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Low hemoglobin is associated with poor functional outcome after non-traumatic, supratentorial intracerebral hemorrhage

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Abstract

Introduction: The impact of anaemia on functional outcome and mortality in patients suffering from non-traumatic intracerebral haemorrhage (ICH) has not been investigated. Here, we assessed the relationship between haemoglobin (HB) levels and clinical outcome after ICH.

Methods: One hundred and ninety six patients suffering from supratentorial, non-traumatic ICH were extracted from our local stroke database (June 2004 to June 2006). Clinical and radiologic computed tomography data, HB levels on admission, mean HB values and nadir during hospital stay were recorded. Outcome was assessed at discharge and 3 months using the modified Rankin score (mRS).

Results: Forty six (23.5%) patients achieved a favorable functional outcome (mRS ≤ 3) and 150 (76.5%) had poor outcome (mRS 4 - 6) at discharge. Patients with poor functional outcome had a lower mean HB (12.3 versus 13.7 g/dl, $P < 0.001$) and nadir HB (11.5 versus 13.0 g/dl, $P < 0.001$). Ten patients (5.1%) received red blood cell (RBC) transfusion. In a multivariate logistic regression model, the mean HB was an independent predictor for poor functional outcome at three months (odds ratio (OR) 0.73, 95% confidence interval (CI) 0.58-0.92, $P = 0.007$), along with National Institute of Health Stroke Scale (NIHSS) at admission (OR 1.17, 95% CI 1.11 - 1.24, $P < 0.001$), and age (OR 1.08, 95% CI 1.04 - 1.12, $P < 0.001$).

Conclusions: We report an association between low HB and poor outcome in patients with non-traumatic, supratentorial ICH. While a causal relationship could not be proven, previous experimental studies and studies in brain injured patients provide evidence for detrimental effects of anaemia on brain metabolism. However, the potential risk of anaemia must be balanced against the risk of harm from red blood cell infusion.

Introduction

Intracerebral hemorrhage (ICH) accounts for approximately 10-15% of acute strokes and is still associated with a mortality up to 30-50% [1]. ICH volume, neurological status on admission, age above 80 years and the presence of intraventricular blood were found to be strong predictors of 30-day mortality [2]. Around 50% of the patients require mechanical ventilation [3] and most are admitted to an intensive care unit [4]. A study including medical and surgical intensive care unit (ICU) patients found a high incidence of anemia in critically ill patients and the nadir hemoglobin (HB) level of <9 g/dl as a predictor of increased mortality and length of hospital stay [5]. At the same time, the number of red blood cell (RBC) transfusions a patient received was independently associated with increased mortality. The current literature supports the idea that many critically ill patients tolerate HB levels as low as 7 g/dl and that a liberal transfusion strategy may in fact lead to worse clinical outcome [5-6]. However, it remains unclear whether a restrictive transfusion threshold is also suitable for neurocritical care patients. Studies including patients suffering from subarachnoid hemorrhage (SAH) [7-9] or traumatic brain injury (TBI) [10-12] provide evidence that low HB is associated with poor functional outcome. A recent study in SAH patients reports that higher HB levels (11.7 ± 1.5 g/dl vs. 10.9 ± 1.2 g/dl) were related with better outcome at discharge and at 3 months [7]. The effects of anemia in patients suffering from supratentorial non-traumatic ICH have not yet been investigated. In the current study, we assessed the impact of anemia on functional outcome and mortality after ICH.

Materials and Methods

Patients

We retrieved all patients suffering from supratentorial ICH that were admitted to our stroke unit or neurological intensive care unit between June 2004 and June 2006 from our local stroke database (n=247). Complete datasets including CT data, baseline NIHSS, mRS at discharge and laboratory tests were available for 196 patients. ICH was diagnosed by computed tomography (CT). Hematoma volume was calculated from the first CT scan using

the a x b x c x 0.5 method [13]. Stroke severity on admission was assessed using the NIHSS (National Institutes of Health Stroke Scale). Functional outcome at discharge was assessed by the attending physician using the modified Rankin Scale (mRS). Functional outcome at 3 months was assessed by a standardized telephone interview using the mRS or by assessing the final reports after end of rehabilitation. Outcome scores were dichotomized into favorable (mRS ≤ 3) and poor functional outcome (mRS 4-6). The study was approved by the local ethics committee (S-406/2009). The data was collected in an anonymized database, therefore the need for informed consent was waived.

