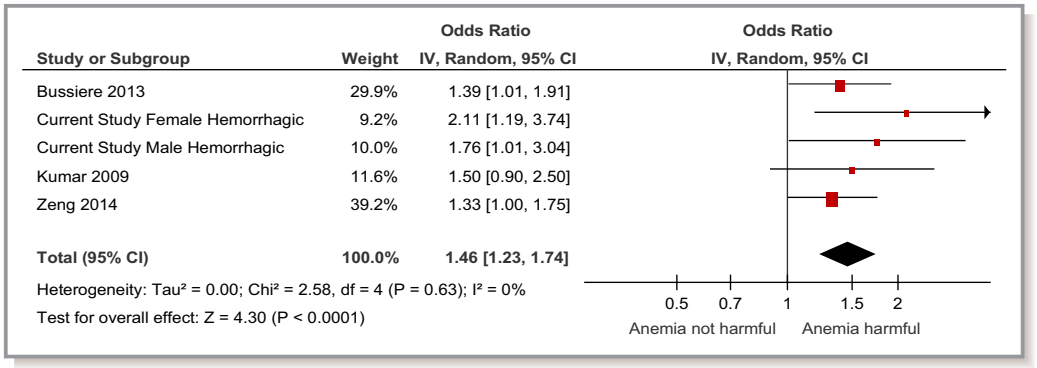

Figure 6. Meta-analysis of studies analyzing the impact of anemia at admission on mortality in hemorrhagic stroke. IV indicates inverse variance.

Table 7. Odds Ratios From Studies Evaluating Association Between Elevated Hemoglobin and Stroke Mortality

Study	Definition of Elevated Hemoglobin	Mortality Time Point	Number of Patients	Odds Ratio (95% CI)
Ischemic stroke				
Park et al[9]	Prespecified quintile	3 months	2681	1.99 (1.02–3.91)
Current study, men	>17 g/dL	In-patient	3298	1.85 (1.03–3.32)
		1 month		1.79 (1.00–3.20)
		3 months		1.86 (1.08–3.18)
		6 months		1.46 (0.86–2.48)
		1 year		1.50 (0.91–2.47)
Current study, women	>15.5 g/dL	In-patient	3653	1.30 (0.87–1.94)
		1 month		1.49 (1.01–2.21)
		3 months		1.19 (0.81–1.75)
		6 months		1.12 (0.78–1.62)
		1 year		1.04 (0.73–1.48)
Hemorrhagic stroke				
Bussiere et al[23]	>16 g/dL	1 year	2406	1.00 (0.74–1.33)
Current study, men	>17 g/dL	In-patient		3.20 (1.19–9.17)
		1 month		2.90 (1.08–7.75)
		3 months		2.08 (0.75–5.78)
		6 months		1.56 (0.56–4.40)
		1 year	513	1.56 (0.56–4.35)
Current study, women	>15.5 g/dL	In-patient	549	2.76 (1.16–6.56)
		1 month		2.11 (0.92–4.82)
		3 months		2.08 (0.91–4.77)
		6 months		2.99 (1.29–6.90)
		1 year		2.63 (1.14–6.05)

those without vascular indications, supporting previous observations that inappropriate prescribing may be more prevalent for women.

The association between anemia and mortality suggests that interventions may improve outcomes. Although previous studies have shown that packed red blood cell transfusions reduce mortality at 30-days in anemic patients with myocardial infarction,[39] a recent systematic review and meta-analysis found that blood transfusion after percutaneous coronary intervention is associated with adverse outcomes,[40] casting doubt on the potential benefits of packed red blood cell transfusions in anemic stroke patients. Observational studies reporting the association between mortality and transfusion in anemic patients with hemorrhagic stroke have had varied results, with one finding a reduction in mortality[41] and another finding no change.[18] To the knowledge of the authors, no studies assessing the impact of packed red blood cell transfusion on anemic ischemic stroke patients have been conducted. Because of the paucity of evidence, guidelines have been unable to specify hemoglobin targets or optimal management options.[11] A randomized controlled trial is required to gauge the impact of transfusions and to establish optimum hemoglobin ranges in patients with acute stroke.

