Health-Related Quality of Life Among Survivors of Intracerebral Hemorrhage: A Hypothesis-Generating Study of One Year Recovery Trajectories and Health Care Decision Making

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Dedication

To all survivors of stroke and to those we have lost, and to their families.

To my mother, Esther.

To my children, Ethan and Mia, and without question, my husband, Ricardo.

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Abstract

Background

Intensive Care Unit clinician-family decision making regarding prognosis and limitation of care occurs early and often in intracerebral hemorrhage (ICH). Recovery in ICH is prolonged and unpredictable, resulting in major challenges to estimating short-term mortality and long-term health-related quality of life (HRQoL). With goals of care decisions centering on prognostic estimates in ICH, further work is needed to examine the influence of early prognostication on withdrawal of life-sustaining treatment (WLST) decisions, and survivor perspectives of their long-term recovery trajectory after severe ICH. Using trial data from Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) and Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III), the purpose of this dissertation is to examine: (1) the demographic and disease-severity predictors of WLST following ICH; (2) the HRQoL of ICH survivors with dichotomized good vs. poor functional outcome over time; and (3) the long-term disposition and HRQoL outcomes of ICH survivors with similar baseline demographic and clinical characteristics of patients who had WLST.

Methods

Aim 1: A retrospective analysis compared no WLST patients (n=861) to WLST patients (n=118) enrolled in the CLEAR III and MISTIE III trials. Multivariable logistic regression was used to estimate the influence of established demographic and clinical severity of disease factors associated with good and poor outcomes, such as age, Glasgow Coma Scale (GCS), ICH location (deep or lobar), and total blood burden, defined by adding ICH and Intraventricular Hemorrhage (IVH) volumes (mL), at stability for WLST patients. Receiver operating characteristic (ROC) curves were used to evaluate the discriminatory power of the predictors of WLST and poor functional recovery of ICH patients at day 365. Rationale for WLST was assessed via standardized questions after goals of care discussions.

Aim 2: A retrospective analysis compared the EQ-5D-3L dimensions and EQ-5D visual analog scale (EQ-VAS) scores of ICH survivors (n=732) enrolled in the CLEAR III and MISTIE III trials with dichotomized "good" (modified Rankin Scale [mRS] 0–3) vs. "poor" (mRS 4–5) functional outcome at days 30, 180, and 365. The EQ-5D-3L dimensions were dichotomized by "no problems" vs. "any problems" and evaluated the percentage of participants by dichotomized mRS at days 30, 180, and 365. The proportion of ICH survivors by dichotomized mRS was evaluated at days 30, 180, and 365.

Aim 3: A matched cohort analysis using a modified severity index compared ICH survivors (n=379) enrolled in MISTIE III to patients who had WLST (n=61) after the first 72 hours. Patient disposition and EQ-VAS of matched survivors were evaluated at days 30, 180, and 365. The mean EQ-VAS at day 365 was compared to the mean EQ-VAS US population norm for persons aged 45–75 years. The rationale for WLST was examined via standardized questions after goals of care discussions.

Results

Aim 1: Of 979 participants, 118 (12%) had WLST. Nearly 73% had WLST performed within the first 30 days following diagnosis of ICH/IVH, with the highest number of WLST cases occurring within the first two weeks following initial presentation. Older age, lower GCS and greater total blood burden were significantly associated with WLST. For every year increase in age, there was a four percent increase in the odds of having WLST performed. Patients with GCS 9-12 were two times more likely to have WLST performed than patients with GCS 13-15. Patients with GCS 3-8 were four times more likely to have WLST performed than patients with GCS 13-15. Patients with total blood burden of > 55 mL were nearly five times more likely to have WLST performed. The area under the ROC curve of 79% indicated that the severity factors were moderately effective in distinguishing between patients who had WLST and those who did not. The severity factors identified 82% of patients with poor functional recovery at day 365. An anticipated dependent outcome was attributed to the rationale for WLST in 62% of WLST cases.

Aim 2: Of 732 survivors, 607 survivors or their proxies completed the EQ-5D-3L dimensions and 557 survivors had EQ-VAS data at all timepoints. At day 30, 80.6% of survivors had a mRS of 4-5. By one year, 61.6% of survivors had a mRS of 0-3. Survivors with mRS 0-3 and mRS 4-5 showed significant differences at days 30, 180, and 365 in all five EQ-5D-3L dimensions, where a significantly higher percentage of survivors with mRS 4-5 reported having "any problems" compared to survivors with mRS 0-3. Survivors with mRS 4-5 reported the highest percentage of "any problems" with mobility at days 30 (99.1%) and 365 (98.3%), usual activities (99.6%) at day 180; and the lowest percentage of "any problems" related to anxiety/depression at days 30 (55.9%), 180 (53.3%), and 365 (56.3%). Proxies of survivors with mRS 4-5 had a significantly higher percentage of those who reported "any problems" with mobility and self-care at days 30, 180, and 365, and with usual activities at days 180 and 365 compared to proxies of survivors with mRS 0-3. EQ-VAS of the survivors increased within the first six months, but not significantly beyond six months to one year. Of the survivors with severe disability in the acute phase, almost 60% achieved functional independence and reported EQ-VAS that approached the EQ-VAS US population norm by one year.

Aim 3: Of 379 survivors in MISTIE III at one year, 90 were matched to patients who had WLST (n=61). Of the 90 matched survivors, 11.1%, 65.6%, and 73.3% returned home by days 30, 180, and 365. The mean (SD) EQ-VAS of matched survivors at days 30, 180, and 365 was 41.9 (24), 62.2 (20.8), and 65.6 (21.8). At day 365, matched survivors living at home (n=66) had mean (SD) EQ-VAS of 70.6 (18.9) as compared to the mean EQ-VAS US population norm of 75. The rationale recorded for WLST was an anticipated dependent state for 38 (62%) of the 61 WLST patients.

Conclusion

These results suggest that the same disease-severity predictors of poor outcome, first described in the late 1980s, continue to influence the decision to withdraw life-sustaining treatment in the critically ill ICH patient population. Yet, the survivors of ICH with severe disability at 30 days following ICH diagnosis demonstrated a significant trend toward functional independence and HRQoL improvement at one year, and nearly half of those with severe disability at one year, reported no problems with anxiety/depression and

pain/discomfort. The HRQoL of ICH survivors with clinical and demographic characteristics similar to those who had WLST, specifically those living at home, approached the US population norm of HRQoL for age-matched persons at one year. Consequently, early prognostication of pessimistic outcomes does not appear to match the potential for acceptable outcomes of ICH survivors. The results of this dissertation study challenge the current goals of care, decision-making practices of early identification of poor ICH outcomes as the solely determinative element of prognosis for the purpose of WLST.

Project Narrative

Shared decision making regarding prognosis and limitation of care occurs early and often between families and Intensive Care Unit clinicians in intracerebral hemorrhage (ICH). Withdrawal of life-sustaining treatment (WLST) is the most common cause of immediate death in critically ill patients with ICH. By contrast, recovery in ICH is prolonged and has been unpredictable, resulting in considerable challenges to estimating short-term mortality and long-term health-related quality of life (HRQoL). With such goals of care decisions centering on early prognostic estimates in ICH, it is essential to examine the influence of early prognostication on WLST decisions, and survivor perspectives of their long-term recovery trajectory after severe ICH. This research has the potential to inform prognostication in ICH with individual, disease-specific, long-term HRQoL data; it can help optimize shared decision making; and could challenge the current practice of early identification of poor ICH outcomes, when goals of care decision making is a priority.

Journal Publication Venues

Manuscript #1

Preconceived Notions about Futility of Care Lead to Withdrawal of Life-Sustaining Treatment following Intracerebral Hemorrhage: A Retrospective Analysis of CLEAR III and MISTIE III

Stroke

Journal of the American Heart Association/American Stroke Association

Not submitted

Manuscript #2

One Year Later: Health-Related Qualify of Life and Functional Recovery of Intracerebral Hemorrhage Survivors in CLEAR III and MISTIE III

Neurocritical Care

Journal of the Neurocritical Care Society

Not submitted

Manuscript #3

Patient Disposition and Health-Related Quality of Life in MISTIE III:

Opportunities to Improve Decision Making with Critically Ill Intracerebral Hemorrhage Patients

Stroke

Journal of the American Heart Association/American Stroke Association

Not submitted

CHAPTER 1:

Dissertation Introduction

Significance

Scope of the Problem

In U.S.-based Neurocritical Care Units, approximately 13% – 15% of patients with acute neurological injuries, including Intracerebral Hemorrhage (ICH), have life-sustaining treatment withheld or withdrawn, accounting for nearly 60% of deaths.[1] For critically ill patients with ICH, the most common cause of immediate death is the decision to withdraw life-sustaining treatment.[2,3] Goals of care decisions, to maintain, limit or withdraw life-sustaining treatment, occur early and often for patients with severe ICH. The decision-making process relies on an informed, shared decision-making model in which surrogate decision makers and clinicians align the patient's preferences and values with the health care team's opinions, beliefs and expectations of the potential for a meaningful recovery. As a consequence, prognostication is a fundamental component of the goals of care decision-making process.