HB levels and transfusions

All HB measurements during hospital stay were extracted from the laboratory database. Routinely, ICU patients have daily laboratory controls, stroke unit patients every other day. In the mean, 7.5 HB values were available for each patient (SD ± 8.0). For every patient, HB on admission, the nadir (lowest value during hospital stay) and the mean HB level (calculated from all available values) was recorded for further analysis. The records of all patients with a nadir of ≤ 10 g/dl were screened for red blood cell (RBC) transfusions and the reason for transfusion. At the moment there is no predefined institutional standard for RBC transfusion in ICH patients. Anemia was defined as a HB level of <12.1 g/l for women and <13.1 g/l for men [14].

Statistical analysis

Distribution of the data was tested using the one-sample Kolmogorov-Smirnov test. Comparisons between groups of patients were made using the χ^2 , Student's *t* test or the Mann-Whitney test where appropriate. Mean HB values in the different outcome categories were compared by using a one-way ANOVA, post-hoc analyses were performed applying Bonferroni adjustment. Homogeneity of variance was tested using the Levene's homogeneity-of-variance test when applying the Student's *t* test and ANOVA. Logistic regression was used to create a model to predict poor outcome (mRS 4-6) at discharge and

at 3 months and in-hospital mortality. The variables age, hemorrhage volume, NIHSS at admission, the presence of intraventricular blood, ICU stay, the need for mechanical ventilation, RBC transfusion, the mean HB level during hospital stay and admission HB were entered into the multivariate model. Because of co-linearity of the included variables, a forward stepwise regression analysis was employed to select which of the variables should be included in a regression model to predict the dependent variable. The procedure applied the variables one by one using a criterion such that the F-statistic for the variable to be added must exceed the level of 0.05. After a variable has been added to the model, the procedure analyzes all included variables and deletes any variable that fails to produce an F-value less than 0.1. After necessary deletions are accomplished, further variable can be added to the model. The procedure terminates when no variable outside the model exceeds the necessary threshold and every variable included is significant. A Cox proportional model was used in order to analyse the risk to develop anemia during hospital stay for both outcome groups. Values of $p < 0.05$ were considered statistically significant in all tests. Statistical analyses were performed using the SPSS software package (SPSS 16.0).

Results

The mean age was 67.1 years (range 29-96, SD 13.5). The median hemorrhage volume was 26.9 ml (range 0.4-383, IQR 60.8) and 78 patients (39%) had intraventricular hemorrhage extension. The most frequent etiologies were hypertension (43%) and ICH due to oral anticoagulants (20%); other etiologies included amyloid angiopathy (16%) and arteriovenous malformations or cavernous angioma (6%). For 7.1% of patients the etiology remained undetermined at the time of discharge.

The mean admission HB was 13.7 g/dl (range 7.4-18.4, SD 1.9), the mean HB during hospital stay was 12.6 g/dl (range 6.3-18.4, SD 2.1) and the mean nadir HB was 11.9 g/dl (range 6.3-18.4, SD 2.3). Only 10 patients (5%) received RBC transfusions during hospital

stay. Mean admission HB of transfused patients was 12.4 g/dl (7.6-16.3, SD 2.7) and mean nadir HB triggering transfusion was 7.9 g/dl (6.3-10, SD 1.2). Reasons for transfusion were surgery (n=5), erosive gastritis (n=1), anemia due to chronic nephropathy (n=1), coronary artery disease (n=1) and undetermined (n=2). None of the included patients encountered major bleedings with need of mass transfusion.