Our study has a number of strengths. The stroke cases were prospectively identified, and the cohort had almost complete follow-up using validated methods. Because a large sample population was used, it was possible to conduct a rigorous analysis by sex and stroke type, enabling us to provide new insights. We were also able to control for a diverse array of confounders, thereby mitigating the effects of residual confounding. The meta-analysis included patients from a wide array of countries, increasing the generalizability of our findings. The inclusion of a large number of participants in the meta-analysis provided sufficient statistical power to obtain results for both stroke subtypes. Finally, all studies included in the meta-analysis were of high methodological quality.

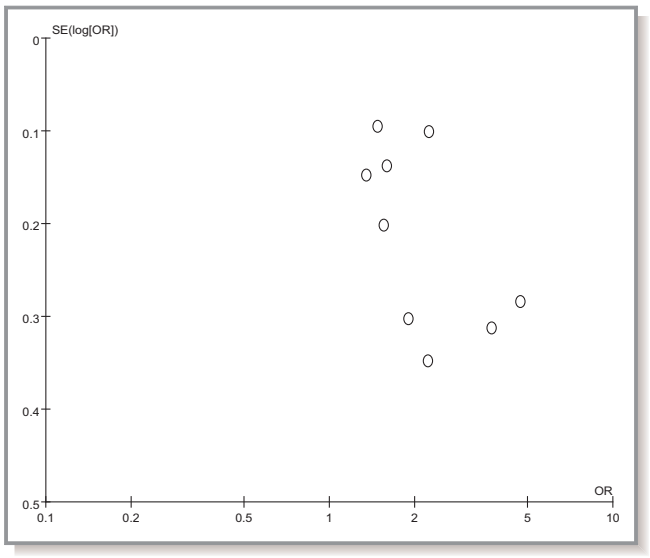

Figure 7. Funnel plot of odds ratios from studies analyzing the impact of anemia at admission on mortality in ischemic stroke.

This study has some limitations. The small sample number of patients with hemorrhagic stroke may have contributed to the nonsignificant *P* values. Some of the models used did not fit the data well. Hosmer–Lemeshow tests were significant for ischemic stroke in men at 3 and 6 months and 1 year (Table 2). Although this result does not alter the associations found, it indicates that for this subgroup, there may be other factors or interactions that might help better predict mortality outcome at these time points. It is possible that we were not able to control for unknown factors. In this registry-based study, we were not able to fully adjust for treatment effect (eg, blood transfusion, use of iron supplements and erythropoietin-stimulating agents). Nonetheless, transfusion for mild to moderate anemia in stroke is not a routine practice, and the likelihood of such confounding is minimal. We were unable to consider the duration of anemia or to assess the impact of abnormal hemoglobin levels subsequent to a stroke; therefore, the independent association between anemia and excess mortality in stroke cannot be described as a causal relationship. The studies in the meta-analysis had high heterogeneity for ischemic stroke (I^2>50%). Finally, the possibility of underrepresentation of studies that reported no significant harm in the relationship between anemia and stroke mortality raises the issue of selective reporting. Consequently, our meta-analysis may have overinflated estimates of the association between anemia and excess mortality risk.

In conclusion, we showed that a significant proportion of stroke patients have anemia at the time of stroke onset and that this is associated with increased mortality up to 1 year. The optimal treatment option in this patient group is unclear. Studies are required to examine the clinical and cost-effectiveness of interventions in this patient population in an acute stroke setting.

Author Contributions

Myint is the Principal Investigator of Norfolk and Norwich University Stroke Register. Myint conceived the study. Bettencourt-Silva performed data linkages. Barlas and McCall analysed the data for cohort study with oversight from Clark. Potter, Bowles and Metcalf are co-investigator of Norfolk and Norwich University Stroke Register. Barlas and Honney performed systematic review & meta-analysis under supervision of Loke. Barlas, Loke and Myint drafted the manuscript. All authors contributed in writing the paper. Myint is the guarantor.

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Disclosures

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