**Intracranial hemorrhage localization: A CT imaging pipeline**John Muschelli$^{1,\ast}$, Natalie L. Ullman$^{2}$, Elizabeth M. Sweeney$^{3}$, Ani Eloyan$^{4}$, Daniel F. Hanley$^{5}$, Ciprian M. Crainiceanu$^{6}$**1 John Muschelli Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA2 Natalie L. Ullman Department of Neurology, Division of Brain Injury Outcomes, Johns Hopkins Medical Institutions, Baltimore, MD, USA3 Elizabeth M. Sweeney, Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA4 Ani Eloyan, Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA5 Daniel F. Hanley Department of Neurology, Division of Brain Injury Outcomes, Johns Hopkins Medical Institutions, Baltimore, MD, USA6 Ciprian M. Crainiceanu Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA E-mail: Corresponding jmuschel@jhsph.edu**

# Abstract

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# Introduction

Intracranial hemorrhage (ICH) is a neurological condition that results in bleeding into tissues and possibly the ventricles of the brain. Bleeding may cause distension of the brain structures and increase in potentially lethal intracranial pressure (ICP). ICH is a serious condition; it accounts for approximately 10-15% of all strokes, corresponding to an estimated 79,500 annual cases and approximately 30,000 deaths in the US and approximately 5 million cases worldwide . In addition to the increased likelihood of death, ICH has debilitating health effects on survivors who do not have full functional recovery after stroke.

The use of computed tomography (CT) scans allows clinical doctors and researchers to qualitatively and quantitatively describe the characteristics of a hemorrhage to guide interventions and treatments. CT scanning is widely available in patients with ICH and is the most commonly used diagnostic tool . While much can be understood from careful CT image inspection, detailed quantification of information at the population level is an open problem. Indeed, it is hard, for example, to quantify from visual inspection alone the percent of a particular anatomic ROI engaged by the stroke, compare locations of strokes across patients, and study the association between specific locations and adverse health outcomes.

To address these problems, we will 1) develop an analytic pipeline based on available neuroimaging tools to register patient CT scans to a CT template; 2) create a 3-dimensional (3D) density map of hemorrhages occurring in a population of patients who survived initial ICH and were enrolled in the MISTIE and ICES clinical trials; 3) provide a detailed quantification of hemorrhage engagement of individual neuroanatomic regions within the brain; 4) determine if differences in location relate to a common disability score: the National Institutes of Health Stroke Scale (NIHSS); and 5) generate a stroke region of engagement that is likely to be associated with adverse health effects and test its predictive performance using within-sample validation ).

It is a matter of debate whether the location of the ICH is relevant to functional outcome in patients who survived to make it to the hospital . For example, found that infratentorial ICH location, intraventricular involvement, and ICH volume, which may represent a number of anatomic locations, all predict 30-day mortality. Conversely, , , and found that the site of ICH univariately was associated with 30-day mortality, but was not statistically associated after adjusting for other covariates. Following the result from that hydrocephalus was an independent predictor of 30-day mortality, found that hydrocephalus was an independent prognostic indicator only for the group with hemorrhages in the putamen and not for those with hemorrhages in the caudate or thalamus. In contrast, other studies have not observed location of the ICH predicting prognosis .

Other trials have estimated the effects of surgery in a sub-population of ICH patients on health outcomes.Phase I of the Surgical Trial in Intracerebral Haemorrhage (STICH) found treatment effects of hemorrhage reduction through early surgery in a subset of patients who had bleeds in the proximity of the brain lobes (1 cm from the cortical surface of the brain) . However, when the effect was re-examined in the second phase of the trial (STICH II), which included only patients with superficial lobar hematomas, the treatment effect was not found to be statistically significant . Although STICH II did identify a statistically significant treatment effect of localization, this may still be an effect of sub-optimal definition of localization. In the “Guidelines for the Management of Spontaneous Intracerebral Hemorrhage” noted that: “other randomized trials have had too few patients to determine outcomes in subgroups by location, randomized only patients with deep ICH, or did not report these results”. Moreover, the localization of ICH and its evolution before and after treatment administration may actually be a crucial baseline or longitudinal characteristic of the stroke that could predict whether treatments are effective, may be a confounding factor of treatment and outcomes, and may relate to ICH recurrence .

