Review

Clinical and Radiographic Predictors of Intracerebral Hemorrhage Outcome

Fawaz Al-Mufti^{a, b} Ahmad M. Thabet^a Tarundeep Singh^a
Mohammad El-Ghanem^{a, b} Krishna Amuluru^{b, c} Chirag D. Gandhi^d

^aDepartments of Neurology, Neurosurgery, and Radiology, Rutgers University-Robert Wood Johnson Medical School, New Brunswick, NJ, USA; ^bDepartment of Neurosurgery, Rutgers University-New Jersey Medical School, Newark, NJ, USA; ^cDepartment of Interventional Neuroradiology, University of Pittsburgh Medical Center Hamot, Erie, PA, USA; ^dWestchester Medical Center, New York College of Medicine, Valhalla, NY, USA

Keywords

Outcome · Intracerebral hemorrhage · Predictors · Poor prognosis

Abstract

Background: Intracerebral hemorrhage (ICH) represents 10–15% of all stroke cases in the US annually. Fewer than 40% of these patients ever reach long-term functional independence, and mortality rate is roughly 40% at 1 month. Due to the high morbidity and mortality rates after ICH, early detection of high-risk patients would be beneficial in directing the management course and goals of care. This review aims to discuss relevant clinical and radiographic characteristics that can serve as predictors of poor prognosis and examine their efficacy in predicting patient outcomes after ICH. **Summary:** A literature review was conducted on various clinical and radiographic factors. They were examined for their predictive value in relation to ICH outcome. Studies that focused on each of these factors were included, and their results analyzed for trends with regard to incidence, patient outcome, and mortality rate. **Key Message:** In this review, we examined clinical and radiographic characteristics that have been found to be significantly associated to a varying degree with poor outcome. Clinical and radiographic predictors of poor patient outcome are invaluable when it comes to identifying high-risk patients and triaging accordingly as well as guiding decision-making.

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Fawaz Al-Mufti, MD
Department of Neurology
Rutgers University-Robert Wood Johnson Medical School
125 Paterson Street, Brunswick, NJ 08901 (USA)
E-Mail fawazalmufti@outlook.com

Introduction

Intracerebral hemorrhage (ICH) represents 10–15% of all 700,000 strokes in the US every year [1]. ICH is a potentially devastating neurologic emergency with long-term functional independence achieved in only 12–39% of cases and mortality rates of 54% at 1 year [2]. Large retrospective cohort studies have shown a significant improvement in mortality rates since 2000 [3], although a meta-analysis of studies between 1980 and 2008 did not show a significant difference in those rates [4].

Prognosis depends on the severity of the clinical presentation, speed of diagnosis, and time of intervention. Due to the nature of ICH to often go unnoticed, prevention may be the most effective approach in lessening the impact ICH has on morbidity [5]. Some risk factors are nonmodifiable, like old age, African-American and Asian ethnicities, male gender, vascular anomalies, and neoplasms; while others are modifiable, like hypertension, coagulopathy, heavy alcohol intake, and illicit drug use.

ICH can be broken down into a few key checkpoints: (1) initial hemorrhagic insult, (2) hematoma expansion, and (3) generalized cerebral edema [6]. Initial hemorrhage is a result of ruptured diseased vessels within the brain. Blood extravasation then leads to formation of a localized edema. The progression from this stage, mainly hematoma expansion and edema, determines patient outcomes. Over the course of hours, bleeding continues leading to progressive accumulation of blood within the brain tissue. Hematoma growth has been determined to occur in a cascaded fashion. Blood extravasation continues from the site of origin and secondary mechanical stresses create rupture of peripheral vessels, leading to ongoing hemorrhage [7]. Expansion creates an increased intracranial pressure that can lead to tissue displacement and potential herniation [8]. Over days after onset, perihematomal edema (PhE) forms secondary to inflammatory processes and oncotic forces [9].

Due to the high morbidity and mortality rates after ICH, early detection of high-risk patients would be beneficial in directing the management course and goals of care. This review aims to discuss relevant characteristics that can serve as predictors of poor prognosis and examine their efficacy in predicting patient outcomes after ICH.

Methods

A literature review was conducted using PubMed, Cochrane, and Google Scholar database searches for original prospective, retrospective, and observational studies on ICH factors (clinical and radiographic) as predictors of outcome, which were published in English. Search was performed using the following terms in varied combinations: “intracerebral hemorrhage, outcome, predictors, spot sign, neutrophil lymphocyte ratio, swirl sign, hemorrhagic stroke, nontraumatic intracerebral hemorrhage, Glasgow Coma Scale (GCS), perihematomal edema (PhE), intraventricular hemorrhage (IVH).” The authors reviewed full texts and reference lists from relevant papers to identify further articles. In some instances, relevant papers from outside the initial search parameters were included if there seemed to be a lack of more current evidence. Studies that focused on each of these factors were analyzed for trends with regard to incidence, patient outcome, and mortality rate.

Results

A total of 51 publications were included, 17 are on radiographic factors and 34 on clinical factors: 4 on patients’ age, 1 on premorbid function state, 3 on initial Glasgow Coma Scale (GCS), 2 on early changes in code status, 7 on systolic blood pressure (SBP), 4 on coagulopathy, 4 on seizures, 4 on fever, 3 on neutrophil/lymphocyte ratio (NLR), 2 on serum

fibrinogen level, 2 on hematoma volume, 2 on hematoma expansion, 3 on radiographic spot sign, 4 on swirl sign, 2 on PhE, 3 on intraventricular hemorrhage (IVH) extension, and 1 on hydrocephalus. Study populations, design aspects, and main findings with statistical results of these studies are summarized in Tables 1, 2.

