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Original Paper

Anemia Predicts Poor Clinical Outcome in Mechanical Thrombectomy Patients with Fair or Good Collateral Circulation

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Keywords

Ischemic stroke · Anemia · Collateral circulation · Mechanical thrombectomy

Abstract

Background and Purpose: Anemia predicts poor clinical outcome of ischemic stroke in the general stroke population. We studied whether this applies to those treated with mechanical thrombectomy for proximal anterior circulation occlusion in the setting of differing collateral circulation. ***Methods:*** We collected the data of 347 consecutive anterior circulation stroke patients who underwent mechanical thrombectomy after multimodal CT imaging in a single tertiary stroke care center. Patients with occlusion of the internal carotid artery and/or the first segment of the middle cerebral artery were included. We recorded baseline clinical, laboratory, procedural, and imaging variables, and the technical, imaging, and clinical outcomes. Differences between anemic and nonanemic patients were studied with appropriate statistical tests and binary logistic regression analysis. ***Results:*** Ninety-four out of the 285 patients eligible for analysis had anemia, and 243 had fair or good collateral circulation (collateral score, CS, >0). Fifty-four percent of the patients experienced good 3-month clinical outcome (modified Rankin Scale ≤2). In pooled analyses of the CS 1–4 and 2–4 ranges, nonanemic patients had good clinical outcome significantly more often (p < 0.001 for both). This effect was not seen in patients with poor collateral circulation (CS = 0). Nonanemic patients had significantly better odds of good clinical outcome (OR = 2.6, 95% CI 1.377–5.030, p = 0.004) in a binary regression model. A 0.1 g/dL increase in hemoglobin improved the odds of good clinical outcome by 2% (OR = 1.02, 95% CI 1.002–1.044, p = 0.03). ***Conclusions:*** Low hemoglobin on admission predicts poor clinical outcome in mechanical thrombectomy patients with fair or good collateral circulation.

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Introduction

Anemia and ischemic stroke are common conditions among the elderly [1]. Anemia has been shown to be related to poorer clinical outcome in the general ischemic stroke population [2–6]. However, very high hemoglobin levels may also have a debilitating effect on the clinical outcome [2, 7]. One report found that anemia has no effect on the 3-month outcome of patients suffering from ischemic stroke [8].

Mechanical thrombectomy (MT) has been proven to be a superior treatment of acute large vessel occlusion (LVO) strokes in several randomized trials [9]. Despite successful recanalization of the ischemic territory in post-MT digital subtraction angiography, the patient occasionally experiences poor clinical outcome. Adequate collateral circulation into the ischemic area is crucial to having a salvageable penumbra and also permits longer delays in achieving reperfusion and a favorable clinical outcome [10, 11]. Thus, the integrity of the collateral circulation is an important predictor of clinical outcome in patients undergoing MT [12, 13].

The objective of this investigation was to clarify how low hemoglobin at presentation influences the 3-month clinical outcome of MT of acute anterior circulation LVO at different integrities of the collateral circulation.

Methods

Participants and Variables

We conducted an observational study on 347 consecutive patients who underwent MT to treat acute anterior circulation occlusion (LVO) in a single stroke center. The patients were treated between December 2014 and December 2017. The inclusion criteria were occlusion of the internal carotid artery (ICA) and/or the first segment of middle cerebral artery (M1). In total, 285 patients met these criteria, and 62 patients were excluded because of a more distal occlusion. The baseline clinical characteristics (Table 1) were collected from the patient records. Hemoglobin values on admission were recovered from the laboratory database. According to the calibration of the local hematological laboratory, a patient was considered anemic when hemoglobin was <11.7 g/dL in females and <13.4 g/dL in males. National Institutes of Health Stroke Scale (NIHSS) scores at presentation, process time points, modified Thrombolysis in Cerebral Ischemia (mTICI) grading evaluated with digital subtraction angiography at the end of the procedure, and procedural complications had prospectively been stored to patient records. A follow-up non-contrast-enhanced computed tomography (NCCT) was performed 24 h after MT. The clinical outcome measure was the 3-month modified Rankin Scale (mRS) evaluated 3 months after the stroke based on a follow-up visit to or a phone interview by a neurologist. Nineteen patients could not be reached for this control. Admission NIHSS could not exactly be evaluated for 9 patients because of sedation during transportation. In 3 cases, NCCT was of such quality that ASPECTS could not be reliably calculated. Admission hemoglobin was missing for 12 patients. The exact onset of symptoms was unknown or unreliable in 12 cases. The study was approved by the institutional review board and adhered to the Declaration of Helsinki. A written consent was not deemed necessary by the review board.

