Predictors of 30-day mortality in patients with spontaneous primary intracerebral hemorrhage

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**Abstract**

**Background:** Intracerebral hemorrhage (ICH) is a life threatening entity, and an early outcome assessment is mandatory for optimizing therapeutic efforts.

**Methods:** We retrospectively analyzed data from 342 patients with spontaneous primary ICH to evaluate possible predictors of 30-day mortality considering clinical, radiological, and therapeutical parameters. We also applied three widely accepted outcome grading scoring systems ([ICH score, FUNC score and intracerebral hemorrhage grading scale (ICH-GS)]) on our population to evaluate the correlation of these scores with the 30-day mortality in our study.

**Results:** From 342 patients (mean age: 67 years, mean Glasgow Coma Scale [GCS] on admission: 9, mean ICH volume: 62.19 ml, most common hematoma location: basal ganglia [43.9%]), 102 received surgical and 240 conservative treatment. The 30-day mortality was 25.15%. In a multivariate analysis, GCS (Odds ratio [OR] =0.726, 95% confidence interval [CI] =0.661–0.796, \( P < 0.001 \)), bleeding volume (OR = 1.012 per ml, 95% CI = 1.007 – 1.017, \( P < 0.001 \)), and infratentorial hematoma location (OR = 5.381, 95% CI = 2.166-13.356, \( P = 0.009 \)) were significant predictors for the 30-day mortality. After receiver operating characteristics analysis, we defined a “high-risk group” for an unfavorable short-term outcome with GCS <11 and ICH volume >32 ml supratentorially or 21 ml infratentorially. Using Pearson correlation, we found a correlation of 0.986 between ICH score and 30-day mortality (\( P < 0.001 \)), 0.853 between FUNC score and 30-day mortality (\( P = 0.001 \)), and 0.924 between ICH-GS and 30-day mortality (\( P = 0.001 \)).

**Conclusions:** GCS score on admission together with the baseline volume and localization of the hemorrhage are strong predictors for 30-day mortality in patients with spontaneous primary intracerebral hemorrhage, and by relying on them it is possible to identify high-risk patients with poor short-term outcome. The ICH score and the ICH-GS accurately predict the 30-day mortality.

**Key Words:** Cerebral hemorrhage, multivariate analysis, prognosis, risk factors, treatment outcome
INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) still poses challenges in neurological and neurosurgical routines in terms of therapeutic decision making. Approximately 10–15% of strokes are caused by intra-axial bleeding, and despite substantial advances in diagnostics and therapy, only approximately 20% of the patients with spontaneous ICH regain functional independency within 3 months after the ictus. Pathogenetically, ICHs are classified into primary and secondary hemorrhages. Primary ICHs occur more frequently than secondary, accounting for approximately 80% of all ICHs. Primary ICHs are caused by a damage of the intracerebral small vessels owing to chronic hypertension or amyloid angiopathy as the underlying pathology. Secondary ICHs are associated with a relevant trauma, tumors, aneurysms, vascular malformations, coagulopathies, or the hemorrhagic transformation of cerebral infarction.

The clinical manifestation of spontaneous ICH varies depending on the location and volume of the hemorrhage, as well as on patient age and presence of other comorbidities. However, the consequences of intracerebral bleeding can be immense. In addition, when one takes into account the economic aspects of patient treatment and care, an early assessment of the prognosis of such patients is very desirable and of significant consequence in terms of treatment optimization and prevention of overtreatment that leads to an expected damaging outcome. Many scoring systems have been introduced and modified to predict the outcome of patients with spontaneous intracerebral bleeding, three of these systems are well-validated and widely accepted for clinical use. The ICH score was developed to estimate the 30-day mortality with value from 0 to 6. The FUNC score ranges from 0 to 11 and was introduced to estimate the functional independence at 90 days. The intracerebral hemorrhage grading scale (ICH-GS) ranges between 5 and 13 points and was designed to predict the outcome and mortality at 30 days.

Considering this background, we performed a study to analyze the short-term course of a large patient group suffering from a primary spontaneous ICH and determine possible predictors of 30-day mortality.

MATERIALS AND METHODS

We retrospectively analyzed data from 342 consecutive patients with the diagnosis of a primary spontaneous intracerebral hemorrhage treated in our institution between January 2005 and December 2013.

The exclusion criteria were secondary ICH caused by trauma, tumors, arteriovenous malformations (AVM) or aneurysms, insufficient medical records and patients with initial absence of brainstem reflexes on admission.

