

## PREDICTING IN-HOSPITAL MORTALITY IN BULGARIAN PATIENTS WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE

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### Abstract

Intracerebral hemorrhage (ICH) is a life-threatening condition associated with high mortality and morbidity. This study aimed to identify the predictors of in-hospital mortality in patients with spontaneous ICH based on initial evaluation. We conducted a retrospective study of patients admitted with ICH between January 2019 and January 2024, collecting demographic, clinical, laboratory, and computed tomographic data. A total of 98 patients were included, with 31 (31.6%) deaths occurring during the hospital stay. Univariate regression analysis identified several potential independent predictors of in-hospital mortality, including lower Glasgow Coma Scale score (GCS), higher National Institutes of Health Stroke Scale (NIHSS) and ICH scores, elevated white blood cell (WBC) count and blood glucose levels, higher hematoma volume, the presence of midline shift, subarachnoid and intraventricular expansions, island sign, satellite sign and irregular shape. However, multivariate regression analysis revealed that only NIHSS score (OR = 1.24, 95% CI = 1.12–1.42,  $p \leq 0.001$ ) and GCS score (OR = 0.15, 95% CI = 0.02–0.67,  $p = 0.02$ ) were independent predictors of in-hospital mortality. In conclusion, our results suggest that lower GCS and higher NIHSS on admission are significant predictors for in-hospital mortality in ICH patients, highlighting their importance for clinical early decision-making.

**Key words:** intracerebral hemorrhage, predictors, in-hospital mortality

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**Introduction.** Intracerebral hemorrhage (ICH), a subtype of stroke, is a devastating condition, defined by brain injury attributable to acute blood extravasation into the brain parenchyma from a ruptured cerebral blood vessel [1]. Non-traumatic ICH comprises 10–15% of all strokes and is associated with high morbidity and mortality [2]. An analysis of European countries using data from the Global Burden of Diseases 2019 identified high mortality rates in those patients, with Bulgaria experiencing over 7600 deaths. Despite the largest relative reduction in mortality rates expected in Bulgaria, the forecast indicates that the country is still going to exhibit one of the highest absolute numbers of deaths [3]. Globally, the 30-day and one-year mortality rates following ICH are approximately 40% and 50%, respectively, with half of the deaths occurring within the first 48 hours [4].

Early identifications of reliable outcome predictors in ICH patients are crucial to guide clinical decision-making and enhance treatment efficacy [2]. Various studies have identified clinical, laboratory and neuroimaging markers that correlate with the outcome after ICH. For clinical evaluation after ischemic stroke, the most widely spread scale is National Institutes of Health Stroke Scale (NIHSS), which correlates with the mortality rate and functional outcome in those patients. Recent studies used the scale in ICH patients and found that it may be considered as a predictive factor for the outcome [5]. Another well-established tool is Glasgow Coma Scale (GCS), which predicts both in-hospital and long-term mortality [6]. However, the most widely recognized prognostic tool for ICH is the ICH score – a simple 6-point clinical grading scale that has been devised to predict 30-day mortality [7]. In addition to clinical scales, certain biochemical and hematological parameters – such as elevated white blood cells count (WBC), glucose level, red cell distribution width (RDW) and platelets count (PC) – play a significant role for the prognosis after ICH [8–11]. Non-contrast computer tomography (NCCT) remains the first-line neuroimaging modality for ICH, due to its accuracy and accessibility. Key NCCT features, including hematoma volume, location, midline shift, intraventricular and subarachnoid expansion have been associated with poor outcome [6, 12–14]. More recently, specific NCCT signs such as the island sign, satellite sign, blend sign, black hole, swirl sign have been identified as markers of poor prognosis in ICH [6, 13, 15, 16]. Despite the identification of numerical prognostic factors, an optimal grading scale for predicting in-hospital mortality following ICH is lacking. The aim of the current study is to explore easily identifiable predictors of in-hospital mortality in patients with spontaneous ICH for use at the time of the first evaluation.

**Materials and methods.** This retrospective study was conducted in Multiprofile Hospital for Active Treatment in Neurology and Psychiatry “St. Naum”, Sofia, Bulgaria, Department of Neurointensive Care between January 2019 and January 2024. All patients with sudden onset acute neurological deficit of vascular origin and confirmed ICH by baseline NCCT, were included in the study. The

