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# Admission Hemoglobin Levels Are Associated With Functional Outcome in Spontaneous Intracerebral Hemorrhage

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**OBJECTIVES:** To test the hypothesis that admission hemoglobin levels are associated with outcome in primary, nontraumatic intracerebral hemorrhage.

**DESIGN:** Individual patient data meta-analysis of three studies of intracerebral hemorrhage.

**SETTING:** Two randomized clinical trials and one multiethnic observational study.

**PATIENTS:** Patients with spontaneous, nontraumatic intracerebral hemorrhage.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Our exposure of interest was admission hemoglobin levels and the primary outcome was 3-month postintracerebral hemorrhage-dichotomized modified Rankin Scale (0–3 vs 4–6). Intermediate outcomes were admission hematoma volume and hematoma expansion defined as 6 mL or 33% increase in hemorrhage size on repeat CT. A total of 4,172 intracerebral hemorrhage patients were included in the study (mean age 63 [SD = 14]; female sex 1,668 [40%]). Each additional g/dL of admission hemoglobin was associated with 14% (odds ratio, 0.86; 95% CI, 0.82–0.91) and 7% (odds ratio, 0.93; 95% CI, 0.88–0.98) reductions in the risk of poor outcome in unadjusted and adjusted analyses, respectively. Dose-response analyses indicated a linear relationship between admission hemoglobin levels and poor outcome across the entire evaluated range (test-for-trend $p < 0.001$). No consistent associations were found between the admission hemoglobin levels and hematoma volume or hematoma expansion.

**CONCLUSIONS:** Higher hemoglobin levels are associated with better outcome in intracerebral hemorrhage. Further research is needed to evaluate admission hemoglobin levels as both a therapeutic target and predictor of outcome.

**KEY WORDS:** anemia; cerebral hemorrhage; Glasgow Coma Scale; hemoglobin A; meta-analysis; prognosis

Spontaneous, nontraumatic intracerebral hemorrhage (ICH) is a devastating condition with high morbidity and mortality (1) and few therapeutic interventions available (2). One strategy to accelerate the development of new therapies is to study biological pathways routinely evaluated in the acute setting that already have safe and effective interventions available (3, 4).



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Low-admission hemoglobin (Hb) levels are associated with worse outcomes in acute coronary syndrome (5) and ischemic stroke (6) and may also play a role in hemorrhagic stroke. A few small, single-center studies have found associations between low admission Hb (7–10) and anemia (9, 11–16) and increased morbidity and mortality in ICH. Proposed mechanisms that would explain this relationship with worse outcome include impaired cerebral oxygen delivery (17) and coagulopathy (18, 19) leading to ICH expansion (10), a powerful predictor of poor outcome (20). Although promising, the existing evidence is limited by the small sample size of existing studies.

We, therefore, aimed to evaluate the relationship between the admission Hb levels and outcome in patients with ICH across multiple studies of this condition, all with excellent ascertainment quality for the collected data. We hypothesize that higher admission Hb levels are associated with better outcomes in these patients. We conducted an individual participant data (IPD) meta-analysis of over 4,000 ICH patients enrolled in the Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 (ATACH-2) clinical trial (21), the Factor Seven for Acute Hemorrhagic Stroke (FAST) clinical trial (22), and the Ethnic/Racial Variation in Intracerebral Hemorrhage (ERICH) observational study (23).

## MATERIAL AND METHODS

### Study Design

We performed an IPD meta-analysis (24) across the ATACH-2, FAST, and ERICH studies. Details about the design and inclusion/exclusion criteria of these studies are available elsewhere (21–23). Briefly, ATACH-2 (NCT01176565) randomized 1,000 ICH patients with elevated systolic blood pressure (> 180 mm Hg) presenting within 4.5 hours of symptom onset to intensive or standard blood-pressure lowering treatment. FAST (NCT00127283) randomized 841 ICH patients presenting within 4 hours of symptom onset to receive recombinant activated factor 7 or placebo. ERICH (NCT01202864) enrolled 3,000 ICH patients, including equal proportions of Whites, Blacks, and Hispanics.

### Standard Protocol Approvals, Registrations, and Patient Consents

Each study included was approved by the appropriate Institutional Review Boards and written informed consent was obtained from each participant or each participant's legal representative.

