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Influence of hematoma location on acute mortality after intracerebral hemorrhage

Ji-Yong Lee, MD, PhD[#], **Caroline King, BA**[*], **Dana Stradling, BSN**[*], **Michael Warren, MA**[*], **Dennis Nguyen**[*], **Johnny Lee**[*], **Mark A. Riola**[*], **Ricardo Montoya, BS**[*], **Dipika Patel**[*], **Vu H. Le, MS**[*], **Susan J. Welbourne, BSN, RN**[^], and **Steven C. Cramer, MD**[*]

[#]Dept. Neurology, Yonsei University Wonju College of Medicine, Wonju, Korea

[*]Dept. Neurology, University of California, Irvine, USA

[^]Dept. Decision Support Services, University of California, Irvine, USA

Abstract

Background and Purpose—The current study aimed to identify predictors of acute mortality after intracerebral hemorrhage (ICH), including voxel-wise analysis of hematoma location.

Methods—In 282 consecutive patients with acute ICH, clinical and radiological predictors of acute mortality were identified. Voxel-based lesion-symptom mapping examined spatial correlates of acute mortality, contrasting results in basal ganglia ICH and lobar ICH.

Results—Acute mortality was 47.9%. In bivariate analyses, one clinical (serum glucose) and two radiological (hematoma volume and intraventricular extension) measures significantly predicted mortality. The relationship was strongest for hematoma volume. Multivariable modeling identified four significant predictors of mortality (ICH volume, intraventricular extension, serum glucose, and serum hemoglobin), although this model only minimally improved the predictive value provided by ICH volume alone. Voxel-wise analysis found that for patients with lobar ICH, brain regions where acute hematoma was significantly associated with higher acute mortality included inferior parietal lobule and posterior insula; for patients with basal ganglia ICH, a large region extending from cortex to brainstem.

Conclusions—For patients with lobar ICH, acute mortality is related to both hematoma size and location, with findings potentially useful for therapeutic decision-making. The current findings also underscore differences between the syndromes of acute deep and lobar ICH.

Intracerebral hemorrhage (ICH) remains a devastating form of stroke, accounting for approximately 10% of all strokes in the US and 30% in Asia [1]. Mortality after ICH approaches 40% in the short-term [2], with reported early mortality rates ranging from 24-51% [3], a rate that has not changed over several decades [4]. Improved prediction of acute mortality after ICH could inform several aspects of clinical decision-making.

A number of predictors of increased mortality after ICH have been identified. These include clinical measures such as elevated serum glucose and increased age, and radiological measures such as intraventricular spread and larger acute hematoma volume [5-7]. Hematoma volume has been recognized as a particularly important biological marker after ICH and a powerful predictor of outcome [8-12], and indeed is a core component of ICH predictive

PLEASE DIRECT CORRESPONDENCE TO: Steven C. Cramer, MD, University of California, Irvine Medical Center, 101 The City Drive South, Building 53 Room 203, Orange, CA 92868-4280, PHONE: (714) 456-6876, FAX: (714) 456-8805, scramer@uci.edu.

Conflicts of Interest

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scores [10-12]. However, the numeric relationship between hematoma volume and mortality is informative but does not consider the spatial distribution of this correlation, i.e., whether the impact of an acute hematoma on mortality varies according to its specific location.

An improved understanding of mortality after ICH might therefore be available from studying the relationship between hematoma location and mortality. At a gross level, it has long been appreciated that mortality after ICH differs when patients are subgrouped by site of ICH origin, for example, the prognosis with brainstem ICH is poorer than with lobar ICH [13]. However, within each of these ICH subgroups, it remains to be determined whether there are specific brain regions where presence of ICH predicts a greater likelihood of early mortality. The current study examined this question in the broader examination of predictors of acute mortality. The main study hypothesis was that there are specific brain regions where occurrence of ICH is associated with a greater likelihood of early mortality. In patients with ischemic stroke, injury to bilateral parietal lobe [14] and bilateral insula [15,16] have been associated with increased mortality, and so a further hypothesis examined in the lobar ICH subgroup was that hematoma in these specific lobar locations would predict increased mortality.