exclusion criteria included: 1. Age under 18 years, 2. Secondary ICH (cerebral aneurysm, arteriovenous malformation, tumour, trauma or hemorrhagic transformation from ischemic stroke). Demographic and clinical data including sex, age, history of hypertension, diabetes mellitus, alcohol consumption, antiplatelet or anticoagulation therapy, GCS, NIHSS were recorded on admission. Laboratory findings at the time of admission, including the RDW, PC, glucose level, WBC count, sodium, international normalised ratio (INR) and creatinine were recorded. All NCCT scans were performed according to the standard radiology department protocol with axial 2.5 mm section thickness on GE/Revolution Evo 64 slice CT. The initial NCCT scan was reviewed to identify ICH location (lobar, thalamic, basal ganglia, cerebellar, brainstem), hematoma volume, hematoma shape, midline shift, presence of intraventricular and subarachnoid expansion. The hematoma volume was calculated using the ABC/2 formula. The hematoma shape was classified as regular and irregular. The specific NCCT signs were reviewed by neuroradiologist who was blinded by the clinical data. The detection and interpretation of satellite sign, island sign, blend sign, black hole sign, swirl sign and sedimentation level were based on the international standards [17]. ICH score was also calculated [7]. Primary outcomes were either survived or died within the hospital.

**Statistical analysis.** The categorical data were presented as percentages. The continuous are reported as mean  $\pm$  standard deviation or with median with Interquartile range (IQR). The demographic characteristics, laboratory and NCCT markers were tested, using Chi-squared tests for categorical and Mann–Whitney U test for continuous data. The univariate and multivariate regressions were used for prediction modelling. The initial multivariate modelling was constructed with predictors selected from the variables with  $p$ -value below 0.1 in univariate regression models. The optimal multivariate regression analysis was obtained using both-directional stepwise regression to find independent predictors of mortality. Odds Ratio (OR) and 95% confidence intervals (CI) were calculated. Receiver operating characteristic (ROC) analysis was calculated to assess the utility of the final multivariate model to predict in-hospital mortality. A  $p$ -value of less than 0.05 was taken as significant. All statistical data were analyzed using R statistical environment.

**Results.** Out of 145 patients with ICH, 98 met the inclusion criteria. The in-hospital mortality rate among these patients was 31.6% ( $n = 31$ ). Demographics and clinical characteristics for both survived and died groups are summarized in Table 1.

A univariate regression model was employed to identify independent predictors of mortality. Among the clinicodemographic characteristics, lower GCS score ( $p < 0.001$ ), higher NIHSS ( $p < 0.001$ ) and elevated ICH scores ( $p < 0.001$ ), were identified as significant independent predictors for mortality. Arterial hypertension exhibited borderline statistical significance. In terms of laboratory

T a b l e 1

Univariate analysis of the association between clinicodemographic findings of patients with intracerebral hemorrhage with in-hospital mortality; SBP – Systolic blood pressure, GCS – Glasgow Coma Scale, NIHSS – National Institutes of Health Stroke Scale; CI – Confidence interval; OR – Odd ratio

Variables	Survived <i>N</i> = 67	Died <i>N</i> = 31	OR (95th CI)	<i>p</i> - value
Age, mean (SD)	68.9 (±13.4)	74.4 (±12.7)	1.03 (1.00–1.07)	0.06
Sex, male, <i>n</i> (%)	35 (52.2)	15 (48.4)	1.17 (0.50–2.75)	0.72
Arterial hypertension, <i>n</i> (%)	58 (86.6)	21 (67.7)	0.33 (0.11–0.91)	0.03
Atrial fibrillation, <i>n</i> (%)	20 (29.8)	8 (25.8)	0.82 (0.11–0.91)	0.68
Diabetes mellitus, <i>n</i> (%)	10 (14.9)	7 (22.6)	1.66 (0.55–4.86)	0.35
Anticoagulant therapy, <i>n</i> (%)	11 (16.4)	4 (12.9)	0.75 (0.19–2.44)	0.65
Antiplatelet therapy, <i>n</i> (%)	12 (17.9)	6 (19.4)	1.10 (0.35–3.18)	0.86
Antihypertensive treatment, <i>n</i> (%)	27 (40.3)	15 (48.4)	1.39 (0.59–3.29)	0.45
Alcohol consumption, <i>n</i> (%)	8 (11.9)	3 (9.7)	–	0.89
Obesity, <i>n</i> (%)	8 (11.9)	1 (3.23)	0.25 (0.01–1.43)	0.20
SBP (mmHg), mean ± SD	163.7 ± 33.3	167.1 ± 43.3	1.00 (0.99–1.01)	0.66
Heart rate (beats/min) (mean ± SD)	82.5 ± 16.1	85.7 ± 21.3	1.01 (0.99–1.03)	0.41
GCS score, median (IQR)	15 (12–15)	7 (3–15)	0.59 (0.46–0.70)	< 0.001
NIHSS score, mean ± SD	7 ± 4.8	18.7 ± 8.7	1.29 (1.18–1.45)	< 0.001
ICH score, mean ± SD	1.3 ± 1.1	3.4 ± 1.2	3.95 (2.45–7.28)	< 0.001

