Survival Analysis and Prediction of Discharge Outcomes of Ischemic Stroke Patients Stratified by Hemorrhagic Transformation Subtype

BOSTON UNIVERSITY

Lillian Yu[1,4], Jack Pohlmann[2,5], Ivy So Yeon Kim, MPH[2,5], Ben Brush, MD[3], Madhav Sambhu[4,6], Lucas Conti[4], Hanife Saglam, MD[3], Katie Milos[5], Michael Cronin[4], Oluwafemi Balogun[5], Stefanos Chatzidakis, MD[3], Ethan Zhang, MS[5], Benjamin Brush, MD[3], Steve Feske, MD[5], Emelia J. Benjamin, MD, ScM[2,4], Josée Dupuis, PhD[2,4], David M. Greer, MD, MA[4,5], Stelios M. Smirnakis, MD, PhD[3,6,7], Charlene J. Ong, MD, MPHS[3,4,5,6]

Lynbrook High School, 1280 Johnson Ave, San Jose, CA 95129[1]; Boston University School of Public Health, 715 Albany St, Boston, MA 02118[2]; Department of Neurology, Brigham & Women's Hospital, 75 Francis St, Boston, MA 02115[3]; Boston University School of Medicine, 85 E Concord St, Boston, MA 02118[4]; Department of Neurology, Boston Medical Center, 1 Boston Medical Center Pl, Boston, MA 02118[5]; Department of Neurology, Harvard Medical School, 25 Shattuck St, Boston, MA 02115[6]; Department of Neurology, Jamaica Plain Veterans Administration Medical Center, 150 S Huntington Ave, Boston, MA 02130[7]

INTRODUCTION

- Between **30% to 40%** of all acute ischemic stroke patients develop hemorrhagic infarcts (HI), which lead to ruptures in cerebral blood vessels known as **hemorrhagic transformations (HT)**
- A major complication of HT is **life-threatening mass effect (LTME)**, which occurs in patients who suffer from a midline-shift (MLS) of greater than or equal to 5 mm or had a decompressive hemicraniectomy procedure
- HT can be categorized by severity into the following subtypes: **parenchymal, petechial, or no hemorrhage**
- Prior studies have analyzed variables of patients who had LTME and HT, but they do not group the patients on when LTME had occurred
- This study accounts for when LTME does occur in a patient when conducting analysis