To determine whether the location of the acute hematoma is associated with differences in acute mortality, voxel-based lesion-symptom mapping (VLSM) [17] was performed on acute head CT scans from consecutive patients with ICH. VLSM statistically assesses clinical-radiological relationships on a voxel-wise basis in stereotaxic space. In VLSM, each voxel in stereotaxic space undergoes statistical analysis to determine if a clinical measure such as behavioral score or mortality rate differs between patients with and patients without a lesion affecting that voxel, with the output of a VLSM analysis being a statistical map that shows where in the brain occurrence of a lesion is associated with a difference in the clinical measure of interest. VLSM takes advantage of the natural variability in brain lesion size and location in order to make this determination. Correction for multiple comparisons can be done in various ways, with a common choice being use of the False Discovery Rate, which calculates the expected proportion of false positives among all reported supra-threshold voxels. VLSM builds upon older methods of lesion overlap by introducing spatial statistics, can identify novel brain areas of interest in contrast to analyses reliant on predefined regions of interest, and its voxel-based approach provides greater spatial resolution than simply describing regional patterns of injury [18]. VLSM has proven useful in previous studies of ischemic stroke [19] but has not been previously applied to the study of ICH.

The current study also provided an opportunity to contrast findings in two large ICH subgroups, those with lobar ICH and those with ICH originating in the basal ganglia, which have in common some aspects of acute disease presentation but differ in many other regards such as pathogenesis [1,20].

Materials and Methods

Subjects

This is a retrospective study of consecutive patients over 18 years of age who were admitted to UC Irvine Medical Center from December, 2000 to June, 2007 with an ICD-9 code of 431, 432, or 432.9 as primary discharge diagnosis. UC Irvine Medical Center is the only academic medical center in Orange County, CA, the fifth most populous U.S. county [21]. Clinical and radiological data were reviewed, and subjects with a primary diagnosis of subarachnoid hemorrhage, subdural hemorrhage, or epidural hemorrhage were excluded, leaving 475 patients. Of these, 193 subjects were further excluded due to either isolated intraventricular hemorrhage; no available CT scan; or known secondary cause of ICH including saccular aneurysm, tumor, ischemic infarction with secondary hemorrhagic

transformation, arteriovenous malformation, or cavernous hemangioma. This left 282 consecutive patients with primary ICH.

For each patient, the first available CT scan for the index ICH was reviewed. CT scans were obtained in the axial plane with in-plane resolution 512 × 512 voxels (0.49 mm × 0.49 mm). Slice thickness was 5 mm supratentorially and 5-10 mm thick infratentorially, with slice number adjusted per head size. ICH location was classified as lobar, basal ganglia, thalamus, pons, or cerebellum based on the clinical radiology report and on review by a single neurologist experienced in vascular disease (J-Y L) who was blinded to clinical data at the time of ICH location determination. For 4 patients with ICH in more than one site, ICH location was defined as the largest site. This study was approved by the UC Irvine IRB.

ICH volume

The volume of the ICH was estimated two ways, each by a single investigator (J-Y L) who was blinded to clinical data, using standard (80/40) window/contrast levels. Note that intraventricular blood and perihematomal edema were not included in volume calculations. Primary analysis measured ICH volume by outlining the hematoma by hand, using MRIcro (http://www.cabiatl.com/mricro/mricro/mricro.html). Secondary analysis measured ICH volume using the ABC/2 method [22], which measures largest ICH diameters in-plane and through-plane.

Clinical and radiological correlations

Baseline clinical and radiological measures of interest were extracted from charts. The 10 clinical measures of interest suggested by review of the literature were age, blood WBC count, serum hemoglobin, platelet count, PTT, PT-INR, serum glucose, sodium, creatinine, and BUN. For each measure, the first value obtained during the index ICH admission was used. No variable had a normal distribution, and none could be transformed to a normal distribution, so non-parametric statistical methods were used. The two radiological measures of interest were hematoma volume and presence of intraventricular extension. The primary outcome measure was acute mortality, i.e., whether or not a patient survived to discharge. The bivariate relationship that each of the 12 predictors had with acute mortality was then determined, using the Wilcoxon rank sums test for continuous measures and Chi square testing for categorical measures, employing a Bonferroni-adjusted alpha=0.00417 (i.e., 0.05/12) to correct for multiple comparisons. Note that pre-admission antiplatelet and anticoagulant use were also of interest but could not be determined in 27% and 26% patients, respectively, and so were not evaluated.

These relationships were also examined using multivariable statistics. Those variables for which the bivariate relationship with survival showed $p < 0.1$ were entered into a multivariable nominal logistic regression model for predicting acute mortality after ICH.

Spatial distribution of clinical correlates

Voxel-wise analysis was performed on the stroke masks created via the hand-drawn method. For right brain ICH, images were flipped along the y-axis. For scans with any 10 mm thick infratentorial CT slices, the resultant stroke mask was adjusted to achieve all slices of 5 mm thickness. Each stroke mask was then converted to a binary image. Next, FLIRT (http://www.fmrib.ox.ac.uk/fsl/flirt/index.html) was used to transform images to MNI standard stereotaxic space. Consistent with the SPM archives, our pilot studies found that the Transm.img image performed better than other reference images for accurate spatial transformation of acute head CT scans, and so this image was used. At times, severely rotated images do not spatially transform well using purely automated methods. Any such

images were manually adjusted then reentered into the spatial transformation algorithm. Accuracy of spatial transformation was verified for each scan.