Table 1 shows the univariate analysis of outcome at discharge. 46 (24%) patients achieved a favorable functional outcome (mRS \leq 3) while 150 (77%) had a poor functional outcome (mRS 4-6). Patients with poor functional outcome were significantly older (62.5 vs. 68.6 years, $P=0.007$) had larger hemorrhages (8.6 vs. 30 ml, $P<0.001$), and a lower mean HB (13.7 vs. 12.3 g/dl, $P<0.001$) and nadir HB (13.0 vs. 11.5 $P<0.001$) during hospital stay. In addition, significantly more patients with poor outcome had intraventricular hemorrhage extension (11% vs. 48%, $P<0.001$), developed anemia during hospital stay (22% vs. 56%, $P<0.001$), needed ICU treatment (15 vs. 51%, $P<0.001$) and mechanical ventilation (4% vs. 37%, $P<0.001$). There was no significant difference in the median duration of hospital stay (7 vs. 6 days, $P=0.32$) or the number of transfused patients between both groups (2% vs.6%, $P=0.302$).

Figure 1 shows the risk to develop anemia during hospital stay for patients with favorable (mRS 0-3) versus poor (mRS 4-6) functional outcome. Poor functional outcome at discharge was associated with higher risk to develop anemia throughout hospital stay ($P=0.029$).

Figure 2 shows patients stratified by mRS category (1-6), excluding the patients that did not survive the first day in hospital (n=17). Mean HB levels were significantly different between groups (14.0, 14.0, 13.4, 13.0, 11.9 and 11.2 mg/dl for mRS 1 to 6 respectively, $F(5,172)=7.71$, $P<0.001$). Post-hoc analysis to compare the different outcome groups separately was performed using Bonferroni adjustment for multiple comparisons; P -values are indicated in Figure 2.

We performed a stepwise logistic regression model to predict unfavorable outcome (mRS 4 to 6) at discharge, including age, hemorrhage volume, baseline NIHSS, the presence of intraventricular hemorrhage extension, ICU stay, the need for mechanical ventilation, RBC transfusion and the mean HB level during hospital stay. In the final model, only NIHSS on admission (OR 1.30, 95% CI 1.17-1.45, $P<0.001$), presence of intraventricular hemorrhage extension (OR 4.50 95% CI 1.23-15.83, $P=0.019$), age (per year, OR 1.04, 95% CI 1.01-1.08, $P=0.021$) and the mean HB (per mg/dl, OR 0.76, 95% CI 0.59-0.97, $P=0.027$) remained independent predictors for poor functional outcome at discharge (Table 2).

In-hospital mortality was 22% (43 patients). In univariate analysis, hemorrhage volume, intraventricular hemorrhage extension, admission status, duration of hospital stay, the need for mechanical ventilation and ICU stay and admission HB levels were associated with in-hospital mortality (Table 3). In the multivariable logistic regression model, NIHSS on admission (OR 1.17, 95%CI 1.10-1.24, $P<0.001$), hemorrhage volume (per ml, OR 1.02, 95% CI 1.01-1.03, $P=0.003$) and age (per year, OR 1.05, 95%CI 1.02-1.09, $P=0.006$) remained independent predictors for in-hospital mortality (Table 4).

Outcome at 3 months was available for 176 (90 %) patients, 20 patients were lost for follow-up. Stepwise logistic regression revealed NIHSS on admission (OR 1.17, 95% CI 1.11-1.24, $P<0.001$), age (per year, OR 1.08, 95% CI 1.04-1.12, $P<0.001$) and the mean HB (per mg/dl, OR 0.73, 95% CI 0.58-0.92, $P=0.007$) as independent predictors of outcome at 3 months (Table 5).

Discussion

In the current study we found lower HB concentrations as independent predictor for poor functional outcome in patients suffering from supratentorial, non-traumatic ICH. Anemia during hospital stay was more likely to occur in patients with poor than with favorable functional outcome.

The design of the current study does not allow determining if the relationship between low HB levels and functional outcome is causative. Based on the current data, it cannot be excluded that anemia simply represents a marker for severity of illness, rather than causing additional brain injury. Critically ill patients usually receive more intravenous fluids, have more blood drawn for laboratory tests and more frequently undergo invasive procedures, all factors leading to lower HB concentrations. However, we found lower HB concentrations to be associated with poor outcome, independent of stroke severity which is the most powerful predictor of outcome of acute ICH.

