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Correlation of leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage

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Abstract

Intracerebral hemorrhage (ICH) is a devastating and common admitting diagnosis to intensive care units in the USA. Despite advances in critical care, patients with ICH often experience early neurological deterioration (END) in the first 72 hours after admission due to a variety of factors, including hematoma and cerebral edema evolution. The purpose of this study was to determine factors associated with END after ICH. Using the Duke University Hospital Neuroscience Critical Care Unit Database, we retrospectively identified patients with an admitting diagnosis of supratentorial ICH from January to December 2010, verified by CT imaging. END was defined as a decrease in the Glasgow Coma Scale score of ≥ 3 or death within the first 72 hours after hemorrhage. The chi-squared or *t*-test analysis was used to compare the groups, as appropriate. Multiple logistical regression modeling was performed to test for associations between likely predictors of END. Of the 89 subjects admitted with supratentorial ICH, we included 83 in the analysis based on complete datasets. Of these, 31 experienced END within 72 hours after onset of symptoms. ICH score, presence of midline shift on imaging, and white blood cell (WBC) count were used in a regression model for predicting END. WBC count demonstrated the greatest association with END. Patients with ICH are prone to END within the first few days after hemorrhage. Elevated WBC count appears predictive of deterioration. These data demonstrate that heightened inflammatory state after ICH may be related to early deterioration after injury.

Keywords

Early neurological deterioration; Intracerebral hemorrhage; Leukocytosis; Outcomes; Risk factors

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1 Introduction

Intracerebral hemorrhage (ICH) is a devastating and relatively common disease, affecting as many as 75,000 people annually in the USA. In the absence of effective treatments, ICH remains associated with poor outcome.¹ Given the high morbidity associated with ICH, there is a wide variation in the aggressiveness of early care at different institutions, which complicates study of the natural history and prognosis of patients with ICH.^{2,3}

Despite advances in the delivery of critical care, patients with ICH often experience early neurological deterioration (END) within the first several days following admission.^{2,4} The causes of END are multifactorial, and include intracranial hypertension secondary to evolution of cerebral edema or hematoma extension,⁵ obstructive hydrocephalus, or secondary metabolic insult.⁶ However, the occurrence of END remains difficult to predict in individual patients.

The ICH score is validated for prediction of prognosis after ICH.⁷ Although several iterations of the ICH score exist, it remains the most reliable measure for prognosis after ICH;⁸ however, it was not designed to determine risk for END. Though emerging evidence suggests biomarkers may be useful,^{9,10} a reliable method for gauging the risk of in-hospital deterioration after ICH is lacking. This information could be of considerable clinical value in guiding initial triage decisions for recommendations on intensive care management or transfer to stroke center. This could, in turn, impact quality improvement initiatives for important outcome metrics, such as length of stay, ventilator days, etc., that have been lacking for ICH thus far.

The current study sought to define clinically useful variables associated with early in-hospital END by identifying unique characteristics, such as markers of increased inflammation.

2 Methods

2.1. Patient population

After approval by the Duke University Institutional Review Board for all aspects of the study, we utilized the Duke University Hospital Neuroscience Critical Care Unit Database for a retrospective review of medical records of consecutive patients with an admission diagnosis of supratentorial, non-traumatic ICH from January to December 2010 ($n=89$). These diagnoses were verified by CT scans, and all patients with concordant diagnoses of trauma, subarachnoid hemorrhage, or other cerebrovascular anomaly were excluded. Patient demographics, ICH scores, CT scans (initial and serial), serial neurological examinations, serial vital signs, and laboratories were abstracted from the Database.

2.2. Patient Analysis

The ICH score was calculated using five characteristics that have been determined to be independent predictors of 30-day mortality.⁷ These characteristics include: Glasgow Coma Scale (GCS) score, ICH volume, presence of intraventricular hemorrhage (IVH), infratentorial origin, and age. Clinical deterioration was defined as a decrease in the GCS score of 3 points or death from the time of presentation examination to 72 hours post-hemorrhage that was unassociated with sedation.