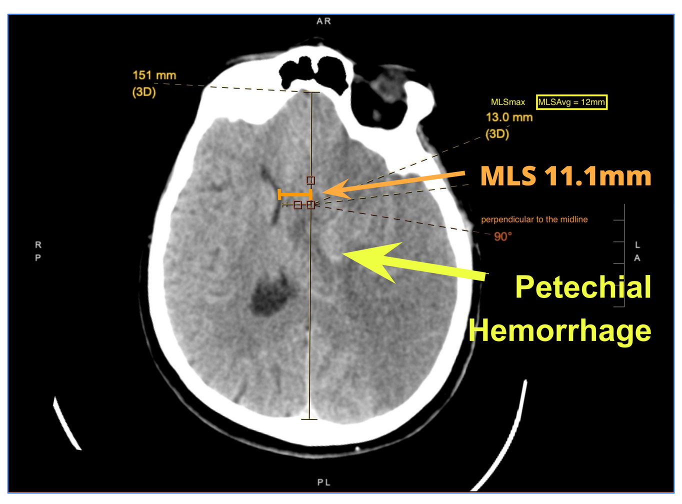

Fig 1. CT Scan of patient with Petechial Hemorrhage and MLS of more than 11 mm

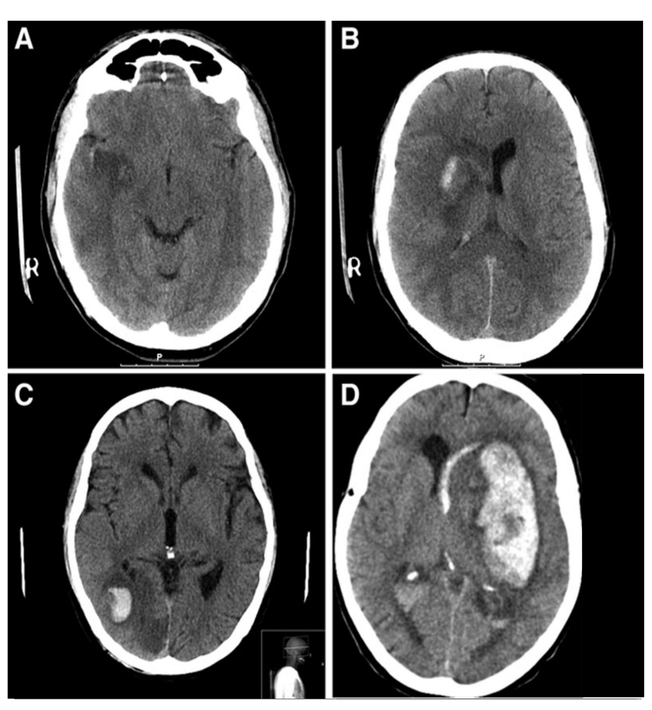

Fig 2. A, Computed tomography (CT) with HI type 1 of right temporal lobe and basal ganglia.
B, CT with HI type 2 of right striatum.
C, CT with parenchymal hematoma (PH) type 1 in right posterior cerebral artery territory.
D, CT with extended PH type 2 of left basal ganglia, capsula interna and externa with additional blood in both lateral ventricles and mass effect causing a shift of midline structures to the right.

Sourced from von Kummer R, et al.[1]

METHODS

- This retrospective study involves **922 patients** admitted to Massachusetts General Brigham hospitals from 2006 - 2021 who suffered from ischemic strokes [Fig 3.]
- **Stratified based on HT subtypes**, the primary predictor of interest
- **Missing data values were imputed** via multiple imputation chain equations
- **Primary outcome of interest**: Death by Discharge; **Secondary outcome of interest**: LTME (after admission) and Status at Discharge