Imaging and Clinical Decision Making

The initial imaging evaluation consisted of NCCT and CT angiography. CT perfusion was optional and performed in 203 cases (71%). The decision to proceed to MT was multidisciplinary involving an acute neurologist and a neurointerventional radiologist. Patients that

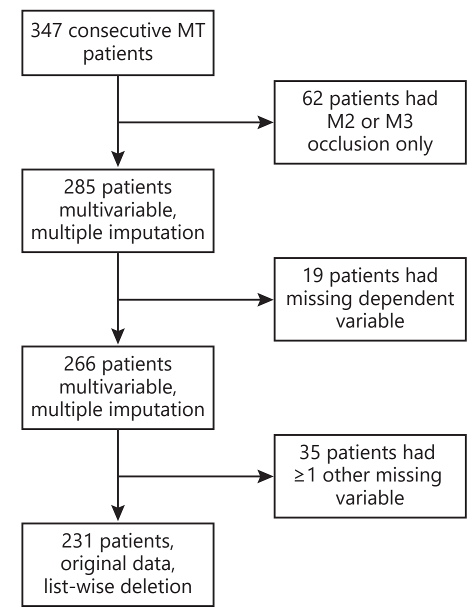

Fig. 1. Flowchart of patient selection and analysis.

were not functionally independent and/or had short life expectancy because of uncontrolled malignant disease were considered noneligible for MT. Patients referred to our institution from other hospitals were reevaluated with at least NCCT upon arrival to rule out bleeding and extensive irreversible ischemic lesions. Image analysis and imaging parameters are described in our previous publication [14].

Recanalization Therapies

Please see the online supplementary Material (for all online suppl. Material, see www.karger.com/doi/10.1159/000510228).

Statistical Analysis

The data were analyzed with SPSS version 25 (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant. Univariable analyses were performed using the maximum number of patients available considering missing data. Group comparisons were performed using the Student t test, the χ^2 test, the Fisher exact test, and the Mann-Whitney U test according to the type and distribution properties of the variable studied. Patients with collateral scores (CS) from 2 to 4 were regarded as having good collateral vessel filling and those with a CS of 1 fair. Patients who had 3-month mRS ≤2 were considered to have experienced good clinical outcome. mTICI scores 2b–3 were considered a good recanalization result. Hemoglobin value was normalized by subtracting the lower bound of the normal range from the value measured on admission for each gender. Multivariable binary logistic regression analyses using good clinical outcome as dependent variable were performed and odds ratios (OR) with 95% confidence intervals (CI) were calculated for each covariate. We discovered no pattern in the distribution of missing data. We used chained equation multiple imputation to generate approximations for the missing data used in the multivariable models, and 1.7% (78/4,482) of the data points were missing in 9/16 variables included in the full model. Both the independent and depended variables were imputed in the full model using 5 iterations.

Table 1. Demographic, baseline, and admission imaging characteristics of all patients by the clinical outcome at 3 months

Characteristics	All patients (n = 285)	RS >2 (n = 122)	mRS ≤2 (n = 144)	P_1
Mean age (SD), years	68 (11)	71 (10)	67 (13)	**0.01**
Female sex, n (%)	115 (40)	55 (45)	52 (36)	0.14
Median NIHSS (IQR) (n = 276)	16.5 (7)	17 (6)	15.5 (8)	**0.005**
Intravenous thrombolysis, n (%)	175 (61)	71 (59)	92 (65)	0.31
ICA occlusions, n (%)	118 (41)	60 (49)	46 (32)	**0.004**
Median ASPECTS (IQR) (n = 282)	9 (3)	8 (3)	9 (2)	**0.01**
Mean onset-to-groin puncture (SD), min (n = 273)	200 (119)	202 (113)	196 (117)	0.72
Collateral score >0, n (%)	243 (85)	94 (81)	133 (93)	**0.004**
mTICI 2b–3, n (%)	261 (92)	109 (89)	136 (95)	0.08
Hypertension, n (%)	139 (49)	68 (56)	64 (44)	0.07
Anemia on admission, n (%)	94 (33)	52 (44)	36 (27)	**0.003**
Mean hemoglobin (SD), g/dL				
Female (n = 110)	12.5 (1.4)	12.2 (1.5)	12.9 (1.3)	**0.02**
Male (n = 163)	13.7 (1.6)	13.5 (1.6)	13.8 (1.7)	0.34
Diabetes, n (%)	46 (16)	25 (21)	20 (14)	0.15
Atrial fibrillation, n (%)	164 (58)	72 (59)	83 (58)	0.82
Coronary artery disease, n (%)	42 (15)	17 (14)	24 (17)	0.54

P_1, p value between groups; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction score; NIHSS, National Institutes of Health Stroke Scale. Boldface denotes statistical significance.