Clinical Predictors of Poor Outcome

Age

Old age is both a risk factor for ICH incidence and a predictor of worse outcome. ICH incidence increases with age (relative risk increase of 1.97 per decade) [10] and is expected to rise with the increase in the overall population age [1].

Numerous studies have demonstrated correlation between age and poor outcome after ICH; however, it is often hard to distinguish between age itself and associated comorbidities, like altered cognitive function and hypertension [11]. Bagg et al. [11] examined age as it relates to functional outcome using a Functional Independence Measure (FIM) instrument scale. Age alone was an independent predictor ($p < 0.001$) of poor functional outcome when measured via total FIM score and Motor FIM score. This association, as indicated earlier, may be explained by comorbidities associated with natural aging. A study by Gonzalez-Perez et al. [4] assessed 30-day mortality as it relates to age of admission. Results showed that age not only increased the prevalence of ICH, but also the 30-day mortality rate. Mortality rate increased from 29.7% in patients aged 20–49 to 54.6% in patients aged 80–89. Age-related mortality rate increased nearly linearly between these two groups ($p < 0.0001$) [4]. Similar findings were reported in a prospective analysis of 549 patients with ICH by Sacco et al. [12], in which older age was associated with an increased risk of 30-day mortality (OR = 1.18, $p < 0.001$).

Premorbid Functional State

The FUNC score was created to predict the likelihood of a patient reaching functional independence after an ICH. Assessed at admission, it takes into account a patient's pre-ICH cognitive impairment, in addition to his age, GCS score, ICH volume, and ICH location. In developing the FUNC score, 418 patients with ICH and 90-day outcome data were studied by Rost et al. [13] to examine the correlation between these predictors and a patient's dependence status at 90 days. In their study, 85% of patients with a FUNC score of 11 reached functional independence. On the other hand, only 4% of patients with a score of 5 achieved independence, and there were no patients with a score of 4 or lower who did. Of the components in the FUNC score, age, GCS, ICH volume, IVH, warfarin use, and pre-ICH cognitive impairment were significantly associated with functional independence ($p < 0.01$). Pre-ICH cognitive impairment was identified as an independent predictor of worse outcomes following ICH. The role of premorbid functional status in rehabilitation following stroke could explain the association of pre-ICH cognitive impairment with worse outcomes due to patients starting at a lower baseline [13].

Initial GCS

ICH is often associated with symptoms and signs of elevated intracranial pressure including decreased level of consciousness that may progress into coma [14]. The GCS is invaluable in assessing patient state of consciousness. More than 20% of ICH patients will deteriorate by 2 or more points in their GCS score between initial assessment by emergency medical services and arrival to an emergency department (ED) [15]. This drop has been termed ED neurological deterioration. Another 15–23% of patients will continue to deteri-

Table 1. Clinical predictors of poor outcome

First author [Ref.], year	Study type	Cases, <i>n</i>	Variable examined	Outcome	OR	<i>p</i> value
<i>Age</i>						
Gonzalez-Perez [4], 2013	Observational database	4,140	Increasing age (20–49 vs. 80–89)	In-hospital mortality rate	N/A	<0.001
Bagg [11], 2002	Prospective	640	Increasing age (<50, 50–59, 60–69, 70–79, >80)	Functional independence measure	N/A	<0.001
Sacco [12], 2009	Prospective	549	Increasing age (<44, 45–54, 55–64, 65–74, 75–84, >85)	30-day mortality	1.18	<0.001
Rosand [35], 2004	Prospective	102	Age >70	3-month mortality	2.4	<0.001
<i>Premorbid functional state</i>						
Rost [13], 2008	Prospective	629	Pre-ICH cognitive impairment	GOS >4	N/A	0.005
<i>Initial GCS score</i>						
Moon [15], 2008	Cohort	98	GCS decline during transport	Intraventricular extension	N/A	<0.001
Fan [16], 2012	Retrospective cohort	619	Early neurological deterioration – GCS decline >2	1-week mortality 30-day mortality Surgical need	4.4 1.8 5.9	<0.001 <0.001 <0.001
Davis [79], 2006	Meta-analysis	218	GCS score on admission	In-hospital mortality Decline in mean Rankin score	0.88 1.46	0.003 <0.001
<i>Early change in code status</i>						
Hemphill [18], 2004	Database sampling	8,233	DNR usage	In-hospital mortality rate	3.28	<0.001
Shepardson [20], 1999	Database sampling	13,337	DNR usage	In-hospital mortality rate	33.9	<0.001
<i>Systolic blood pressure</i>						
Leira [8], 2004	Prospective	266	10 mm Hg increase in BP	48 h – early neurological deterioration	1.17	<0.001
Ohwaki [101], 2004	Retrospective	76	BP >145	48 h – ICH expansion	1.063	<0.001
Dandapani [26], 1995	Retrospective	87	BP >145	30-day mortality	5.64	<0.010

Table 1 (continued)