### Definition of ICH

All studies enrolled patients with a primary, nontraumatic ICH, defined as an acute neurologic deficit with associated new intraparenchymal blood documented on neuroimaging. ICH cases secondary to tumors, vascular malformations, or hemorrhagic conversion of an ischemic stroke were excluded.

### Exposure and Outcome

Our exposure of interest was baseline Hb levels, as measured on routine admission laboratories. Hb measurements were converted to mg/dL. Patients missing admission Hb levels or 3-month outcome data were excluded. Our primary outcome was functional outcome 3 months after the ICH, as measured by the modified Rankin scale (mRS). The mRS is a 7-point ordinal scale with 0 corresponding to full recovery and 6 corresponding to death (25).

### Neuroimaging Analysis

Baseline and follow-up head CT scans were obtained in all three studies. The determination of ICH location, ICH volume, and intraventricular hemorrhage (IVH) presence was performed centrally by blinded investigators in each study. ICH volumes were measured using manual or semiautomatic segmentation of the parenchymal hematoma. ICH location was classified as lobar or nonlobar, as the former is mainly linked to cerebral amyloid angiopathy and the latter to long-standing hypertension (26). Nonlobar hemorrhages included those compromising the thalami or basal ganglia and those located below the tentorium and primary IVHs. Hematoma expansion was defined as 6 mL or 33% increase in hemorrhage size on a follow-up scan (24 hr after the initiation of treatment in ATACH-2 and FAST trials and the first available repeat neuroimaging study in ERICH).

### Statistical Methods

Categorical variables are presented as count (%) and continuous variables as mean (SD) or median (interquartile range), as appropriate.

***Exposure and Outcome Modeling***. We modeled admission Hb levels as a continuous variable and functional outcome as a dichotomous variable, defining good outcome as mRS 0–3 and poor outcome as 4–6 (25, 27). In sensitivity analyses, we dichotomized Hb values as anemia (< 12 mg/dL for women and < 13 mg/dL for men) or no anemia. For analysis involving intermediate neuroimaging endpoints, we modeled ICH volume as a continuous variable and ICH expansion as a dichotomous variable.

***Association Testing***. The primary analyses involved a one-stage IPD meta-analysis, implementing multivariable, mixed-effects logistic regression modeling to test for association between the admission Hb levels and outcome. As a secondary analysis, we conducted a two-stage IPD meta-analysis, fitting multivariable logistic regression models for each study separately, with subsequent pooling of study-specific results using fixed-effects and random-effects (with inverse-variance weighting) meta-analyses. Multivariable models included universal confounders (gender and race), the components of the ICH score (age, ICH location, ICH volume, presence of IVH, and Glasgow Coma Scale), and anticoagulation (only for ERICH study). We used $\tau^2$, Q, and $I^2$ to assess heterogeneity. In sensitivity analyses, we: 1) adjusted for the trial intervention when analyzing ATACH-2 and FAST data, 2) excluded anticoagulated participants from ERICH, 3) included participants from clinical trials only, 4) included only participants with prestroke mRS compatible with independence, 5) analyzed only participants with Hb levels outside the usual transfusion threshold (7 mg/dL), and 6) dichotomized outcome as an mRS of 0–2 versus 3–6. In stratified analyses, we evaluated lobar and nonlobar hemorrhages separately. Finally, we performed secondary analysis looking at Hb measurements at intermediate time points (24, 48, and 72 hr after randomization) and the change between baseline and 72 hours in ATACH-2, the only study with these data available.

***Association Testing for Intermediate Neuroimaging End Points***. We used the same analytical approach to test for association between the admission Hb levels and admission hematoma volume and hematoma expansion and further tested if the relationship between the Hb levels and ICH volume changed after log-transforming ICH volume.

***Dose-Response Analyses***. We evaluated the shape of the dose-response curve between the admission Hb levels and ICH outcome by estimating the unadjusted risk of poor outcome across the strata of admission Hb levels. To assess this dose-response curve further, we calculated the predicted probabilities of poor outcome based on our regression models across the strata of the admission Hb levels using five-fold cross-validation and used generalized additive models to explore potential ceiling effects.

### Data Availability

Anonymized data from the ATACH-2 and ERICH studies are publicly available via the National Institute of Neurologic Disorders and Stroke Archive of Clinical Research Datasets. Anonymized data from the FAST trial is accessible upon reasonable request from the study's sponsor.