However, even the coarse classification of hemorrhage location is complicated, which may lead to labeling confusion even among the best trained neuroimage scientists. Indeed, a hemorrhage may extend into multiple brain areas, may affect different tissue classes, and may break through the ventricular wall causing the hemorrhage to spread to other areas of the brain. Such problems would challenge even the best scientists, as it becomes time-onerous to do anything more than calling a single region as the primary affected anatomic region (i.e. caudate or putamen) or describing the edge of a hemorrhage by an average or minimum distance to a given landmark . Also, increased long- or short-term disability that corresponds to a significant difference in hemorrhage volume may modulated by hemorrhage location. Alternatively, hemorrhage increases after a stabilization period may result in no changes in functional indices depending on the brain regions involved. Hence, there is a need for detailed information of brain hemorrhage location and its association with the stroke severity, while controlling for volume. Such detailed localization information can be obtained by registering scans to a common template and by using the detailed anatomical information in the template to provide refined anatomical localization information.

Previous CT neuroimaging studies have not used registration-to-template-based methods for detailed location quantification, most likely due to a lack of a CT template brain. Registration to template space is a crucial first step for the type of analysis we are describing here, as most brain atlases that segment that brain are available in this space. Recently, published the first CT template of healthy adults together with its MNI (Montreal Neurological Institute) space representation. Along with this template, released software for CT image registration to the template. This is an important analytic step forward over the previous available tools. Indeed, previous studies have used average CT images as a template, but the patient population consisted of people affected by a specific neurological condition (cerebrovascular infarcts) and were not in MNI space . In addition, many other studies have co-registered CT images to concurrent (or temporally proximal) MRI images from the same patient, some that were and some that were not in MNI space. This is very useful when structural MRIs are concurrently acquired with CT images. In the clinical trials we investigate here the CT images have always been acquired according to the trial protocol, whereas MRI sequences were only acquired according to the local practices, which varied quite a bit by modality and frequency. Other methods have used CT image registration directly to an MRI template, but using a CT template provides a simpler registration as the reference image and template image are the same modality .

Most importantly, this type of detailed mapping of strokes has never been done in the context of the highly visible MISTIE and ICES stroke clinical trials. MISTIE is the Minimally Invasive Surgery plus recombinant-tissue plasminogen activator (rtPA) for Intracerebral Evacuation and ICES is the Intraoperative CT-Guided Endoscopic Surgery for ICH (ICES) trials. MISTIE was a phase II clinical trial with the goal of determining the safety, efficacy, and long-term effects of treatment of ICH using thrombolytics. ICES was a simultaneous phase I trial with the same inclusion/exclusion criteria as MISTIE and the goal to determine the effect of endoscopic surgery as opposed to thrombolytic therapy for hematoma removal. No treatment effects are of interest in our analysis as any scan, demographic, or functional measure was taken prior to randomization.

# Materials and Methods

## Patients

The study consists of 111 patients from MISTIE () and ICES () recruited from 26 centers. Patients were eligible if: he/she were aged 18 to 80 years old with a spontaneous ICH of greater than cc that did not require an extraventricular drain (EVD), were non-pregnant, had a historical Rankin Scale score of and a diagnosis that excluded other conditions such as ruptured aneurysms, arteriovenous malformations, or other neurovascular anomaly (for full criteria, see ). CT and clinical data were previously collected as part of the Johns Hopkins Medicine IRB-approved ICES and MISTIE research studies with written consent provided by participants. Each site adhered to local ethical procedures and consented in participation of the study. All clinical data was deidentified by using a unique patient identifier and CT images were anonymized to remove any patient identifying information.

The NIHSS score was recorded at enrollment into the study; patients did not have an NIHSS at enrollment and were excluded from the analysis of NIHSS and location. Histograms of NIHSS score, age, sex, and disease duration are shown in Figure [fig:histdem], and the descriptive statistics of age, sex and NIHSS score are shown in Table [t:dem]. The NIHSS scores indicate a large heterogeneity of disease burden, with a range between (no stroke symptoms) to (severe stroke). The age of the patients is between 33 and 80 years old. Women comprise 31.5% of the dataset.

[Figure [fig:histdem] here.]

[Table [t:dem] here.]

## Imaging Data

CT images were acquired for all patients, with site-specific scanning parameters. Scans were acquired using GE (), Siemens (), Philips (), and Toshiba () scanners. Gantry tilt was seen in 87 scans. Slice thickness of the image varied within the scan reconstruction for 14 scans, which we will refer to as variable slice thickness. An example of this is if a scan was reconstructed with mm slices at the top and bottom of the brain, which are not of interest, but with 5mm slices in the middle where the hematoma is seen (Figure [f:reg]). Therefore, the scans analyzed had different voxel dimensions and image resolution prior to registration to the template. Different reconstructions are not available via the data-acquiring center, and represent how scans are presented for evaluation in many diagnostic cases.