Table 2. Anemia, etiological breakdown (n = 94)

	n (%)
B_{12} deficiency	2 (2.1)
Iron deficiency	2 (2.1)
GI bleeding	3 (3.2)
Urinary tract bleeding	1 (1.1)
Soft tissue bleeding	2 (2.1)
Postoperative anemia	1 (1.1)
Blood thinning medication	2 (2.1)
Immune suppression sequelae	1 (1.1)
Chronic rheumatoid disease	4 (4.3)
Chronic renal failure	2 (2.1)
Mild anemia of unclear etiology after diagnostic workup	74 (78.7)

Results

Baseline Characteristics

The inclusion criteria were met by 285 patients (Fig. 1), and 118 patients (41%) had ICA as the most proximal site of occlusion, the rest in the M1 segment. The baseline characteristics along with differences between the patients with good (mRS ≤2) and poor 3-month clinical outcome are summarized in Table 1. The median NIHSS on admission was 16.5 (IQR 7), the mean onset-to-groin puncture time was 200 min (SD 119 min), and 243 patients (85%) had fair or good collateral circulation (CS 1–4). Ninety-four patients (33%) had anemia (etiological factors are outlined in Table 2). Anemia was usually mild, i.e., hemoglobin levels were

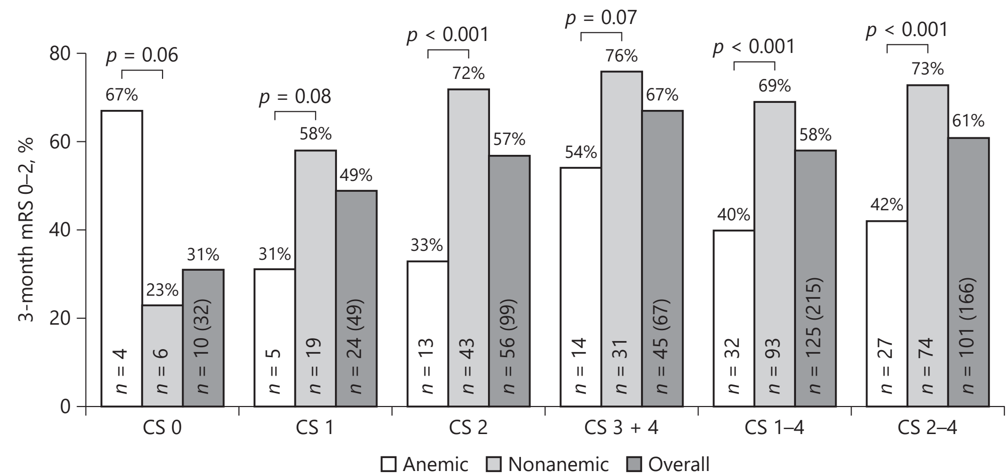

Fig. 2. The proportion of good clinical outcome (3-month modified Rankin Scale, mRS, ≤2) in the anemic and nonanemic groups in proximal occlusions by collateral score (CS). Brackets indicate statistically significant differences between 2 groups. *n*, number of patients in each group.

0.9 g/dL below the lower limit of the median (IQR 1 g/dL). The 3-month mRS was recorded from 266 patients of whom 144 (54%) had good clinical outcome. Advanced age, high NIHSS score, ICA occlusion, acute ischemic changes on the admission NCCT, poor collaterals, suboptimal recanalization result, and low hemoglobin value on admission especially in females were significantly associated with poor clinical outcome. There were no significant differences in baseline variables between these patients and the 19 patients with missing 3-month mRS apart from the proportion of ICA occlusions that was higher in the latter group (63.2 vs. 39.8%, $p = 0.05$).