First author [Ref.], year	Study type	Cases, <i>n</i>	Variable examined	Outcome	OR	<i>p</i> value
Sakamoto [27], 2013	Prospective	211	Mean achieved BP	Early neurological deterioration – GCS decline >2 points Hematoma expansion (>33%) Unfavorable outcome (mRS 4–6 at 3 months)	4.45 1.86 2.03	<0.010 <0.010 <0.010
Tsivgoulis [28], 2014	Systematic review	3,315	BP-lowering treatment	3-month mortality/dependency (mRS 3–6) Hematoma growth attenuation Mortality rate	0.87 N/A 1.01	0.062 0.038 0.914
Arima [29], 2010	Randomized controlled trial	346	BP-lowering treatment to <140 mm Hg	Slowed hematoma growth	N/A	<0.050
Takeda [83], 2013	Prospective	201	BP >160 mm Hg	Hematoma expansion (>33%)	8.77	0.001
<i>Coagulopathy</i>						
Liotta [3], 2013	Database review	52,993	Warfarin-associated ICH	Mortality rate	1.35	<0.001
Filbotte [33], 2004	Prospective	183	Warfarin associated ICH	Hematoma expansion (>33%)	6.2	<0.001
Rosand [34], 2004	Prospective	435	Warfarin-associated ICH	Mortality rate	2.2	<0.010
Cucchiara [102], 2008		303	Warfarin-associated ICH	Mortality rate	N/A	0.006
<i>Seizures</i>						
Passero [44], 2002	Prospective	761	Lobar hemorrhage	Seizure incidence	4.05	<0.001
Mullen [46], 2013	Database sampling	13,033	Seizures	In-hospital mortality	0.62	0.003
Messe [48], 2009	Randomized controlled trial	295	Antiepileptic use	Poor outcome at 90 days (NIHSS decline)	6.8	0.001
Naidech [49], 2009	Prospective	98	Antiepileptic use	Poor outcome at 90 days (NIHSS decline)	9.8	0.020
<i>Fever</i>						
Honig [50], 2015	Prospective	95	Central fever	Intraventricular extension	4.667	<0.001
Castillo [53], 1998	Prospective	260	Hyperthermia (1st 24 h)	Increased infarct volume	3.23	<0.001
Rincon [52], 2013	Database sampling	303	Central fever	Hematoma expansion (>33%)	1.5	0.040

Table 1 (continued)

First author [Ref.], year	Study type	Cases, <i>n</i>	Variable examined	Outcome	OR	<i>p</i> value
Schwarz [54], 2000	Prospective	251	Central fever	Hematoma expansion (>33%) Higher neurological deficit	N/A 3.06	<0.001 <0.001
<i>Hyperglycemia</i>						
Fogelholm [60], 2005	Database sampling	329	Hyperglycemia	28-day mortality rate	1.22	<0.0001
Kimura [61], 2007	Prospective	100	Hyperglycemia (>150 mg/dL)	Early in-hospital mortality	37.5	0.030
Passero [62], 2003	Prospective	764	Hyperglycemia (diabetics) Hyperglycemia (non-diabetics)	30-day mortality 3-month mortality 30-day mortality 3-month mortality	1.31 1.24 1.29 1.27	<0.010 <0.010 <0.010 <0.010
Oddo [63], 2008	Prospective	20	Tight glycemic control (<13 mg/dL)	Mortality rate	7.36	0.020
<i>Neutrophil/lymphocyte ratio</i>						
Leira [8], 2004	Prospective	266	Absolute neutrophil count	Early neurological deterioration – GCS decline >2 points	2.08	<0.001
Lattanzi [69], 2016	Retrospective	177	Neutrophil/lymphocyte ratio >4.58	3-month mortality	1.16	<0.001
Wang [70], 2016	Observational	224	Neutrophil/lymphocyte ratio >7.35	30-day mortality	1.09	<0.001
<i>Serum fibrinogen level</i>						
Leira [8], 2004	Prospective	266	Serum fibrinogen >523 mg/dL	Early neurological deterioration – GCS decline >2 points	5.59	<0.001
Van den Herik [103], 2012	Case-control	211	Serum fibrinogen increase	Unfavorable outcome (mRS 4–6 at 3 months)	4	<0.001

ICH, intracerebral hemorrhage; GOS, Glasgow outcome scale; END, early neurological deterioration; DNR, do not resuscitate; BP, blood pressure; GCS, Glasgow Coma Scale; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil/lymphocyte ratio.