## Hemorrhage Segmentation

To co-register the CT scan to the template, the hemorrhage was excluded from the algorithm, i.e. “masked out”, using manual ICH segmentations. ICH was first designated on CT scans using the OsiriX imaging software (OsiriX v. 4.1, Pixmeo; Geneva, Switzerland). Expert readers employed a semiautomated threshold-based approach using a Hounsfield unit (HU) range of to to select potential regions of ICH . Binary image masks were created for the hemorrhage region of interest (ROI) by setting pixel intensities to if classified as hemorrhage, and otherwise.

## Image Processing: Brain Extraction, Reorientation, Co-registration

DICOM images of the scan and the binary mask were exported from OsiriX. Images with gantry tilt were corrected using a customized MATLAB (The Mathworks, Natick, Massachusetts, USA) user-written script (<http://bit.ly/1ltIM8c>). Images were then converted to the Neuroimaging Informatics Technology Initiative (NIfTI) data format using dcm2nii (2009 version, provided with MRIcro ). Images were constrained to values and Hounsfield units (HU) to remove potential image rescaling errors and artifacts. No interpolation was done for images with a variable slice thickness. Thickness was determined from the first slice converted and was assumed homogeneous throughout.

Brains were extracted to remove skull, eyes, facial and nasal features, extracranial skin, and more importantly non-human elements of the image captured by the CT scanner, such as the gantry, pillows, or medical devices. Using a variant of a previously published brain extraction protocol , brains were extracted using the brain extraction tool (BET) , a function of the FSL neuroimaging software (v5.0.4). Images were thresholded to a brain tissue range (- HU) and BET was applied, using a fractional intensity threshold of . An image with its brain-extracted counterpart can be seen in Figure [fig:bet].

The brain-extracted image was used in automated estimation a transformation to center the image to the line between anterior commissure (AC) and posterior commissure (PC) using a custom MATLAB script (<http://bit.ly/1gUqMDw>). The full image and binary mask were re-centered using this transformation matrix, which is required for the statistical parametric mapping, version 8, (SPM8, Wellcome Trust Centre for Neuroimaging, London, United Kingdom) spatial co-registration algorithm. The binary hemorrhage mask was smoothed using a Gaussian smoother with a full width at half maximum (FWHM) of mm. The image was masked by the inverse of the smoothed hemorrhage mask.

The image was then spatially co-registered to the CT template using the Clinical toolbox , which employs SPM8’s unified normalization–segmentation routine . The smoothed hemorrhage mask was transformed into the template space using the estimated co-registration transformation. The co-registered smoothed hemorrhage mask was then thresholded using the following rule: where denotes voxel for smoothed mask for person , denoted . If a voxel was thresholded to , that voxel was declared as ICH in template space for that scan.

## Assessing Registration

Determining the quality of co-registration was done qualitatively by visual inspection. Again, one main goal of this analysis is to quantify the location of ICH on the template brain, which is conditional on the registration algorithm working “reasonably well”. We acknowledge that visual inspection is subjective but there is no gold standard for assessing registration results and analysis of registration quality is not commonly done with large deformations of tissue as in patients with ICH.

[CRITERIA from NATALIE]

No scans were excluded due to inadequate registration.

## Histograms of ICH in the Brain

To visualize the localization of lesions, we first combined information from co-registered masks of 111 patients. Using the resulting co-registered masks we obtained the -dimensional (3D) histogram of the ICH localization for our study population. More precisely, for every voxel location in the template space, we calculated the proportion of patients who have an ICH at that particular voxel.

## ICH Localization and Engagement

As co-registered scans are in MNI space, we can use previously segmented and labeled atlases of the brain to label where ICH occurred. We used the MNI structural atlas , Eve-I , and Eve-II . The MNI structural atlas segments gray matter (GM) regions, but has no labels for ventricular regions and white matter (WM) regions. Eve-I and Eve-II both segment WM and GM regions, but ventricular regions are left as background. We therefore categorized any region within the brain labeled background in Eve-I or Eve-II as a ventricular region, though this may not be entirely accurate.

From these atlases, we determined overlap of ICH with each labeled regions on a per-scan level, calculating the percent of ICH engaged with each region. From these percentages, we can calculate the region most engaged, similar to the categorization that is currently done with hemorrages, or finer detail of how much engagement the hemorrhage has with each region. Similarly, we can do a weighted percentage of engagement for the 3D histogram based on the population.