Effect of Anemia on the 3-Month Clinical Outcome in Different CS Categories

The dichotomized 3-month clinical outcomes of anemic and nonanemic patients with different collateral statuses are described in Figure 2. As expected, the 3-month clinical outcome was consistently better in patients with higher CS. Nonanemic patients had significantly better outcomes in the CS = 2 groups (mRS ≤2, 72 vs. 33%, $p < 0.001$). There was a statistical trend in the same direction in the CS = 1 and CS = 3–4 groups ($p = 0.08$ and $p = 0.07$, respectively). Paradoxically, anemic patients had a trend towards better outcomes in the CS = 0 group. However, this result is based on a small number of patients and is probably coincidental. In pooled analyses of the CS 1–4 and 2–4 ranges (vs. CS = 0 and CS = 0–1, respectively), nonanemic patients experienced good outcome significantly more often ($p < 0.001$ for both). Figure 3 depicts shift analysis of the 3-month mRS in anemic and nonanemic patients with CS 1–4 (fair to good collateral circulation). The proportion of patients in mRS categories 0–2 is larger in the nonanemic group whereas anemic patients had significantly higher mortality (mRS = 6, $p < 0.001$).

Anemia and Hemoglobin Value Are Independent Predictors of Good 3-Month Clinical Outcome

Binary logistic modeling for the dichotomized 3-month clinical outcome was performed using all the baseline and imaging variables described in Table 1 as covariates considering that they are all theoretically meaningful predictors of clinical outcome. Multiple imputation

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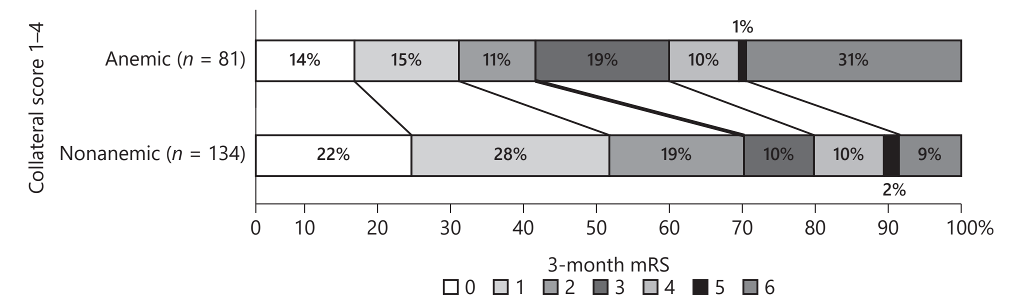

Fig. 3. The distributions of 3-month modified Rankin Scale (mRS) in the anemic and nonanemic groups in proximal occlusions, collateral scores 1–4. The thick line indicates the division between functional independence (mRS ≤2, left-hand side) and dependence (right-hand side).

was used to generate approximations for missing data to avoid 54 patients from being dropped in list-wise deletion. The results for dichotomized hemoglobin (anemic/nonanemic) are outlined in Table 3. Not having anemia improved the odds of good clinical outcome 2.6-fold (95% CI = 1.377–5.030, $p = 0.004$). Younger age, higher ASPECTS (admission NCCT), higher CS, higher mTICI score, and more distal sites of occlusion were also significantly associated with good clinical outcome. The analysis was repeated using hemoglobin values normalized with respect to the lowest normal range value (online suppl. Table 1). A 0.1 g/dL increase in hemoglobin improved the odds of good clinical outcome by 2% (OR = 1.02, 95% CI 1.002–1.040, $p = 0.03$). Models with no imputation (original data, $n = 231$) and the independent variables only being imputed ($n = 266$) were calculated as sensitivity analyses (online suppl. Tables 2–5). The results for the 2 hemoglobin variables remained essentially unchanged in all these models.

Discussion

Rapid and effective recanalization of the occluded vessel is a crucial determinant of a good clinical outcome in the treatment of acute anterior circulation ischemic stroke [15, 16]. Good clinical outcome (mRS ≤2) is achieved only in roughly half of the anterior circulation stroke patients despite high rates (85–90%) of successful reperfusion with modern MT treatments [17–20]. Our results are in agreement with these observations. The integrity of the collateral circulation is an established predictor of clinical outcome whereas studies on anemia have yielded conflicting results. We studied the interplay of these 2 potentially modifiable factors and found both to be significant and independent predictors of clinical outcome, with anemia being associated with poor outcome especially among those who have good or fair collateral circulation.