Table 2. Radiographic predictors of poor outcome

First author [Ref.], year	Study type	Cases, <i>n</i>	Variable examined	Outcome	OR	<i>p</i> value
<i>Hematoma location</i>						
Broderick [77], 1993	Retrospective	188	Lobar hemorrhage	30-day mortality	39%	N/A
			Deep hemorrhage	30-day mortality	45%	N/A
			Pontine hemorrhage	30-day mortality	44%	N/A
			Cerebellar hemorrhage	30-day mortality	64%	N/A
<i>Hematoma volume</i>						
Broderick [77], 1993	Retrospective	188	Volume >60 cm ³	30-day mortality	N/A	<0.0001
Takeda [83], 2013	Prospective	201	Volume >16 mL	Hematoma expansion >33%	5.05	0.018
<i>Hematoma expansion</i>						
Leira [8], 2004	Prospective	266	Hematoma expansion	Early neurological deterioration	N/A	<0.010
Davis [79], 2006	Meta-Analysis	218	Hematoma expansion	In-hospital mortality	1.05	<0.001
<i>Spot sign</i>						
Wada [78], 2007	Prospective	39	Spot sign	Hematoma expansion >33%	8.5	0.003
Tsukabe [84], 2014	Prospective	83	Spot sign (on admission)	Hematoma expansion >33%	N/A	<0.001
			Spot sign (48 h follow-up)	Hematoma expansion >33%	N/A	<0.00001
Rizos [85], 2013	Prospective	101	Spot sign	Hematoma expansion >33%	5.27	<0.001
<i>Swirl sign</i>						
Boulois [7], 2016	Cohort	1,029	Hematoma heterogeneity	Hematoma expansion >33%	3.42	<0.001
Barras [86], 2009	Prospective	90	Hematoma heterogeneity	Hematoma expansion >33%	N/A	<0.046
Takeda [83], 2013	Prospective	201	Hematoma heterogeneity	Hematoma expansion >33%	7.81	0.004
Selariu [104], 2012	Prospective	203	Swirl sign	30-day mortality	2.6	<0.001
<i>Perihematomal edema</i>						
Gebel [87], 2002	Prospective	142	Baseline relative edema volume	Poor 3-month outcome	0.09 per 1 mL increase	0.016
Staykov [88], 2011	Prospective	219	Increase in PHE volume	In-hospital mortality	N/A	0.014
<i>Intraventricular hemorrhage</i>						
Leira [8], 2004	Prospective	266	Intraventricular hemorrhage	Early neurological deterioration	2.66	<0.01
Bhattathiri [95], 2006	Prospective	1,033	Intraventricular hemorrhage	Poor 3-month outcome	N/A	<0.00001
Hallevi [96], 2008	Retrospective	406	Intraventricular hemorrhage	Poor outcome (mRS 4–6)	2.25	0.001
<i>Hydrocephalus</i>						
Diringer [100], 1998	Prospective	81	Hydrocephalus	90-day mortality rate	1.26	<0.0001

PHE, perihematomal edema; IVH, intraventricular hemorrhage; mRS, modified Rankin scale.

orate within the first few hours of hospitalization [16]. Decline in GCS in the ED was found to be independently associated with a 4.4-fold increase in 1-week mortality (11.0 vs. 2.5%, $p < 0.001$), 1.8-fold increase in 30-day mortality (36.4 vs. 19.6%, $p < 0.001$), and a 5.9-fold increased need for surgical intervention (65 vs. 11.1%, $p < 0.001$) [16]. The 2015 American Heart Association/American Stroke Association (AHA/ASA) Guidelines for the Management of Spontaneous ICH recommend that standardized disease severity scores such as the GCS and ICH score should be utilized to help facilitate clear communication between medical providers [17].

Early Change of Code Status

Do-not-resuscitate (DNR) orders are common in the setting of patients with neurological impairment. Many studies have found associations between DNR usage in hospitals and poor patient outcomes after spontaneous ICH. A multicenter study of 8,233 patients found that usage of DNR orders varied greatly across the hospitals studied. Hospitals were broken down into quartiles based on DNR use. Mortality rate increased significantly with DNR usage (p trend = 0.01). After adjusting for race, age, gender, insurance, and use of mechanical ventilation, every 10% increase in DNR use rate increased the mortality rate by 13% [18]. Hospitals reporting the lowest DNR use were more likely to be teaching hospitals or trauma centers. Being made DNR within 24 h after admission increased mortality rate 2.4, 2.6, 2.8, and 3.3-fold ($p < 0.001$) in quartiles 1, 2, 3, and 4, respectively. An increase in DNR use was an independent predictor of patient mortality as compared to an individual lacking a DNR order [19]. It suggests that the mortality risk of patients treated in high DNR use hospitals is related to an aspect of the medical care provided there. Similarly, Shepardson et al. [20], in 13,337 consecutive stroke admissions across 30 hospitals, noted that DNR usage was associated with a higher in-hospital mortality rate compared to those patients without a DNR order (40 vs. 2%, $p < 0.001$). Other studies focused on the potential relation between withdrawal of care discussion and probability of poor outcome. In a retrospective analysis of 383 patients with multiple types of intracranial hemorrhage, Weimer et al. [21] explored whether withdrawal of life support therapy decision would accurately identify patients with high probability of poor outcome. The results showed that the majority of patients undergoing withdrawal of life support therapy may be expected to have either died or remained significantly disabled despite maximum therapy. When stratifying by hemorrhage type, ICH was associated with high median predicted probability of poor outcome and death.

Systolic Blood Pressure

Hypertension is the most common cause of primary ICH, accounting for 60–70% of all cases [22]. A history of hypertension, in a trial of 370 patients, was determined to double the risk of ICH occurrence (OR = 2.55, 95% CI 1.72–3.79) [23]. Chronic hypertension leads to reduced elasticity of deep small arterioles and increased susceptibility to spontaneous rupture [24]. Common locations for hypertension-related ICH are the putamen (46% of all ICH patients), thalamus (18%), caudate (4%), pons (13%), and cerebellum (4%) [25].

After the initial insult, sustained hypertension in the early stages of ICH can create a risk of continuous hemorrhage, increased ICH volume, and worsened severity of the stroke [26]. In a study by Sakamoto et al. [27] ($n = 211$), a 10 mm Hg increase in uncontrolled SBP was found to be associated with poor outcomes. Outcomes assessed were early neurological deterioration (OR = 4.45, 95% CI 2.03–9.74), hematoma expansion (OR = 1.86, 95% CI 1.09–3.16), and unfavorable outcome measured by a Rankin disability scale score of 4–6 (OR = 2.03, 95% CI 1.24–3.33).

