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Predictors and Temporal Trends of Withdrawal of Life-Sustaining Therapy After Acute Stroke in the Florida Stroke Registry

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OBJECTIVES: Temporal trends and factors associated with the withdrawal of life-sustaining therapy (WLST) after acute stroke are not well determined.

DESIGN: Observational study (2008–2021).

SETTING: Florida Stroke Registry (152 hospitals).

PATIENTS: Acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) patients.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Importance plots were performed to generate the most predictive factors of WLST. Area under the curve (AUC) for the receiver operating curve were generated for the performance of logistic regression (LR) and random forest (RF) models. Regression analysis was applied to evaluate temporal trends. Among 309,393 AIS patients, 47,485 ICH patients, and 16,694 SAH patients; 9%, 28%, and 19% subsequently had WLST. Patients who had WLST were older (77 vs 70 yr), more women (57% vs 49%), White (76% vs 67%), with greater stroke severity on the National Institutes of Health Stroke Scale greater than or equal to 5 (29% vs 19%), more likely hospitalized in comprehensive stroke centers (52% vs 44%), had Medicare insurance (53% vs 44%), and more likely to have impaired level of consciousness (38% vs 12%). Most predictors associated with the decision to WLST in AIS were age, stroke severity, region, insurance status, center type, race, and level of consciousness (RF AUC of 0.93 and LR AUC of 0.85). Predictors in ICH included age, impaired level of consciousness, region, race, insurance status, center type, and prestroke ambulation status (RF AUC of 0.76 and LR AUC of 0.71). Factors in SAH included age, impaired level of consciousness, region, insurance status, race, and stroke center type (RF AUC of 0.82 and LR AUC of 0.72). Despite a decrease in the rates of early WLST (< 2 d) and mortality, the overall rates of WLST remained stable.

CONCLUSIONS: In acute hospitalized stroke patients in Florida, factors other than brain injury alone contribute to the decision to WLST. Potential predictors not measured in this study include education, culture, faith and beliefs, and patient/family and physician preferences. The overall rates of WLST have not changed in the last 2 decades.

KEY WORDS: ischemic stroke; intracerebral hemorrhage; subarachnoid hemorrhage; temporal trends; withdrawal of life-sustaining therapy

Ischemic and hemorrhagic strokes are associated with high morbidity and mortality (1–3). Overall, one-third of severe stroke patients can reach independence at 6–12 months follow-up (4, 5). Among all stroke types, subarachnoid hemorrhage (SAH) is associated with better functional outcomes when compared with acute ischemic stroke (AIS) and intracerebral hemorrhage

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KEY POINTS

Question: What are the factors associated with the decision to withdraw of life-sustaining therapy (WLST) in acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH)?

Findings: In the Florida Stroke Registry of 309,393 AIS, 47,485 ICH, and 16,694 SAH patients; 9%, 28%, and 19%, respectively, had WLST. Most common predictors of WLST were age, level of consciousness, disease severity, state region, race, insurance status/type, ambulation at baseline, and center type. Overall rates of WLST were stable in the last 2 decades.

Meaning: In acute hospitalized stroke patients, factors other than brain injury alone contribute to the decision to WLST.

(ICH) (4). Patient and family values and preference, self-fulfilling prophecy (driven by poor prognosis beliefs), and cognitive biases in prognosis shortly after injury may lead to the decision to withhold or withdraw of life-sustaining therapies (WLST) (6–9). WLST is more commonly seen after ICH and SAH than AIS (9–11). Factors such as age, stroke severity, and impaired level of consciousness may influence WLST decisions (10–13). The temporal trends and predictors of WLST decision during hospitalization are not well studied.

In this study, we aimed to investigate factors associated with WLST decisions in hospitalized acute stroke patients (AIS, ICH, SAH) using data from Florida Stroke Registry (FSR) hospitals participating in the American Heart Association (AHA) Get With The Guidelines-Stroke (GWTG-S). We hypothesized that factors not related directly to injury and age may contribute to WLST decision. Additionally, we aimed to study the temporal trends of overall rates of WLST, early WLST (< 2 d), later WLST, and mortality by stroke type. We hypothesized an overall decrease in WLST over the study period following the 2015 ICH AHA/ASA guidelines recommending against early do-not-resuscitate (DNR) orders and the advancement the field made in stroke management (14).