T a b l e 2

Univariate analysis of the association laboratory findings of patients with intracerebral hemorrhage with in-hospital mortality; HBG – hemoglobin; WBC – white blood cell; PC – platelet count; RDW – red cell distribution width; Glu – glucose; INR – international normalised ratio; CI – Confidence interval; OR – Odd ratio

Parameters	Survived <i>N</i> = 67	Died <i>N</i> = 31	OR (95th CI)	<i>p</i> - value
HBG, g/L, mean ± SD	139.1 ± 17.7	143.8 ± 17.1	1.02 (0.99–1.04)	0.21
WBC, 10 <sup>9</sup> /L, mean ± SD	9.9 ± 3.6	12.4 ± 3.9	1.19 (1.06–1.36)	0.006
PC, 10 <sup>9</sup> /L, mean ± SD	285 ± 192.8	283.7 ± 127	1.00 (0.99–1.0)	0.97
RDW, %, mean ± SD	14.3 ± 2.1	14.7 ± 1.8	1.09 (0.88–1.35)	0.42
Glu, mmol/L, mean ± SD	7.5 ± 2.4	9.7 ± 3.1	1.32 (1.13–1.59)	0.001
Na <sup>+</sup> , mmol/L, mean ± SD	138.8 ± 3.9	138.9 ± 3.3	1.01 (0.90–1.13)	0.91
INR, mean ± SD	1.5 ± 1.0	1.3 ± 0.5	0.71 (0.27–1.27)	0.36
Creatinine, μmol/L, mean ± SD	88.8 ± 48.6	92.2 ± 41.5	1.00 (0.99–1.01)	0.68

parameters, higher WBC count ( $p = 0.006$ ) and elevated blood glucose levels ( $p = 0.001$ ) were found to be independent predictors of mortality (Table 2).

Regarding neuroimaging, NCCT findings showed that larger hematoma volume ( $p < 0.001$ ), irregular shape ( $p = 0.011$ ), midline shift ( $p = 0.028$ ), presence of subarachnoid ( $p = 0.043$ ) and intraventricular ( $p < 0.001$ ) expansions were

T a b l e 3

Univariate analysis of the association between non-contrast computer tomography findings of patients with intracerebral hemorrhage with in-hospital mortality; CI – Confidence interval; OR – Odd ratio

Variables	Survived <i>N</i> = 67	Died <i>N</i> = 31	OR (95th CI)	<i>p</i> - value
Hematoma vol., mL, median (IQR)	11.1 (3.3–40.1)	53.7 (5.2–115)	1.02 (1.01–1.03)	< 0.001
Irregular shape, <i>n</i> (%)	33 (49.3)	24 (77.4)	3.53 (1.39–9.89)	0.011
Lobar, <i>n</i> (%)	37 (55.2)	18 (58.1)	1.12 (0.48–2.69)	0.79
Basal ganglia, <i>n</i> (%)	15 (22.4)	6 (19.3)	0.83 (0.27–2.32)	0.73
Thalamic, <i>n</i> (%)	12 (17.9)	5 (16.1)	0.88 (0.26–2.65)	0.83
Brainstem, <i>n</i> (%)	3 (4.5)	4 (12.9)	3.16 (0.66–16.96)	0.15
Cerebellar, <i>n</i> (%)	0 (0.0)	1 (3.2)	–	–
Midline shift, <i>n</i> (%)	19 (28.4)	16 (51.6)	2.69 (1.12–6.60)	0.028
Intraventricular expansion, <i>n</i> (%)	19 (28.4)	20 (61.3)	–	< 0.001
Subarachnoid expansion, <i>n</i> (%)	8 (11.9)	9 (29)	3.02 (1.03–9.02)	0.043
Island sign, <i>n</i> (%)	8 (11.9)	9 (29)	3.02 (1.03–9.02)	0.043
Satellite sign, <i>n</i> (%)	17 (25.4)	15 (48.4)	2.76 (1.13–6.82)	0.026
Blend sign, <i>n</i> (%)	8 (11.9)	1 (3.2)	0.25 (0.01–1.43)	0.20
Black hole sign, <i>n</i> (%)	16 (23.8)	10 (14.9)	1.52 (0.58–3.87)	0.38
Swirl sign, <i>n</i> (%)	30 (44.8)	19 (28.4)	1.95 (0.83–4.75)	0.13
Sedimentation level, <i>n</i> (%)	4 (5.9)	2 (6.4)	1.09 (0.15–5.90)	0.93

associated with increased mortality risk. Additionally, specific NCCT signs, including the island sign ( $p = 0.043$ ) and satellite sign ( $p = 0.026$ ) were linked to a higher risk of death (Table 3).