Prognosis in ICH is often uncertain. Prognostic models to aid in the prediction of mortality and functional outcomes for critically ill patients with ICH have been developed; however, current models possess several limitations.[1,2,4–7] Outcome models for ICH were originally designed to provide population-based estimates of outcomes, which creates challenges in applying predictions at the individual level.[1] Additionally, existing ICH outcome models include variables that are extrapolated from patient populations in whom withdrawal of life-sustaining treatment (WLST) was performed.[1] Most importantly, current prediction models in ICH fail to address the long-term health-related quality of life (HRQoL) as perceived by survivors of ICH, a factor of significant interest to surrogate decision makers, particularly in the context of goals of care decision making.[1] Thus, decisions were often not informed by carefully validated long-term HRQoL data from surviving ICH patients. Accordingly, the utilization of mortality data and prognostic models may create a "self-fulfilling prophecy" and maintain high mortality rates in ICH.[1,2] Lastly, given the uncertainties surrounding long-term

prognosis following ICH, significant variability exists among clinicians in predicting outcomes for patients with ICH; thus, the delivery of prognosis to surrogate decision makers results in exceedingly pessimistic or overly optimistic prognostic estimates.[1,2,8] Consequently, deficiencies in prognostic opinions of outcomes early after ICH may significantly influence the decision to pursue WLST while negating the influence of patient-reported HRQoL outcomes, and may leave surrogates unprepared to make a high-quality decision, a decision that is congruent with the patient's preferences and values.

Given the sudden and unexpected nature of ICH, goals of care decisions are often made without the guidance of a pre-existing advance directive, or if present, an advance directive that is poorly applicable or not applicable at all.[9] Thus, surrogate decision makers are asked to use substituted judgement in making decisions on the behalf of a patient that lacks decision-making capacity. Such decisions often center on the decision-maker's ability to predict the patient's likelihood of achieving an acceptable level of recovery and adapting to a new life with disability.[5,9] This process may be prone to unintended errors if family-clinician conversations about goals of care are anchored on flawed prognostic models that are primarily focused on survival and functional recovery, without addressing a patient's ability to reframe their internal preferences and values in a new disability state.[1,5,9] Consequently, surrogate decision makers often express doubt, guilt and regret surrounding these consequential decisions leading to psychological stress and long-term psychological morbidity.[1,10–15] Post-traumatic stress with moderate to severe risk for post-traumatic stress disorder was high (82%) among 284 family members who participated in end-of-life decisions.[10] Within one year of a critically ill relative's death, 34% of surrogates met criteria for at least one psychiatric illness.[16] Nearly one-third of surrogates of patients with stroke experienced clinically significant grief or stress reactions as a result of making a goals of care decision.[15]

Impact of Dissertation Research

Using longitudinal, validated data from two, well-monitored, NIH-sponsored clinical trials, Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III)[17] and Minimally Invasive

Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III),[18] this dissertation will: 1) analyze the predictors of WLST in ICH; 2) evaluate the HRQoL of ICH survivors with good vs. poor outcomes; and 3) describe the long-term patient disposition and HRQoL for ICH survivors with similar baseline disease severity to ICH patients who had WLST.

This research has the potential to inform current prognostication with individual disease-specific long-term HRQoL data and could challenge the current practice of early identification of poor ICH outcomes followed by the delivery of clinical opinions, beliefs, and expectations of recovery in association with goals of care decision making. An informed, shared decision-making framework that allows for the use of ICH survivor-based HRQoL data has the potential to: 1) provide insight into the current clinical paradigm of early prediction of pessimistic outcomes; 2) improve future prognostication of recovery after ICH; and 3) allow for future research focused on optimizing data and process driven surrogate decision-maker experiences in dealing with future health uncertainties and making high-quality, consequential decisions.

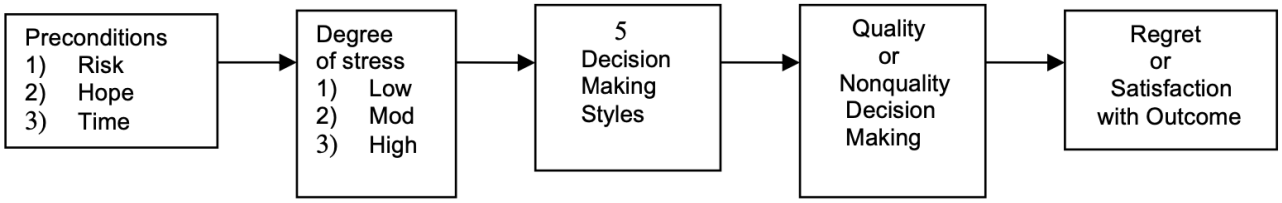
Theoretical Framework

Janis and Mann's *Theory of Conflict in Decision Making*, briefly depicted in Figure 1, forecasts decision-making behavior for consequential decisions, defined as decisions "which are emotionally laden and motivationally driven, in which perceived losses exist no matter which alternative is chosen."[19–22] The theorists, Janis and Mann, describe three preconditions, *risk* associated with the consequences of the decision, *hope* for finding a better solution, and the *time* pressure of making a difficult decision. The preconditions of risk, hope and time influence the degree of stress a decision maker experiences and impacts the decision-making style adopted by the decision maker.[19,20,22] The decision-making style assumed by the decision maker leads to either quality or non-quality decision making resulting in decision satisfaction or later decision regret. The most optimal range of stress is the moderate range to ensure adherence to quality decision making. Janis and Mann describe a "normative" decision-making style termed, *vigilance*, which is associated with a moderate range of stress required to make high-quality decisions based on the optimization of clarifying the objectives and values involved in the decision, surveying the options and alternatives, searching and examining information, and

weighing the gains and losses of the consequences of the decision. This decision-making style leads to less regret and more satisfaction.[19,20,22]

The *Theory of Conflict in Decision Making* will be used in three ways for this ***dissertation and program of research***: 1) as a foundation for understanding factors, specifically in relation to prognostication, affecting the deliberation process in goals of care decision making; 2) as a basis for understanding decisional conflict and decision regret among the surrogate decision makers of critically ill patients with ICH in **future research**; and 3) as the underpinning guide for the development of decision-making interventions that include ICH survivor-reported outcomes and surrogate data to target decisional conflict and decision regret in this **program of research**.

Figure 1. Model of Better Decision Making.



Adapted by Hollen PJ from Janis and Mann's *Theory of Conflict in Decision Making*.[19–22] From Hollen PJ, Gralla RJ, Jones RA, et al. A theory-based decision aid for patients with cancer: Result of feasibility and acceptability testing of DecisionKEYS for cancer. *Support Care Cancer*. 2013;21:889-899. doi:10.1007/s00520-012-1603-8. Copyright 2012 by Springer-Verlag.

Specific Aims

Intracerebral hemorrhage (ICH), a devastating subtype of stroke, accounts for an estimated 30% of all stroke-related deaths and leads to catastrophic disability among survivors each year.[23,24] Approximately 30% – 50% of patients with ICH will die within 30 days and only 20% of ICH survivors are predicted to regain their premorbid functional state at 6 months.[24,25] The course of recovery in ICH is prolonged and unpredictable, resulting in considerable challenges in estimating a long-term meaningful outcome.[1,2,5] For patients predicted to have a "poor outcome," death is often the result of a decision to withdraw life-sustaining treatment, currently the most common cause of immediate death in patients with ICH.[2,23] Yet, what constitutes a meaningful recovery is difficult to define as an acceptable quality of life can only be determined by the patient, not observers of the patient.[1,2,5] To avoid the potential for survival with unwanted, severe disability, the surrogate decision makers of incapacitated patients with ICH are tasked with making a consequential, goals of care decision – to maintain or forego life-sustaining treatment. Neurocritical care clinician teams are tasked with guiding families through the complex decision-making process of establishing goals of care. Despite best efforts, significant challenges exist in prognosticating outcomes for ICH patients that may impact the quality of the decision-making process.[1,2]

Prognostication is a fundamental component of goals of care discussions between clinicians and surrogate decision makers. Existing prognostic models for ICH focus primarily on mortality and observer measured functional recovery, while not utilizing patient-reported health-related quality of life (HRQoL) outcomes.[1,6,26] An observer's measure of functional outcome fails to capture a person's ability to reframe their internal values and adapt to a new state with disability. Discrepancies between functional outcome and patient-reported HRQoL have been described in patients with ischemic stroke;[27,28] however, there is a paucity of literature describing the long-term HRQoL of ICH survivors, creating an unacceptable gap in essential knowledge. To address this knowledge gap as a **broad goal**, an initial investigation in a program of research aimed at integrating decision-making science with innovative palliative care-based delivery mechanisms is proposed to optimize the goals of care decision-making process for patients with acute neurologic injury. The **major objective** of this retrospective, secondary data analysis, using validated data from two NIH-sponsored,

randomized clinical trials, CLEAR III and MISTIE III, is to analyze the current demographic and disease-severity predictors of withdrawal of life-sustaining treatment (WLST) following ICH, to evaluate the HRQoL of ICH survivors with good vs. poor outcomes over time, and to describe the long-term disposition and patient-reported HRQoL outcomes of ICH survivors with similar baseline demographic and clinical characteristics to ICH patients who had WLST performed in the acute phase of injury. The **specific aims** of this hypothesis generating study are as follows:

1. To identify the demographic and disease severity predictors of withdrawal of life-sustaining treatment (WLST) following ICH.
2. To evaluate the HRQoL of ICH survivors with dichotomized good vs. poor functional outcome at days 30, 180, and 365 following diagnosis of ICH.
3. To describe the long-term disposition and HRQoL outcomes of ICH survivors with similar baseline demographic and clinical characteristics as ICH patients who had WLST.

Longitudinal studies evaluating the long-term outcomes of survivors of ICH are urgently needed. Understanding the HRQoL of patients with ICH will allow for the development of a decision-making framework that integrates survivor-based HRQoL data with patient preferences and values to optimize the goals of care decision-making process. Utilizing patient-generated outcomes has the potential to examine the recovery trajectory of ICH survivors, better describe recovery in patient-centered terms, concordantly improve health care resources for neurorehabilitation and reintegration into society for ICH survivors, and optimize goals of care decision making.[29] This investigation will contribute to methodologically sound research to enhance the science of palliative/goals of care decision making as well as the potential to define and disseminate the benefits of patient-reported outcomes following acute brain injury and its impact on goals of care decisions.

