Predictors of Outcome in Warfarin-Related Intracerebral Hemorrhage

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Background: Intracerebral hemorrhage (ICH) associated with warfarin sodium therapy is becoming more common as the use of this medication increases in the aging population.

Objective: To delineate factors associated with early mortality, determine variables responsible for poor functional outcome, and evaluate possible reasons for expansion of hemorrhage and associated parenchymal edema.

Design: Retrospective study of clinical and radiologic information for 88 patients with warfarin-associated ICH.

Setting: A single hospital.

Patients: Eighty-eight consecutive patients with warfarin-associated ICH.

Methods: Patients were included if the international normalized ratio (INR) at presentation with ICH was 1.5 or greater. Computed tomographic scans were reviewed for volumetric analysis of hematoma and perihematomal edema volume. Outcome variables included 7-day mortality, hematoma enlargement, and functional outcome based on the modified Rankin Scale score.

Results: Seven-day mortality (39.8%) was associated with a lower Glasgow Coma Scale sum score and larger ICH volume at presentation. Univariate analysis revealed that a lower Glasgow Coma Score sum score, larger initial ICH volume, higher initial and 48-hour maximum glucose concentrations, and higher percentage of ICH expansion were significantly associated with poor functional outcome at hospital discharge. At multivariate analysis, only Glasgow Coma Score and ICH volume remained significantly associated with functional outcome measured at hospital discharge and at the last follow-up visit. Conversely, INR at presentation, time to INR correction, initial blood pressure, and enlargement of edema were not associated with functional outcome either at hospital discharge or at the last follow-up. Neither serum glucose concentration at admission nor highest level during the first 48 hours had any correlation with ICH or parenchymal edema enlargement. In addition, neither initial INR nor time to INR correction correlated with expansion of ICH or parenchymal edema.

Conclusions: Lower level of consciousness at presentation and larger initial ICH volume predict poor prognosis in patients with warfarin-associated ICH. In our study population, INR at presentation was not associated with functional outcome.

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functional outcome, and evaluate possible reasons for expansion of hemorrhage and associated parenchymal edema.

METHODS

We reviewed medical records for all consecutive patients with ICH treated at Saint Mary's Hospital (Mayo Clinic, Rochester, Minnesota) from January 1, 1997, to December 31, 2005. Inclusion criteria included radiologically documented ICH, treatment with warfarin at the time of the bleeding, international normalized ratio (INR) of 1.5 or greater at diagnosis of ICH, and clinical and neuroimaging data available for review. Patients with underlying structural brain lesions or hemorrhagic conversion of ischemic infarctions were excluded from the analysis. Eighty-eight consecutive patients were eligible for the study.

Medical records and brain computed tomographic (CT) scans were reviewed by 2 investigators (A.Y.Z. and A.A.R.). For patients who had been transferred from an outside hospital, initial head CT scans and INR from that hospital were included in the analysis. We collected clinical information on age, sex, comorbid conditions, initial blood pressure (BP), initial Glasgow Coma Scale (GCS) sum scores, reasons for anticoagulation therapy, initial INR and time to correction of INR (defined as INR ≤ 1.4), and serum glucose concentration at admission and during the first 48 hours after admission. Radiologic data collected included location of the parenchymal hematoma, extent to the ventricular system, and initial volume and subsequent enlargement of the hematoma and perihematomal edema.

When available, multiple CT scans were reviewed for each patient. Volume of ICH and edema were measured manually using the previously described ABC/2 method. For measurements of parenchymal edema, CT hypodensity surrounding the ICH was measured using the same method. Edema volume was obtained by subtracting the ICH volume from the total lesion volume. No volume measurements were obtained in cases of intraventricular hemorrhage without measurable parenchymal hematoma. The investigators measuring the CT scans were blinded to clinical information and to the chronological order of the scans to avert potential bias in the measurements.

Death was classified as early if it occurred within 7 days of ICH onset or delayed if it occurred later. Functional outcome was assessed using the modified Rankin scale (mRS) and dichotomized as good (score of 0-3) or poor (score of 4-6) at discharge. Functional evaluation (mRS) and diastolic blood pressure (BP) were assessed at discharge and last follow-up visit, and the percentage increase in ICH volume. At univariate analyses, associations between binary outcome variable and various continuous variables were assessed using the Wilcoxon rank sum test. Further multivariate analysis was performed using logistic regression in the case of these binary outcome variables. The final multivariate model was selected based on P value and C statistic, which is a measure of the area under the curve. Assessment of goodness of fit for these models was performed using the Hosmer-Lemeshow goodness-of-fit test. In addition, receiver operating characteristic analysis was performed to identify optimal cutoff points in continuous variables for the prediction of binary outcomes.