## RESULTS

A total of 4,841 ICH patients were enrolled in ATACH-2, FAST, and ERICH. After excluding 669 patients who had missing data for admission Hb levels or outcome, a total of 4,172 ICH patients (mean age 63 [SD = 14]; 1,668 [40%] were female) were included in the study, including 905 from ATACH-2, 2,521 from ERICH, and 746 from FAST (**Table 1**). There were 976 lobar (23%) and 3,167 nonlobar (76%) hemorrhages (29 with missing location). The mean admission Hb was 13.8 (1.9) g/dL when considering all studies together, and 14.3 (1.7), 14.0 (1.6), and 13.6 (2.0), respectively, when evaluating each study separately (**Table 2**). Poor outcomes were observed in 1,940 patients (47%) when considering all studies, and 346 (38%), 359 (48%), and 1,235 (49%), respectively, when evaluating each study separately (Table 2). Among all participants, 770 (18.5%) died.

### Admission Hemoglobin Levels and ICH Outcome

We found a significant association between the higher admission Hb levels and the lower risk of poor outcome (**Table 3**). The primary analysis combining IPD across studies and implementing multivariable mixed-effects logistic regression indicated that each additional g/dL of admission Hb was associated with a 7%

## TABLE 1.
### Demographic Characteristics by Study

| Variable | Overall (*n* = 4,172) | Antihypertensive Treatment of Acute Cerebral Hemorrhage-II (*n* = 905) | Ethnic/Racial Variations of Intracerebral Hemorrhage (*n* = 2,521) | Recombinant Factor VIIa in Acute Intracerebral Hemorrhage (*n* = 746) |
|---|---|---|---|---|
| Age (yr), mean (SD) | 62.56 (13.69) | 62.23 (13.03) | 62.10 (14.14) | 64.57 (12.71) |
| Female, *n* (%) | 1,668 (40.0) | 342 (37.8) | 1,047 (41.5) | 279 (37.4) |
| White race, *n* (%) | 1,080 (31.5) | 239 (26.4) | 841 (33.4) | Not applicable |
| Hypertension, *n* (%) | 3,101 (76.4) | 716 (81.2) | 1,883 (75.0) | 502 (75.3) |
| Diabetes, *n* (%) | 889 (21.7) | 179 (19.8) | 625 (24.8) | 85 (12.7) |
| Hyperlipidemia, *n* (%) | 967 (24.2) | 217 (25.5) | 671 (27.0) | 79 (11.8) |
| Atrial fibrillation, *n* (%) | 316 (7.9) | 32 (3.6) | 256 (10.5) | 28 (4.2) |
| Ever smoker, *n* (%) | 1,423 (37.1) | 399 (44.1) | 1,009 (44.5) | 15 (2.2) |
| Anticoagulation, *n* (%) | 287 (6.9) | 0 (0.0) | 287 (11.4) | 0 (0.0) |
| Lobar intracerebral hemorrhage, *n* (%) | 976 (23.4) | 104 (11.5) | 778 (30.9) | 94 (13.1) |
| Intraventricular hemorrhage present, *n* (%) | 1,574 (38.6) | 234 (26.4) | 1,069 (43.6) | 271 (36.7) |

## TABLE 2.
### Exposure and Outcomes

| Variable | Overall (*n* = 4,172) | Antihypertensive Treatment of Acute Cerebral Hemorrhage-II Trial (*n* = 905) | Ethnic/Racial Variations of Intracerebral Hemorrhage Study (*n* = 2,521) | Recombinant Factor VIIa in Acute Intracerebral Hemorrhage Trial (*n* = 746) |
|---|---|---|---|---|
| Hemoglobin (g/dL), mean (SD) | 13.84 (1.91) | 14.26 (1.73) | 13.63 (2.02) | 14.03 (1.62) |
| Intracerebral hemorrhage volume (mL), mean (SD)[a] | 19.99 (23.88) | 13.70 (12.05) | 21.39 (26.14) | 22.88 (25.35) |
| Hematoma expansion, *n* (%) | 781 (24.0) | 195 (24.3) | 370 (21.5) | 216 (29.9) |
| Poor outcome[b], *n* (%) | 1940 (46.5) | 346 (38.2) | 1235 (49.0) | 359 (48.1) |
| Death, *n* (%) | 770 (18.5) | 66 (7.3) | 554 (22.0) | 150 (20.1) |

[a]Missing data for baseline intracerebral hemorrhage volume = 92.
[b]Poor outcome defined as modified Rankin Scale ≥ 4 at 3-mo follow-up.

decrease in risk of poor outcome (odds ratio [OR], 0.93; 95% CI, 0.88–0.98; $p = 0.006$). These results remained unchanged when implementing two-stage meta-analysis using either fixed-effects (OR, 0.93; 95% CI, 0.89–0.97; $p = 0.0007$) or random-effects (OR, 0.92; 95% CI, 0.86–0.99; $p = 0.038$) approaches. Importantly, there was no heterogeneity across study-specific estimates ($\tau^2 = 0.0003$, $I^2 = 0.0\%$, and Q = 0.85 [$p = 0.65$]).