References

1. Frontera JA, Curtis JR, Nelson JE, et al. Integrating Palliative Care Into the Care of Neurocritically Ill Patients: A Report From the Improving Palliative Care in the ICU Project Advisory Board and the Center to Advance Palliative Care. *Crit Care Med*. 2015;43:1964-1977. doi:10.1097/CCM.0000000000001131
2. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology*. 2001;56:766-772.
3. Zahuranec DB, Brown DL, Lisabeth LD, et al. Early care limitations independently predict mortality after intracerebral hemorrhage. *Neurology*. 2007;68(20):1651-1657. doi:10.1212/01.wnl.0000261906.93238.72
4. Cai X, Robinson J, Muehlschlegel S, et al. Patient Preferences and Surrogate Decision Making in Neuroscience Intensive Care Units. *Neurocrit Care*. 2015;23(1):131-141. doi:10.1007/s12028-015-0149-2
5. Creutzfeldt CJ, Holloway RG. Treatment decisions after severe stroke: Uncertainty and Biases. *Stroke*. 2012;43(12):3405-3408. doi:10.1161/STROKEAHA.112.673376
6. Hemphill, JC, Bonovich, DC, Besmertis, L, Manley, GT, Johnston S. The ICH Score: A Simple, Reliable Grading Scale for Intracerebral Hemorrhage. *Stroke*. 2001;32:891-897.
7. Ariesen MJ, Algra A, Worp HB Van Der, Rinkel GJE. Applicability and relevance of models that predict short term outcome after intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 2005;76:839-844. doi:10.1136/jnnp.2004.048223
8. Zahuranec DB, Fagerlin A, Sánchez BN, et al. Variability in physician prognosis and recommendations after intracerebral hemorrhage. *Neurology*. 2016;86(20):1864-1871. doi:10.1212/WNL.0000000000002676
9. Voumard RR, Kiker WA, Dugger KM, et al. Adapting to a New Normal after Severe Acute Brain Injury: An Observational Cohort Using a Sequential Explanatory Design. *Crit Care Med*. 2021;49(8):1322-1332. doi:10.1097/CCM.0000000000004947

10. Azoulay E, Kentish-Barnes N, Chevret S, et al. Risk of Post-traumatic Stress Symptoms in Family Members of Intensive Care Unit Patients. *Am J Respir Crit Care Med*. 2005;171:987-994. doi:10.1164/rccm.200409-1295OC

11. Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med*. 2007;356(5):469-478. doi:10.1056/NEJMoa063446

12. Curtis JR, Treece PD, Nielsen EL, et al. Randomized Trial of Communication Facilitators to Reduce Family Distress and Intensity of End-of-life Care. *Am J Respir Crit Care Med*. 2016;193(2):154-162. doi:10.1164/rccm.201505-0900OC

13. Gries CJ, Engelberg RA, Kross EK, et al. Predictors of symptoms of posttraumatic stress and depression in family members after patient death in the ICU. *Chest*. 2010;137(2):280-287. doi:10.1378/chest.09-1291

14. Barnato AE, Arnold RM. The Effect of Emotion and Physician Communication Behaviors on Surrogates' Life-Sustaining Treatment Decisions. *Crit Care Med*. 2013;41(7):1686-1691. doi:10.1097/CCM.0b013e31828a233d

15. Trevick SA, Lord AS. Post-traumatic Stress Disorder and Complicated Grief are Common in Caregivers of Neuro-ICU Patients. *Neurocrit Care*. 2017:1-8. doi:10.1007/s12028-016-0372-5

16. Siegel MD, Hayes E, Vanderwerker LC, Loseth DB, Prigerson HG. Psychiatric illness in the next of kin of patients who die in the intensive care unit. *Crit Care Med*. 2008;36(6):1722-1728. doi:10.1097/CCM.0b013e318174da72

17. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet*. 2017;389(10069):603-611. doi:10.1016/S0140-6736(16)32410-2

18. Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial [Supplementary appendix]. *Lancet*. 2019;393(10175):1021-1032.

19. Janis IL, Mann L. Coping with Decisional Conflict. *Am Sci*. 1976:657-667.

20. Janis IL, Mann L. *Decision Making: A Psychological Analysis of Conflict, Choice and Committment*. New York: The Free Press; 1977.

21. Janis IL, Mann L. A theoretical framework for decision counseling. In: Janis IL, ed. *Counseling on Personal Decisions: Theory and Research on Short-Term Helping Relationships.* New Haven: Yale University Press; 1982:47-72.

22. Hollen PJ, Gralla RJ, Jones RA, et al. A theory-based decision aid for patients with cancer: Results of feasibility and acceptability testing of DecisionKEYS for cancer. *Support Care Cancer*. 2013;21:889-899. doi:10.1007/s00520-012-1603-8

23. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet*. 2009;373:1632-1644.

24. Caceres JA, Goldstein JN. Intracranial Hemorrhage. *Emerg Med Clin North Am*. 2012;30(3):771-794.

25. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo Hi, Hanley DF. Spontaneous Intracerebral Hemorrhage. *N Engl J Med*. 2001;344(19):1450-1460.

26. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: The FUNC score. *Stroke*. 2008;39(8):2304-2309. doi:10.1161/STROKEAHA.107.512202

27. Vahedi K, Benoist L, Kurtz A, et al. Quality of life after decompressive craniectomy for malignant middle cerebral artery infarction [1]. *J Neurol Neurosurg Psychiatry*. 2005;76(8):1181-1182. doi:10.1136/jnnp.2004.058537

28. Polding LC, Tate WJ, Mlynash M, et al. Quality of Life in Physical, Social, and Cognitive Domains Improves with Endovascular Therapy in the DEFUSE 3 Trial. *Stroke*. 2021;52(4):1185-1191. doi:10.1161/STROKEAHA.120.031490

29. Menon DK, Bryant C. Time for change in acquired brain injury. *Lancet Neurol*. 2019;18(1):28. doi:10.1016/S1474-4422(18)30463-0

CHAPTER 2:

Preconceived Notions about Futility of Care Lead to Withdrawal of Life-Sustaining Treatment following Intracerebral Hemorrhage:

A Retrospective Analysis of CLEAR III and MISTIE III

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Abstract

Objectives: Withdrawal of life-sustaining treatment (WLST) is a common cause of death in patients with intracerebral hemorrhage (ICH) and intraventricular hemorrhage (IVH). In a contemporary cohort of ICH/IVH patients, we aimed to determine if previously described predictors of poor outcome continue to influence WLST decisions in ICH patients.

Methodology: We retrospectively compared no WLST patients (n=861) to WLST patients (n=118) enrolled in the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) and Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III) trials. Multivariable logistic regression was used to estimate the influence of clinical factors, age, Glasgow Coma Scale (GCS), ICH location (deep or lobar), and total blood burden, defined by adding ICH and IVH volumes (mL), at stability for WLST patients. Receiver operating characteristic (ROC) curves were used to evaluate the discriminatory power of the predictors of WLST and poor functional recovery of ICH patients at day 365. Rationale for WLST was assessed via standardized questions after goals of care discussions.

Results: Of 979 participants, 118 (12%) had WLST. The multivariable analysis showed that age at consent (Adjusted Odds Ratio [AOR], 95% Confidence Interval [CI]: 1.04 [1.02-1.06]), GCS 9-12 (AOR, 95% CI: 2.16 [1.07, 4.36]), and GCS 3-8 (AOR, 95% CI: 4.15 [2.09, 8.22]), compared to GCS 13-15, and total blood burden > 40 mL to ≤ 55 mL (AOR, 95% CI: 2.81 [1.36, 5.80]) and > 55 mL (AOR, 95% CI: 4.72 [2.34, 9.53]), compared to total blood burden ≤ 30 mL, were significantly associated with higher odds of WLST. The area under the ROC curve of 79% indicated that the severity factors were moderately effective in distinguishing between patients who had WLST and those who did not. The severity factors identified 82% of patients with poor functional recovery at day 365. An anticipated dependent outcome was attributed to the rationale for WLST in 62% of WLST cases.

Conclusion: Older patients with lower GCS and larger hematoma volume had higher odds of undergoing WLST. Our results suggest that early prognostication continues to lead to a self-fulfilling prophecy, which could be perpetuating high mortality in ICH. The avoidance of early pessimistic predictions may improve the ability to prognosticate recovery more accurately for ICH patients.

Trial Registration: URL: https://clinicaltrials.gov/ct2/show/NCT00784134; Unique Identifier: NCT00784134; URL: https://clinicaltrials.gov/ct2/show/NCT01827046; Unique Identifier: NCT01827046

Non-Standard Abbreviations and Acronyms

Adjusted Odds Ratio (AOR)

Akaike Information Criterion (AIC)

Area Under the Receiver Operating Characteristic Curve (AUC)

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III)

Computed Tomography (CT)

Confidence Interval (CI)

External Ventricular Drain (EVD)

Functional Outcome in Patients with Primary Intracerebral Hemorrhage (FUNC)

Glasgow Coma Scale (GCS)

Interquartile Range (IQR)

Intracerebral hemorrhage (ICH)

Intraventricular hemorrhage (IVH)

Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III)

modified Rankin Scale (mRS)

National Institutes of Health Stroke Scale (NIHSS)

Receiver operating characteristic (ROC)

Withdrawal of life-sustaining treatment (WLST)

Introduction

Intracerebral hemorrhage (ICH), a devastating subtype of stroke, accounts for an estimated 30% of all stroke-related deaths.[1,2] The withdrawal of life-sustaining treatment (WLST) is the most common cause of immediate death in critically ill patients with intracerebral hemorrhage (ICH).[3,4] Prognosis in ICH is often uncertain, leading to significant challenges in goals of care decision making, the decision to maintain, limit or withdraw life-sustaining treatment. Goals of care decision making for critically ill patients with ICH relies on an informed, shared decision-making model in which surrogate decision makers and clinicians align prognostic estimates with the patient's preferences and values.[5,6] To inform general prognosis, several prognosticating models for ICH have been developed throughout the years.