Antihypertensive medications were noted to ameliorate the incidence of ICH and associated poor outcomes. A meta-analysis of 3,315 patients showed that intensive BP reduction

was found to be associated with lower unfavorable 3-month functional outcomes and mortality. In addition, they found that blood pressure reduction was associated with quicker attenuation of hematoma growth and ICH progression [28]. Significant associations have been noted between aggressive SBP reduction within 24 h and attenuation of hematoma growth ($p < 0.05$). In a study by Arima et al. [29], SBP reduction to between 130 and 140 mm Hg within 24 h of admission with ICH, showed the highest protective effect against hematoma growth. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) found that intensive lowering of SBP to <140 mm Hg significantly reduced the risk of poor outcomes ($p < 0.05$). In addition, intensive blood pressure-lowering showed no significant adverse effects [30]. To further study the efficacy of early, intensive antihypertensive treatment, the NIH had funded the Antihypertensive Treatment of Acute Cerebral Hemorrhage trial (ATACH-II). This trial enrolled 1,000 patients within 4.5 h of ICH, a hematoma volume <60 mL, and SBP >180 mm Hg. Whereas INTERACT2 results suggested a benefit of blood pressure lowering, ATACH-II did not [31]. The difference lay in the more rapid and intensive lowering of SBP in the ATACH-II trial. Combined results suggest that blood pressure reduction to 140 mm Hg is beneficial but more so in a controlled manner like in INTERACT2 [30, 31]. The 2015 AHA/ASA ICH guidelines recommend targeting an SBP goal of <140 mm Hg for ICH patients with a presenting SBP between 150 and 220 mm Hg and no contraindication for treatment, and that it is reasonable to lower SBP for patients who present with an SBP >220 mm Hg, but a specific target blood pressure is not specified [17].

Coagulopathy

Coagulopathy is a risk factor for primary ICH. 6.6% of ICH patients in the US from 2005 to 2008 were using warfarin [3]. Novel oral anticoagulants (NOACs) have a lower risk of ICH than warfarin. Other causes of coagulopathy include platelet deficiency or dysfunction, congenital or acquired coagulation factor deficiencies, and liver disease [32].

Coagulopathy is also associated with worse ICH outcomes, commonly in the setting of the use of vitamin K antagonists [3, 33, 34]. The risk of ICH occurrence and expansion is higher with warfarin and the NOAC than with antiplatelet agents [35]. Although randomized trials in atrial fibrillation patients showed that NOACs have about half the incidence of ICH compared to warfarin [36], subsequent studies noted that baseline ICH volume, hematoma expansion, mortality, and functional outcome at 90 days were similar following NOAC-associated ICH and vitamin K antagonist-associated ICH [37].

In terms of outcomes, warfarin has been noted to significantly increase the ICH-related 30-day mortality rate in multiple studies. Rosand et al. [34] observed a doubling in mortality rate in patients on warfarin therapy, 52 compared to 25.8%. Liotta and Prabhakaran [3] ($n = 52,993$) discovered in their review of warfarin-associated ICH (WAICH), that incidence rose from 2005 to 2008 by 2% and was associated with a 35% higher mortality rate than non-WAICH patients (OR = 1.35, 95% CI 1.24–1.47, $p < 0.001$). Another study of 183 cases by Flibotte et al. [33] supports these findings; warfarin was the sole predictor of hematoma expansion (OR = 6.2, 95% CI 1.7–22.9, $p < 0.001$) and consequent patient mortality rate. Since WAICH expansion occurs rapidly, abrupt reversal with vitamin K in addition to fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) may be crucial in stopping progression and improving outcomes [38, 39]. Not only PCC provides rapid administration and INR correction compared to FFP, in one study its use was associated with improved 3-month outcome in patients with WAICH [40]. In patients with factor Xa inhibitor-associated ICH, the available data are not sufficient to support the efficacy of available reversal agents. Nevertheless, the neurocritical care society and society of critical care medicine advises the administration of reversal agents to correct anti-factor Xa-associated coagulopathy. Due to better correction and lower risk of thromboembolism, it seems favorable to use 4-factor PCC or acti-

vated PCC. Regarding direct thrombin inhibitor-associated ICH, it is recommended to use idarucizumab (5 g i.v. in two divided doses) as the reversal agent. Other methods of reversal are the use of PCC and or dialysis in certain patients or if idarucizumab is not available [41].

Seizures

The incidence of seizures after ICH is roughly 15–20%, most of which are nonconvulsive in nature [42, 43]. Seizures after ICH can be divided clinically into early onset (<2 weeks) or late onset (>2 weeks), and their origin varies. Early-onset seizures are thought to be due to a sudden mass development within the brain parenchyma that disrupts the brain's natural architecture. Late-onset seizures after ICH are mechanistically described as irregular electrical activity due to scar tissue formation [44].

In a large clinical series, 761 patients with spontaneous ICH were observed for occurrence of seizure, the predictive value it may hold, and the utility of prophylactic antiepileptic therapy. Seizures occurred in 4.2% of all patients ($n = 761$) within 24 h ("immediate") and in 8.1% within 30 days after ICH ("early"). Immediate seizures, occurring within 24 h, were associated with smaller hematoma volumes, and with lobar ICH. Analysis showed that lobar location of hemorrhage held the most predictive value for immediate seizures (OR 4.05; $p < 0.00001$) [45]. Another study by Neshige's group analyzed data from 1,920 patients after ICH and confirmed the associations made by Passero et al. [45] showing significant relationships between seizures and lobar/cortical hemorrhage ($p < 0.001$), nonhypertensive ICH ($p < 0.001$), and neurological deficits ($p < 0.001$).