**TABLE 3.**
**Hemoglobin Association With Outcome (Modified Rankin Scale ≥ 4) at 3-mo After Intracerebral Hemorrhage**

| | All Patients ($n = 4,172$) | | Lobar ($n = 976$) | | Nonlobar ($n = 3,167$) | |
|---|---|---|---|---|---|---|
| **Study or Analysis Strategy** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** |
| Study-specific results | | | | | | |
| Antihypertensive Treatment of Acute Cerebral Hemorrhage-II trial | 0.88 (0.79–0.99) | 0.028 | 0.68 (0.47–0.98) | 0.04 | 0.90 (0.80–1.01) | 0.09 |
| Ethnic/Racial Variations of Intracerebral Hemorrhage study | 0.93 (0.88–0.98) | 0.01 | 0.94 (0.85–1.04) | 0.23 | 0.92 (0.86–0.98) | 0.01 |
| Recombinant Factor VIIa in Acute Intracerebral Hemorrhage trial | 0.95 (0.84–1.07) | 0.37 | 1.01 (0.69–1.49) | 0.95 | 0.92 (0.81–1.05) | 0.21 |
| Combined analyses | | | | | | |
| One-stage IPD meta-analysis | 0.93 (0.88–0.98) | 0.006 | 0.93 (0.75–1.14) | 0.47 | 0.92 (0.87–0.98) | 0.007 |
| Two-stage IPD meta-analysis (fixed effects) | 0.93 (0.89–0.97) | 0.0007 | 0.93 (0.85–1.02) | 0.10 | 0.92 (0.87–0.97) | 0.001 |
| Two-stage IPD meta-analysis (random effects) | 0.92 (0.86–0.99) | 0.039 | 0.89 (0.56–1.40) | 0.37 | 0.92 (0.90–0.94) | 0.003 |

IPD = individual participant data, OR = odds ratio.
Missing data for intracerebral hemorrhage (ICH) location = 29. Models adjusted by age, sex, race, ICH location (except in stratified analyses by location), ICH volume, presence of intraventricular hemorrhage, Glasgow Coma Scale, and, in Ethnic/Racial Variations of Intracerebral Hemorrhage study, anticoagulation use. Heterogeneity (all patients): $\tau^2 = 0.0003$, $I^2 = 0.0\%$, and Q = 0.85 ($p = 0.65$). Heterogeneity (lobar): $\tau^2 = 0.0216$, $I^2 = 33.2\%$, and Q = 2.99 ($p = 0.22$). Heterogeneity (nonlobar): $\tau^2 = < 0.0001$, $I^2 = 0.0\%$, and Q = 0.07 ($p = 0.97$).

Sensitivity analyses including the trial intervention in ATACH-2 and FAST did not change the results nor did the exclusion of anticoagulated participants from ERICH (OR, 0.93; 95% CI, 0.89–0.97; $p < 0.001$). Additionally, analysis including only participants from clinical trials, only those with prestroke mRS compatible with independence, or only those outside the usual transfusion threshold yielded consistent results, as did dichotomizing mRS as 0–2 versus 3–6. Analyses stratified by hemorrhage location yielded similar results in nonlobar hemorrhages but did not reach statistical significance in lobar ICH (Table 3). Finally, we performed secondary analysis using Hb measurements at 24, 48, and 72 hours in the ATACH-2 study. Hb levels at all these three time points were associated with outcome (24 hr $p = 0.05$, and 48 and 72 hr both $p < 0.001$). A positive change in Hb levels was also associated with outcome (OR, 0.73; 95% CI, 0.62–0.84; $p < 0.001$).