While emphasis has been placed on the development of models to aid in the prediction of mortality and functional outcomes for patients with ICH, these models can predict for a proportion of patients and are challenging to apply at the individual level.[7–9] Moreover, some of the most widely-accepted prediction models in ICH are biased by the inclusion of early WLST.[3,5,7] As a consequence, the reliance on preconceived population-based estimates of morbidity and mortality seems to create a "self-fulfilling prophecy" and perpetuate high mortality rates in ICH.[3,7] As a result of this critical bias, international organizations and societies have recommended the avoidance of WLST for patients with devastating brain injuries within 72 hours of presentation, but with the exception of individuals with prior do-not-resuscitate, do-not-intubate or other care limitation orders.[10–12]

In a large, contemporary cohort of patients with ICH/IVH enrolled in the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) and Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III) trials, we aimed to determine if the previously described clinical predictors of poor outcome, identified through analytical models that did not consider the effects of WLST and first described in the late 1980s, continue to influence the decision to withdraw life-sustaining treatment, leading to self-fulfilling prophecies in the ICH/IVH patient population.

Methods

Data Source

Data was obtained from the CLEAR III[13] and MISTIE III[14] trials. Briefly, CLEAR III was a randomized, double-blinded, prospective phase 3 trial of the combination of external ventricular drain placement (EVD) and low dose alteplase for clearance of IVH, performed at 73 hospitals in the USA, Canada, Europe, South America and Asia. Eligible patients were aged 18 to 80 years with a diagnosis of IVH and obstructive hydrocephalus of the third or fourth ventricle. They had known symptom onset within 24 hours of the initial, diagnostic computed tomography (CT), and spontaneous, supratentorial ICH of ≤ 30 mL that remained stable (hematoma growth of < 5 mL) on repeat CT scan at least 6 hours after EVD placement, and a pre-morbid modified Rankin Scale (mRS) of 1 or less.[13] The primary outcome of CLEAR III was to assess the clinical efficacy of EVD placement plus alteplase, as measured by a dichotomized mRS of less than 3 vs. more than 3 at day 180.[13]

MISTIE III was a randomized, controlled, open-label, blinded endpoint, phase 3 explanatory trial of image-guided, catheter-based removal plus fibrinolysis of ICH of ≥ 30 mL, performed at 78 hospitals in the USA, Canada, Europe, Australia, and Asia. Eligible patients were aged 18 years or older with a spontaneous, non-traumatic, supratentorial ICH of ≥ 30 mL due to cerebral small-vessel disease. They had a Glasgow Coma Scale (GCS) of 14 or less or National Institutes of Health Stroke Scale (NIHSS) score of 6 or higher, a pre-morbid (mRS) score of 0 or 1, and an ICH that remained stable (hematoma growth of < 5 mL) for at least 6 hours after diagnostic CT scan.[14] The primary aim of MISTIE III was to determine if the MISTIE procedure could improve functional outcome, as measure by mRS of 0 to 3, at day 365 following ICH.[14]

Patients with expressed care limitations were excluded from CLEAR III and MISTIE III. Discussions between clinicians and surrogate decision makers involving prognosis and goals of care decisions were conducted according to each institution's policies, and in conjunction with their respective institutional codes of medical ethics. The medical management of all enrolled patients was in concordance with the CLEAR III protocol[13] and MISTIE III protocol,[14] both of which followed the American Heart Association guidelines for the

treatment of spontaneous ICH.[15] Trial inclusion factors utilized the concept of abstaining from WLST early during active treatment.

Withdrawal of Life-Sustaining Treatment

WLST was defined as the discontinuation of life-sustaining therapies (i.e., mechanical ventilation, hemodynamic support, artificial nutrition) at any timepoint during the study period. WLST cases were captured at days 30, 180 and 365.

Total Blood Burden

Total blood burden was defined by adding the ICH and IVH volumes in millimeters (mL) at stability. Given the known neuro-inflammatory effects of intraventricular and intraparenchymal blood, the rationale for the use of total blood burden in this study was to combine the study populations from the CLEAR III and MISTIE III trials.

Rationale for WLST

Rationale for WLST determination was assessed via standardized questions after family conferences. Respondents were instructed to indicate the rationale for the decision to pursue WLST. Respondents included attending physicians, site principal investigators, and others (i.e., residents/fellows, nurse practitioners, palliative care). Responses were categorized as: (a) dependent outcome anticipated; (b) dependent outcome anticipated, living will; (c) dependent outcome anticipated, prior statement by patient; (d) dependent outcome anticipated, prior statement by patient, living will; (e) living will; (f) living will, prior statement by patient; (g) prior statement by patient; and (h) unknown. A data manager (RA) reviewed the CLEAR III and MISTIE III case report forms of patients who had WLST to identify the attributed rationale for the decision to withdraw life-sustaining treatment.

Statistical Analysis

We performed a retrospective comparison of 861 patients who did not have WLST to 118 patients who had WLST, enrolled in the CLEAR III and MISTIE III trials. Normally distributed continuous variables were summarized as means with standard deviations and non-normally distributed variables were reported as medians with interquartile range (IQR). For univariate assessments, Student's t-test or Wilcoxon rank sum test for continuous variables based on the normality distribution was used, and $\chi 2$ test or Fisher's exact test for categorical variables were used. Patients were grouped into two categories: no WLST and WLST. Demographic and ICH clinical characteristics were compared between no WLST and WLST groups using appropriate univariate analysis. Variables with a predetermined significance of p-value < 0.1 and variables considered to be clinically associated with WLST were entered into the multivariable logistic regression models and compared using Akaike Information Criterion (AIC) to select the optimal set of covariates of each model. Multivariable logistic regression (MLR) was used to estimate the influence of clinical factors [age, GCS, ICH location (*deep or lobar*), and total blood burden] for WLST patients, as well as for ICH patients with poor functional recovery, as defined by mRS 4-6, at day 365. Receiver operating characteristic (ROC) curves were used to evaluate the discriminatory power of the predictors of WLST and poor functional recovery of ICH patients at day 365.

Age in years was captured at time of consent. GCS and ICH location were captured at time of randomization. Deep ICH location was defined as hemorrhage involving the thalami or basal ganglia. ICH and IVH volume were captured following the stability CT scan done at least 6 hours after diagnostic CT showing clot stability (defined as hematoma growth of < 5 mL) as measured by ABC/2 method.[16] Hematoma volumes were measured using volumetric software OsiriX MD (version 9.0.1). Total blood burden was distributed based on the quartiles of the blood volumes in the trials.

Statistical analyses were performed using Stata (version 16.0, College Station, TX) and R (version 4.0.2, R Project for Statistical Computing). All analyses were two-tailed, and significance level was determined by $p < 0.05$.

Standard Protocol Approvals, Registrations, and Patient Consents

Each of the trial sites included in the CLEAR III and MISTIE III trials obtained institutional review board or ethics committee approval from their respective institutions.[13,14] This study was approved by the Johns Hopkins Medicine Institutional Review Board. CLEAR III and MISTIE III are registered with ClinicalTrials.gov, NCT00784134 and NCT01827046. Written informed consent for participation in the CLEAR III and MISTIE III trials were obtained from all participants (or legal representatives or surrogates when applicable).

Data Availability Statement

CLEAR III and MISTIE III trials data, including de-identified participant data, are available at the National Institute of Neurological Disorders and Stroke (NINDS) data archive (https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets). Those seeking access must complete a NINDS data request form and receive approval.

Results

Out of 999 randomized participants in the CLEAR III and MISTIE III trials, 20 (2%) were excluded from analysis due to lost to follow-up or withdrawal of consent. The remaining 979 (98%) participants were analyzed, with 118 (12.1%) having WLST performed and 861 (87.9%) not having WLST (figure 1). The number of WLST cases amongst the two trials were nearly equal with CLEAR III having 57 deaths attributed to WLST and MISTIE III having 61 deaths attributed to WLST. Nearly 73% of WLST cases occurred within the first 30 days following diagnosis of ICH/IVH (figure 2). The median number of days from ictus or stroke to WLST was 17.5 (IQR 11.5-36, p=0.6) for WLST patients in CLEAR III and 15 (IQR 9-41, p=0.7) for WLST patients in MISTIE III.

The demographic and clinical characteristics of patients who did not have WLST performed (n=861) and patients who had WLST (n=118) are shown in table 1. Patients who underwent WLST were of older age,

higher white representation, more severe GCS (3-8), lobar ICH, greater total blood burden (mL) during stability scans, and higher rates of hyperlipidemia at baseline. There was those no difference in treatment effect between patients who did not have WLST and patients who had WLST (table 1). The demographic and clinical characteristics of patients who died of causes other than WLST (n=129) and patients who had WLST (n=118) are shown in table S1. Patients who died of causes other than WLST had higher rates of deep ICH and lower total blood burden (mL) than patients who had WLST (table S1). A univariate analysis of the demographic and clinical factors associated with good functional outcome (mRS 0-3) and poor functional outcome (mRS 4-6) at day 365, excluding patients who had WLST, is shown in table S2. Patients who had poor functional recovery were older, had larger ICH volume, lower GCS, and had higher rates of IVH, deep ICH location, and diabetes (table S2).