METHODS

The University of Miami's institutional review board approved this study on March 5, 2020. The study title is "Hispanic Stroke Prevention/Intervention Research Program (HSPIRP)" Institutional Review Board no. 20120987. Each participating center received institutional ethics approval to enroll patients in the Registry without requiring individual patient consent under the common rule or a waiver of authorization and exemption from subsequent review by their institutional review board. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Study Population

Using the FSR, we identified patients with a final diagnosis of AIS, ICH, and SAH between 2008 and 2021. We identified the WLST status through a question during hospitalization on whether the patient underwent comfort measures only or WLST as documented in GWTG-S as a discrete data element. Additionally, we identified the timing of WLST as following: day 0 or 1 of presentation (early), day 2 or after (late) (10–12). The WLST timing was collected as a dichotomous variable in the registry.

Case Identification and Data Abstraction

Originally funded by the National Institute of Neurologic Disorders, the stroke registry included data from GWTG-S participating hospitals in Florida and Puerto Rico (2010–2017) and was referred to as the Florida-Puerto Rico Collaboration to Reduce Stroke Disparities (15, 16). Since 2017, the registry continued as the FSR with funding support through the state of Florida (COHAN-A1). Deidentified retrospective and prospective data from hospitalized patients with the primary diagnosis of ischemic stroke, transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage, and stroke not otherwise specified are included in the registry.

Data collected included patient demographics (age, sex, race/ethnicity), insurance status (private, Medicare, Medicaid, and self/none), comorbidities (prior history of smoking, alcohol/drug use, hypertension, diabetes, obesity, atrial fibrillation or flutter, coronary artery disease, peripheral vascular disease, prior stroke, heart failure), prior ambulation status, IV thrombolysis or endovascular treatment, surgical treatments (such as external ventricular drain or craniectomy), hospital level characteristics (stroke center type—omprehensive, primary, or thrombectomy capable), and disease severity (as measured by the National Institutes of Health Stroke Scale [NIHSS], ICH score, Glasgow Coma Scale (GCS) score, World Federation of Neurosurgical Societies, Hunt and Hess score [WFNS Grading Scale]) (17–23). Florida state was divided into the following regions: east central, west central, north, panhandle, and south. Impaired level of consciousness was identified using one of the GTWG-S questions on the presence of altered level of consciousness on initial examination findings as previously described (10, 11). Additionally, we studied in-hospital mortality, ambulation status on discharge (independent, need assistance, unknown), and discharge disposition (home/inpatient rehab or other).

Statistical Analysis

The primary goal was to identify factors associated with WLST decision after AIS, ICH, and SAH. The secondary goal was to identify the temporal trends of overall, early (< 2 d), late WLST decision, and mortality over the study period, stratified by stroke subtype (AIS, ICH, and SAH).

For patient characteristics, continuous variables were summarized as median with first and third quartiles (Q1 and Q3). Pearson chi-square and Kruskall-Wallis tests were used to compare descriptive statistics.

Primary Outcome Analysis. We generated importance plots using random forest (RF) for factors associated with WLST. This method allows for selecting the variables that are most relevant to the decision of WLST. It provides a list of most significant variables by a mean decrease in Gini. The variables included in the importance plots were those with low missingness less than 5% and those that are clinically relevant for the WLST decision (consensus between the co-authors). We included the following factors in the importance plot for AIS: age, sex, race, insurance status, history of smoking, history of drugs/alcohol use, hypertension, diabetes, obesity, atrial fibrillation or flutter, coronary artery disease, peripheral vascular disease, prior stroke or transient ischemic attack (TIA), prior ambulation status, stroke center type, NIHSS, IV thrombolysis, endovascular treatment, state region, and impaired level of consciousness. For the ICH importance plot, we included the following factors: age, sex, race, insurance status, history of smoking, history of drugs/alcohol use, hypertension, diabetes, obesity, atrial fibrillation or flutter, coronary artery disease, peripheral vascular disease, prior stroke or TIA, prior ambulation, stroke center type, surgical treatments, state region, and impaired level of consciousness. We did not include ICH score due to high missingness. For SAH importance plot, we included the following factors: age, sex, race, insurance status, history of smoking, history of drugs/alcohol use, hypertension, diabetes, obesity, atrial fibrillation or flutter, coronary artery disease, peripheral vascular disease, prior stroke or TIA, prior ambulation, stroke center type, state region, and impaired level of consciousness. We did not include Hunt and Hess score due to high missingness. These factors were selected based on their potential relevance for the WLST decisions.