Anemia has been generally linked to poor clinical outcome in ischemic stroke patients [2–6]. We observed this linkage also in anterior circulation MT patients. Akpinar et al. [21] reported poor clinical outcome in a small cohort of moderately and severely anemic LVO patients treated with MT. Our data confirm and further elucidate this finding to especially concern patients with good or fair collateral circulation. Tanne et al. [2] proposed that anemia and clinical outcome are nonlinearly correlated so that patients having either very low or high hemoglobin concentrations experience worse clinical outcomes. Our results suggest a more linear mode of action throughout the hemoglobin range: Lower hemoglobin values predicted

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Table 3. Logistic regression analysis of good clinical outcome at 3 months (mRS ≤2), dichotomized hemoglobin value, multiple imputation (n = 285)

	OR	Sig.	95% CI
Nonanemia	2.63	**0.004**	1.377–5.030
Age	0.96	**0.02**	0.936–0.993
ASPECTS, admission NCCT	1.20	**0.04**	1.007–1.441
Hypertension	0.58	0.07	0.320–1.053
Diabetes	0.69	0.34	0.321–1.486
NIHSS, admission	0.95	0.07	0.893–1.004
mTICI 2b–3	3.26	**0.05**	1.014–10.461
Male	1.53	0.17	0.832–2.812
Collateral score	1.59	**0.009**	1.125–2.234
Non-ICA occlusion	2.26	**0.009**	1.230–4.135
Onset-to-groin puncture	1.00	0.60	0.996–1.002
Atrial fibrillation	1.07	0.82	0.588–1.952
Ischemic heart disease	1.62	0.25	0.713–3.655
IV thrombolysis	1.00	1.00	0.539–1.859

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; ICA, internal carotid artery; IV, intravenous; mTICI, modified Thrombolysis in Cerebral Infarction score; NCCT, non-contrast-enhanced computed tomography; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio. Boldface denotes $p < 0.05$.

worse outcome not only in anemic patients but also within the normal range. This finding is theoretically sensible considering the increased oxygen transfer capacity per each additional unit of hemoglobin. However, there were only few patients with very low or high hemoglobin concentrations in our cohort (online suppl. Fig. 1), and the follow-up period was shorter. LVO patients have larger ischemic parenchymal volumes than the average patient in the general ischemic stroke population and correspondingly suffer from a more severe condition. Thus, reduced oxygen delivery because of anemia potentially has a larger impact on LVO patients. This may in part explain the differences between our findings and the previously published studies that address the general stroke population [2–8]. In our data, anemia appeared to have a paradoxical beneficial effect on outcome in the absence of visible collateral circulation (CS = 0). This finding is based on a small number of patients and is probably artifactual considering that there is no conceivable mechanism for this effect.

Onset-to-reperfusion time is a well-established prognostic factor with longer delays contributing towards poorer clinical outcomes. We found no significant difference in onset-to-groin puncture times between the good and poor clinical outcome groups. This may be explained by brain imaging being the primary patient selection method. Still, prolonged duration of MT was associated with worse outcome and lower mTICI scores (data not shown). Successful reperfusion (mTICI 2b-3) was an independent predictor of good clinical outcome. However, the difference in successful reperfusion rates was relatively small between the 2 outcome groups (95 vs. 89%). This small difference highlights variations in the rate of expansion of the infarct core [22] which is heavily dependent on the intracranial collateral flow [23–25].

The inherent limitation of this study is the observational and retrospective design. The single, tertiary high-volume stroke care center setup potentially limits the generalizability of the findings. Missing data and the multiple imputation method may introduce biases and increase variability. However, the percentage of missing data is small, and the results were robust in sensitivity analyses.

Conclusions

Low hemoglobin on admission predicts poor clinical outcome in mechanical thrombectomy patients with fair or good collateral circulation.

Acknowledgment

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Statement of Ethics

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Pirkanmaa Hospital District Science Center (R14551). For this type of study formal consent is not required.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest relevant to this manuscript.

Funding Sources

There are no funding sources to declare.

Author Contributions

J.-P.P.: conception and design of the work; acquisition analysis and interpretation of data, drafting of the work, and final approval; S.P.: conception and design of the work; acquisition analysis and interpretation of data, revising of the work, and final approval; E.H. and P.J.: acquisition of clinical data, revising of the work and final approval; N.S.: conception of the work, analysis and interpretation of data, revising the work, and final approval.

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