The absolute difference of mean HB levels between both outcome groups was 1.4 mg/dl, corresponding to a reduction of blood oxygen content around 10% [$(1.39 \times \text{HB concentration} - \text{O}_2 \text{ Sat}/100) + (0.003 \times \text{PaO}_2)$]. A reduction of mean HB levels from 14 to 11.9 mg/dl as found for patients with mRS 1 versus 6 respectively makes a difference in blood oxygen content of 20%, roughly assuming similar PaO₂ levels. Previous studies in SAH patients report a comparable magnitude of absolute differences in HB levels between outcome groups [7-8]. Moreover, there is a large body of literature including patients suffering from TBI [10-12], SAH [7-9] or ischemic stroke [15-17] suggesting that anemia or even relative anemia may not be tolerated in the setting of acute brain injury. In patients with acute brain injury, physiological compensatory mechanisms such as an increase in cerebral blood flow (CBF) [18-19] may fail, rendering them more vulnerable for fluctuations in blood oxygen content. Possible mechanisms include impairment of cerebrovascular autoregulation and metabolic disturbances of the injured brain [20]. While some studies have reported intact autoregulation in the perihematoma region in the acute and subacute phase of ICH [21-22], it has recently been demonstrated that global cerebral autoregulation can be impaired in ICH patients. Additionally, loss of cerebrovascular pressure reactivity was associated with poor outcome [23]. Failure of autoregulation may impede a compensatory increment in CBF as response to anemia and thus render ICH patients more vulnerable to a decrease in blood oxygen content.

In addition, animal studies provide evidence that anemic hypoxia may exacerbate primary neurological injury [24-25]. Although the concept of an ischemic penumbra in hemorrhagic stroke has increasingly been challenged [26-27], new hypotheses claim the presence of a metabolic penumbra [28-29]. Recent studies do not point towards a general lack of oxygen in the perihematoma region, but rather to a changed metabolism [29] with low rates of oxygen use [26, 30]. However, the exact timing of metabolic and inflammatory processes in the perihematoma zone remains to be elucidated. Moreover, it is conceivable that the metabolic and oxygen demand may change during the course of the disease. So far, there are no studies in humans suffering from acute ICH investigating the effect of low HB levels on the perihematoma zone. Only animal studies in dogs that were exposed to chronic anemia before induction of experimental ICH provide evidence for an altered brain metabolism in anemic animals [31-32]. While chronic anemic hypoxia promoted a decrease in metabolic demands and an increase in cerebral blood flow, these adaptive responses deteriorated at induction of ICH [31]. In the acute phase of ICH, anemia was associated with an increased critical threshold of brain oxygenation and progressive deterioration of cerebral hemodynamics.

While we found an independent association between low HB and worse functional outcome, HB levels during hospital stay were not predictive for in-hospital mortality. Only hemorrhage volume, age and admission status remained independent predictors for in-hospital mortality in the multivariate model. This may be explained by the overwhelming influence of hemorrhage volume on mortality and the fact that 40% of patients who died, died on the first day of hospital stay. Of interest, admission HB levels differed significantly between both groups in univariate analysis. This finding is in line with a recent study including almost 700 patients suffering from non-traumatic ICH investigating the role of anemia on admission (day 1) on the clinical course of acute ICH [33]. Although patients with anemia on admission (25.8% of patients) were at higher risk of death at 30 days in univariate analysis, this effect did not persist in a multivariate model including hemorrhage volume. Interestingly, the authors report that the presence of anemia on admission was associated with larger ICH

volume and thereby hypothesize that the presence of anemia may contribute to hemorrhage growth. Another explanation may be that admission HB levels rather are a marker for poor physiological status on admission. Unfortunately, scores for physiologic illness such as the APACHE II score were not available due to the retrospective design of our study.