We then studied the top factors associated with the decision to WLST using logistic regression (LR) and RF models. We generated area under the curve (AUC) for the receiver operating curve to evaluate the performance of LR and RF models. We used 70/15/15 for training/testing/validation. We performed three methods to test the calibration of our models: Brier score, average absolute difference, and Spiegelhalter's z test (24, 25). Brier score and average absolute difference include components of discrimination and calibration evaluation, whereas Spiegelhalter's z test is designed to measure calibration only.

Secondary Outcome Analysis. R-square (R^2) and p values were reported for overall, early, late WLST, and mortality in the regression trend analysis.

The level of statistical significance was set at p less than 0.05. All statistical analyses were performed using Statistical Analysis System Version 9.4 software (SAS Institute, Cary, NC), MATLAB 2021b (Mathworks, Natick, MA), and R (3.6.0., The R Foundation, Indianapolis, IN).

Data Availability Statement

FSR analyses are available per request sent to the FSR Biostatistics Core and after approval of the FSR Publication Committee.

RESULTS

Study Population

We studied 309,393 AIS, 47,485 ICH, and 16,694 SAH patients between 2008 and 2021. WLST during hospitalization occurred in 9% of AIS (33% early WLST), 28% of ICH (50% early WLST), and 19% of SAH (47% early WLST) patients. In-hospital mortality for patients who had WLST versus patients without WLST was 25% versus 1% for AIS, 50% versus 6% for ICH, and 64% versus 6% for SAH. Patients who had WLST were overall more likely to be older (77 vs 70 yr), more likely to be women (57% vs 49%), more likely to be White (76% vs 67%), had greater stroke severity on NIHSS greater than or equal to 5 (29% vs 19%), more likely to be treated in comprehensive stroke centers (52% vs 44%), more likely to have Medicare insurance (53% vs 44%), less likely to be uninsured (8% vs 13%), more likely to undergo surgical treatments (1.2% vs 0.3%), and more likely to have impaired level of consciousness (38% vs 12%). Other characteristics stratified by the WLST decision are summarized in **Table S1** (http://links.lww.com/CCX/B209). Patients' characteristics are described by stroke type in **Tables S2–S4** (http://links.lww.com/CCX/B209).

Factors Associated With WLST Decision After AIS, ICH, and SAH

Most predictive factors associated with the decision to WLST in AIS were age, stroke severity, state region, insurance status, stroke center type, race, and level of consciousness (RF AUC of 0.93 and LR AUC of 0.85). Most predictive factors in ICH were age, impaired level of consciousness, state region, race, insurance status, stroke center type, and ambulation status at baseline (RF AUC of 0.76 and LR AUC of 0.71). Most predictive factors in SAH were age, impaired level of consciousness, state region, insurance status, race, and stroke center type (RF AUC of 0.82 and LR AUC of 0.72) (**Fig. S1**, http://links.lww.com/CCX/B209).

When stratifying data by region, West Central Florida has higher WLST across stroke subtypes (**Tables S5–S7**, http://links.lww.com/CCX/B209). However, patients in the West Central region had overall more comorbidities (hypertension, diabetes, obesity, coronary artery disease, peripheral vascular disease, and prior stroke), and were more predominantly White (Tables S5–S7, http://links.lww.com/CCX/B209).

The calibration methods of our models' discrimination are summarized in (**Table S8**, http://links.lww.com/CCX/B209). Overall, the RF models had higher discrimination accuracy but lower calibration, whereas the LR models had lower discrimination accuracy but higher calibration.

Temporal Trends of Overall, Early (< 2 d), Late WLST Decision, and Mortality

In acute strokes (ischemic and hemorrhagic), we found a significant decrease in early WLST (on day 0 or 1 of admission) (R^2 0.8, $p < 0.001$); an increase in late WLST (≥ 2 d) (R^2 0.7, $p < 0.001$); and an overall stable rate of WLST (R^2 0.5, $p < 0.001$). The rate of mortality has declined over the study period (R^2 0.7, $p < 0.001$).

In patients with AIS, we found a significant decrease in early WLST from 4% in 2008 to 2% in 2021 (R^2 0.9, $p < 0.001$) and a stable late WLST (≥ 2 d) from 6.1% in 2008 to 6.2% in 2021 (R^2 0.4, $p = 0.01$). There was an overall decrease in WLST from 10% in 2008 to 8.5% in 2021 (R^2 0.7, $p \le 0.001$), and mortality from 4.3% in 2008 to 3.1% in 2021 (R^2 0.7, $p \le 0.001$) (**Fig. S2**, http://links.lww.com/CCX/B209).