VLSM was then used to determine the spatial distribution of brain regions where presence of acute hematoma was associated with a significantly greater likelihood of early mortality. For each brain voxel, VLSM calculated a statistical score that compared the mortality rate among patients who had ICH in that voxel with the mortality rate among patients who did not have ICH in that voxel [17]. The map produced by VLSM thus describes where in the brain occurrence of ICH was associated with a significant difference in acute mortality. A non-parametric form of VLSM was employed using the program MRIcron (http://www.cabiatl.com/mricro/mricron/index.html) to generate voxel-wise statistical scores via the Liebermeister measure, appropriate for categorical predictor variables [23]. Thresholds for significance were defined using the False Discovery Rate at $p<0.05$, an approach that conservatively corrects for multiple comparisons in spatial statistics. These spatial statistics were evaluated in the two largest ICH subgroups, those with ICH arising from basal ganglia (n=94), as well as those with lobar ICH (n=86).

Results

Subjects

Of the 282 patients, 61% were male and 39% female, 88% had a history of hypertension, and 30% percent had a history of diabetes mellitus. Baseline values for the 10 clinical and 2 radiological measures of interest appear in Table 1. Each measure was available in >97% of patients except for PT-INR (available in 94%) and PTT (available in 87%). None of these measures varied significantly according to side of ICH. The site of ICH origin was basal ganglia in 94 (Figure 1A), lobar in 86 (Figure 1B), thalamus in 60, cerebellum in 23, and pons in 19 patients. The overall incidence of intraventricular hemorrhage was 50.4%, the rate of which differed according to ICH subgroup ($p<0.005$), being higher in thalamic (72%) and basal ganglia (48%), and lower in lobar (43%) and pontine (37%) ICH subgroups.

Clinical and radiological correlates of acute mortality

Overall, 47.9% of patients died during the hospitalization for the index ICH. This did not vary by ICH subgroup. Table 1 presents the bivariate relationships that each baseline clinical and radiological measures of interest had with acute mortality, across all subjects. Among clinical variables, age, WBC count, and serum glucose were related to mortality, but only serum glucose remained significant after correction for multiple comparisons. Both of the radiological variables showed a significant bivariate relationship with mortality. Note that the bivariate relationship to acute mortality was much stronger for the radiological measures as compared to the clinical: r^2 was 0.21 for ICH volume, 0.09 for intraventricular extension, and 0.06 for serum glucose. These bivariate relationships remained true when only the 94 patients in the basal ganglia ICH subgroup were examined, and when only the 86 patients in the lobar ICH subgroup were examined.

In the multivariable nominal logistical model for predicting acute mortality after ICH (Table 2), four variables remained significant: acute hematoma volume (determined with the hand-drawn method), presence of intraventricular hemorrhage, first measured serum glucose, and first measured serum hemoglobin. Note that r^2 for this model = 0.23, which was only minimally better than the value obtained in bivariate statistics with ICH volume alone.

The method of measuring ICH volume had little effect on results. Across all subjects, the median ICH volumes for the hand-drawn method (35.4 cc) were tightly correlated with values found using the ABC/2 method (30.1 cc, $r=0.99$, $p<0.0001$). Furthermore, this remained true when the two ICH volume measurement methods were compared within each

of the four quartiles of ICH volume, and evaluated separately for each of the five ICH origin sites. The relationship between ICH volume and mortality (Table 1) was identical when using the ABC/2 method.

Spatial distribution of the relationship between hematoma and mortality

VLSM defined the brain areas where presence of acute hematoma was significantly associated a difference in a clinical measure. Results were diffuse for basal ganglia ICH and more focal for lobar ICH. Thus for the subgroup with ICH originating in basal ganglia, the brain region where occurrence of acute ICH was associated with a significant increase in acute mortality was a large area that extended from cortical gray matter to brainstem, within and inside of the main hematoma region (Figure 2A). For the subgroup with lobar ICH, the brain regions where occurrence of acute ICH was associated with a significant increase in acute mortality were the inferior parietal lobule, posterior insula, and the posterolateral thalamus (Figure 2B). For both subgroups, there were no brain regions where acute ICH was associated with a significant decrease in acute mortality.