Though prevalence is high, the impact seizures have on patients' prognosis is unclear. Some studies have found that seizures in the setting of acute ICH do not negatively affect outcomes [43, 45, 46] while others have found that they were associated with worse outcomes [46, 47]. Likewise, studies of the impact of anticonvulsant medications in ICH have had conflicting results. Passero et al. [45] reported that antiepileptic drugs (AED) significantly reduced clinical seizures after lobar ICH. In contrast, several studies have reported a lack of effect of AED especially in the acute period. Furthermore, worse outcome was noted especially with the use of phenytoin [48, 49]. The 2015 AHA/ASA ICH guidelines recommend that ICH patients with an unexpected decreased level of consciousness should be screened for electrographic seizures with continuous EEG monitoring, and recommend against prophylactic AEDs, but do recommend that clinical and electrographic seizures in patients with a decreased level of consciousness should be treated with AEDs [17].

Fever

Fever has been reported in 30–40% of all ICH cases [50, 51], which may be secondary to an infection or neurogenic. Infection-related fever is the most prevalent, and it could be due to a concurrent or hospital-acquired infection [51]. In that study, 37.6% of ICH patients were febrile; 22.7% of patients had a documented infection; while 14.8% developed fever without an infection [51]. Neurogenic fever is a diagnosis of exclusion with no identified causative agent. Initial hemorrhage and the associated mass effect of the hematoma, have been hypothesized to induce neuronal and cell death leading to an inflammatory state that leads to an elevation in body temperature [52]. It could also be due to lesions at the anterior region of the hypothalamus, which regulates temperature [53]. Fever has been noted to be more prevalent following lobar or basal ganglia ICHs, with the highest prevalence if IVH is present [54, 55]. There is also evidence to support that intracranial temperature is significantly higher in ICH patients as compared to core temperature, correlated with a rise in intracranial pressure.

Fever has been described to directly impact neurological decline [56]. It has been associated with both hematoma expansion and worse outcomes [54, 57]. Rincon et al. [52] analyzed the effect of a rise in temperature at admission and then 24, 48, 72, and 168 h after

ICH on patient outcome. A cumulative change rise in temperature at 72 h was associated with increased hematoma expansion and poor outcome at 90 days. Another study included 251 patients to investigate the prognostic significance of fever on admission and following 72 h in spontaneous ICH. 9% of patients had normal temperatures through the 72-h study. Of the rest, fever duration was <24 h in 34%, 24–48 h in 36%, and >48 h in 21%. Increased duration of fever was significantly associated with significantly worse outcome as assessed on discharge with the Glasgow Outcome Scale (GOS) score [54]. The 2015 ICH guidelines recommend treating fever in the setting of ICH, although current studies have failed to show improved outcomes with controlled normothermia in this setting [58, 59].

Hyperglycemia

Hyperglycemia in ICH patients has been associated with worse outcomes in several studies [60–62]. Kimura et al. [61] aimed to examine the association of plasma glucose and the risk for early death in 100 patients. Admission plasma glucose levels were significantly higher in patients who died within 14 days as compared to those who survived ($p < 0.0001$). Glucose levels >150 mg/dL were independent predictors of early death. Amongst 764 patients with ICH, Passero et al. [62] found that high plasma glucose was associated with greater incidence of infectious and cerebral complications and also served as an independent predictor of 30-day and 3-month mortality. High blood glucose levels on admission were associated with more severe strokes, supporting evidence that hyperglycemia is associated with poor patient outcomes [61, 62]. However, the concern has been raised that aggressive treatment of elevated blood glucose may lead to systemic or cerebral hypoglycemia and potentially worsen outcomes [63–65]. Tight glycemic control is achieved with intensive insulin therapy with variable target ranges. In a study by Oddo et al. [63], two target levels were categorized: “tight” (80–120 mg/dL) and “intermediate” (121–180 mg/dL). The patients under “tight” control had increased prevalence of low plasma glucose levels (65 vs. 36% in “intermediate,” $p < 0.01$) and brain energy crisis (25 vs. 17% in “intermediate,” $p < 0.01$). Brain energy crisis, a condition of starvation where brain function is reduced, was defined as a glucose level <13 mg/dL. This state was associated with an increased mortality rate [63]. However, Vespa et al. [64] found that intensive therapy does not offer functional outcome or mortality advantage. The 2015 AHA/ASA ICH guidelines recommend close monitoring of the glucose level and avoiding either hyperglycemia or hypoglycemia [17].

Neutrophil/Lymphocyte Ratio

NLR is used as a marker for inflammation within the vascular bed, a commonly hypothesized mechanism for injury in ICH [66, 67]. Within hours after the initial insult, neutrophils are recruited around the growing hematoma and contribute to cellular injury. As such, the increase in NLR holds predictive value as to the severity of the hemorrhagic insult in ICH and existing inflammatory changes [68].

Several studies have examined the correlation between NLR and patient outcome after ICH. A study of 177 patients by Lattanzi et al. [69] examined the predictive value of NLR in terms of patient outcome. An absolute neutrophil count above the upper limit, and absolute lymphocyte count below the lower limit, and $\text{NLR} > 4.58$ as defined by the study were independently associated with 1.7- and 2-fold increase in 90-day mortality (OR = 1.22, 0.57, 1.16, respectively; $p < 0.001$ each). Another study of 224 patients by Wang et al. [70] found that an $\text{NLR} > 7.35$ was associated with a significantly higher mortality rate; 31.6 compared to 4.8% in those with an $\text{NLR} < 7.35$ upon admission. In those surviving ICH, Leira et al. [8] found that absolute neutrophil count was an independent predictor of early neurological deterioration. Various studies demonstrate that NLR holds predictive value for patient outcome due to its correlation with severity of inflammation; however, they differ on significant NLR cutoffs.