To define possible risk factors for death within 30 days, we created a data file that included the following parameters: Age, sex, initial neurologic status, medical history for the presence of comorbidities and consumption of antiplatelet and anticoagulant drugs, radiographic features, as well as type of treatment (surgical or conservative therapy).

The cornerstone of our work was assessing the short-term outcome, with short-term mortality as the primary outcome of interest. Therefore, we defined the primary endpoint of this study as death or follow-up of maximum 30 days.

The neurological outcome was estimated using the modified Rankin Scale (mRS). The outcome was defined as favorable if the mRS score was ≤2 and unfavorable when the mRS score was >2. The initial neurologic status was determined by the Glasgow Coma Scale (GCS) on arrival of the patient in our emergency department and before treatment commencement.

Comorbidities, such as hypertension, diabetes, history of tobacco abuse (consumption of more than 5 cigarettes per day at least 2 days every week for at least 12 months) and alcohol abuse (consumption or more than 24 doses per week for men and 16 for women), and the use of antiplatelet or anticoagulant drugs were also collected.

The initial imaging data (mainly computed tomography [CT] of the head) were reviewed to obtain possible radiographic risk factors, including location, volume and depth of bleeding. Furthermore, we also looked for the presence of interventricular hemorrhage (IVH) or accompanying subarachnoid hemorrhage (SAH). The hematoma volume was estimated on the initial head CT scan using the ABC/2 method, in which A is the greatest diameter on the largest hemorrhage slice, B is the diameter perpendicular to A, and C is the number of axial slices with bleeding multiplied by the slice thickness. The hematoma location was subdivided into supratentorial including lobular as well as basal ganglia, and infratentoriell including cerebellum as well as brainstem. The depth of the bleeding from the cortical surface (≤10 mm versus >10 mm) was also measured on the first head CT scan on admission. These images were made in our institution and there was always a written radiological report. The findings in the images’ written radiological reports were compared with our own assessments, which gave us a form of intraobserver agreement.

To analyze the influence of treatment (conservative versus surgical) on the short-term outcome, we defined two groups. Group I comprised patients who underwent initial conservative therapy with medical treatment. Group II
included the patients who underwent an early surgical evacuation of the bleeding within the first 72 h after the diagnosis of the ICH along with medical treatment. The placement of an external ventricular drainage was considered a tool for neurological monitoring within the bounds of the medical treatment and not as a primary active surgical treatment. Decision for surgery was made in each case by a responsible neurosurgeon individually, which was mainly based on the radiological features of the hemorrhage and the neurological status of the patient.

Finally, we determined three validated outcome grading scores\(^{[12,18,19]}\) for the patients in our cohort, to measure the correlation between their predictive ability and our results regarding the 30-day mortality.

**Statistical analysis**
First, an univariate logistic regression was used to assess the strength of association between the collected variables and the 30-day mortality. The assessed variables included age, gender, GCS, ICH volume, ICH location, IVH, SAH, arterial hypertension, diabetes, tobacco abuse, alcohol abuse, use of anticoagulation and/or antiplatelet therapy, and the kind of therapy (conservative therapy versus surgery). Multivariate analysis, with the 30-day mortality as dependent variable, on variables found to be significant by univariate analysis, was performed in a second step. We also derived cutoff values after performing receiver operating characteristics (ROC) analysis using the Youden Index. A Hosmer and Lemeshow test was used to assess the goodness of fit for the multivariate model. Results are reported as odds ratios (OR) together with a 95% confidence interval (CI). Pearson correlation analysis was performed to determine the correlation between applied outcome grading scores and 30-day mortality. The significance level was set to be 0.05. The analysis was performed using the Statistical Package for the Social Sciences, Version 22 (SPSS Inc., Chicago, IL, USA).

**RESULTS**
A total of 342 patients (mean age 67 ± 11.2 years; 172 males, 50.3%) with the diagnosis spontaneous primary ICH for whom sufficient medical records existed fulfilled the inclusion criteria. Mean GCS score on admission was 9 ± 3.66 (range: 3–15). The main characteristics of our patient cohort are summarized in Table 1.

Arterial hypertension was present in 86.5% (n = 296), a history of diabetes in 28% (n = 96), a history of tobacco abuse in 5.8% (n = 20), and alcohol abuse in 8.8% (n = 30) of the patients.

A preoperative therapy that affected hemostasis comprising either antiplatelet (n = 76) or anticoagulant therapy (n = 88) was identified in 164 patients (48%).