## Anemia at Admission and ICH Outcome

The results outlined above remained consistent when categorizing ICH patients as anemic or nonanemic. The primary analysis combining IPD across studies indicated that anemic versus nonanemic patients had a 49% higher risk of poor outcome (OR, 1.49; 95% CI, 1.17–1.89; $p = 0.001$). These results remained unchanged when implementing two-stage meta-analysis using either fixed-effects (OR, 1.54; 95% CI, 1.26–1.88; $p < 0.0001$) or random-effects (OR, 1.54; 95% CI, 1.21–1.95; $p = 0.015$). There was no heterogeneity ($\tau^2 = 0.0025$; $I^2 = 0.0\%$, and Q = 0.55 [$p = 0.76$]).

## Dose-Response Analysis

To evaluate whether the association between the admission Hb levels and the poor outcome was only driven by anemia, we evaluated how this association

changed across different strata of the exposure. We found a consistent linear relationship between the admission Hb levels and the ICH outcome across a wide range of evaluated values. We observed this linear correlation when both estimating unadjusted risks of poor outcomes across different strata of admission Hb levels (test-for-trend $p < 0.0001$) (**Fig. 1**) and formally testing the association between the Hb levels and the predicted risks from the adjusted regression model ($p < 0.0001$). No ceiling effect was identified.

### Admission Hemoglobin Levels and ICH Volume and Expansion

We evaluated whether the observed association between the admission Hb levels and the outcomes was mediated by admission hematoma volume and hematoma expansion. Mean time to follow-up CT in ERICH was 24.1 hours (SD = 40). For this analysis, we excluded patients with primary IVHs (e.g., those without any intraparenchymal blood) and those with missing data for hematoma expansion. These exclusions led to an effective sample size of 4,035 ICH cases for the analysis of admission hematoma volume and 3,215 for the analysis of hematoma expansion. The primary analysis did not find an association between the admission Hb levels and these neuroimaging markers (**Table 4**). Sensitivity analysis using log-transformed ICH volume as outcome did not change the results. Study-specific analyses did reveal an inverse association between the admission Hb levels and ICH volume in ERICH (beta = –1.09; 95% CI, –1.60 to –0.58; $p < 0.0001$). We did not find significant associations for hematoma expansion. Sensitivity analysis including time from symptom onset to CT did not significantly change the results.

## DISCUSSION

We report the results of a large observational study evaluating whether admission Hb levels are associated with functional outcome in spontaneous, nontraumatic ICH. We pooled IPD from ERICH, a multiethnic prospective observational study of ICH, and ATACH-2 and FAST, two landmark clinical trials that evaluated aggressive blood pressure reduction and activated Factor VII, respectively, in this condition. We found that higher admission Hb levels were associated with a lower risk of poor outcome in ICH, with consistent effect estimates across the included studies. We also found that this association held across a wide range of evaluated Hb levels and that it was stronger for nonlobar hemorrhages. We did not find a consistent association between the admission Hb levels and admission hematoma volume or hematoma expansion.

Our findings confirm the existing evidence for an association between the admission Hb levels and functional outcome in ICH. A small, single-center study found that low Hb levels were associated with worse functional outcome, and this association was mediated by a higher risk of hematoma expansion (10). Although promising, these results were limited by the small sample size and single-center design of the study. A meta-analysis on this topic based on summary statistics (not using IPD) including seven studies showed that anemia at admission (defined as Hb < 12 g/dL for women and < 13 g/dL for men) was associated with higher