The multivariable logistic regression model for WLST is shown in table 2. Race lost significance when controlling for the other covariates. The multivariable analysis showed that age at consent (Adjusted Odds Ratio [AOR], 95% Confidence Interval [CI]: 1.04 [1.02-1.06]), GCS 9-12 (AOR, 95% CI: 2.16 [1.07, 4.36]), and GCS 3-8 (AOR, 95% CI: 4.15 [2.09, 8.22]), compared to GCS 13-15, and total blood burden of > 40 mL to $\leq$ 55 mL (AOR, 95% CI: 2.81 [1.36, 5.80]) and $>$ 55 mL (AOR, 95% CI: 4.72 [2.34, 9.53]), compared to total blood burden $\leq$ 30 mL, were significantly associated with higher odds of WLST. No association between deep ICH location (AOR, 95% CI: 0.86 [0.55, 1.36]) and WLST and total blood burden $>$ 30 mL to $\leq$ 40 mL (AOR, 95% CI: 0.55 [0.20,1.55]), compared with total blood burden $\leq$ 30 mL, and WLST. The multivariable logistic regression model of poor functional outcome at day 365 is shown in table S3. The multivariable analysis showed that age at consent (AOR, 95% CI: 1.08 [1.06, 1.09]), GCS 9-12 (AOR, 95% CI: 1.74 [1.16, 2.62]), and GCS 3-8 (AOR, 95% CI: 3.80 [2.45, 5.89]), compared to GCS 13-15, and total blood burden $>$ 30 to $\leq$ 40 mL (AOR, 95% CI: 2.97 [1.85, 4.77]), $>$ 40 mL to $\leq$ 55 mL (AOR, 95% CI: 5.41 [3.31, 8.86]) and $>$ 55 mL (AOR, 95% CI: 7.75 [4.65, 12.9]), compared to total blood burden $\leq$ 30 mL, were significantly associated with higher odds of poor functional outcome.

The area under the ROC curve (AUC) for the predictors of WLST (0.7943) demonstrated moderate to good discriminatory power in identifying WLST, but the Hosmer Lemeshow goodness-of-fit test indicated a poor fit (p=0.0003) (figure 3). The AUC for the predictors of poor functional recovery (mRS 4-6) at day 365 (0.8216) demonstrated good discriminatory power. The Hosmer Lemeshow goodness-of-fit test indicated a good fit (p=0.3692).

The attributed rational for WLST decisions are shown in table 3. Of the 118 patients who had WLST, dependent outcome anticipated was cited as the rationale for WLST in 73 (62%) of the 118 WLST cases in CLEAR III and MISTIE III.

Discussion

Our study demonstrated that older age, lower GCS and greater total blood burden were statistically associated with WLST. For every year increase in age, there was a four percent increase in the odds of having WLST performed. Patients with GCS of 9 to 12 were two times more likely to have WLST performed than patients with GCS of 13 to 15. Patients with GCS of 3 to 8 were four times more likely to have WLST performed than patients with GCS of 13 to 15. Patients with total blood burden of greater than 55 mL were nearly five times more likely to have WLST performed. Of the 118 patients that had WLST performed, nearly 73% had WLST performed within the first 30 days following diagnosis of ICH/IVH, with the highest number of WLST cases occurring within the first two weeks following initial presentation.

The AUC for the predictors of WLST was not as robust as the AUC for the predictors of poor functional outcome, which excluded patients who had WLST, as well as demonstrated that identifying WLST based on the demographic and clinical characteristics of poor outcome may be problematic with additional factors influencing this decision. The AUC for the predictors of poor functional recovery at one-year following ICH demonstrated good discriminatory power in identifying poor outcome in 80% of cases. However, this is challenged by the inability to accurately predict the remaining 20% of patients with ICH, resulting in considerable uncertainty in providing prognostic estimates to surrogate decision makers during the goals of care

decision-making process. Importantly, an anticipated dependent outcome was documented as the attributing rationale for WLST in 62% of WLST cases in the CLEAR III and MISTIE III trials. These findings suggest that the clinical predictors of poor outcome following ICH, first described in the late 1980s, continue to influence the decision to withdraw life-sustaining treatment in the critically ill ICH patient population.

In the late 1980s, Portenoy and colleagues identified that low GCS, intraventricular extension of hemorrhage and hematoma volume were predictive of outcome following ICH.[17] Tuhrim and colleagues added to the literature by identifying that low GCS, hemorrhage size and pulse pressure could be used to accurately identify 92% of ICH patients as alive or dead at 30 days following the ictus.[18] In the late 1990s, Broderick and colleagues described that hematoma volume, in conjunction with GCS on presentation, was a predictor of 30-day mortality and morbidity after ICH. Patients with a hematoma volume of 60 cm^3 or more and a GCS of 8 or less had a 30-day predicted mortality of 91%.[16] Diringer and colleagues added to the literature by identifying that hydrocephalus was an independent predictor of mortality after ICH.[19] These early investigations of mortality and morbidity predictors after ICH were followed by the development of outcome prediction models, with two of the most widely accepted being the ICH score[8] and Functional Outcome in Patients with Primary Intracerebral Hemorrhage (FUNC) score.[20] These ICH outcome prediction models prognosticate survival and functional outcome, and have been formulated with the implicit and unstated assumption that WLST is part of the natural history of the most severely injured ICH patients.[3,5,7] The practice of utilizing demographic and clinical predictors of morbidity and mortality in the ICH population has been challenged, and continues to be scrutinized.[3,4,21–23]

In the early 2000s, Becker and colleagues noted that preconceived notions about futility of care may lead to WLST, creating a self-fulfilling prophecy in ICH. The investigators identified that WLST was performed more frequently in patients with lower GCS and larger hematoma volumes; yet, a high proportion of patients with low GCS and larger hematoma volumes not only survived, but achieved functional independence, thus, challenging the identified clinical predictors of poor prognosis after ICH.[3] More recently, Shah and colleagues demonstrated that up to 40% of severely ill ICH and IVH patients with a poor functional outcome at

30 days were able to reach a good functional outcome at 1 year.[21] Significant recovery of patients with other forms of devastating brain injury that occurs over an extended period of time has been recently reported. Using data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) trial, McCrea and colleagues reported that 52.4% of severe traumatic brain injury patients reached a good functional outcome at one year, with 19.3% reporting no disability at this time point.[24]

Since Becker's seminal publication, investigators have also reported on the challenges associated with providing the surrogate decision makers of severely ill ICH patients with prognostic information to aid with consequential goals of care decisions. Zahuranec and colleagues demonstrated that early care limitations can independently predict mortality after ICH.[4] Additionally, the same authors advised caution when applying predictive models at the individual level.[23] Zahuranec and colleagues reported on the substantial variability in physicians' prognosis and recommendations after ICH.[25] More recently, Alkhachorum and colleagues reported on how altered level of consciousness in ICH and severe ischemic stroke is associated with an increased mortality resulting from an increased rate of WLST.[26,27]

Despite a growing body of literature demonstrating that critically ill patients with acute neurologic injury predetermined to have a poor prognosis not only survive, but achieve functional independence,[21,28] the results of this retrospective analysis suggest that reliance on early demographic and clinical characteristics may impair the ability to accurately predict future recovery for patients with ICH. Furthermore, recommendations for the management of ICH from international societies suggest the avoidance of WLST for the first 48 to 72 hours after diagnosis of ICH, but whether this professional opinion is the correct time frame has not been tested.[10,11,29]

Our study has limitations. First, goals of care decision making following ICH is multifaceted and may be impacted by cultural and religious beliefs, as well as explicitly stated patient wishes prior to the stroke. Such factors were not evaluated in this analysis. Additionally, although anticipated outcome was noted to be a medically-attributed rationale for WLST in 62% of the WLST cases in CLEAR III and MISTIE III, it is unclear how the demographic and clinical predictors investigated in this study impacted the goals of care decision-

making process. Furthermore, complications related to the hospital course were not captured in this study, and may have impacted the decision to pursue WLST. Lastly, since the rates of WLST reported in CLEAR III and MISTIE III are the result of large, randomized clinical trials, they may not be a true reflection of the current prognostication and goals of care decision-making practice in otherwise standard intensive care unit practice.

Conclusion

Our results demonstrate that ICH patients who were older, had a lower GCS score and larger hematoma volume on presentation had higher odds of having WLST performed. Of the 118 patients who had WLST, nearly 73% had WLST performed within 30 days following the diagnosis of ICH. In light of evidence dating back to the work of Becker and colleagues, which first described the "self-fulfilling prophecy" paradigm in ICH, the same clinical predictors of preconceived poor outcome appear to still influence the decision to withdraw life-sustaining treatment in the critically ill ICH/IVH patient population. While there are many factors that influence the decision to withdraw life-sustaining treatment for critically ill ICH patients, this study supports the recommendation that an examination of the practice of early prognostication of pessimistic outcomes, based on the previously established population-based demographic and clinical predictors of poor outcome, becomes a "red flag" for change. The avoidance of early pessimistic predictions may improve the ability to prognosticate recovery more accurately for ICH patients and improve shared decision making.

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Supplemental Material

Tables S1- S3

References

1. Caceres JA, Goldstein JN. Intracranial Hemorrhage. *Emerg Med Clin North Am*. 2012;30(3):771-794.

2. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo Hi, Hanley DF. Spontaneous Intracerebral Hemorrhage. *N Engl J Med*. 2001;344(19):1450-1460.

3. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology*. 2001;56:766-772.