The most common location of the bleeding was the basal ganglia (43.9%, n = 158) followed by lobular (38%, n = 134), cerebellar (10.4%, n = 36), and brainstem (4.1%, n = 14) hemorrhage.

The mean ICH volume was 62.19 ± 59.46 ml (range: 5–382 ml). IVH was found on the initial CT of 198 patients (58%) and accompanying SAH in 32 patients (9.4%). Mean midline shift was 6.5 ± 4.8 mm and the minimum depth of the hematoma from the cortical surface was ≤10 mm in 100 patients (29.2%) and >10 mm in 242 patients (70.8%).

One hundred and two patients (29.8%) underwent an early surgical treatment for the bleeding. Of these, 10 patients had a stereotactic evacuation and 16 patients received an additional craniectomy. Two hundred and forty patients (70.2%) were treated conservatively without surgical evacuation of the hemorrhage.

**Short-term outcome**
Eighty six patients died within 30 days following the bleeding and hence the 30-day mortality was 25.15%.

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**Table 1: Characteristics of 342 patients with a spontaneous intracerebral hemorrhage**

| Patients (n) | 342 |
|---|---|
| Male/female, n (%) | 172 (50.3)/170 (49.7) |
| Age (years), mean±SD | 67 ± 11.2 |
| Glasgow Coma Scale (GCS) on admission, mean±SD | 9 ± 3.66 |
| GCS=3-8, n (%) | 130 (38) |
| GCS=9-12, n (%) | 132 (38.6) |
| GCS≥13-15, n (%) | 80 (23.4) |
| Comorbidities, n (%) | |
| Hypertension | 296 (86.5) |
| Diabetes | 96 (28) |
| Smoking | 20 (5.8) |
| Alcohol | 30 (8.8) |
| Use of AC or AP, n (%) | 164 (48) |

**Hemorrhage characteristics**

| Location, n (%) | |
|---|---|
| Basal ganglia | 158 (43.9) |
| Lobular | 134 (38) |
| Cerebellum | 36 (10.4) |
| Brainstem | 14 (4.1) |
| Intraventricular hemorrhage, n (%) | 198 (58) |
| ICH volume (ml), mean±SD | 62.91 ± 59.22 |
| Subarachnoidal hemorrhage, n (%) | 32 (9.4) |
| Midline shift (mm), mean±SD | 6.5 ± 4.8 |
| Depth ≤10 mm%/> 10 mm, n (%) | 100 (29.24)/240 (70.765) |

**Treatment**

| Surgery/BMT, n (%) | 102 (29.82)/240 (70.18) |

AC: Anticoagulation therapy, AP: Antiplatelet therapy, GCS: Glasgow coma scale, IVH: Intraventricular hemorrhage, ICH: Intracerebral hemorrhage, SAH: Subarachnoidal hemorrhage, SD: Standard deviation, BMT: Best medical treatment
Half of these patients died within the first 48 h following bleeding. An unfavorable outcome (mRS > 2) was documented in 262 patients (76.7%) at the end of the short-term follow-up [Table 2].

The univariate analysis showed the following variables as significant predictors of death within 30 days after ictus of spontaneous ICH: Initial neurological state, baseline volume of ICH, midline shift on initial head CT, localization of ICH (supra- vs. infratentorial), use of oral anticoagulants, presence of IVH and type of treatment (conservative vs. operative). In the second step, we performed a multivariate logistic regression analysis on variables found to be significant after univariate analysis with the 30-day mortality as the dependent variable.

Hereafter initial GCS (OR = 0.726 per one point on GCS, 95% CI = 0.661–0.796, P < 0.001), the volume of the bleeding (OR = 1.012 per ml, 95% CI = 1.007–1.017, P < 0.001), and the infratentorial location of the ICH (OR = 5.381, 95% CI = 2.166–13.556, P = 0.009) were significant predictors for the 30-day mortality. The use of oral anticoagulants was not a significant prognostic factor in our multivariate analysis, although there was a tendency towards significance in terms of higher 30-day mortality [Table 3].

On performing an ROC analysis (using the Youden Index), a cutoff value of 11 was determined for the GCS. In addition, cutoff values for the volumes for supratentorial bleeding and infratentorial could be identified as 32 ml and 21 ml respectively. This “high-risk group” of spontaneous ICH patients with an initial GCS <11 and ICH volume >32 ml supratentorially or 21 ml infratentorially showed a 30-day mortality exceeding 50% and an unfavorable outcome (mRS > 2) in almost 100% [Figure 1].