2.3. Imaging Analysis

All subjects entered into the database were diagnosed with CT-scan proven ICH. The imaging scans used for analysis were the image for diagnosis (occurred on admission) a the

next subsequent scan that occurred within 72 hours after admission. A blinded neurologist assessed the CT scans in the following manner: on the CT slice with the largest area of ICH, the largest diameter (*A*) of the hematoma was measured in centimeters. The dimension of the hemorrhage perpendicular to the largest diameter represented the second diameter (*B*) in centimeters. The height of the hematoma was calculated by multiplying the number of slices involved by the slice thickness, providing the third diameter (*C*). The three diameters were multiplied and then divided by two ($ABC/2$) to obtain the volume of ICH in cubic centimeters.¹¹ For the purpose of determination of the *C* diameter, the first and last slices where hematoma is first and last noted were not counted. After tabulation of the estimated volume, all subjects were dichotomized into groups of either hematoma volume of >30 mL or volume of < 30 mL on initial CT scan. All subjects were also dichotomized into groups of either increase in hemorrhage volume of >20% or increase in hemorrhage volume of <20% between baseline and subsequent CT scans. Additionally, IVH was defined as an intraventricular hyperdense image not attributable to calcification or the choroid plexus. Midline shift (MLS) of the septum pellucidum was measured in millimeters (mm) by a blinded neurologist and corrected for magnification by using the scale provided on each CT scan. MLS was calculated as the distance from the center of the anterior horns of the lateral ventricles on the CT slice containing the third ventricle to a perpendicular line connecting the anterior and posterior insertions of the falx cerebri. Because individual measurements were recorded in mm, only MLS of > 1 mm were considered to be significant and recorded. Finally, after recording MLS, subjects were dichotomized based on whether MLS increased by >1 mm between the baseline and subsequent CT images.

2.4. Laboratory Analysis

All laboratory analyses were completed at Duke University Hospital. White blood cell count (WBC) were analyzed in the hematology laboratory as standard of care. The collection of laboratory data occurred in a blinded fashion in regards to the status of a subject's END.

2.5. Statistical Analysis

The Student's *t*-test was used to analyze patient demographics and outcome scores. ICH score as a full ordinal scale was analyzed with non-parametric Wilcoxon, then dichotomized using chi-squared analysis. Other dichotomized variables, such as age, hemorrhage volume, change in hemorrhage volume, leukocyte threshold, and change in MLS, were analyzed using chi-squared analysis. Univariate analysis was used to measure the effects of all variables on change in GCS score of > 3 points or death in the first 72 hours after admission. Latency to CT imaging was defined as the time in minutes between the onset of ICH and the first (diagnostic) CT image obtained. Logistical regression was used to measure the effect on selected variables on decrease in GCS score of > 3 points or death in the first 72 hours after admission for multivariate modeling. Statistical significance was assumed with $p < 0.05$. All values are expressed as mean + standard deviation (SD). Analysis were performed on JMP Pro v9 (Statistical Analysis Software, Research Triangle Park, NC, USA).

3 Results

Of the 89 total patients with supratentorial ICH, 83 subjects were included in the analysis based on complete datasets within the medical records. Patient demographics are noted in Table 1. Of this cohort, 31 (37%) experienced clinical deterioration within 72 hours after onset of symptoms. Twenty-two (43%) demonstrated MLS by CT scan exceeding 1 mm within the first three days of admission, and 37 (45%) patients had WBC counts exceeding 10,000/mL³ within the first three days of admission. ICH location included 29 (33%) having basal ganglia ICH, 17 (19%) having thalamic ICH, 42 (47%) having lobar ICH, and one (1%) having both basal ganglia and lobar ICH locations.

ICH scores ranged from 0 to 5 (mean=1.65 + 1.22). Sixteen (18%) scored 0, 27 (31%) scored 1, 27 (31%) scored 2, nine (10%) scored 3, eight (9%) scored 4, and one (1%) scored 5. An ICH score > 2 was associated with subacute deterioration ($p<0.001$; odds ratio [OR] =7.19, confidence interval [CI] =2.23–23.19). Of the individual elements comprising the ICH score, presence of IVH was most closely associated with subacute deterioration ($p=0.002$, OR=4.85, CI=1.76–13.33). Although not a factor in the ICH score, an MLS of > 1 mm during the first three days after injury was a significant predictor of subacute deterioration ($p=0.038$, OR=3.83, CI=1.12–13.08). The average latency from symptom onset to admission CT scan was 348.3 + 641.6 minutes for the total population. Initial imaging times were not associated with END during the first three days (400.1 + 727.5 minutes for subjects with END compared to 315+587.7 minutes for subjects without END). Although all subjects received admission CT scans for diagnosis, 51 of the total subject population obtained imaging that allowed for serial analysis. In this smaller cohort, although progression of MLS of > 1 mm on serial scans was also associated with deterioration ($p=0.038$, OR=3.83, CI=1.12–13.08), hematoma extension of > 20% increase between baseline and follow-up imaging was not ($p=0.318$).