The Spearman rank correlation test was used to assess the association between ICH expansion (percentage) and other continuous variables of interest. Further, multivariate linear regression was used to assess predictors of ICH enlargement while adjusting for potential covariates of interest. All tests were 2-sided, and P < .05 was considered statistically significant. Analysis was performed using commercially available software (SAS version 9; SAS Institute, Inc, Cary, North Carolina).

RESULTS

We identified 88 consecutive patients eligible for the study. Fifty-three patients (60%) were men, and the average patient age was 76 years (age range, 45-91 years). A history of hypertension before ICH was documented in 50 patients (57%). Indications for anticoagulation therapy were atrial fibrillation in 45 patients (51%), history of deep vein thrombosis or pulmonary embolism in 19 patients (22%), artificial heart valve in 15 patients (17%), and various other conditions in the remaining 9 patients (10%). All patients were treated with a standard antihypertensive regimen (intravenous sodium nitroprusside, labetalol hydrochloride, or nicardipine hydrochloride) to maintain mean arterial pressure less than 130 mm Hg. Reversal of INR was achieved by administration of vitamin K and fresh frozen plasma in 83 patients. Four patients also received recombinant factor VII in addition to fresh frozen plasma and vitamin K.

Median (range) INR at admission was 3.2 (1.5-15.7). In 17 patients (19%), INR was not normalized because of early death or family request for restriction of care. In the remainder of patients, the median time to reversal of INR was 7.3 hours (2-96 hours). Median serum glucose concentration at admission was 135 mg/dL (77-370 mg/dL) \( \text{[to convert to millimoles per liter, multiply by 0.0555]} \), and the median highest serum glucose concentration within 48 hours of admission was 172 mg/dL (90-379 mg/dL). Median time to first repeat CT scan was 14 hours (1.5-401 hours) after the initial CT scan. Twenty-two patients (25%) did not undergo a second CT because of early death or limitations of care requested by the families.

Thirty-five patients died within 7 days after ICH (7-day mortality, 39.7%), and an additional 3 died within 30 days after ICH (30-day mortality, 43.2%). Palliative care was provided to 29 of these patients following family request. Three additional patients died within 1 year after ICH, and 11 others died more than 1 year after ICH.

FACTORS INFLUENCING 7-DAY MORTALITY

Univariate analysis using the Wilcoxon rank sum test indicated that there was a significant association between the initial ICH volume and 7-day mortality \( (P < .01) \) \( \text{(Table 1).} \) Worse level of consciousness at presenta-
tion also had a significant effect on 7-day mortality; pa-
tients who died within 7 days after ICH had a median
GCS sum score of 9 (P < .01). Glucose concentration at
admission and maximal glucose measurement within 48
hours (P < .01 for both) and higher percentage of ICH
expansion were also associated with early death (P = .03).
There was no correlation between early death and sys-
tolic or diastolic BP, initial INR, time to reversal of INR,
or enlargement of perihematomal edema. At multivari-
ate logistic regression analysis (Table 1), GCS (P < .01),
diastolic BP (P = .04), and initial ICH volume (P < .01)
were associated with 7-day mortality.

## FACTORS INFLUENCING FUNCTIONAL OUTCOME AT HOSPITAL DISCHARGE

Univariate analysis showed significant association be-
 tween functional outcome at hospital discharge and ini-
tial GCS (P < .01), initial ICH volume (P < .01), per-
centage of ICH expansion (P = .03), and maximum glucose
concentration at 48 hours (P = .04) (Table 2). Glucose
concentration at admission, INR at presentation, time to
INR reversal, systolic or diastolic BP at admission, and
percentage of enlargement of perihematomal edema were
not associated with functional outcome at discharge.

Further analysis of the influence of initial clinical find-
ings on outcome revealed that a GCS sum score of 13 had
94% specificity and 56% sensitivity for the prediction of
poor outcome. Multivariate logistic regression analysis
including variables significant at univariate analysis (Table 2)
narrowed associations of mRS score at discharge to GCS (P = .04) and initial ICH volume (P = .02). Patients with poor outcome had a median initial ICH volume of 17.4 mL, whereas patients with good outcome had much smaller hematomas at admission (5 mL; P < .01).