Discussion

The current study examined clinical and radiological predictors of acutely mortality after ICH, and extended this analysis by applying a voxel-wise approach to examine the three-dimensional relationship between hematoma location and acute mortality. ICH volume was the most significant predictor of acute mortality, in bivariate and in multivariable modeling. Voxel-wise analysis revealed that, for the subgroup of patients with lobar ICH, mortality was more likely when the acute ICH involved specific regions that included inferior parietal lobule and posterior insula, findings that are consistent with prior work in ischemic stroke. These spatial relationships with mortality differed from those found among the subgroup of patients with ICH originating in the basal ganglia, underscoring the differences in the syndrome of ICH across subgroups. These results provide insights that might be of value to therapeutic decision-making in the acute ICH setting.

Current results support the hypothesis that there are specific brain regions where occurrence of ICH is associated with a greater acute mortality rate in patients with lobar ICH, but not in patients with ICH originating in the basal ganglia. In the subgroup with lobar ICH, presence of acute hematoma in inferior parietal lobule, posterior insula, and posterolateral thalamus (Figure 2B) was associated with a significant increase in the acute morality rate. Two of these regions overlap with findings from studies of patients with ischemic stroke. First, prior reports described increased early death when ischemic stroke injury involvement of the insula on either side of the brain [15,16]. The early deaths in these reports were cardiac in nature. Second, Rincon et al [14] found increased cardiac mortality, albeit over a 4 year follow-up period, when ischemic stroke injured the parietal lobe on either side of the brain. Cardiac events were at the center of these ischemic stroke studies, raising the question of a cardiac contributor to death in the current cohort, but the proximate mechanism of death was not available in the current study. On the one hand, the fact that brain regions associated with increased mortality overlap between ischemic stroke and ICH might suggest similarities in the mechanisms of death between these two forms of stroke. On the other hand, cardiac arrest is an uncommon cause of death among patients with acute ICH [24], and so the association between mortality and ICH affecting insula or inferior parietal lobe might be mediated through non-cardiac mechanisms such as specific behavioral sequelae. An alternative possibility is that ICH affecting posterior insula or inferior parietal lobule might in fact be linked to increased mortality through cardiovascular mechanisms but only in an indirect way, for example, by altering mean arterial blood pressure and so cerebral perfusion pressure.

The current findings could theoretically be useful to clinical decision-making in some acute ICH settings. Conceivably, knowledge that a patient's ICH carries a higher risk of acute mortality by virtue of its location could help with prognosis, guide level of care, or inform the risk-benefit analysis for acute interventions. The current findings might also be useful for design of future ICH investigations. In this regard, note that the STICH trial suggested that favorable outcome from early surgery was more likely if the acute hematoma was within 1 cm of the cortical surface [25], but did not consider which cortical surface, i.e., whether this finding varied in relation to hematoma location. Future studies of surgical efficacy after ICH might benefit from incorporating data on hematoma location.

The current study also provided an opportunity to further contrast deep and lobar ICH. These two ICH subgroups share some clinical similarities but show differences in other regards such as pathogenesis, frequency of intraventricular extension, and hematoma shape [20,26]. The divergent findings in the three-dimensional relationship between hematoma location and mortality rate (Figure 2) further underscore differences between basal ganglia and lobar ICH.

Strengths of the current study include use of consecutive cases from a single center, and CT analyses by a single examiner using metrics reliably extracted from acute head CT scans. The current results corroborate prior reports of excellent agreement between ABC/2 method and the hand-drawn method for hematoma measurement [22,27]; the ABC/2 method is more rapid but an ICH outline is needed for VLSM analyses. Weaknesses include the retrospective approach, which limited availability of some data such as long-term outcome measures, the proximate cause of death, and the rate with which care was withdrawn [24]. Also, the patient mix at our hospital includes many indigent patients. Such patients have a greater prevalence of chronic diseases, reduced access to care, and higher stroke case fatality rates [28]. This might account in part for the mortality rate of 47.9% in the current cohort, which is at the higher end of literature estimates for acute ICH [3], and for the absence of mortality differences across ICH subgroups--factors that might potentially limit generalization of current results. An additional weakness was the inability to evaluate the impact of pre-admission antiplatelet and anticoagulant use. Despite these limitations, the current study, by examining the spatial distribution of clinical-radiological relationships, provides new insights into mortality after acute ICH.