4. Zahuranec DB, Brown DL, Lisabeth LD, et al. Early care limitations independently predict mortality after intracerebral hemorrhage. *Neurology*. 2007;68(20):1651-1657. doi:10.1212/01.wnl.0000261906.93238.72

5. Creutzfeldt CJ, Holloway RG. Treatment decisions after severe stroke: Uncertainty and Biases. *Stroke*. 2012;43(12):3405-3408. doi:10.1161/STROKEAHA.112.673376

6. Cai X, Robinson J, Muehlschlegel S, et al. Patient Preferences and Surrogate Decision Making in Neuroscience Intensive Care Units. *Neurocrit Care*. 2015;23(1):131-141. doi:10.1007/s12028-015-0149-2

7. Frontera JA, Curtis JR, Nelson JE, et al. Integrating Palliative Care Into the Care of Neurocritically Ill Patients: A Report From the Improving Palliative Care in the ICU Project Advisory Board and the Center to Advance Palliative Care. *Crit Care Med*. 2015;43:1964-1977. doi:10.1097/CCM.0000000000001131

8. Hemphill, JC, Bonovich, DC, Besmertis, L, Manley, GT, Johnston S. The ICH Score: A Simple, Reliable Grading Scale for Intracerebral Hemorrhage. *Stroke*. 2001;32:891-897.

9. Ariesen MJ, Algra A, Worp HB Van Der, Rinkel GJE. Applicability and relevance of models that predict short term outcome after intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 2005;76:839-844. doi:10.1136/jnnp.2004.048223

10. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(7):2032-2060. doi:10.1161/STR.0000000000000069

11. Souter MJ, Blissitt PA, Blosser S, et al. Recommendations for the Critical Care Management of Devastating Brain Injury: Prognostication, Psychosocial, and Ethical Management: A Position Statement for Healthcare Professionals from the Neurocritical Care Society. *Neurocrit Care*. 2015;23(1):4-13. doi:10.1007/s12028-015-0137-6

12. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014;9(7):840-855. doi:10.1111/ijs.12309

13. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet*. 2017;389(10069):603-611. doi:10.1016/S0140-6736(16)32410-2

14. Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet*. 2019;393(10175):1021-1032. doi:10.1016/S0140-6736(19)30195-3

15. Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41(9):2108-2129. doi:10.1161/STR.0b013e3181ec611b

16. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage: A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24(7):987-993. doi:10.1161/01.STR.24.7.987

17. Portenoy RK, Lipton RB, Berger AR, Lesser ML, Lantos G. Intracerebral haemorrhage: A model for the prediction of outcome. *J Neurol Neurosurg Psychiatry*. 1987;50(8):976-979. doi:10.1136/jnnp.50.8.976

18. Tuhrim S, Dambrosia JM, Price TR, et al. Prediction of intracerebral hemorrhage survival. *Ann Neurol*. 1988;24(2):258-263. doi:10.1002/ana.410240213

19. Diringer MN, Edwards DF, Zazulia AR. Hydrocephalus: A previously unrecognized predictor of poor

outcome from supratentorial intracerebral hemorrhage. *Stroke*. 1998;29(7):1352-1357. doi:10.1161/01.STR.29.7.1352

20. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: The FUNC score. *Stroke*. 2008;39(8):2304-2309. doi:10.1161/STROKEAHA.107.512202

21. Shah VA, Thompson RE, Yenokyan G, et al. One-Year Outcome Trajectories and Factors Associated with Functional Recovery among Survivors of Intracerebral and Intraventricular Hemorrhage with Initial Severe Disability. *JAMA Neurol*. 2022;79(9):856-868. doi:10.1001/jamaneurol.2022.1991

22. Morgenstern LB, Zahuranec DB, Sánchez BN, et al. Full medical support for intracerebral hemorrhage. *Neurology*. 2015;84(17):1739-1744. doi:10.1212/WNL.0000000000001525

23. Zahuranec DB, Morgenstern LB, Sánchez BN, Resnicow K, White DB, Hemphill JC. Do-not-resuscitate orders and predictive models after intracerebral hemorrhage. *Neurology*. 2010;75(7):626-633. doi:10.1212/WNL.0b013e3181ed9cc9

24. McCrea MA, Giacino JT, Barber J, et al. Functional Outcomes over the First Year after Moderate to Severe Traumatic Brain Injury in the Prospective, Longitudinal TRACK-TBI Study. *JAMA Neurol*. 2021;78(8):982-992. doi:10.1001/jamaneurol.2021.2043

25. Zahuranec DB, Fagerlin A, Sánchez BN, et al. Variability in physician prognosis and recommendations after intracerebral hemorrhage. *Neurology*. 2016;86(20):1864-1871. doi:10.1212/WNL.0000000000002676

26. Alkhachroum A, Bustillo AJ, Asdaghi N, et al. Withdrawal of life-sustaining treatment mediates mortality in patients with intracerebral hemorrhage with impaired consciousness. *Stroke*. 2021;52(12):3891-3898. doi:10.1161/STROKEAHA.121.035233

27. Alkhachroum A, Bustillo AJ, Asdaghi N, et al. Association of Acute Alteration of Consciousness in Patients With Acute Ischemic Stroke With Outcomes and Early Withdrawal of Care. *Neurology*. 2022;98(14):E1470-E1478. doi:10.1212/WNL.0000000000200018

28. Jakobsson J, Redebrandt HN, Tobieson L, et al. Long-Term Functional Outcome and Quality of Life

After Surgical Evacuation of Spontaneous Supratentorial Intracerebral Hemorrhage: Results from a Swedish Nationwide Cohort. *World Neurosurg*. 2022:351-363. doi:10.1016/j.wneu.2022.11.013

29. Wartenberg KE, Hwang DY, Haeusler KG, et al. Gap Analysis Regarding Prognostication in Neurocritical Care: A Joint Statement from the German Neurocritical Care Society and the Neurocritical Care Society. *Neurocrit Care*. 2019;31(2):231-244. doi:10.1007/s12028-019-00769-6

Tables

Table 1. Baseline characteristics of ICH patients who did not have life-sustaining treatment withdrawn and patients who had life-sustaining treatment withdrawn in the CLEAR III and MISTIE III trials.

Characteristic	**No WLST, n=861**	**WLST, n=118**	***p*-value**
	Treatment: 439 (51%), Control: 422 (49%)	Treatment: 53 (44.9%), Control: 65 (55.1%)	0.216
Age of consent (years)	60.0 (51.0, 68.0)	66.0 (57.2, 76.0)	**<0.001**
Male, sex	503 (58%)	69 (58%)	>0.9
Hispanic, ethnicity	113 (13%)	15 (13%)	>0.9
Race			**0.025**
White	576 (67%)	95 (81%)	
African-American	226 (26%)	20 (17%)	
Other	53 (6.2%)	3 (2.5%)	
Not reported	6 (0.7%)	0 (0%)	
GCS at Randomization			**<0.001**
GCS (13-15)	261 (30%)	13 (11%)	
GCS (9-12)	331 (38%)	40 (34%)	
GCS (3-8)	268 (31%)	65 (55%)	
Missing	1	0	
Deep ICH Location*	615 (71%)	73 (62%)	**0.045**
Missing	0	1	
Stability ICH Volume (mL)	25.7 (7.7, 43.7)	31.1 (10.7, 59.1)	**0.004**
Stability IVH Volume (mL)	7.5 (0.4, 21.1)	12.4 (1.5, 39.3)	**<0.001**
Stability IVH Presence	693 (80%)	105 (89%)	**0.026**
Stability Total Blood Burden (mL)	38.5 (28.5, 53.3)	57.0 (47.5, 73.2)	**<0.001**
Stability Total Blood Burden (mL) by Category			
≤ 30 mL	248 (28.8%)	11 (9.3%)	**<0.001**
> 30 to ≤ 40 mL	212 (24.6%)	6 (5.1%)	
> 40 to ≤ 55 mL	211 (24.5%)	35 (29.7%)	
> 55 mL	190 (22.1%)	66 (55.9%)	
Hyperlipidemia	241 (28%)	45 (38%)	**0.023**
Diabetes	167 (19%)	26 (22%)	0.5
Hypertension	811 (94%)	112 (95%)	0.8

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; and WLST, withdrawal of life-sustaining treatment.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

Table 2. Multivariable logistic regression model of WLST.

Covariates	**Odds Ratio (95% CI), *p*-value**
Age at consent, years	1.04 (1.02, 1.06), ***p*<0.0001**
GCS group	
GCS (13-15)	Reference
GCS (9-12)	2.16 (1.07, 4.36), ***p*=0.033**
GCS (3-8)	4.14 (2.09, 8.22), ***p*<0.0001**
Total Blood Burden (mL)	
≤ 30 mL	Reference
> 30 mL to ≤ 40 mL	0.55 (0.20, 1.55), *p*=0.261
> 40 mL to ≤ 55 mL	2.81 (1.36, 5.80), ***p*=0.005**
> 55 mL	4.72 (2.34, 9.53), ***p*<0.0001**
Deep ICH Location*	0.86 (0.55, 1.36), *p*=0.519

CI indicates Confidence Interval; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; and WLST, withdrawal of life-sustaining treatment.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

Table 3. Rationale for WLST in the CLEAR III and MISTIE III trials.

Response Option	CLEAR III (n=57)	MISTIE III (n=61)	Total (n=118)	Dependent Outcome Anticipated
	n (%)	n (%)	n (%)	n (%)
Dependent outcome anticipated	18 (32%)	18 (30%)	36 (31%)	**73 (62%)**
Dependent outcome anticipated; living will	1 (2%)	2 (3%)	3 (3%)	
Dependent outcome anticipated; prior statement by patient	13 (23%)	15 (25%)	28 (24%)	
Dependent outcome anticipated; prior statement by patient; living will	3 (5%)	3 (5%)	6 (5%)	
Living will	3 (5%)	2 (3%)	5 (4%)	
Living will; prior statement by patient	1 (2%)	0 (0%)	1 (1%)	
Prior statement by patient	14 (25%)	12 (20%)	26 (22%)	
Unknown	4 (7%)	9 (15%)	13 (11%)	

Rationale data were obtained from CLEAR III and MISTIE III case report forms.

Figures with Figure Legends

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram depicting the phases of the CLEAR III and MISTIE III trials leading to WLST vs. no WLST. CLEAR III indicates Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage; MISTIE III, Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation; and WLST, withdrawal of life-sustaining treatment.