In patients with ICH, we found a significant decrease in early WLST from 16.4% in 2008 to 13% in 2021 (R^2 0.8, $p < 0.001$) and an increase in late WLST (≥ 2 d) from 12% in 2008 to 15.3% in 2021 (R^2 0.7, $p < 0.001$). The rate of the overall WLST was stable from 28.4% in 2008 to 28.7% in 2021 (R^2 0.3, $p = 0.05$), with a significant decrease in mortality from 21.3% in 2008 to 15.1% in 2021 (R^2 0.6, $p = 0.001$) (Fig. S2, http://links.lww.com/CCX/B209).

In patients with SAH, we found a significant decrease in early WLST from 10.7% in 2008 to 7.2% in 2021 (R^2 0.5, $p = 0.002$) and a slight increase in late WLST (≥ 2 d) from 9.2% in 2008 to 10.5% in 2021 (R^2 0.3, $p = 0.03$). There was a slight decrease in the overall WLST from 19.9% in 2008 to 17.8% in 2021 (R^2 0.2, $p = 0.2$), with a significant decrease in mortality from 19.6% in 2008 to 12.8% in 2021 (R^2 0.7, $p < 0.001$) (Fig. S2, http://links.lww.com/CCX/B209).

DISCUSSION

In this prospective large multicenter stroke registry between 2008 and 2021, we found the following rates of WLST in different stroke subtypes; 9% in AIS, 28% in ICH, and 19% in SAH. Most predictive factors associated with the decision to WLST in all stroke subtypes prior to the stroke, level of consciousness, stroke severity, state region, race, insurance status, ambulation status at baseline, and stroke center type. There is an overall decrease in rates of early WLST (< 2 d), and mortality in all stroke subtypes, but an increase in rates of late WLST. These findings indicate that in addition to individual stroke factors, hospital system level factors and region had a role in WLST decisions. Although hospital system levels and region are related, we suggest there is an independent effect which is affected by factors not measured in our study, including education, culture, race, economic status, faith and beliefs, and patient and family preferences.

Stroke is associated with high morbidity and mortality; however, over one-third of patients after severe acute brain injury can reach independence at 6–12 months follow-up (5, 7, 26, 27). The decision of early DNR is associated with an increase in mortality independent of demographics, stroke size, and location (28, 29). The deaths of acute ischemic and hemorrhagic strokes in ICUs are commonly preceded by WLST (13, 30–32). The average predicted probability of in-hospital death among WLST patients was 35% had they continued maximal therapy among intracranial hemorrhage patients (33). In this study, we found high rates of WLST after acute stroke despite improvement in mortality and the progress the field has made regarding therapeutic interventions in stroke and critical care. We found higher rates of WLST in hemorrhagic strokes when compared to ischemic stroke; consistent with prior literature. These higher rates might in part be related to impaired level of consciousness, cerebral edema, and herniation syndromes that are seen more commonly after hemorrhagic strokes (9–11). The rates of WLST were stable overtime in comparison to the mortality rates (in decline), highlighting the limitation of the current prognostication practices. The most recent AHA/ASA ICH guidelines (published in 2022) recommended against the use of a baseline severity score (such as ICH score) to be used for forecasting individual prognosis or limiting life-sustaining treatment (34). The 2015 AHA/ASA ICH guidelines recommended to postpone DNR orders early, before the second day (14). Despite observing a decline in early WLST rates, we found an associated increase in late WLST rates, resulting in a stable WLST rates after ICH. Unlike the ICH guidelines, AHA/ASA guidelines for AIS and SAH lack any recommendations regarding WLST (35, 36). The temporal trends in this population-level study highlight the persistent pessimism in clinical practice that may result in a premature WLST after acute stroke and subsequently a fatal outcome—"self-fulfilling prophecy" (6–8). It is interesting to note the concomitant decrease in early WLST, the increase in late WLST, and the overall decrease in mortality in all stroke subtypes, despite the significant advances in care for AIS and SAH patients in comparison to ICH. This might be in part related to the overall improvement of care (i.e., medical, surgical, and critical care) for acute brain injury patients in the last years.