## FACTORS INFLUENCING LONG-TERM OUTCOME

Fifty patients survived for 30 days after ICH, including 47
who survived longer than 1 year. Four patients had no long-
term follow-up. At univariate analysis, initial GCS (P < .01),
initial ICH volume (P < .01), percentage of ICH expansion
(P = .02), and glucose concentration at admission (P = .02)
were significantly associated with long-term outcome
(P = .03) (Table 3). Multivariate logistic regression analysis
indicated that lower GCS sum score (P = .01) and larger
initial ICH volume (P = .02) were independently asso-
ciated with poor long-term outcome (Table 3).

## FACTORS INFLUENCING ICH EXPANSION

Patients with good outcome at discharge (mRS score 0-3)
had a median (range) ICH expansion of 14.9% (−23.8%
to 56.9%), and patients with poor outcome had a me-
dian ICH expansion of 30.5% (−56.3% to 87.0%). A nomi-
nal logistic fit comparing these parameters demon-
strated that enlargement of ICH by 47% had 95% speci-
ficity and 37% sensitivity for predicting poor out-
come (mRS score, 4-6). Volume of ICH in excess of 73.4
mL had 100% specificity in predicting poor outcome.
There was no correlation between the degree of enlarge-
ment of edema and functional outcome.

Analysis using the Spearman rank correlation indi-
cated that there was no statistically significant correla-
tion (P > .05) between expansion of ICH or perihema-
tomal edema and initial GCS, initial INR, time to INR
correction, initial systolic BP, glucose concentration at
admission, or the highest glucose concentration during
the first 48 hours after admission. Multivariate linear re-
gression analysis adjusting for the listed covariates indi-
cated that initial systolic BP was the only significant pre-

### Table 1. Factors Influencing 7-Day Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>≤7 Days (n = 35)</th>
<th>&gt;7 Days (n = 53)</th>
<th>P</th>
<th>ORb (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td>.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial ICH volume, mL</td>
<td></td>
<td></td>
<td>.01</td>
<td>1.09 (1.03 to 1.15)</td>
<td>.01</td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>9 (3 to 15)</td>
<td>15 (8 to 15)</td>
<td>.01</td>
<td>0.59 (0.41 to 0.87)</td>
<td>.01</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td>.33</td>
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<tr>
<td>Systolic</td>
<td>188.5 (106 to 230)</td>
<td>160 (88 to 290)</td>
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<td></td>
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</tr>
<tr>
<td>Diastolic</td>
<td>86 (37 to 190)</td>
<td>82 (30 to 149)</td>
<td>.32</td>
<td></td>
<td></td>
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<tr>
<td>Glucose concentration, mg/dL</td>
<td></td>
<td></td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>168 (81 to 368)</td>
<td>124 (77 to 370)</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum at 48 h</td>
<td>219.5 (141 to 379)</td>
<td>144 (90 to 345)</td>
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<tr>
<td>Initial INR</td>
<td>3.3 (1.9 to 11.1)</td>
<td>3.05 (1.5 to 15.7)</td>
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<td></td>
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<tr>
<td>Time to INR reversal, h</td>
<td>5 (2 to 47)</td>
<td>7.5 (3 to 96)</td>
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<td></td>
</tr>
<tr>
<td>ICH expansion, %</td>
<td>41.7 (0 to 87)</td>
<td>19.23 (−56.3 to 63.6)</td>
<td>.03</td>
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<td></td>
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<tr>
<td>Perihematomal edema expansion, %</td>
<td>47.5 (−58.5 to 86.7)</td>
<td>29.43 (−58.5 to 92.1)</td>
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### Table 2. Factors Influencing ICH Expansion

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Abbreviations: CI, confidence interval; ICH, intracranial hemorrhage; INR, international normalized ratio; OR, odds ratio; ellipsis, not applicable.

a Evaluations made using the Wilcoxon rank sum test.

b Reported for 1-U increase in predictor variable.
dictor for ICH expansion (P = .04) but did not have any association with expansion of edema.

In this analysis of outcome predictors in patients with warfarin-associated ICH, we found that stupor or coma and larger hematoma volume were the main determinants of poor functional outcome. Detailed radiologic analysis of ICH volume showed that in patients with poor functional outcome, hematoma enlargement was common but often lower than one-third of baseline volume. Early hyperglycemia was more common in patients who died or recovered poorly. Conversely, neither INR nor time to correction of INR correlated with mortality, functional outcome, or enlargement of the ICH.
mal perihematomal edema did not have any correlation with functional outcome.

The poor outcome in patients with warfarin-associated ICH in this series is consistent with previously reported studies that reported 6-month mortality ranging from 23% to 58%. As in previous studies, initial ICH volume and low GCS sum score had significant correlation with early death. In our population, patients who died within 7 days of ICH had a median GCS of 9. Although the low average GCS sum scores in patients who died was expected, we found that a much higher GCS was associated with poor functional outcome (mRS score > 3). This is slightly higher than previously reported and most likely reflects that patients with any decreased level of consciousness at presentation are at higher risk of deterioration.