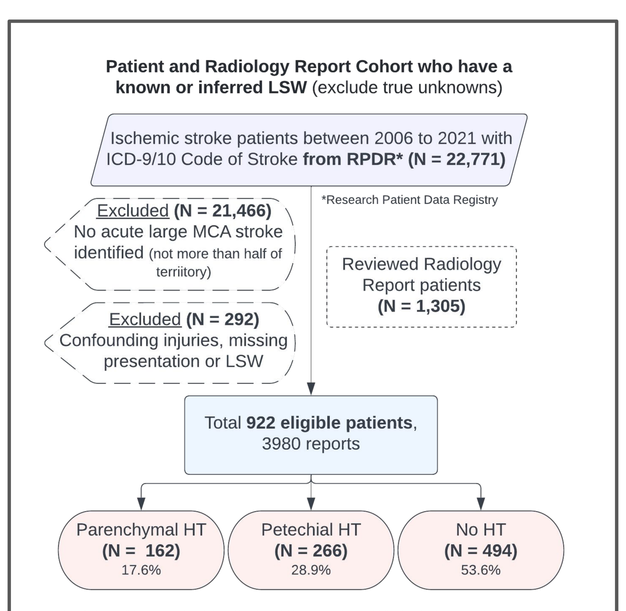

Fig 3. Inclusion Criteria Flowchart

Comparative Box Plot of Glucose at Admission Stratified by LTME and HT Subtype

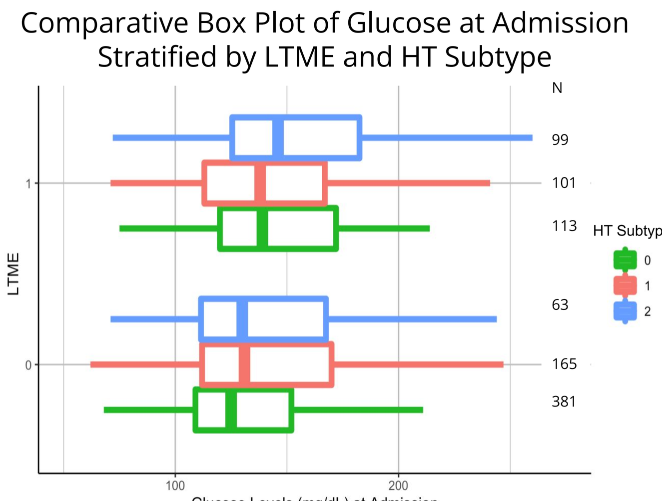

Fig 4. Outliers are excluded from this box plot

Density Estimation Plot of Age Stratified by HT Subtype

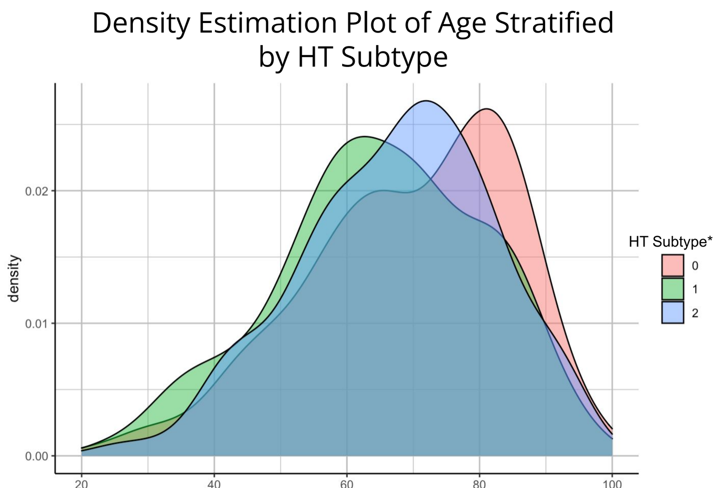

Fig 5.

**0 = None*
1 = Petechial
2 = Parenchymal

- **Kaplan-Meier, Log-rank Tests, and Cox Proportional-Hazards Models** were employed to determine how HT subtypes and LTME influenced different time to events and survival probabilities.
- Supervised machine learning classification and feature selection models **Random Forests and K-Nearest Neighbor (KNN) algorithms** were trained to take into account confounding biomarkers and risk factors revealed from univariate logistic regression analyses
- Secondary cohort of 183 patients used as validation group for the ML models
  - Patients were admitted to Boston Medical Center from 2006 to 2022 identified as having NIHSS greater than or equal to 15

RESULTS

Survival Analysis: Log-Rank tests on Kaplan Meier Curves

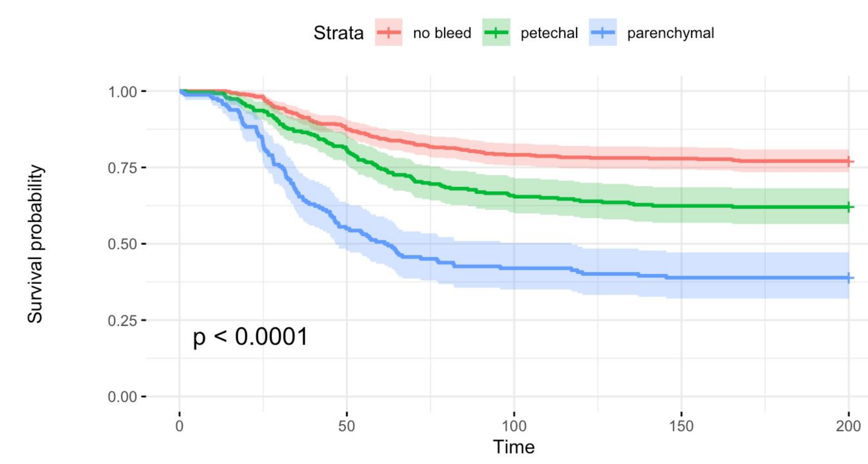

Fig 6. Days to LTME of Patients Stratified by HT Subtype

Comparing survival and time to event probabilities stratified by HT subtype:

- **χ^2 = 4.9 (df = 2), p= 0.08 for time to Death Discharge**
- **χ^2 = 6.1 (df = 2), p= 0.05 for time to Cerebral Edema Death Discharge**
- **χ^2 = 107 (df = 2), p < 0.01 for time to LTME**