We also tested the presence of significant serum glucose concentration on presentation as another manifestation of acute stress response, finding that neither presentation hyperglycemia (defined as glucose >140 g/dL, $p=0.105$) nor hypoglycemia (defined as glucose < 60 g/dL, $p=0.431$) were associated with subacute deterioration. Further, we tested the potential for intubation and mechanical ventilation to confound any potential associations. We found, however, that of the total subjects, 38 were intubated prior to admission to the ICU and were evenly split (as a percentage) between subjects with END (47.2%) and those without (45.8%). There were no subjects intubated in the first three days who were not intubated prior to admission; thus, no subject with a natural airway on admission was mechanically ventilated during the first three days after admission. In addition to assessing traditional radiographic and clinical variables, we tested the hypothesis that an inflammatory state might contribute to subacute deterioration (Table 2). We found that WBC > 10,000/mL³ upon presentation or within the first 72 hours was highly associated with subacute deterioration ($p=0.014$, OR=4.22, CI=1.28–13.86). This appeared to be a threshold effect, as the association was much less robust when a threshold of 15,000/mL³ was used ($p=0.283$). Interestingly, there was no association with febrile state and subacute deterioration ($p=0.197$), nor was there an association between pneumonia and deterioration ($p=0.742$).

To better define the associations between these variables, we performed multivariate regression models including MLS of > 1 mm, hemorrhage volume of > 30 mL, and WBC count of > 10,000/mL³. Although initial hemorrhage volume and the amount of MLS were associated ($p<0.001$, c-index=0.744, CI=0.612–0.835), leukocytosis was also associated with the total amount of MLS on the initial CT scan ($p=0.040$, c-index=0.243, CI=0.012–0.445) but not with hemorrhage volume ($p=0.160$).

Finally, we performed a multivariate regression using pre-identified variables with a p value < 0.10 in the univariate analysis. Using these variables in a regression model, WBC count demonstrated the highest association with clinical deterioration, as defined by decrease in GCS score ($p=0.05$, OR=5.00, CI=1.00–24.98; c-index=0.695) while no other variable demonstrated significant association in this model (Table 3).

4 Discussion

END after ICH has been associated with an increased length of hospital stay, poor functional outcome, and mortality.^{4,5} The ability to assess risk of in-hospital deterioration would have

significant clinical utility in guiding early management and triage decisions. Although several models have been developed to predict prognosis,¹²⁻¹⁴ there remains no validated model to predict patients at highest risk for END. In the current study, we find that, after correction for traditional prognostic variables, such as age and radiographic findings, initial leukocytosis was associated with END within the first three days of admission.

Further, in the current study, we find that although progressive MLS was associated with subacute deterioration, the relationship between hematoma extension and deterioration was not as strong. Although approximately 25% of patients may experience symptomatic hemorrhage extension within 24 hours of presentation,¹⁵ our data suggest that other factors, such as progressive cerebral edema secondary to neuroinflammatory responses, may also play an important role in contributing to subsequent END from secondary cerebral edema.⁹

Our current findings extend the association of ICH Score beyond prognosis to END. In addition to the traditional clinical and radiographic features reflected in the ICH score, we find that leukocytosis within the first 72 hours is independently associated with END. This finding is consistent with a growing understanding that neuroinflammatory responses may be associated with increased cerebral edema and exacerbation of secondary injury⁴ and agrees with previously published data associating neutrophil count with early deterioration after ICH.⁴

Interestingly, elevated temperature within the first three days was not significantly predictive of early deterioration. Further, as neither fever nor presence of positive culture, was associated with this deterioration, it seems plausible that the initial leukocytosis may have been related to systemic inflammatory state immediately following injury, rather than possible infection. The association between progressive MLS and leukocytosis (not hemorrhage extension) lends credence to an enhanced inflammatory response resulting in greater perihematomal edema formation.

Further the idea that leukocytosis is associated with END has been borne out in other forms of acute CNS injury, such as delayed ischemic deficit in patients with subarachnoid hemorrhage.¹⁶ Adding credence to this line of reasoning, a more recent report demonstrated that systemic inflammatory response syndrome criteria were associated with delayed ischemic deficit in the setting of subarachnoid hemorrhage.¹⁷ Further in preclinical model of traumatic brain injury, WBC accumulation has been described within the first 4 to 48 hours after induced injury, suggesting that WBC accumulation may interfere with the cerebral microcirculation and contribute to secondary brain damage.¹⁸ Finally, Pozzilli and colleagues¹⁹ demonstrated that 72 hours after ischemic stroke, peripheral leukocyte counts were at their peak and were associated with a significantly larger infarct size, impaired neurological exam, and poor clinical outcome.