To refine the prediction model, a multivariable regression analysis was performed. Due to the collinearity between ICH score, Intraventricular expansion and GCS, only GCS was selected for inclusion in the final model. After stepwise regression analysis, two variables remained as independent predictors of in-hospital mortality included: NIHSS score (OR = 1.24, 95% CI = 1.12–1.42,  $p < 0.001$ ) and GCS (OR = 0.15, 95% CI = 0.02–0.67,  $p = 0.02$ ) (Table 4). On the ROC curve analysis, the area under curve for the significant predictors was 0.833 (95%

T a b l e 4

Results of multivariate analysis of predictors of in-hospital mortality; GCS – Glasgow Coma Scale; NIHSS – National Institutes of Health Stroke Scale; SE – Standard error; CI – Confidence interval; OR – Odd ratio

Variables	Regression coefficient	SE	OR	95th CI	<i>p</i> -value
NIHSS	0.216	0.060	1.24	1.12–1.42	< 0.001
GCS	–1.921	0.850	0.15	0.02–0.67	0.02
Arterial hypertension	–1.239	0.850	0.29	0.05–1.47	0.14

CI 0.748–0.917). The model performs well with high accuracy (88%), sensitivity (95%) and positive predictive value (88%). It shows good discrimination between the two groups, but there is potential for improving specificity (71%). The kappa value (70%) also suggests significant agreement between predicted and actual values.

**Discussion.** Outcomes in patients with ICH remain poor with no specific medical treatment. The goal of our study was to identify independent prognostic factors for in-hospital mortality in patients with spontaneous ICH, based on initial evaluation. The mortality rate in the present study was 31.6%. The in-hospital mortality in different countries varies from 13.7% to 45.2% [18, 19]. In our population elevated WBC count and blood glucose levels were found to be independent predictors of mortality. A meta-analysis among 17 studies involving 6527 patients concluded that hyperglycemia significantly increased the risk of mortality in patients with spontaneous intracerebral hemorrhage (RR = 2.36, 95% CI 1.79–3.12). Additionally, this analysis indicated that hyperglycemia raises the risk of both short-term mortality (RR = 3.97, 95% CI 2.13–7.43) and long-term mortality (RR = 1.53, 95% CI 1.14–2.05) [8]. One potential mechanism for this association is that hyperglycemia exacerbates acute blood-brain barrier disruption compared to normoglycemia [9]. Data on the impact of WBC count in relation to mortality in ICH patients remains controversial. However, several recent studies have associated elevated WBC count on admission with increased mortality at 90 days following ICH [10]. Furthermore, a meta-analysis evaluating WBC count as a prognostic factor found that increased count at admission was significantly associated with both overall and long-term mortality [11].

Radiological findings also appear closely associated with mortality prediction in the patients with ICH. The results of the current study align with previous findings of baseline hematoma volume [6, 12], midline shift [13], subarachnoid expansion [14], island sign [15, 16], satellite sign [15], intraventricular hemorrhage [6] and irregular shape [13] which are significant variables influencing the prognosis. However, we did not identify any association between the in-hospital mortality and other variables, including age, gender, blend sign, swirl sign, black hole sign and location of hemorrhage. The ICH score proved statistically significant, as some of its components – such as the GCS, hematoma volume and intraventricular extension – are highly relevant to patient's outcome. Many studies have concluded that this simple clinical grading scale facilitates risk stratification at the time of ICH presentation [7].

Both-sided stepwise regression analysis reduced our model to just two predictors – NIHSS and GCS. Lower GCS scores were associated with a greater risk of in-hospital mortality. Our findings are consistent with numerous studies that demonstrate the ability of this scale to predict both in-hospital and 30-day mortality. The importance of the scale is supported by the fact that it is a component in multiple prognostic models for mortality after ICH [6]. Our study confirmed

that increased NIHSS score upon admission impacts ICH outcomes unfavourably. Prior studies have shown that admission NIHSS correlates with case fatality rates. MAHDY et al. [20] reported a highly statistically significant relation ( $p = 0.001$ ) between the 30-day mortality and NIHSS. A study of KAZARYAN et al. [5] showed that the NIHSS predicts 3-month disability and case fatality outcomes with substantial accuracy, performing comparably with the ICH score. Widely documented in routine clinical care, the NIHSS deficit severity score can serve as a valuable measure for clinical prognosis, therapy development, and case-mix risk adjustment in patients with ICH. In addition, combining the NIHSS and the ICH score in unified model may improve the prognostic performance of each score alone.

**Limitations.** Several limitations must be acknowledged in this study. A retrospective design may not be as robust as a prospective or interventional study due to potential recall and selection biases. In addition, the insufficient sample size may limit representativeness, potentially leading to overestimation, underestimation, or uncertainty in our findings.

**Conclusion.** In conclusion, intracerebral hemorrhage is associated with high mortality and morbidity. Different clinical, laboratory and radiological findings at admission may be effective in prognosticating mortality. However, in our study the multivariable regression analysis revealed that only low GCS and higher NIHSS independently can predict mortality.

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