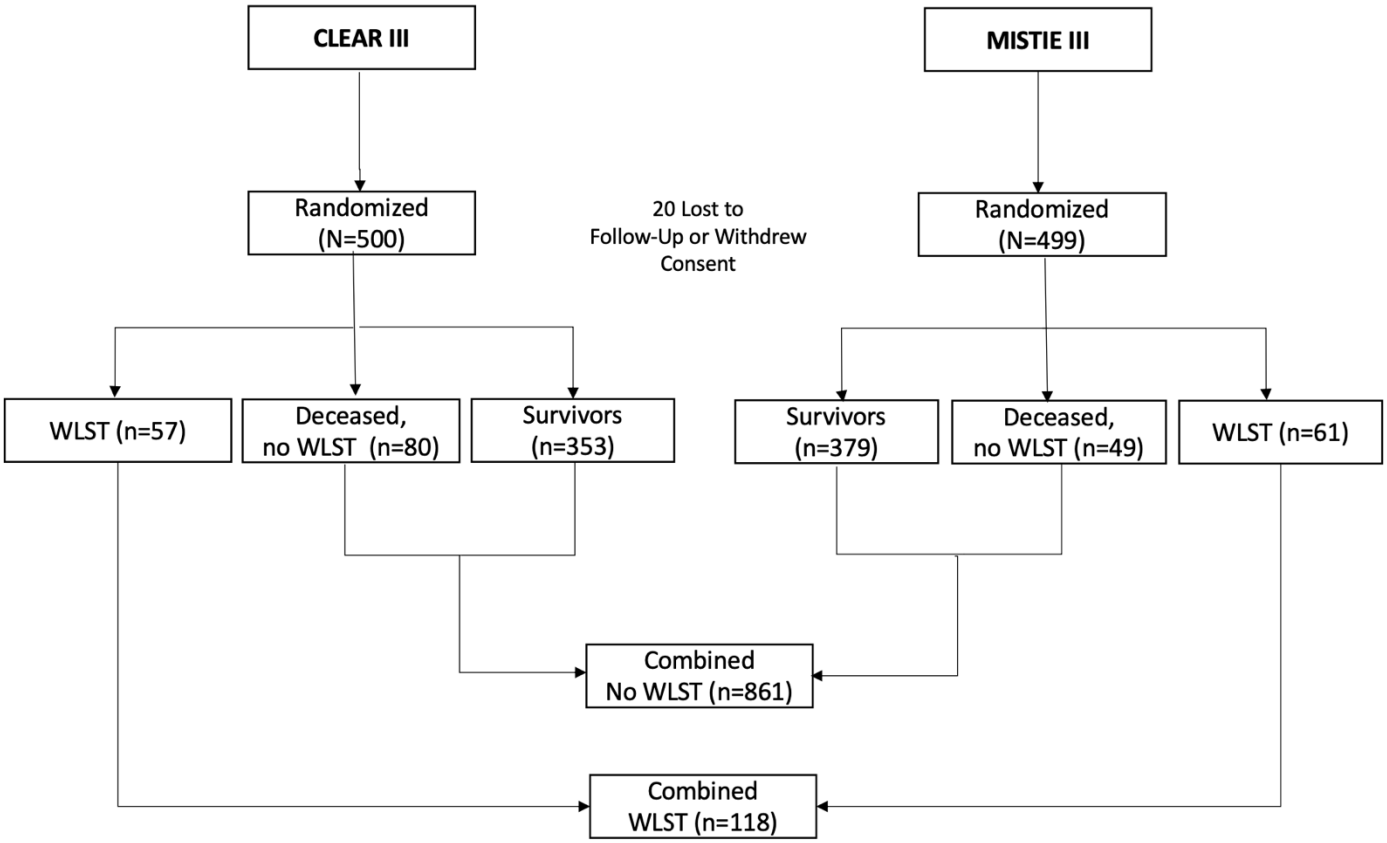

Figure 2. Number (%) of withdrawal of life-sustaining treatment cases by timepoint in the CLEAR III and MISTIE III trials. WLST indicates withdrawal of life-sustaining treatment.

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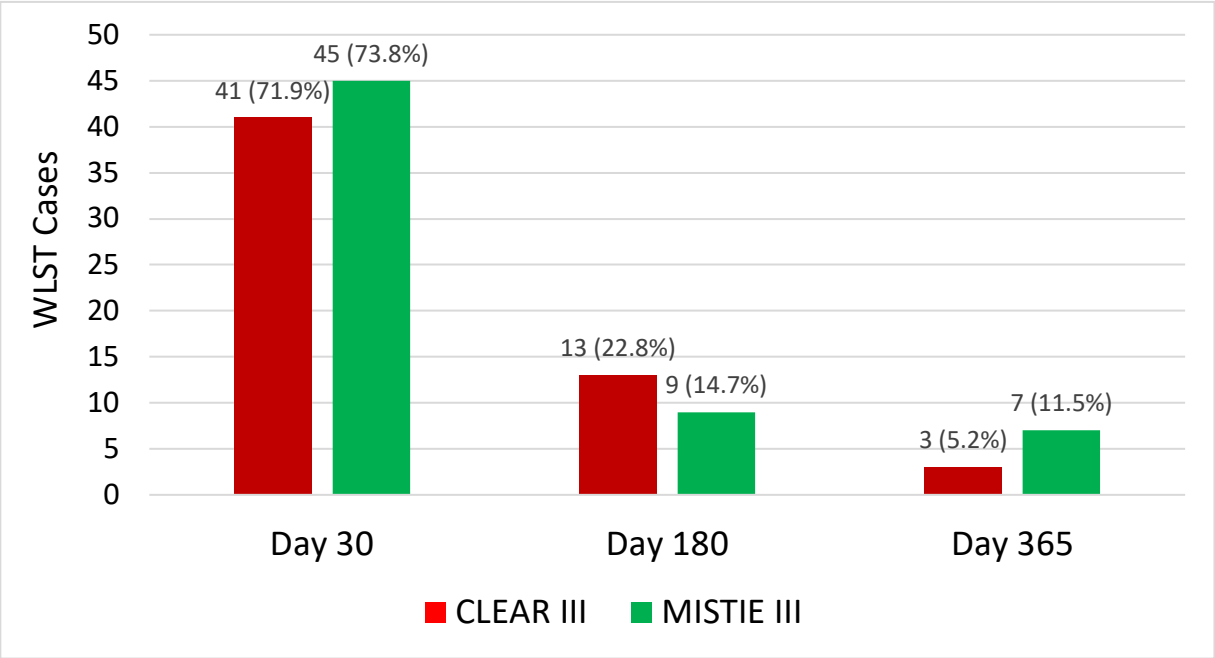
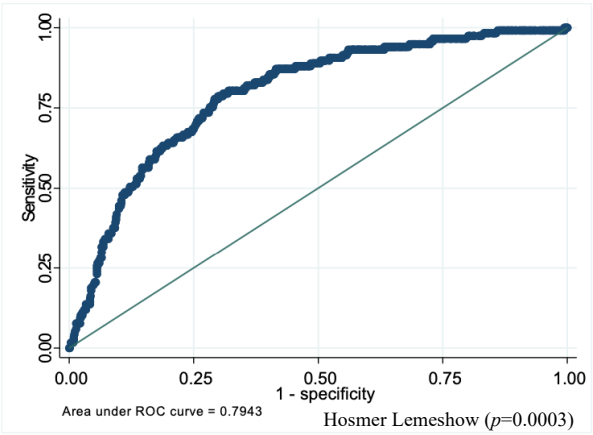
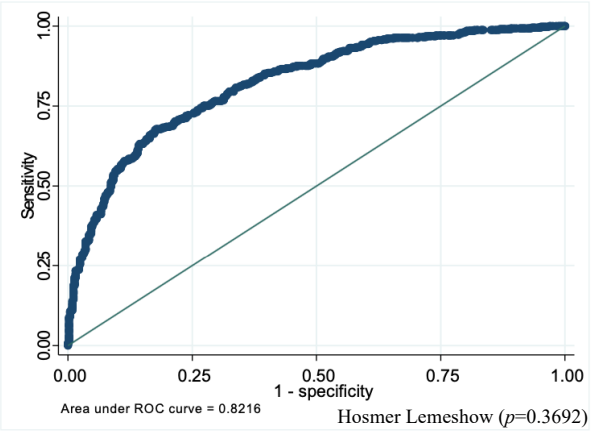


Figure 3. Receiver operating characteristic curves for the performance of the demographic and clinical factors of ICH patients to predict withdrawal of life-sustaining treatment (Model 1) and poor functional recovery (mRS 4-6) of ICH patients at day 365 (Model 2). ROC indicates receiver operating characteristic; and mRS, modified Rankin Scale.



Model 1



Model 2

Supplemental Material

Table S1. Baseline characteristics of ICH patients who died of causes other than WLST and patients who had WLST in the CLEAR III and MISTIE III trials.