Our findings also point to the importance of systemic and neuroinflammatory responses in mediating secondary brain injury and influencing patient outcomes. Several studies have demonstrated that ICH is accompanied by inflammation in both humans^{18, 20} and preclinical models.²¹⁻²⁴ Wu and colleagues²² demonstrated that administration of macrophage inflammatory protein to rats with ICH exacerbated damage of the blood brain barrier by recruitment of leukocytes and neutrophils further contributing to cerebral edema and secondary brain injury. Thus, therapeutic strategies that target modification of systemic and/or neuroinflammatory responses following acute brain injury may hold promise.

It should be noted that we used GCS to define END rather than NIH Stroke Scale (NIHSS). Though the NIHSS has been used previously to define END,^{25, 26} it has not previously been the gold standard, as other studies have used the Canadian Stroke Scale⁴, a level of consciousness score,⁵ or both GCS and NIHSS.¹⁵ Thus, for the purposes of creating an

early care decision-making tool to assist with triage of aggressive care (e.g., intubation and mechanical ventilation, resuscitation, etc.), we chose GCS as our definition of END. However to assess the internal validity of our sample, we analyzed the inclusion of NIHSS in our dataset. Of our total subject population, 60 subjects had NIHSS scoring on admission that allowed them to be used for analysis. We defined END by NIHSS as an increase of greater than 2 between 2 consecutive measurements. The positive predictive value of NIHSS for END (with GCS as the gold standard) was 60% and a negative predictive value of 87.5%. Conversely, the positive predictive value in our cohort of GCS for END (with NIHSS as the gold standard) is 70.6% and negative predictive value is 81.4%. Further, we re-analyzed key univariates and found retained significant interactions; however, the overall multivariate model dropped its adjusted c-index to 0.295 and MLS was the only variable that retained significance in the model ($p=0.0152$; IVH: $p=0.0528$; WBC: $p=0.0821$). Though the NIHSS and GCS were highly correlative with each other in our subject population, we retained the use of GCS as our definition for END because we felt it better reflected decision-making tools in the acute stages after ICH.

While there remains a need to demonstrate that treatment of causes of END result in improved morbidity and mortality after ICH, correlation between the two was not the expressed purpose of this study. We feel that early deterioration is important in its relationship to increased utilization of resources and early aggressiveness of care. It is clear that lack of early, aggressive care results in worse outcome;² thus, the ability to predict which patients are likely to deteriorate in the first 72 hours may result in improved ability to triage care towards those patients in most need; i.e., transfer from community hospital to tertiary care facility with specialized neurointensive care and/or determining intensity of nursing care. Thus, in our attempt to create a tool useful for in-hospital decision-making, whether END may or may not be related to long-term outcome may not be as critical as whether variables exist to assist clinicians in making these early stage decisions.

There are several limitations to the present study that should be addressed. These findings are based on a relatively small sample size of retrospective patient data collected at a single site. One advantage to the current study is that all patients cared for at the Duke University Neuroscience Critical Care Unit have standardized protocols for management of ICH. As noted above, practice patterns in the care of patients with ICH may vary widely, and the generalizability of our findings should be confirmed with prospective multicenter trial. It is also worth noting that we included a fairly homogenous patient population with non-traumatic supratentorial ICH, and the results may not be applicable to patients with infratentorial hemorrhage, or hemorrhage associated with trauma or vascular anomalies. In addition, in order to create tools useful in the clinical setting after acute ICH, we made the a priori decision to dichotomize many of the variables, such as hemorrhage volume, MLS, and WBC, based on the use of similar stratification in other published works.^{7,9} Thus, they were not treated as continuous variables in our model. However, given the success of the use of clinical tools using similar stratification, such as the ICH Score, our decision to treat variables in this manner erred on the side of being more useful at the bedside. Also, the evolution of imaging to detect subtle findings, such as the 'spot sign',²⁷ will likely necessitate its inclusion in future predictive models. Finally, our analysis of our cohort was limited by incomplete data regarding serial imaging. Although all subjects obtained imaging that allowed for baseline assessment and dichotomization of hemorrhage and edema volume, we are not able to draw definitive associations between hemorrhage and edema evolution over the first 3 days after injury and END nor was the study appropriately powered to detect such changes. Thus, we cannot overstate the preliminary nature of these data.

In conclusion, our key finding was that initial WBC count $> 10,000/\text{mL}$ ³ was predictive of END within the first 72 hours after ICH. Also, MLS of $> 1 \text{ mm}$ on serial scans was

associated with increased leukocytosis, while hematoma volume of > 30 mL was not. As such, our findings may serve preliminary data for a clinically useful tool in assessing risk of END in patients presenting with ICH. However, ongoing prospective research is needed to confirm these findings.