Serum Fibrinogen Level

Serum fibrinogen level is a measure of blood coagulation and also an acute phase reactant. Like NLR, fibrinogen level is reflective of the level of inflammation and tissue damage around the hematoma. In a study using univariate analysis with logistic regression model, serum fibrinogen level >523 mg/dL was found to be significantly associated with early neurological degeneration ($p < 0.001$) [8]. Another study of 135 ICH events, using a multivariable model, found that for every standard deviation increase (66.2 mg/dL) in serum fibrinogen, there was a 1.35-fold greater risk of ICH occurrence ($p < 0.001$) [71]. Increased absolute fibrinogen levels were found to be associated with unfavorable outcomes.

Radiographic Predictors of Poor Outcome

Noncontrast computerized tomography (CT) is the most widely used tool for the diagnosis and evaluation of ICH. Head CT scan helps defining the hematoma location, size, and associated IVH and hydrocephalus. These properties of a hematoma and the ongoing hemorrhage have been shown to be effective for predicting patient prognosis.

Hematoma Location

The 30-day mortality rate in ICH is between 44 and 51%, with variation based on the location and volume of the hemorrhage [72]. Deep hemorrhages consist of those originating in the basal ganglia, thalamus, internal capsule, cerebellum, brain stem, or ventricles. In these hemorrhages, blood accumulation leads to hematoma expansion within the brain's white matter, adjacent to the ventricular system. Lobar hemorrhages, usually secondary to amyloid angiopathy, are those originating in the cortex and subcortical white matter. The risk of recurrence of ICH is higher in cases associated with cerebral amyloid angiopathy (10–20% per year) [73] as compared to cases associated with hypertension (<2% per year, if hypertension is well controlled) [74]. As a whole, independent of hemorrhage volume, cerebellar ICH was the highest predictor of 30-day mortality rate, considering the limited space in the posterior fossa and higher risk of herniation.

Hematoma Volume

For any given location in the brain, the volume of ICH is the strongest predictor of 30-day mortality rates. While planimetric computerized methods can be used, hematoma volume can be “hand calculated” quite accurately using the ABC/2 method which estimates the volume of a spheroid [75, 76].

In a study of 30-day mortality rates based on ICH volume, Broderick et al. [77] found that ICH volumes <30 cm³ showed the following 30-day mortality rates: 57 for cerebellar, 23 for deep, and 7% for lobar, while ICH volumes between 30 and 59 cm³ showed the following rates: 75 for cerebellar, 64 for deep, 60 for lobar, and 100% for pontine; and finally ICH volumes >60 cm³ showed the following rates: 93 for deep and 71% for lobar (no cerebellar or pontine hemorrhages were this large in the studied population). As hemorrhage volume increased, the patients' 30-day mortality rates were significantly worse ($p < 0.0001$), indicating a strong predictive value of hemorrhage volume at presentation.

Hematoma Expansion

Another primary indicator of patient prognosis is expansion of the hematoma following the initial hemorrhagic insult. Clinically, it is challenging to assess for early hematoma expansion after the insult because of delayed presentation to the ED. However, most literature defines hematoma expansion as an increase in hematoma volume by >33% [78].

Hematoma expansion has been reported in 38–76% of patients within 3 h after the time of symptom onset and 26% of patients within 1 h after initial CT scan [6] as well as 50% of patients on anticoagulation [33, 79]. Although the precise mechanism of hematoma expansion is unclear, it may be attributable to persistent bleeding or re-bleeding from the initial blood vessel rupture or new foci of bleeding at the periphery of the lesion, often attributed to ischemia, poor venous flow, and local coagulopathy [80, 81]. Large hematoma and a heterogeneous pattern can also be predictive of potential expansion [82, 83]. The higher volume of hematoma expansion is associated with worse outcomes [79]. Recent ongoing research shows that certain radiographic markers, including the spot sign and swirl sign, are effective in identifying patients who are at risk for hematoma expansion and poor outcome.

Spot Sign

Utilizing postcontrast CT, a spot sign can be visualized as a focus of contrast extravasation in an expanding hematoma. It is a radiological marker that can indicate an active, ongoing hemorrhage in the brain parenchyma and help identify high-risk patients. Wada et al. [78] described the spot sign and its potential predictive value. In their study, 39 patients with spontaneous ICH were examined using postcontrast CT. Hematoma expansion occurred in 10 out of the 13 patients within this population that demonstrated the spot sign. The criterion for hematoma expansion was an increase in volume between 33 and 50% [78]. Tsukabe et al. [84] collected similar data in another study. Postcontrast CT spot sign was observed in 24.1% of patients on admission and 53% on follow-up. Presence of spot sign held a strong predictive value for hematoma expansion ($p < 0.001$ at admission and $p < 0.00001$ on follow-up). Rizos et al. [85], in a prospective study of 101 patients, examined the predictive value of spot sign upon admission with regard to hematoma expansion and clinical outcome. 26.7% of patients exhibited a spot sign on admission in addition to higher initial hematoma volumes (36.0 vs. 14.39 mL, $p = 0.005$). At 24 h after ICH, patients with spot sign exhibited greater hematoma expansion ($p < 0.001$). However, no significant increase in the 3-month outcome was found.