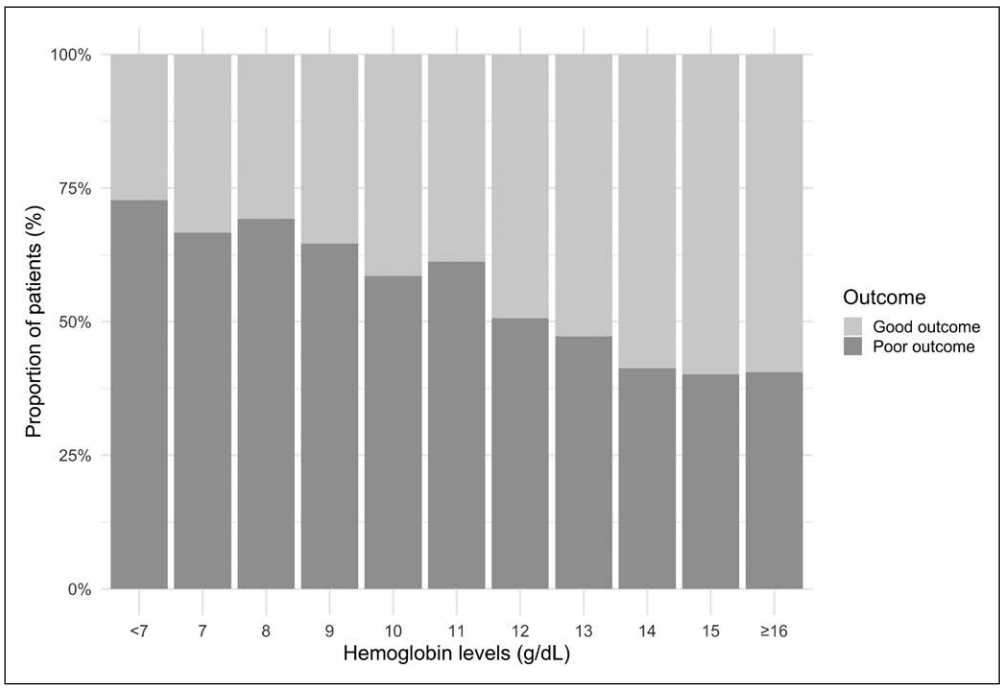


**Figure 1.** Dose-response analysis. Proportion of patients with poor outcome in each hemoglobin level subgroup.

**TABLE 4.**
**Hemoglobin Association Intracerebral Hemorrhage With Baseline Volume and Intracerebral Hemorrhage Expansion**

| | ICH Volume | | ICH Expansion | |
|---|---|---|---|---|
| **Study or Analysis Strategy** | **Beta (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** |
| Study-specific results | | | | |
| Antihypertensive Treatment of Acute Cerebral Hemorrhage-II trial | 0.14 (−0.35 to 0.62) | 0.58 | 0.98 (0.88–1.09) | 0.745 |
| Ethnic/Racial Variations of Intracerebral Hemorrhage study | −1.09 (−1.60 to −0.58) | < 0.0001 | 0.94 (0.88–1.01) | 0.077 |
| Recombinant Factor VIIa in Acute Intracerebral Hemorrhage trial | 0.24 (−0.86 to 1.35) | 0.67 | 1.03 (0.92–1.16) | 0.58 |
| Meta-analysis | | | | |
| One-stage IPD meta-analysis | −0.35 (−1.24 to 0.55) | 0.45 | 0.99 (0.92–1.05) | 0.71 |
| Two-stage IPD meta-analysis (fixed effects) | −0.38 (−0.72 to −0.05) | 0.026 | 0.97 (0.92–1.02) | 0.20 |
| Two-stage IPD meta-analysis (random effects) | −0.30 (−2.17 to 1.58) | 0.57 | 0.97 (0.87–1.09) | 0.40 |

ICH = intracerebral hemorrhage, IPD = individual participant data, OR = odds ratio.
Intracerebral hemorrhage (ICH) volume models: models adjusted by age, sex, race, ICH location, and anticoagulation use (only in Ethnic/Racial Variations of Intracerebral Hemorrhage study [ERICH]). Heterogeneity: $\tau^2 = 0.4236$, $I^2 = 84.5\%$ (54.0–94.8%), and Q = 12.93 ($p = 0.0016$). ICH expansion models: models adjusted by age, sex, race, ICH location, baseline ICH volume, treatment (in Antihypertensive Treatment of Acute Cerebral Hemorrhage-II and Recombinant Factor VIIa in Acute Intracerebral Hemorrhage trial), and anticoagulation use (only in ERICH). Heterogeneity: $\tau^2 = 0.0008$, $I^2 = 0.0\%$ (0.0–89.2%), and Q = 1.92 ($p = 0.38$).

mortality and worse outcome (13). These results were limited by the high meta-analytic heterogeneity of the pooled estimates and the limited modeling strategy of the exposure.

By addressing the limitations outlined above, our study provides important new evidence linking admission Hb levels to functional outcome in ICH. We combined IPD from three well-phenotyped studies of ICH to achieve the power necessary to evaluate appropriately the hypothesis of interest. In addition, the availability of admission Hb levels allowed us to model the exposure as a continuous variable and assess whether the observed associations held across different strata of this variable. We found a linear association between the Hb levels and outcome. However, visual inspection of Figure 1 shows that the proportion of patients with poor outcome stabilizes around 14 mg/dL. Furthermore, in stratified analyses, we found that the relationship held for nonlobar but not for lobar ICH. One possible explanation is that smaller changes in brain oxygenation could have more significant consequences in patients with nonlobar ICH. Follow-up studies should evaluate whether the known biological differences across these subtypes play a role in explaining our findings.