The main limitations of the current study include the small number of transfused patients and the retrospective, observational design that does not shed light on the underlying metabolic processes. However, while the latter was beyond the scope of the current study, further studies invasively assessing the parenchymal metabolic effects of anemia and RBC transfusion in ICH patients seem justified. In the current study, only 10 (5.1%) of patients received RBC transfusions during hospital stay. RBC transfusion was included as variable in multivariable models, however, the number of transfused patients was too low to provide solid data on the effect of RBC transfusion on outcome parameters. In order to exclude the possibility that poor outcomes were primarily related to transfusion, rather than anemia, we repeated our analysis after excluding the 10 transfused patients from the multivariate models. In this repeat analysis, mean HB did not remain an independent predictor for poor outcome at discharge but stayed an independent predictor in the model for outcome at 3 months (see additional file 1 for details). However, evidence exists from previous studies including TBI [10, 12] or SAH [34-35] patients that despite some putative beneficial physiological effects, RBC transfusion was associated with additional risks and poorer outcome. In addition, Zygun and colleagues recently have assessed the effect of red blood cell transfusion on cerebral oxygenation and metabolism in TBI patients [36]. They report that transfusion of RBC resulted in improved brain tissue oxygenation, however without noticeable effect on cerebral metabolism as measured by lactate-pyruvate ratio. There is currently no data available for ICH patients.

Conclusions

In summary, in the current study we found an association between low HB and poor functional outcome in patients with non-traumatic ICH, as was previously reported for patients suffering from SAH, TBI and ischemic stroke. Although none of the studies in brain injured patients has so far proven a causative relationship between anemia and poor outcome, physiological and observational studies provide evidence for possible detrimental effects of anemia on brain metabolism. However, the potential risk of anemia must be balanced against the potential risk of harm from allogenic RBC infusion. Further trials are needed investigating the local metabolic effects of anemia and RBC transfusion in ICH patients.

Key messages

- Poor functional outcome at discharge and at 90 days was associated with lower mean HB levels during hospital stay in patients suffering from non-traumatic, supratentorial ICH.
- Based on the currently available data it could not be elucidated if the presence of anemia promotes further brain injury or if it rather represents a marker of severe illness.
- Further trials are needed to investigate if RBC transfusion in acute ICH may lead to improved outcome.

Abbreviations

ICH: Intracerebral hemorrhage; HB: hemoglobin; RBC: blood cell; mRS: modified Rankin score; NIHSS: National Institute of Health Stroke Scale; SAH: subarachnoid hemorrhage; TBI: traumatic brain injury; CT: computed tomography; ICU: intensive care unit; PaO₂: partial pressure of arterial oxygen.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JD and MS contributed equally and planned and designed the study and performed the statistical analysis. JD wrote the first draft of the manuscript. PH performed data acquisition. MS, KH, MS, LK, JB and SP critically revised the manuscript. TS contributed to conception of the study and critically revised the manuscript.

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Figure legends

Figure 1: Cumulative Hazard to develop anaemia during hospital stay for both outcome groups separately. During their hospital stay, patients with poor functional outcome (mRS 4-6) had a higher risk to develop anaemia compared to those with favourable outcome at discharge.

Figure 2: Mean HB values and outcome at discharge. Mean HB levels were significantly different between all groups ($F(5, 172)=7.71, P<0.001$). Significant differences between group means are indicated by the bars (post-hoc analysis using Bonferroni adjustment for multiple comparisons).

Table 1: Univariate analysis of functional outcome at discharge

Variable	mRS 0-3 (n=46)	mRS 4-6 (n=150)	P
Age (years) (mean, SD)	62.5 (13.4)	68.6 (13.1)	0.007 ^a
Sex (male, n, %)	29 (63.0)	101 (67.3)	0.136 ^c
Hemorrhage volume (ml) (median, IQR)	8.6 (24.0)	30 (66.4)	<0.001 ^b
Intraventricular hemorrhage extension (n, %)	5 (10.9)	72 (48.0)	<0.001 ^c
NIHSS on admission (median, IQR)	4 (3)	16 (23)	<0.001 ^b
Admission HB (g/dl) (mean, SD)	14.2 (1.6)	13.6 (2.0)	0.052 ^a
Mean HB (g/dl) (mean, SD)	13.7 (1.8)	12.3 (2.0)	<0.001 ^a
Nadir HB (g/dl) (mean, SD)	13.0 (1.9)	11.5 (2.3)	<0.001 ^a
Anemia during hospital stay (n, %)	10 (21.7)	84 (56.0)	<0.001 ^c
HB measurements (n) (median, IQR)	4 (4.3)	5 (8.5)	0.22 ^b
Hospital stay (days) (median, IQR)	7 (8)	6 (8)	0.32 ^b
ICU stay (n, %)	7 (15.2)	76 (50.7)	<0.001 ^c
Mechanical ventilation (n, %)	2 (4.3)	55 (36.9)	<0.001 ^c
RBC transfusion (n, %)	1 (2.2)	9 (6.0)	0.302 ^c