In our population, admission hyperglycemia and maximal glucose concentration within the first 48 hours after ICH correlated with worse clinical recovery at univariate analysis but not multivariate analysis. This effect of hyperglycemia had not been previously discussed in detail in patients with warfarin-associated ICH, although in 1 study, hyperglycemia was associated with larger baseline volume of ICH. Studies in patients with spontaneous ICH have shown a significant correlation between baseline glucose concentration and 30-day and 3-month mortality. In another trial, elevated glucose concentration was associated with ICH growth. The pathophysiologic reasons for the association of hyperglycemia with worse outcome remain to be elucidated. Our study did not find any correlation between hyperglycemia and hematoma expansion or perihematomal edema, although some experimental data suggest that hyperglycemia might cause increased edema and perihematomal cell death. Hyperglycemia could directly cause deleterious effects on the acutely injured brain or result from sympathetic stress response corresponding to the magnitude of damage produced by the ICH. The lack of independent association between glucose concentration and functional outcome in our multivariate analysis seems to support the latter premise.

We identified no correlation between mortality and initial INR or time to reversal of INR, contrary to a previous study that concluded that intensity of anticoagulation correlated with the risk of early death. This might be explained by possible bias generated by exclusion of 17 patients who died before INR reversal. In addition, conventional reversal of INR with vitamin K and fresh frozen plasma therapy requires hours, and it is not known whether ultrarapid correction of INR with recombinant factor VII or prothrombin complex concentrate could have a beneficial effect on mortality or morbidity.

Expansion of ICH was associated with greater risk of fatal outcome. Mean ICH enlargement was 30% in patients with poor outcome vs 15% in those with good outcome. The enlargement of ICH significantly correlated with outcome even after adjusting for initial ICH volume. We found that degrees of hematoma enlargement smaller than the commonly used cutoff of 33%, even if not readily apparent initially, may have substantial functional effect. Intracranial hemorrhage volume greater than 73 mL had 100% specificity for predicting poor outcome. Enlargement of ICH volume by 47% had 95% specificity for prediction of poor outcome, demonstrating the devastating consequences of massive hematoma expansion. In our population, parenchymal edema did not have a significant effect on outcome. Although initial systolic BP was associated with hematoma expansion at multivariate analysis, the lack of association at univariate analysis makes the clinical significance of this finding questionable.

In our experience, time to reversal of anticoagulation therapy did not correlate with hematoma enlargement. These findings are different from those of a previous study that indicated reduced incidence of hematoma expansion with early (within 2 hours) complete INR reversal. Hematoma enlargement may even occur after full reversal of INR with the administration of fresh frozen plasma and vitamin K therapy. The effect of ultrarapid correlation of INR with newer hemostatic treatments awaits formal evaluation.

Our study has limitations. One potentially powerful confounder in our retrospective analysis is related to the frequent occurrence of withdrawal of support or early death in the most severely affected patients. One-fourth of our patients did not have a follow-up CT scan, a major potential confounder in our analysis of the incidence and effect of ICH expansion. The same problem applies to time to reversal of anticoagulation because 17 of the patients who died early did not have documented normalization of INR. Patients with incomplete data were excluded from the multivariate logistic regression analysis, which may have introduced bias by not considering the most severe cases. We used the ABC/2 method rather than more precise computerized planimetry techniques for measuring volumes of hematoma and edema. The ABC/2 method has been well validated; however, the resulting volumes are most commonly analyzed as dichotomized rather than as continuous variables. Thus, our findings must be interpreted with this caveat in mind.

Warfarin-associated ICH is a growingly and daunting problem for which therapies are limited. The current focus on rapid reversal of anticoagulation therapy may be justified on the basis of previous data; however, time to reversal of INR using conventional hemostatic therapies did not affect outcome in our patients. Further studies are needed to identify modifiable factors that might influence outcome in these patients.

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Author Contributions: Dr Rabinstein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Claassen, Manno, and Rabinstein. Acquisition of data: Zubkov, Claassen, and Manno. Analysis and interpretation of data: Zubkov, Claassen, and Manno. Drafting of the manuscript: Manno. Critical revision of the manuscript for important intellectual content: Zubkov, Mandrekar, Claassen, Wijdicks, and Rabinstein. Statistical analysis: Mandrekar. Administrative, technical, and material support: Zubkov, Claassen, and Manno. Study supervision: Wijdicks and Rabinstein.
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