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Table 1

Demographics of patients with leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage

	Total	Early neurological deterioration		
	N=89	Yes (N=31)	No (N=52)	p value
Age (years) mean $\pm$ SD (range)	65.9 $\pm$ 15.2 (38–94)	67.6 $\pm$ 14.3 (44–91)	65.3 $\pm$ 15.8 (38–94)	0.504
Female; N(%)	52 (58.4)	19 (61.3)	29 (55.8)	0.622
Race/ethnicity; N(%)	41 (46.1)	14(45.2)	24 (46.2)	0.804
Caucasian	45 (50.6)	7(54.8)	26 (50.0)	
African American	1 (1.1)	0	1 (1.9)	
Hispanic/Latino	2 (2.3)	0	1 (1.9)	
Asian				
ICH location; N(%)	29 (32.6)	9(29.0)	18(34.6)	0.318
BG	17(19.1)	3(9.7)	12(23.1)	
Thalamuse	42(47.2)	18(58.1)	22(42.3)	
Lobar	1(1.1)	1(3.2)	0	
BG + lobar				
ICH score; N(%)	16 (18.2)	2 (6.7)	13 (25.0)	<0.001
0	27(30.7)	8 (26.7)	14 (26.9)	
1	27 (30.7)	7 (23.3)	20 (38.5)	
2	9 (10.2)	7 (23.3)	2 (3.8)	
3	8 (9.1)	5 (16.7)	3 (5.8)	
4	1 (1.1)	1 (3.3)	0	
5	0	0	0	
6				
Latency to CT image (min); Mean $\pm$ SD (range)	348.3 $\pm$ 641.6 (30–10,080)	315 $\pm$ 587.7 (35–10,080)	400.1 $\pm$ 727.5 (30–3240)	0.431

Subjects were dichotomized into groups based on the presence or absence of early neurological deterioration defined as change in GCS score of > 3 or death during the first 72 hours after onset of ICH. Latency to CT imaging was defined as the time in minutes between the onset of ICH and the first (diagnostic) CT image obtained. BG=basal ganglia, GCS=Glasgow coma scale, ICH=intracerebral hemorrhage, N=number, SD=standard deviation

Table 2

Univariate analyses of patients with leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage

	Total	Early neurological deterioration		
	N=89	Yes (N=31)	No (N=52)	p value
ICH score; N(%)	70 (79.5)	17 (56.7)	47 (90.4)	<0.001
2	18 (20.5)	13 (43.3)	5 (9.6)	
3				
ICH location; N(%)	29 (32.6)	9 (29.0)	18 (34.6)	0.372
BG	17 (19.1)	3 (9.7)	12 (23.1)	
Thalamus Lobar	42 (47.2)	18 (58.1)	22 (42.3)	
BG + lobar	1 (1.1)	1 (3.2)	0	
HV enlargement; N(%)	N= 51 12 (23.1)	N= 18 6 (31.6)	N= 33 6 (18.2)	0.4175
MLS increase; N(%)	N= 51 22 (43.1)	N= 18 11 (61.1)	N= 33 11 (33.3)	0.038
IVH; N(%)	47 (53.4)	23 (76.7)	21 (40.4)	0.002
Age > 80 years; N(%)	22 (24.7)	6 (19.4)	11 (21.2)	0.844 3
WBC; N(%)	64(71.9)	27(87.1)	32(61.5)	0.014

BG = basal ganglia, HV enlargement=hematoma volume enlargement >20% increase from baseline CT scan to subsequent image within 72 hours after ICH, ICH=intracerebral hemorrhage, IVH=presence of intraventricular hemorrhage on initial CT scan, MLS increase=midline shift enlargement >1 mm from baseline CT scan to subsequent image at 72 hours after ICH, N=number, and WBC=white blood cell count>10,000/mL³.

Table 3

Multivariate regression analysis of patients with leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage

Effect	Point estimate	95 Confidence Interval		p value
MLS	3.259	0.866	12.260	0.0805
WBC	5.004	1.002	24.978	0.0497 *
ICH score	2.233	0.266	18.758	0.4593

* When variables from the univariate analyses were included together in a multivariate model, only leukocytosis (white blood cell count (WBC) >10,000/mL³) during the first 72 hours after intracerebral hemorrhage retained significance.

ICH=intracerebral hemorrhage, MLS increase=midline shift enlargement >1 mm from baseline CT scan to subsequent image at 72 hours after ICH, and WBC=white blood cell count >10,000/mL³.