Characteristic	HR[1]	95% CI[1]	p-value
HT subtype			
0	—	—	
1	1.82	1.39, 2.38	<0.001
2	3.86	2.94, 5.06	<0.001

[1] HR = Hazard Ratio, CI = Confidence Interval

Fig 7. Hazard Ratios of LTME Stratified by HT Subtype

Note: data was treated as right censored for patients who met their discharge time and no longer followed

Comparing survival probabilities stratified by LTME:

- **χ^2 = 5.7 (df = 1), p= 0.02 for time to Death Discharge**
- **χ^2 = 31.4 (df = 1), p< 0.01 for time to Cerebral Edema Death by Discharge**

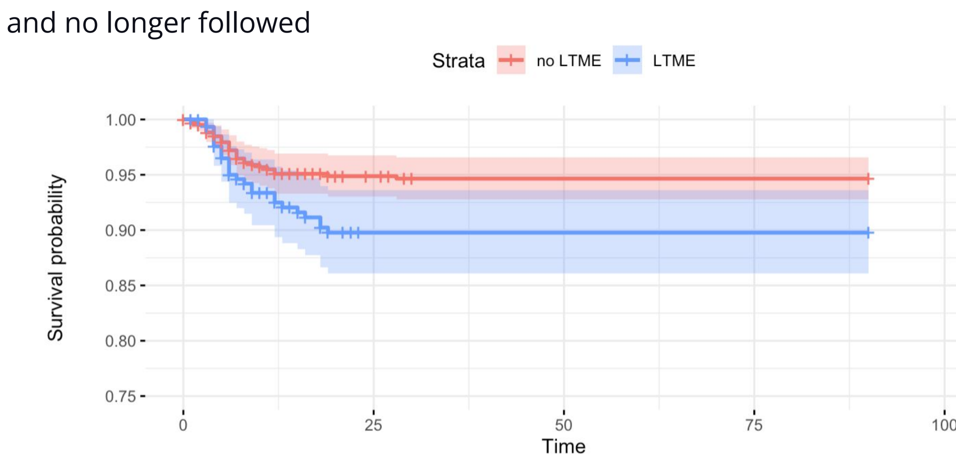

Fig 8. Days to Death Discharge of Patients Stratified by LTME

Random Forest Models

Validation on BMC dataset:

85.24% Accuracy for determining death at discharge

Confusion matrix

Prediction

True Value

	0	1	Class error
0	129	3	0.02
1	24	27	0.47

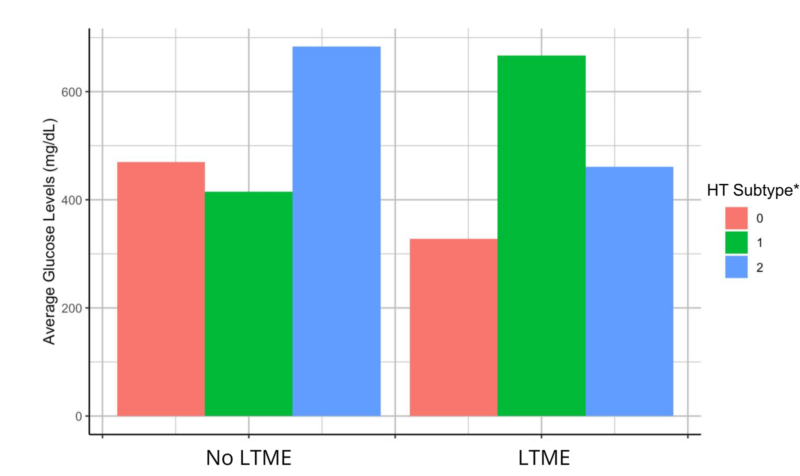

Fig 9. Average Glucose Levels at Admission Stratified by LTME and HT subtype

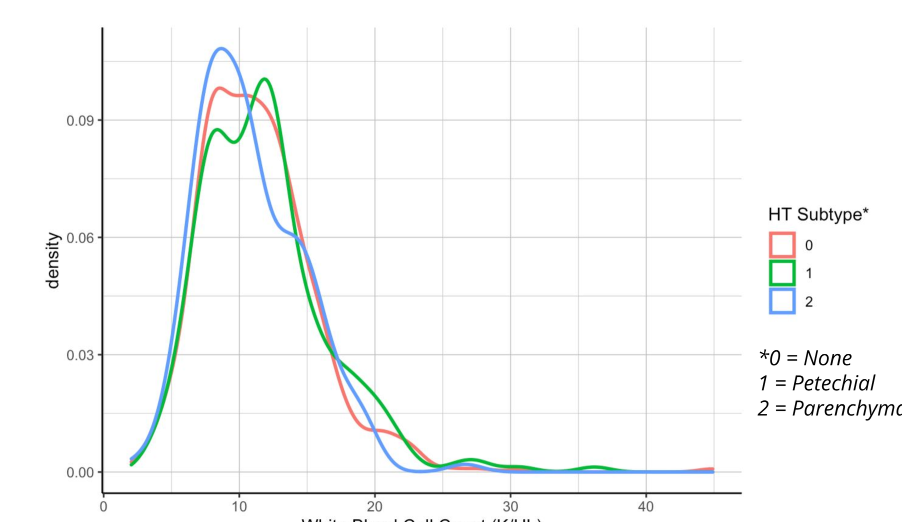

Fig 10. Density Estimation Plot for White Blood Cell Count at Admission Stratified by HT Subtype

**0 = None*
1 = Petechial
2 = Parenchymal

Most misclassifications occurred from classifying patients who died at discharge as patients who did not die at discharge, which may have been due to other competing risk factors or confounding variables.