^a Student *t*-test^b Mann-Whitney-U test^c Chi square test

mRS: modified Rankin Scale; SD: standard deviation; NIHSS: National Institutes of Health Stroke Scale; HB: hemoglobin; IQR: interquartile range; ICU: intensive care unit; RBC: red blood cell

Table 2: Final stepwise logistic regression model to predict poor outcome (mRS 4-6) at discharge (included variables: age, hemorrhage volume, NIHSS at admission, the presence of intraventricular blood, ICU stay, the need for mechanical ventilation, RBC transfusion and the mean HB level during hospital stay)

Variable	Coefficient	P	OR (95% CI)
NIHSS on admission (per point)	0.261	<0.001	1.30 (1.17-1.45)
Presence of intraventricular hemorrhage extension	1.503	0.019	4.50 (1.23-15.83)
Age (per year)	0.043	0.021	1.04 (1.01-1.08)
Mean HB (per mg/dl)	-0.281	0.027	0.76 (0.59-0.97)

OR: odds ratio; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; HB: hemoglobin, ICU: intensive care unit; RBC: red blood cell; HB: hemoglobin

Table 3: Univariate analysis of factors associated with in-hospital mortality

Variable	mRS 0-5 (n=153)	mRS 6 (n=43)	P
Age (years) (mean, SD)	66.1 (13.8)	71.1 (11.1)	0.028 ^a
Sex (male, n, %)	100 (65.4)	30 (69.8)	0.589 ^c
Hemorrhage volume (ml) (median, IQR)	17.1 (36.5)	88 (108.9)	<0.001 ^b
Intraventricular hemorrhage extension (n, %)	49 (32.9)	28 (65.1)	<0.001 ^c
NIHSS on admission (median, IQR)	10 (12)	34 (10)	<0.001 ^b
Admission HB (g/dl) (mean, SD)	13.9 (1.8)	13.2 (2.3)	0.040 ^a
Mean HB (g/dl) (mean, SD)	12.8 (2.0)	12.2 (2.4)	0.150 ^a
Nadir HB (g/dl) (mean, SD)	11.9 (2.2)	11.7 (2.7)	0.516 ^a
Anemia during hospital stay (n, %)	71 (46.4)	23 (53.5)	0.411 ^c
Hospital stay(days) (median, IQR)	7 (9)	2 (43)	<0.001 ^b
ICU stay (n, %)	53 (34.6)	30 (69.8)	<0.001 ^c
Mechanical ventilation (n, %)	33 (21.6)	24 (57.1)	<0.001 ^c
RBC transfusion (n, %)	7 (4.6)	3 (7)	0.527 ^c

^a Student *t*-test^b Mann-Whitney-U test^c Chi square test

mRS: modified Rankin Scale; SD: standard deviation; NIHSS: National Institutes of Health Stroke Scale; HB: hemoglobin; IQR: interquartile range; ICU: intensive care unit; RBC: red blood cell

Table 4: Final stepwise logistic regression model to predict in-hospital mortality (included variables: age, hemorrhage volume, NIHSS at admission, the presence of intraventricular blood, ICU stay, the need for mechanical ventilation, RBC transfusion and the admission HB)

Variable	Coefficient	P	OR (95% CI)
NIHSS on admission (per point)	0.109	<0.001	1.17 (1.11-1.24)
Hemorrhage volume (per ml)	0.015	0.003	1.02 (1.01-1.03)
Age (per year)	0.052	0.006	1.05 (1.02-1.09)

OR: odds ratio; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; ICU: intensive care unit; RBC: red blood cell; HB: hemoglobin