Swirl Sign

Similar to the spot sign, the swirl sign (detected on noncontrast CT) has been described as a marker of ongoing extravasation of blood within a hematoma. It is observed as a region of hypodensity within the hematoma that disrupts its uniformity. Hematomas that demonstrate the swirl sign are heterogeneously dense, a trait that Barras et al. [86] examined in their Randomized Controlled Trial. This study focused on the physical properties of ICHs upon presentation and demonstrated that there was a correlation between the size and density of hematomas and their propensity for expansion. In their study, they found that hematomas that were larger and more heterogeneous in density had greater growth between the baseline and 24-h CT scans [86]. A larger-scale retrospective analysis by Boulois et al. [7] showed similar results in a cohort of 1,029 patients with ICH. 52.8% of patients with hematoma expansion had observed hypodensities, whereas only 21.9% without hematoma expansion had hypodensities ($p < 0.001$). Using univariate analysis, warfarin use, presence of spot and swirl signs were significantly associated with hematoma expansion between two cohorts [7]. Selariu's group, examining the correlation of swirl sign with 30-day mortality rates, found similar results in a study of 203 patients. Swirl sign was seen in 30% of the population; 30-day mortality was 61% in patients demonstrating swirl sign compared to 21% of those not demonstrating it ($p < 0.001$).

Perihematomal Edema

These may develop as early as 1 h after ICH, show peak growth by 7 days, may last for weeks after injury, and have been associated with worse outcomes [87, 88]. The mass created

by the edema may contribute to the increased mortality rate and neurological deterioration. Between days 7 and 11 after ICH, PhE volume nearly doubled from 32.6 to 63.7 mL, in a study done by Staykov et al. [88] ($n = 219$). They found that ICH volume strongly correlated with absolute PhE volume ($p < 0.001$). An increase in the absolute volume was found to be significantly associated with worse patient outcome and mortality rate. These findings are supported by the work done by Gebel et al. [87] who, in addition, noted that a larger baseline-relative edema volume (edema volume divided by hematoma volume) was associated with a significant decrease in poor 3-month outcome (OR 0.09 per 1-mL increase, $p = 0.016$). The etiology of this is likely multifactorial and includes blood-brain barrier damage, lysis of red blood cells, and white blood cell recruitment, in addition to release of plasma proteins, thrombin, hemoglobin, iron, matrix metalloproteinases, interleukins, and other inflammatory mediators [9, 25, 89–93].

Intraventricular Hemorrhage

IVH is present in about 45% of ICH patients. As blood fills the ventricular system, clots can form within the CSF leading to obstruction of CSF flow and consequently obstructive hydrocephalus and generalized edema [94]. IVH is consistently associated with worse outcomes across studies. It was found to be associated with a 2.6-fold increase in the risk of early neurological deterioration in a study by Leira et al. [8]. IVH is an indicator of more severe ICH progression, and has been associated with better patient outcome when absent as compared to when present (31.4 vs. 15.1%, $p < 0.00001$). This is compounded by the presence of hydrocephalus, which decreases favorable outcome to 11.5%. Favorable outcome is defined as functional independence and survival [95]. In a similar study, Hallevi et al. [96] identified IVH in 45% of their study population and examined incidence with regard to ICH location and volume, in addition to looking at patient outcomes. Larger ICH volumes were significantly associated with IVH presence ($p < 0.001$). Those presenting with IVH had a 2-fold increase in poor outcome (OR 2.25, $p < 0.001$). All relevant studies provide evidence that IVH is significantly associated with increased mortality and poor outcomes. Therapeutic intervention involving decompression and removal of blood from the ventricular system is of utmost importance in treatment of these patients [97].

Hydrocephalus

IVH occurs in 40% of patients with primary ICH, and is considered a predictor of poor outcome [98]. In a retrospective study by Herrick et al. [99], patients with lower GCS, severe IVH, and smaller ICH volume were more likely to have an external ventricular drain (EVD) placed. Placement of EVD was associated with reduced mortality and improved short-term outcomes after adjusting for severity factors.

Diringer et al. [100] first examined patients with ICH and their development of hydrocephalus after ictus. From the 81 patients studied, 40 developed hydrocephalus. Patients with hydrocephalus were younger (57 vs. 67) and more frequently had deep hemorrhages. Patients with hydrocephalus had a higher prevalence of ventriculostomy placement. Compared to those without hydrocephalus, those with had significantly higher 90-day mortality rates of 51% compared to 2% (OR 1.26, 95% CI 1.13–1.42, $p < 0.0001$). Presence of hydrocephalus in patients presenting with ICH is a serious complication and is a strong independent predictor of poor outcome.

Conclusion

Given the profound morbidity and mortality associated with ICH, these clinical and radiographic predictors of poor patient outcome are of important prognostic value. Currently, studies show that <40% of patients regain functional independence after ICH, and mortality rate is 40% at 1 month and 54% at 1 year [2]. Indication of patient outcome, based on presentation upon admission, holds value when triaging patients and making care decision. Efforts can be made to provide effective intervention immediately to delay or prevent ensuing neurological damage. One concern with outcome prediction is that prediction of a high mortality rate may skew early decision-making and limit the care given to individuals who would otherwise be treatable. Due to this nature of outcome prediction, current care guidelines recommend aggressive initial treatment of all ICH patients regardless of factors present upon admission [17].

Disclosure Statement

All authors have no conflict of interest.

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