Severity of the neurologic injury, the diagnosis of stroke, level of consciousness, and older age are among the reported factors contributing to the decision of WLST (10, 11, 13, 37). A GWTG study based on data collected between 2009 and 2013 found the following factors to be associated with early WLST: older age, female sex, white race, Medicaid and self-pay/no insurance, arrival by ambulance, arrival off hours, baseline nonambulatory status, and stroke type (12). In addition to disease severity, we found that older age, level of consciousness, state region, white race, insurance status, ambulation status at baseline, and stroke center type are important factors contributing to the decision of WLST. Our results are consistent with prior publications regarding older age, baseline functional status, level of consciousness and race (10–13). The higher rates of WLST in comprehensive stroke centers may reflect a sicker population (with more comorbidities, and more severe strokes) than those in other center types. Interestingly, WLST patients were less likely to be uninsured and more likely to be insured with Medicare. This may be related to age as patients with Medicare are older (65 yr and older). The differences we found in the rates of WLST by region might be related to an overall sicker patient population in West Central Florida. The RF (supervised machine learning) performed persistently better than LR in all stroke subtypes in predicting WLST. These results could be related to the ensemble nature of RF which combines the results of multiple decision trees to predict more accurately nonlinear data.

The results of this study carry important clinical implications and considerations regarding the decision of WLST and the practice of WLST in the last 2 decades across multiple hospitals. Even though there are decreasing rates of early WLST, the overall WLST decision rate is stable (2008–2021). The current prognostication scores (such as the ICH score and the Hunt and Hess scales) fail to account for WLST (34). It is critical for clinicians to consider WLST decisions with caution and to avoid the self-fulfilling prophecy when managing patients after acute strokes. More studies are needed to understand the nature and the factors (e.g., education, patient and family preferences, religion) associated with the WLST decisions. Future studies should focus on long-term, patient- and family-centered outcomes, and on discovery of biomarkers early after injury to help clinicians and families navigate the prognostic uncertainty. It is also important to reconsider and challenge the cutoff of 2 days for the timing of WLST, since the first period of hospitalization is still considered "early" after injury.

The study has multiple limitations. The FSR is an AHA GWTG-S with limited information on important relevant data to WLST such as physiologic parameters (blood pressure, heart rate, intracranial pressure, etc.), medications administered or withdrawn during hospitalization, code status (DNR), palliative care involvement, prior advanced directives, detailed clinical examination beyond the NIHSS examination (e.g., brainstem reflexes, motor, and cognitive examination), and imaging findings (edema, herniation, midline shift, etc). Furthermore, the variables included in the importance plots were decided via a consensus of the co-authors which may have a bias risk. Additionally, the data lack the long-term cognitive and functional outcomes after hospitalization. Long-term follow-up outcomes are important measures to fully assess the impact of the self-fulfilling prophecy in this population. Important scores such as GCS, ICH score, Hunt and Hess, WFNS Grading Scale have high missingness, making the interpretation of stroke severity challenging in our ICH and SAH population. This study does not include patient- and family-centered measures to understand the shared decision-making and how the discussion of WLST was communicated. Additionally, we did not have data on spiritual, religious, and cultural beliefs for patients and their families, nor data on educational level, financial status, and other social factors; all important factors to consider when making WLST decisions. Finally, we had no data on the withdrawal of specific treatments, such as mechanical ventilation vasopressors use, feeding tube placement, and tracheostomy. Despite these limitations, the results of this study are important, emphasizing the high and overall stable rates of WLST in acute stroke despite improvement in the management of these patients in the last 2 decades. Factors not related to the injury alone could contribute to the decision of WLST. Although WLST can lead to death, not all WLST cases are inappropriate. For patients who present with devastated injuries with prior existing advance care directives, WLST is appropriate to honor the patient and family wishes.

CONCLUSIONS

In summary, WLST is common after AIS, ICH, and SAH and often decided early. In acute hospitalized stroke patients, factors other than brain injury alone contribute to the decision to WLST. Despite the decreased rates of early WLST (< 2 d), the overall rates of WLST are stable in the last 2 decades.

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Drs. Alkhachroum, Asdaghi, and Gardener were involved in study concept and design. Drs. Zhou, Gardener, Ying, and Gutierrez were involved in acquisition of data. Drs. Zhou, Ying, Alkhachroum, Manolovitz, Asdaghi, and Gardener were involved in analysis and interpretation of data. Drs. Alkhachroum, Zhou, Asdaghi, Gardener, Ying, Gutierrez, Samano, Bass, Sur, Rose, Jameson, Massad, Kottapally, Merenda, Starke, O'Phelan, Romano, Claassen, Sacco, and Rundek were involved in drafting the article. Drs. Zhou, Gardener, Manolovitz, and Ying were involved in statistical analysis. Drs. Alkhachroum, Gutierrez, and Asdaghi were involved in study supervision.

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