**Surgery versus nonsurgical treatment**

Concerning the influence of the type of treatment (conservative vs. surgery) on the short-term outcome in our study, statistical analysis of the entire cohort showed a trend towards lower mortality in the early surgery group compared to the conservatively treated group (15.7% vs. 29.2%), although this result was not statistically significant (P = 0.097). The outcome at 30 days after bleeding in both groups, that is, surgery and conservative treatment, is illustrated in Figure 2.

Notably, the distribution of the characteristics with regard to the volume and depth of hemorrhage between the patients (surgery vs. nonsurgery), was significantly different in both therapy groups [Table 4]. Therefore, we narrowed the selection criteria and analyzed a subgroup of patients with lobar supratentorial bleeding, volumes between 10 and 200 ml and a GCS of 9–13. Sixty four matching patients were identified (males: 30 [46%], mean age: 71.5 ± 7.6 years, mean ICH volume: 71.41 ± 37.13 ml, mean GCS: 11.5 ± 1.4). Of these, 36 patients (56.3%) underwent surgical evacuation and 28 patients (43.8%) received medical treatment. The regression analysis identified no significant benefit of early surgical treatment, neither regarding the mortality nor concerning the morbidity within our study follow-up time. Moreover, the baseline volume of the ICH and the GCS on admission continued to be the most decisive predictors of 30-day mortality even in this subgroup [Table 5].

**Predicting 30-day mortality using outcome grading scores**

We applied three known and validated outcome grading scores to our cohort to determine their correlation with 30-day mortality. The distribution of the study cohort with regard to the grading scores and the correlation with 30-day mortality are presented in Figure 3 and Table 6.

When using the ICH score and the ICH-GS, the 30-day mortality increased in accordance with increases in the scores’ values. The FUNC score correlated negatively to the functional outcome as documented in 262 patients (76.7%) at the end of the short-term follow-up [Table 2].

![Table 2: Characteristics of both study groups referring to the 30-day mortality](image)

**Table 2: Characteristics of both study groups referring to the 30-day mortality**

| Characteristic                          | Survived  | Died within 30 days |
|----------------------------------------|-----------|---------------------|
| No. of patients                        | 256 (74.85%) | 86 (25.15%)         |
| Male (%) / Female (%)                  | 124 (48.4) / 132 (51.6) | 48 (55.8) / 38 (44.2) |
| Mean age in years ± SD                 | 76 ± 11   | 68 ± 12             |
| Mean GCS on administration ± SD        | 10 ± 3    | 6 ± 3               |
| Comorbidities (%)                      |           |                     |
| Hypertension                           | 224 (87.3) | 72 (83)             |
| Diabetes                               | 76 (29.6) | 20 (23.3)           |
| Smoking                                | 14 (5.5)  | 2 (2.3)             |
| Alcohol                                | 22 (8.6)  | 8 (9.3)             |
| Use of AC or AP (%)                    | 114 (44.5)| 50 (58)             |
| Imaging features                       |           |                     |
| Location (infra vs. supratentorial) (%)|           |                     |
| Basal ganglia                          | 130 (50.8)| 28 (32.6)           |
| Lobular                                | 96 (37.5) | 38 (44.2)           |
| Cerebellium                            | 22 (8.6)  | 14 (16.3)           |
| Brainstem                              | 8 (3.1)   | 6 (7)               |
| Presence of IVH (%)                    | 136 (53.1)| 62 (72.1)           |
| Mean ICH volume in ml ± SD             | 48 ± 46.12| 104.42 ± 73.62      |
| Presence of SAH (%)                    | 22 (8.6)  | 10 (11.6)           |
| Midline shift in mm ± SD               | 4.4 ± 3.2 | 8.2 ± 5.1           |
| Depth ≤ 10 mm (%) / > 10 mm (%)        | 72 (28%)  | 28 (32.6%)          |
| Surgery (%) / BMT (%)                  | 86 (33.6%)| 16 (18.6%)          |
|                                         | 170 (66.4)| 70 (81.4)           |

**Table 2: Characteristics of both study groups referring to the 30-day mortality**

AC: Anticoagulation therapy, AP: Antiplatelet therapy, GCS: Glasgow coma scale, IVH: Intraventricular hemorrhage, ICH: Intracerebral hemorrhage, SAH: Subarachnoidal hemorrhage, SD: Standard deviation, BMT: Best medical treatment.
Pearson correlation showed correlations of 0.986 between ICH score and 30-day mortality ($P < 0.001$), 0.853 between FUNC score and 30-day mortality ($P = 0.001$), and 0.924 between ICH-GS and 30-day mortality ($P = 0.001$).