Table 5: Final stepwise logistic regression model to predict poor outcome (mRS 4-6) at 3 months (included variables: age, hemorrhage volume, NIHSS at admission, the presence of intraventricular blood, ICU stay, the need for mechanical ventilation, RBC transfusion and the mean HB level during hospital stay)

Variable	Coefficient	P	OR (95% CI)
NIHSS on admission (per point)	0.157	<0.001	1.17 (1.11-1.24)
Age (per year)	0.076	<0.001	1.08 (1.04-1.12)
Mean HB (per mg/dl)	-0.319	0.007	0.73 (0.58-0.92)

OR: odds ratio; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; ICU: intensive care unit; RBC: red blood cell; HB: hemoglobin

Additional files

Additional file 1: Additional logistic regression models. Logistic regression models after exclusion of 10 patients who had received RBC transfusions.

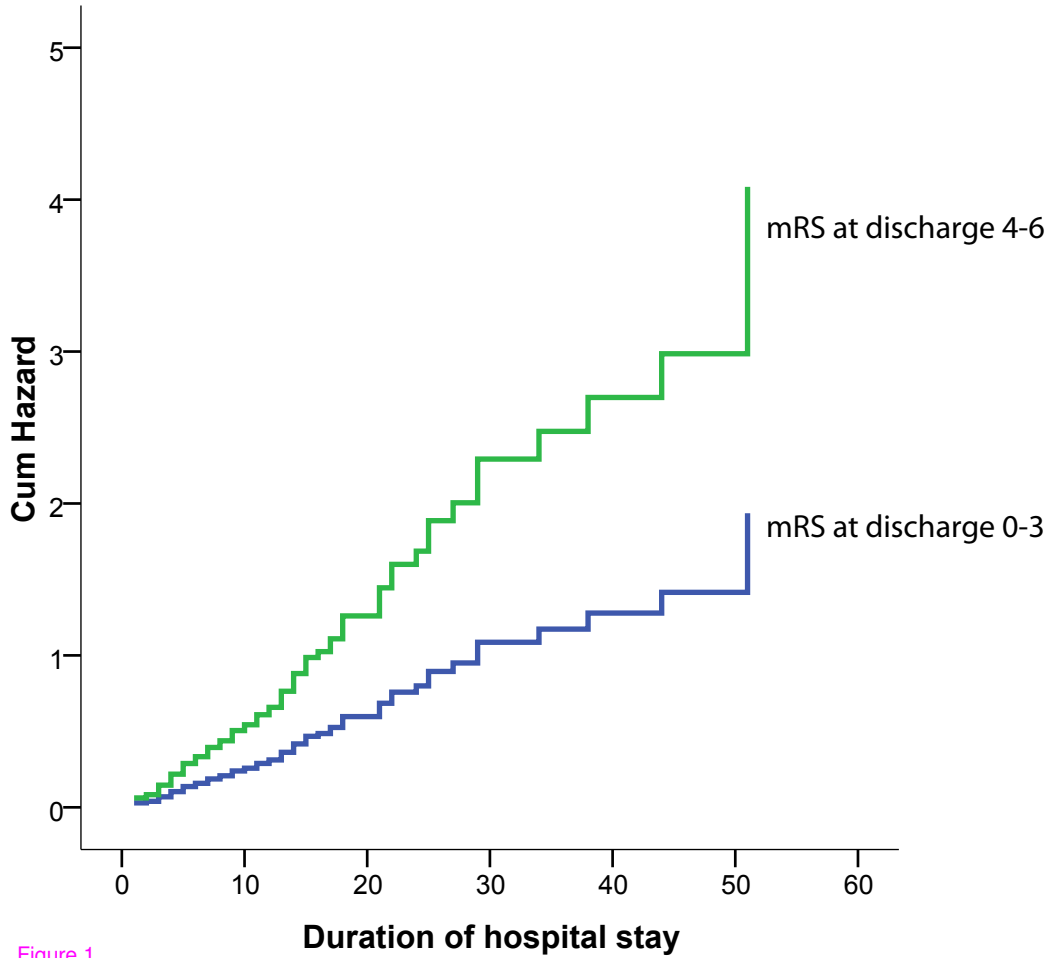


Figure 1

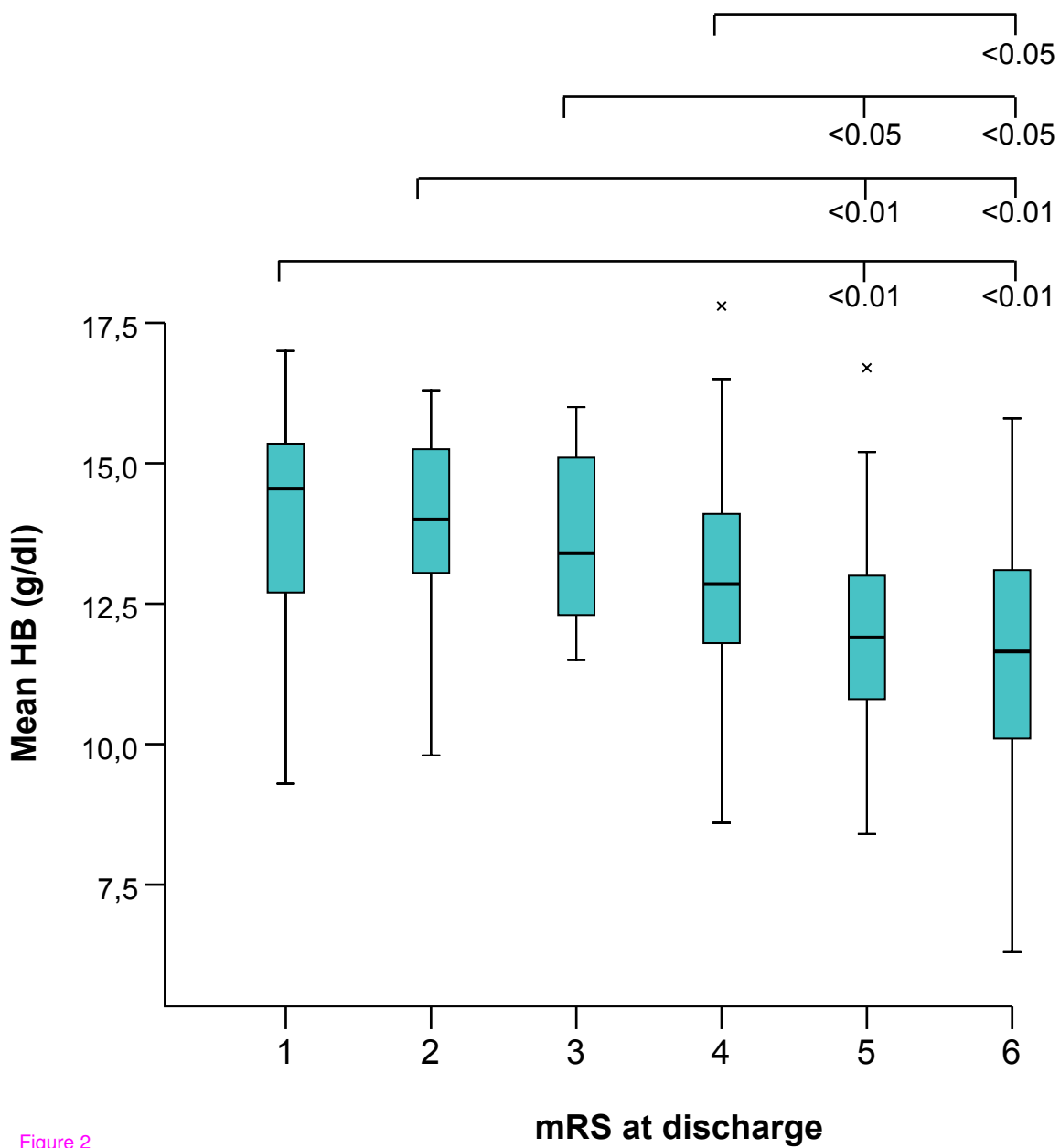


Figure 2

Additional files provided with this submission:

Additional file 1: Additional logistic regression models.doc, 33K

<http://ccforum.com/imedia/1322793793380081/supp1.doc>