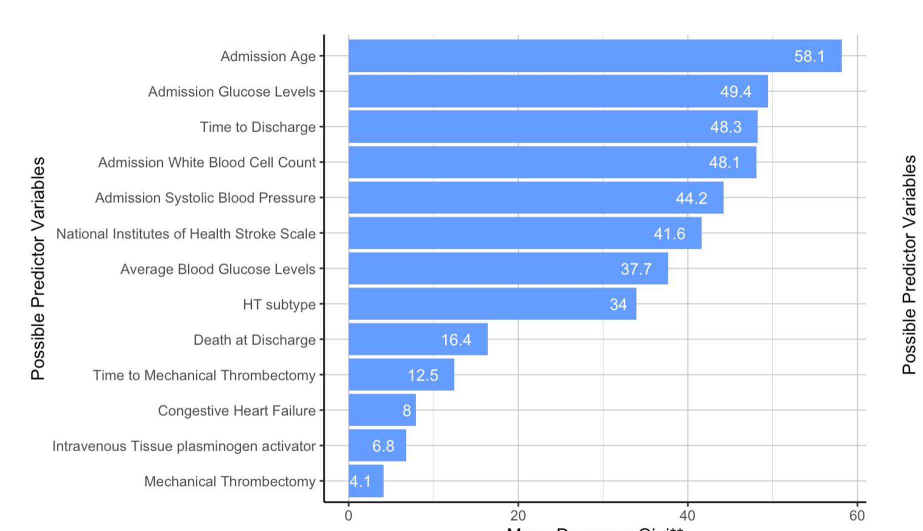

Fig 11. Predictor Importance for LTME

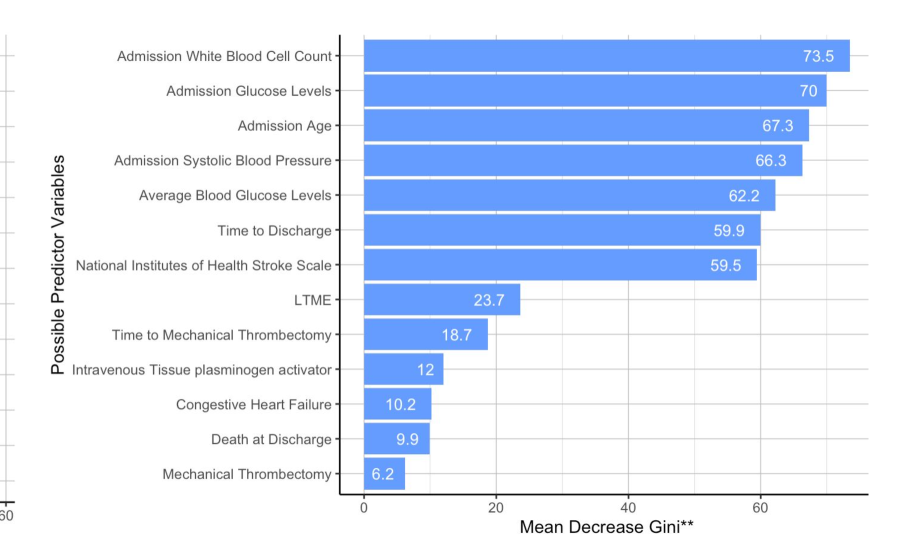

Fig 12. Predictor Importance for HT subtype

***The mean decrease in Gini coefficient is a measure of how each variable contributes to the homogeneity of the nodes and leaves in the resulting random forest. The greater the mean decrease Gini score, the higher the importance of the variable in the model.*

KNN Models

Most optimal at predicting LTME with 28 K-Neighbors

88.52% Accuracy on Validation Cohort

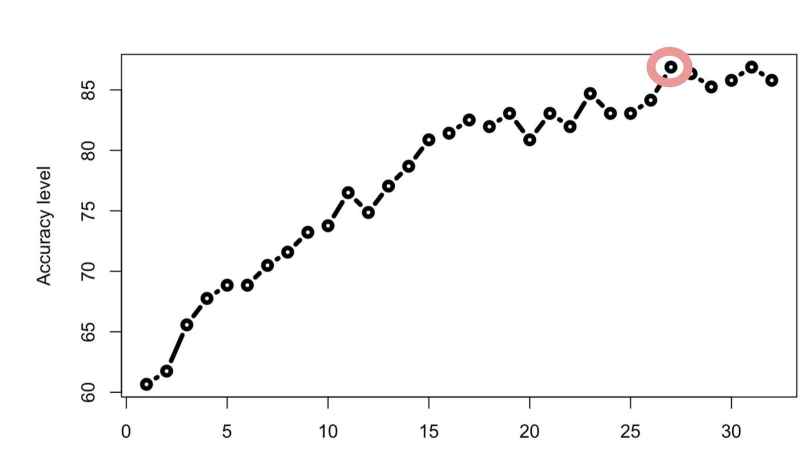

Fig 13. Accuracy of KNN varying by K-Neighbors

The strongest predictors agrees with Random Forest model.

CONCLUSIONS/DISCUSSION

- There is **evidence of a difference in time to events** for parenchymal hemorrhage patients compared to petechial hemorrhage patients for death by discharge, cerebral edema death by discharge and LTME
- **Most significant predictors for LTME and HT** include **age, glucose levels at admission and white blood cell count at admission**
  - Results agrees with Marsh EB, et al.[2], however prior anticoagulation does not appear to be associated with HT as Marsh EB, et al.[2] results suggest (more specifically warfarin)
- Glucose levels at admission may be potentially confounded by diabetic and non-diabetic patients; therefore we consider **HbA1C** (average blood glucose levels measured across a period of 3 months) to account for the **differing glucose levels in diabetic patients**
  - Further study into **longitudinal trends** of glucose levels may improve predictions and associations between glucose levels and HT subtype
- The **success of the trained Random Forest and KNN models** on classifying patient outcomes beyond the primary cohort serves as a indicator that results **may be generalized** to Ischemic stroke patient populations that had large MCA strokes, provided further training and testing

References

1. von Kummer R, Broderick JP, Campbell BCV, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. Stroke. 2015;46(10):2981-2986. doi:10.1161/STROKEAHA.115.010049
2. Marsh EB, Llinas RH, Schneider ALC, Hillis AE, Lawrence E, Dziedzic P, Gottesman RF. Predicting Hemorrhagic Transformation of Acute Ischemic Stroke: Prospective Validation of the HeRS Score. Medicine (Baltimore). 2016 Jan;95(2):e2430. doi: 10.1097/MD.0000000000002430. PMID: 26765425; PMCID: PMC4718251.

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