**DISCUSSION**

Spontaneous intracerebral hemorrhage remains an important and frequent medical emergency, often with severe and devastating consequences for the patient. Optimal management is still under discussion and subject of many studies in the medical literature dealing inter alia with various treatment options[1,14] and potential predictive models.[5,12,13,21] Nevertheless early prognosis of ICH is difficult to assess causing persistent uncertainty concerning the “best initial treatment” including surgical, nonsurgical and best supportive care options. With this background, we performed our study evaluating the short-term outcome and attempting to predict the 30-day mortality.

The 30-day mortality of patients with spontaneous ICH has been reported as ranging from 25 to 52%.[2,10,20] The low rate at 25% in our study might be explained by our exclusion criteria. Patients with an initial absence of brainstem reflexes in whom the nontreatment concept was clear were not included in the study group.

Concerning the short-term outcome, 23.4% of the patients had a favorable outcome after 30 days. In a meta-analysis, Van Asch et al. presented a functional outcome with independency rates of between 12 and 39% corresponding to our data.[27]
Consistent with other previously published studies neither gender nor age was a significant outcome predictor. Our study even showed no significant association between the 30-day outcome and the presence of comorbidities such as hypertension, diabetes, tobacco abuse, or alcohol abuse. Patients with a history of oral anticoagulants showed a tendency in term of of higher 30-day mortality.

Concerning possible risk factors for a poor outcome, our study confirmed the initial neurological status and the volume of ICH as the strongest predictors of outcome as described in others. The initial hemorrhage volume and the associated cerebral edema result in an increased intracranial pressure with a consecutive delayed influence on the medical course.

Our statistical model revealed that a bleeding volume of more than 32 ml supratentorially and 21 ml infratentorially correlated with a poor short-term outcome (death or dependence) of >80% and approaching 100% when combined with an initial GCS of 11 or less.

Flemming et al. identified 40 ml as a critical volume predicting a poor outcome in his study with a population of patients with lobar hemorrhage who were primarily medically treated. In contrast, Hemphill et al. presented a volume of 30 ml as the cutoff value, whereas Nilsson et al. described 60 ml as the cutoff point. Clearly, the cutoff values of critical volume and critical GCS differ in the published studies. This may be explained by the use of different outcome scales and varyingly defined follow-up times.
The location of the hemorrhage was also a significant risk factor for 30-day mortality. An infratentorial location correlated with a high 30-day mortality in our study which is consistent with results from other studies.[12,23] Previous studies, however, revealed conflicting results showing no significant influence in case of an infratentorial bleeding location.[2,25]

Patients who underwent surgical therapy had a higher survival rate compared to patients who received the conservative best medical treatment. However, this survival advantage was not statistically significant. In addition, the rate of functional disability was higher in surviving patients in the surgical therapy group, especially in the subgroup with a GCS of <11 on admission and baseline ICH volume of >32 ml supratentorially and >21 ml infratentorially. Hence, further prospective studies evaluating the long-term outcome of these patients are necessary.

Several limitations have to be considered when interpreting our data. First, the retrospective character disposes to an incomplete documentation of the various analyzed variables. Second, because the decision on the treatment modality (surgical or conservative) was made individually by different physicians, it probably contributed to the diverse distribution of the variables in both therapy groups. However, our study confirms some existing data, using a relatively big cohort of patients, and additionally defines a “high-risk” group for an unfavorable outcome.

Our study also compared three validated outcome grading scores and showed that the ICH score and the ICH-GS accurately predict short-term mortality. The FUNC score, originally designed to estimate the 90-day outcome, correlated to a lesser degree with the mortality at 30 days in our study cohort.

**CONCLUSION**

The GCS score on admission, together with baseline volume and localization of the hemorrhage are strong predictors for 30 day-mortality in patients with spontaneous primary ICH. An admission GCS of less than 11 and ICH volume of more than 32 ml supratentorially and 21 ml infratentorially define a high-risk group of patients for developing a poor short-term outcome. The ICH score and the ICH-GS accurately predict the 30-day mortality.

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**Conflicts of interest**

There are no conflicts of interest.
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