## Prediction of NIHSS Based on Hemorrhage Location

We evaluated the association between hemorrhage location and stroke severity as measured by the total NIHSS score by a series of models. In the population, patients had an ICH at a total of 1045174 voxels. We limited our analysis of NIHSS to voxels in the template space where more than 10 patients exhibit lesions, which included 166202 voxels. At each of these voxels, we ran a linear regression model of the type

$\label{eq:nihss\_regression}
{\rm NIHSS}\_i=\beta\_0+\beta\_1(v) {\rm ICH}\_i(v)+X^t\_i γ + \epsilon\_{iv},$

where ${\rm NIHSS}\_i$ is the total NIHSS score for patient , ${\rm ICH}\_i(v)$ is a binary covariate that indicates whether patient has a ICH at voxel of the template space, is a vector of patient-specific confounders with effects and are treated as independent homoscedastic errors. We also ran a simple Wilcoxon rank-sum test on NIHSS at every voxel. The vector of confounders, , either was excluded for “unadjusted” voxel-level models, or contains a combination of patient-specific confounders, age, sex, and total baseline ICH volume (TICHVol) in an adjusted model.

P-values of voxel-vise regression of NIHSS scores on ICH presence, corresponding to the test , or in the case of the Wilcoxon rank-sum test: for the distribution of NIHSS were calculated for each model. We corrected the p-values using a Bonferroni correction with . Some of the voxels were identical for presence for ICH over the population, i.e. voxels 1 and 2 each had the same people having ICH and same people not having ICH at that location. We excluded these from the correction, using only then number of unique tests ().

We created a region of interest (ROI) by selecting voxels by the p-value from the undadjusted linear model, excluding . We thresholded the image based on the p-value (, , ) and by taking the top-ranked voxels based on p-value (, , ). For each scan, we calculated the percent of voxels in the ROI that hemorrhage overlapped. Thus, if a patient’s hemorrhage covered the entire ROI, the ROI coverage would be . We then put this patient-level ROI coverage into a linear regression adjusted for the confounders above: ${\rm NIHSS}\_i = \beta\_0 + \beta\_1 {\rm Coverage}\_i + \gamma\_1{\rm Age}\_i +\gamma\_2{\rm Gender}\_i +\gamma\_3{\rm TICHVol}\_i + \epsilon\_{i}$ We compared the , adjusted , and Akaike information criterion (AIC) of this model with the same model, replacing ROI coverage with an indicator of reader-specified clot location in order to determine whether using voxel-level information improved prediction of NIHSS .

# Results

## Image Registration

The registered images for patients are shown in Figure [f:reg] with overlays (in pink) of the manually segmented blood in native space (left panel) the co-registered image and mask in template space (middle panel) and the overload mask onto the template (right panel). The slices shown are at the centroid (average location) of the hemorrhage mask. We chose one patient with variable slice thickness with a large hemorrhage (Figure [f:reg], , and ) and one patient with a small hemorrhage (Figure [f:reg], , and ). Images indicate that gross brain features remain relatively unchanged, but large deformations of tissue are preserved with registration. Also, the non-linear registration accounts for variable slice thickness.

[Figure [f:reg] here.]

## Histograms of ICH in the Brain

The resulting image of the density of hemorrhages is shown in Figure [fig:StrokeHist] . In this image, voxels colored brighter correspond to a higher proportion of patients with hemorrhage at that voxel. The 3D histogram indicates that lesions are distributed medially deep in the brain in this cohort, with a lower concentration close to the cortical surface and higher in the left side of the brain. Combining left and right sides of the brain by folding at the mid-sagittal plane may indicate similar bleeds between patients, although on different sides of the brain. We do not see a high prevalence in the very anterior or posterior areas of brain. We also do not see brain stem bleeds, which were excluded in our criteria.

The histogram of the prevalence of hemorrhages over voxels (Figure [fig:StrokeHist]  shows a large number of voxels with low prevalence of hemorrhage, but some voxels have a high prevalence ( of the population).

These observations above may be an artifact of the inclusion criteria and may not generalize to other populations, but no spatial location was preferred for inclusion. Regardless, creating these population images actually allows us to determine if this location density does generalize to other populations given their density map.

[Figure [fig:StrokeHist] here.]