Unlike prior studies, we did not find a consistent association between the admission Hb levels and hematoma volume or expansion, two possible mediators of the observed association with outcome. Possible explanations for the null results for hematoma volume are the relatively low hematoma volume seen in ATACH-2 and the exclusion of anticoagulated patients from both clinical trials. Regarding hematoma expansion, the inclusion of interventional trials whose therapeutic effect was aimed at reducing hematoma expansion could bias these results toward the null. Notably, we did find an association between the admission Hb levels and hematoma volume and a trend toward a protective effect of higher baseline Hb levels on hematoma expansion in ERICH, results that emphasize the need for further research in this area, with a focus on possible mediating mechanisms.

There is significant experience with the utilization of blood products in the hyperacute, acute, and subacute periods of acute brain injury, including subarachnoid hemorrhage and traumatic brain injury. However, the efficacy of such interventions has been variable in the literature. A small retrospective study investigating packed RBC transfusions in ICH concluded that this interventions was safe and was associated with improved survival at 30 days in multivariable analyses adjusting for ICH score variables (28), but a more recent study found worse outcomes in patients receiving transfusions (29). Combined with prior reports, this study suggests that Hb levels may be a potential target for clinical interventions, but further research is needed to establish a causal association. Alternatively, low Hb levels could be a mediator of poor outcomes in patients with other comorbidities.

Our study has a number of limitations. Being an exploratory analysis of existing studies, the presented results could correspond to false-positive associations caused by multiple testing. Furthermore, the overrepresentation of nonlobar ICH, explained by different factors depending on the study, resulted in a lower number of lobar hemorrhages; therefore, the lack of statistical significance of the analysis focused on lobar ICH should be interpreted with caution, as it could be due to limited statistical power. Additionally, the three studies had a different distribution of outcomes, as ATACH-2 had significantly better outcomes. In addition, the lack of data on transfusions and the exclusion criteria of both randomized clinical trials may limit the generalizability of our results. However, the strength of the association and consistency of the estimates across the included studies and analytical strategies provides significant reassurance against this scenario. Even if replicated across different cohorts, the observational nature of our study precludes the possibility of making any causal inferences. The observed association could be the result of bias caused by confounding by underlying serious comorbidities (like cancer) that both lower Hb levels and increase the risk of poor outcome. Preclinical studies using animal models, genetic analyses, and randomized clinical trials are needed to determine whether the association between the admission Hb levels and outcome in ICH represents a causal relationship. Even in the absence of a causal link justifying therapeutic interventions, admission Hb levels would still hold significant value as a very early biomarker for poor outcome in this condition. These early biomarkers of future prognosis are particularly helpful to select appropriately patients for clinical trials.

## CONCLUSIONS

In conclusion, we report a large IPD meta-analysis that pooled data from the ATACH-2, FAST, and ERICH studies to examine the relationship between the admission Hb levels and functional outcome after ICH. We found that higher admission Hb levels were associated with better outcomes and that this association was stronger for nonlobar hemorrhages. Further research is needed to evaluate admission Hb level as both a therapeutic target and early predictor of outcome.