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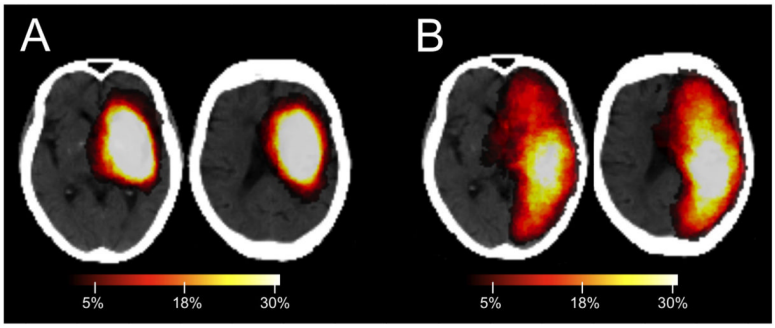

Figure 1.
The percent of subjects whose acute hematomas affected each voxel is presented for [A] basal ganglia ICH and [B] lobar ICH.

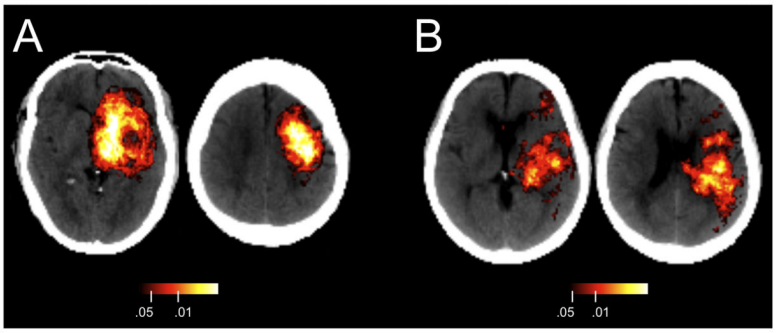

Figure 2.

Representative slices of VLSM statistical results, superimposed on a single subject head CT. [A] For the subgroup with ICH originating in basal ganglia, the brain region where acute ICH was associated with a significant increase in acute mortality was diffuse, extending from cortical gray matter to brainstem. [B] Results differed for the subgroup with lobar ICH, among whom acute ICH was associated with a significant increase in acute mortality in areas that included inferior parietal lobule, posterior insula, and posterolateral thalamus. Colorbars represent the p values using False Discovery Rate.

Table 1
Baseline clinical and radiological measures and their bivariate relationship to mortality

Clinical Measure	Median overall (25%-75% IQR)	Median for patients who died	Median for patients who survived	p
Age (years)	64.3 (52.6 - 75.7)	67.7	60.0	0.02
Serum hemoglobin (g/dL)	13.9 (12.7 - 14.9)	13.8	14.2	0.07
Platelet count ($\times 10^9$/L)	237 (183 -286)	237	234	0.67
PTT (sec)	27.6 (25.5 - 31.5)	27.6	27.5	0.74
PT-INR	1.05 (0.97 - 1.18)	1.05	1.05	0.72
Blood WBC count (per uL)	10.9 (8.3 - 13.9)	11.8	10.3	0.01
Serum glucose (mg/dl)	151 (119 - 191)	161	138	<0.0001
Serum sodium (mEq/L)	138 (135 - 140)	138	138	0.38
Serum creatinine (mg/dL)	1.0 (0.8 - 1.2)	1.0	1.0	0.40
BUN (mg/dL)	16 (12 -22)	17	16	0.51
ICH volume (cc)	35.4 (13.3 - 82.0)	70.6	21.0	<0.0001
Presence of intraventricular extension?	50.4%	68.1%	34.0%	<0.0001

Table 1 presents baseline clinical and radiological measures, the bivariate relationship that each had with acute mortality, and the values for those who died vs. survived. Three variables survived the Bonferroni adjusted p =0.00417: serum glucose, ICH volume, and presence of intraventricular extension. Note, however, that while all three were significant, their relationship to mortality differed, as r^2 was 0.21 for ICH volume, 0.09 for intraventricular extension, and 0.06 for serum glucose.

Table 2
Multivariable nominal logistic model for predicting acute mortality after ICH

Variable	p	Odds Ratio	95% CI
Serum hemoglobin (per one unit increase in g/dL)	0.028	1.18	1.02 - 1.37
Serum glucose (per one unit increase in mg/dl)	0.009*	0.99	0.989 - 0.99
ICH volume (per one unit increase in cc)	<0.0001	0.99	0.99997 - 0.99998
Presence of intraventricular extension?	0.0025	1.58	1.18 - 2.13

Table 2 presents the multivariable nominal logistic model for predicting acute mortality after ICH. Four variables survived as significant predictors, the most significant of which was ICH volume. Note that the predictive value of the overall model ($r^2 = 0.23$, $p < 0.0001$) was minimally different from that provided by ICH volume alone, indicating the central importance of this radiological measure.