## ICH Localization and Engagement

[Tables [t:nihss] and  [t:gcs] here]

## Prediction of NIHSS Based on ICH Location

We run several versions of model ([eq:nihssregression]) starting with the simplest case and then building the model by incorporating different choices of potential confounders to investigate their effects on the statistically significant association between ICH locations and NIHSS. More precisely, the five linear models are:

rll & $ {\rm NIHSS}\_i =$ &

$\beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \epsilon\_{iv}, $ & $ {\rm NIHSS}\_i = $ &

$ \beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \gamma\_1(v){\rm Age}\_i + \epsilon\_{iv}, $ & $ {\rm NIHSS}\_i = $ &

$ \beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \gamma\_2(v){\rm Gender}\_i + \epsilon\_{iv}, $ &$ {\rm NIHSS}\_i = $ &

$ \beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \gamma\_3(v){\rm TICHVol}\_i \epsilon\_{iv},$ &$ {\rm NIHSS}\_i = $ &

$ \beta\_0+\beta\_1(v) {\rm ICH}\_i(v) + \gamma\_1(v){\rm Age}\_i +\gamma\_2(v){\rm Gender}\_i +\gamma\_3(v){\rm TICHVol}\_i + \epsilon\_{iv},$

where denotes a model. Also, we’ll denote as the voxel-wise Wilcoxon rank-sum test on NIHSS.

The p-values for each model are presented in Figure [f:mods], with cooler (blue) colors representing higher p-values and hotter (red) colors representing lower p-values. Colors correspond to p-values (dark blue), , (light blue), (green), (yellow), (orange) (red). We see that there may be some relationship to medial hemorrhages with NIHSS seen in the unadjusted model (Figure ) and the Wilcoxon rank-sum test (Figure ).

[Figure [f:mods] here.]

No voxels were significantly related to NIHSS in any model using the Bonferroni correction.

## Prediction of NIHSS using a Region of Interest

[Figure [f:roi] here.]

# Discussion

We began this project to describe the locations of intracranial hemorrhages in a population of patients. With this framework, we have shown how using automated tools allows us to more finely and objectively describe locations of ICH within the brain. Although this analysis focused on patients from a single trial cohort, these tools can be applied to large-scale epidemiologic studies to better understand ICH distribution in specific patient populations of interest and help predict patient outcomes.

The current description of hemorrhages are reliant on one specific registration technique and one atlas for determination of areas. Future research should focus on different approaches and atlases. However, at this time the current software is the sole CT-only registration software and CT template published and available. Though we have seen promising results, a healthy CT template was used for registration. Thus, brains with large deformations are registered to the template that was constructed from typical brains. In future studies, we may want to create a study-specific template for population-level analysis. However, in that case, comparisons between analyses may be impossible as templates changes from study to study.

Another important open question is what brain structures and features need to be preserved during registration of brains with ICH. This problem extends to healthy brains as well, since atrophy and other morphological changes occur with ageing. For example, large deformations may shift and compress ventricles resulting in misclassifying ICH within ventricles.

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# Tables

[ht]

|  |  |
| --- | --- |
|  | N (%) or Mean (SD) |
| Age in Years: Mean (SD) | 60.8 (11.2) |
| Gender: Female | 35 (31.5%) |
| NIHSS: Mean (SD) | 22.1 (8.7) |
| Race |  |
| Caucasian not Hispanic | 59 (53.2%) |
| African American not Hispanic | 35 (31.5%) |
| Hispanic | 12 (10.8%) |
| Asian or Pacific Islander | 5 (4.5%) |

[t:dem]

[H]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number of Voxels | P-value | Adjusted R$^2$ | R$^2$ | AIC |
| Location Model |  | 0.146 | 0.177 | 14.62 |
| 1000 | 0.0005 | 0.236 | 0.265 | 2.47 |
| 2000 | 0.0009 | 0.234 | 0.263 | 2.81 |
| 2422 | 0.0010 | 0.247 | 0.275 | 0.98 |
| 3000 | 0.0013 | 0.244 | 0.272 | 1.46 |
| 19047 | 0.0100 | 0.254 | 0.282 | 0.00 |
| 47736 | 0.0500 | 0.248 | 0.276 | 0.77 |

[t:nihss]

[H]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number of Voxels | P-value | Adjusted R$^2$ | R$^2$ | AIC |
| Location Model |  | 0.084 | 0.118 | 16.76 |
| 1000 | 0.0002 | 0.214 | 0.243 | 0.00 |
| 2000 | 0.0004 | 0.213 | 0.242 | 0.09 |
| 3000 | 0.0006 | 0.212 | 0.241 | 0.25 |
| 4669 | 0.0010 | 0.212 | 0.241 | 0.23 |
| 22858 | 0.0100 | 0.191 | 0.221 | 3.17 |
| 52368 | 0.0500 | 0.166 | 0.197 | 6.44 |

[t:gcs]

# Figure Legends

[ht!]

![](data:None;base64,)

[fig:histdem]

[htbp] [fig:bet]

[htbp] [f:reg]

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[fig:StrokeHist]

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[f:mods]

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[f:roi]