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## REFERENCES

1. Gross BA, Jankowitz BT, Friedlander RM: Cerebral intraparenchymal hemorrhage: A review. *JAMA* 2019; 321:1295–1303
2. Cordonnier C, Demchuk A, Ziai W, et al: Intracerebral haemorrhage: Current approaches to acute management. *Lancet* 2018; 392:1257–1268
3. Mei H, Xia T, Feng G, et al: Opportunities in systems biology to discover mechanisms and repurpose drugs for CNS diseases. *Drug Discov Today* 2012; 17:1208–1216
4. Fagan SC. Drug repurposing for drug development in stroke. *Pharmacotherapy* 2010; 30(7 PART 2):51S–54S
5. Stucchi M, Cantoni S, Piccinelli E, et al: Anemia and acute coronary syndrome: Current perspectives. *Vasc Health Risk Manag* 2018; 14:109–118
6. Kellert L, Schrader F, Ringleb P, et al: The impact of low hemoglobin levels and transfusion on critical care patients with severe ischemic stroke: STroke: RelevAnt Impact of HemoGlobin, Hematocrit and Transfusion (STRAIGHT)–an observational study. *J Crit Care* 2014; 29:236–240
7. Chang TR, Boehme AK, Aysenne A, et al: Nadir hemoglobin is associated with poor outcome from intracerebral hemorrhage. *Springerplus* 2013; 2:379
8. Diedler J, Sykora M, Hahn P, et al: Low hemoglobin is associated with poor functional outcome after non-traumatic, supratentorial intracerebral hemorrhage. *Crit Care* 2010; 14:R63
9. Barlas RS, Honney K, Loke YK, et al: Impact of hemoglobin levels and anemia on mortality in acute stroke: Analysis of UK regional registry data, systematic review, and meta-analysis. *J Am Heart Assoc* 2016; 5:1–16
10. Roh DJ, Albers DJ, Magid-Bernstein J, et al: Low hemoglobin and hematoma expansion after intracerebral hemorrhage. *Neurology* 2019; 93:e372–e380
11. Li Z, Zhou T, Li Y, et al: Anemia increases the mortality risk in patients with stroke: A meta-analysis of cohort studies. *Sci Rep* 2016; 6:1–8
12. Kuramatsu JB, Gerner ST, Lücking H, et al: Anemia is an independent prognostic factor in intracerebral hemorrhage: An observational cohort study. *Crit Care* 2013; 17:R148
13. Zhang S, Pan X, Wei C, et al: Associations of anemia with outcomes in patients with spontaneous intracerebral hemorrhage: A meta-analysis. *Front Neurol* 2019; 10:1–9
14. Zeng YJ, Liu GF, Liu LP, et al: Anemia on admission increases the risk of mortality at 6 months and 1 year in hemorrhagic stroke patients in China. *J Stroke Cerebrovasc Dis* 2014; 23:1500–1505
15. Bussière M, Gupta M, Sharma M, et al; Investigators of the Registry of the Canadian Stroke Network: Anaemia on admission is associated with more severe intracerebral haemorrhage and worse outcomes. *Int J Stroke* 2015; 10:382–387
16. Kumar MA, Rost NS, Snider RW, et al: Anemia and hematoma volume in acute intracerebral hemorrhage. *Crit Care Med* 2009; 37:1442–1447
17. Kramer AH, Zygun DA: Anemia and red blood cell transfusion in neurocritical care. *Crit Care* 2009; 13:R89
18. Livio M, Gotti E, Marchesi D, et al: Uraemic bleeding: Role of anaemia and beneficial effect of red cell transfusions. *Lancet* 1982; 2:1013–1015
19. Roeloffzen WW, Kluin-Nelemans HC, Bosman L, et al: Effects of red blood cells on hemostasis. *Transfusion* 2010; 50:1536–1544
20. Dowlatshahi D, Demchuk AM, Flaherty ML, et al; VISTA Collaboration: Defining hematoma expansion in intracerebral hemorrhage: Relationship with patient outcomes. *Neurology* 2011; 76:1238–1244
21. Qureshi AI, Palesch YY, Suarez JI: Intensive blood-pressure lowering in cerebral hemorrhage. *N Engl J Med* 2016; 375:e48
22. Mayer SA, Brun NC, Begtrup K, et al; FAST Trial Investigators: Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; 358:2127–2137
23. Woo D, Rosand J, Kidwell C, et al: The ethnic/racial variations of intracerebral hemorrhage (ERICH) study protocol. *Stroke* 2013; 44:e120–e125

24. Tierney JF, Vale C, Riley R, et al: Individual participant data (IPD) meta-analyses of randomised controlled trials: Guidance on their use. *PLoS Med* 2015; 12:e1001855
25. Broderick JP, Adeoye O, Elm J: Evolution of the modified Rankin scale and its use in future stroke trials. *Stroke* 2017; 48:2007–2012
26. Falcone GJ, Biffi A, Brouwers HB, et al: Predictors of hematoma volume in deep and lobar supratentorial intracerebral hemorrhage. *JAMA Neurol* 2013; 70:988–994
27. Bamford JM, Sandercock PA, Warlow CP, et al: Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989; 20:828
28. Sheth KN, Gilson AJ, Chang Y, et al: Packed red blood cell transfusion and decreased mortality in intracerebral hemorrhage. *Neurosurgery* 2011; 68:1286–1292
29. Roh DJ, Carvalho Poyraz F, Magid-Bernstein J, et al: Red blood cell transfusions and outcomes after intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 2020; 29:105317