Characteristic	**Deceased, No WLST n=129**	**WLST n=118**	***p*-value**
Age of consent (years)	65.0 (56.0, 73.0)	66.0 (57.2, 76.0)	0.2
Male, sex	70 (54%)	69 (58%)	0.5
Hispanic, ethnicity	17 (13%)	15 (13%)	>0.9
Race			0.2
African-American	33 (26%)	20 (17%)	
Other	4 (3.1%)	3 (2.5%)	
White	92 (71%)	95 (81%)	
GCS at Randomization			0.8
GCS 13-15	17 (13%)	13 (11%)	
GCS 9-12	46 (36%)	40 (34%)	
GCS 3-8	66 (51%)	65 (55%)	
Deep ICH Location*	102 (79%)	73 (62%)	**0.004**
Missing	0	1	
Stability IVH Presence	118 (91%)	105 (89%)	0.5
Stability Total Blood Burden (mL)	45.5 (33.2, 62.8)	57.0 (47.5, 73.2)	**<0.001**
Stability Total Blood Burden (mL) by Category			**<0.001**
≤ 30 mL	23 (18%)	11 (9.3%)	
> 30 to ≤ 40 mL	33 (26%)	6 (5.1%)	
> 40 to ≤ 55 mL	28 (22%)	35 (30%)	
> 55 mL	45 (35%)	66 (56%)	
Hyperlipidemia	40 (31%)	45 (38%)	0.2
Diabetes	38 (29%)	26 (22%)	0.2
Hypertension	122 (95%)	112 (95%)	>0.9

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; and WLST, withdrawal of life-sustaining treatment.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

Table S2. Univariate assessment of factors associated with good functional recovery (mRS 0-3) and poor functional recovery (mRS 4-6), excluding patients who had WLST.

Characteristic	**Poor mRS (4-6), n=410**	**Good mRS (0-3), n=451**	***p*-value**
Treatment group	208 (51%)	231 (51%)	0.9
Male, sex	245 (60%)	258 (57%)	0.4
Race			0.5
African-American	105 (26%)	121 (27%)	
Not reported	2 (0.5%)	4 (0.9%)	
Other	21 (5.1%)	32 (7.1%)	
White	282 (69%)	294 (65%)	
Hispanic, ethnicity	55 (13%)	58 (13%)	0.8
Age of consent (years)	63.0 (55.0, 71.0)	57.0 (48.0, 64.5)	**<0.001**
Stability ICH volume (mL)	31.6 (13.6, 48.7)	17.4 (4.7, 38.9)	**<0.001**
Stability IVH volume (mL)	8.1 (0.7, 22.1)	6.8 (0.1, 20.0)	**0.014**
Stability IVH Presence (yes)	353 (86%)	340 (75%)	**<0.001**
Stability Total Blood Burden (mL)	45.7 (34.4, 60.2)	33.4 (24.2, 45.6)	**<0.001**
Stability Total Blood Burden (group)			**<0.001**
≤ 30 mL	64 (16%)	184 (41%)	
> 30 to ≤ 40 mL	98 (24%)	114 (25%)	
> 40 to ≤ 55 mL	117 (29%)	94 (21%)	
> 55 mL	131 (32%)	59 (13%)	
GCS at Randomization	9.0 (7.0, 11.0)	11.0 (9.0, 14.0)	**<0.001**
Missing	0	1	
GCS at Randomization (group)			**<0.001**
GCS 13-15	74 (18%)	187 (42%)	
GCS 9-12	161 (39%)	170 (38%)	
GCS 3-8	175 (43%)	93 (21%)	
Missing	0	1	
Hyperlipidemia	118 (29%)	123 (27%)	0.6
Diabetes	106 (26%)	61 (14%)	**<0.001**
Hypertension	390 (95%)	421 (93%)	0.3
Deep ICH Location*	339 (83%)	276 (61%)	**<0.001**

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; and WLST, withdrawal of life-sustaining treatment.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

Table S3. Multivariable logistic regression model of poor functional recovery (mRS 4-6) at day 365.

Covariates	**Odds Ratio (95% CI), *p*-value**
Age at consent, years	1.08 (1.06, 1.09), ***p*<0.0001**
GCS group	
GCS (13-15)	Reference
GCS (9-12)	1.74 (1.16, 2.62), ***p*=0.007**
GCS (3-8)	3.80 (2.45, 5.89), ***p*<0.0001**
Total Blood Burden (mL)	
≤ 30 mL	Reference
> 30 mL to ≤ 40 mL	2.97 (1.85, 4.77), ***p*<0.0001**
> 40 mL to ≤ 55 mL	5.41 (3.31, 8.86), ***p*<0.0001**
> 55 mL	7.75 (4.65, 12.9), ***p*<0.0001**
Deep ICH Location*	7.58 (4.88, 11.8), ***p*<0.0001**

CI indicates Confidence Interval; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; and mRS, modified Rankin Scale.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

CHAPTER 3:

One Year Later: Health-Related Qualify of Life and Functional Recovery of Intracerebral Hemorrhage Survivors in CLEAR III and MISTIE III

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Keywords

Intracerebral hemorrhage, intraventricular hemorrhage, health-related quality of life, functional outcome

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Daniel F. Hanley, MD	Johns Hopkins University, Baltimore, MD	Study concept and design, analysis, interpretation of data, critical revision of the manuscript for important intellectual content, and managed study funding and personnel

Abstract

Objectives: Functional outcomes in Intracerebral Hemorrhage (ICH) have been reported, but few studies have described the long-term health-related quality of life (HRQoL) of ICH survivors, a perspective that includes domains related to physical, mental, emotional, and social functioning. Using validated data from the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) and Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III) trials, we aimed to describe the HRQoL of ICH survivors with large bleeds, including those with good functional recovery and those with severe disability over time.

Methodology: A retrospective, descriptive analysis compared the EQ-5D-3L dimensions and EQ-5D visual analog scale (EQ-VAS) of ICH survivors (n=732) enrolled in the CLEAR III and MISTIE III trials by dichotomized “good” (modified Rankin Scale [mRS] 0–3) vs. “poor” (mRS 4–5) functional outcome at days 30, 180, and 365. The EQ-5D-3L dimensions were dichotomized by "no problems" vs. "any problems" and evaluated by the percentage of participants (survivor, proxy, and unknown respondent) reporting “any problems” by mRS 0-3 vs. mRS 4-5 at days 30, 180, and 365. The proportion of ICH survivors with good vs. poor functional outcome was evaluated by timepoint.

Results: Of 732 survivors, 607 survivors or their proxies completed the EQ-5D-3L dimensions and 557 survivors had EQ-VAS data at all timepoints. At day 30, 586 (80.6%) survivors had a mRS of 4-5. By one year, 451 (61.6%) survivors had a mRS of 0-3. Survivors with mRS 0-3 and mRS 4-5 showed significant differences at days 30 (p<0.0001, p=0.001 for anxiety/depression]); 180 (p<0.0001, p=0.01 for anxiety/depression); and 365 (p<0.0001, p=0.001 for anxiety/depression) in all five EQ-5D-3L dimensions, where a significantly higher percentage of survivors with mRS 4-5 reported having “any problems” compared to survivors with mRS 0-3. Survivors with mRS 4-5 reported the highest percentage of “any problems” with mobility at days 30 (99.1%) and 365 (98.3%), usual activities (99.6%) at day 180; and the lowest percentage of “any problems” related to anxiety/depression at days 30 (55.9%), 180 (53.3%), and 365 (56.3%). Proxies of survivors with mRS 4-5 had a significantly higher percentage of those who reported “any problems” with mobility (day 30, p<0.0001; day

180, $p<0.0001$; day 365, $p<0.0001$) and self-care (day 30, $p<0.0001$; day 180, $p<0.0001$; day 365, $p<0.0001$), and with usual activities at day 180 ($p=0.024$) and day 365 ($p=0.005$), compared to proxies of survivors with mRS 0-3. The median (interquartile range [IQR]) EQ-VAS of survivors with mRS 0-3 vs. mRS 4-5 was 70 (60-80) vs. 40 (20-55) at day 30; 77 (60-90) vs. 50 (35-70) at day 180; and 80 (65-90) vs. 50 (40-70) at day 365. The median (IQR) increase for EQ-VAS between days 30 to 180 was 20 (5-40; $p<0.0001$) and 16.5 (0-35; $p<0.0001$) for days 30 to 365. Of 557 survivors with EQ-VAS available at all timepoints, at day 30, 427 (76.7%) survivors had mRS 4-5, of which 252 (59%) survivors achieved mRS 0-3 at day 365. Of these 252 survivors, the median (IQR) was 50 (30-60) at day 30, 70 (50-80) at day 180, and 73.5 (60-80) at day 365, which approached the EQ-VAS US population norm of 75 for age-matched persons.

Conclusion: HRQoL impairments vary with the level of functional recovery. Participants with poor functional outcome reported having more problems with HRQoL dimensions, specifically with mobility, than those with good functional recovery. ICH survivors with severe disability reported the lowest percentage of problems related to anxiety/depression. EQ-VAS of ICH survivors increases in the first six months, but not significantly from six months to one year. Of the survivors with severe disability in the acute phase, almost 60% achieved functional independence and reported a HRQoL state which approached the EQ-VAS US population norm.

Trial Registration: URL: https://clinicaltrials.gov/ct2/show/NCT00784134; Unique Identifier: NCT00784134; URL: https://clinicaltrials.gov/ct2/show/NCT01827046; Unique Identifier: NCT01827046

Non-Standard Abbreviations and Acronyms

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III)

Computed Tomography (CT)

EQ-5D three-level version (EQ-5D-3L)

EQ-5D visual analog scale (EQ-VAS)

External Ventricular Drain (EVD)

Glasgow Coma Scale (GCS)

Health-related Quality of Life (HRQoL)

Interquartile Range (IQR)

Intracerebral hemorrhage (ICH)

Intraventricular hemorrhage (IVH)

Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III)

modified Rankin Scale (mRS)

National Institutes of Health Stroke Scale (NIHSS)

Introduction

Intracerebral hemorrhage (ICH) is a devastating subtype of stroke leading to severe disability among survivors.[1,2] The recovery trajectory for survivors of ICH is prolonged, and the potential for a meaningful outcome is challenging to predict.[3–5] Outcomes research in ICH has focused primarily on survival and functional recovery,[3,6] with much less attention to the assessment of long-term health-related quality of life (HRQoL) of ICH survivors with varying degree of disability. HRQoL encompasses domains related to physical, mental, emotional, and social functioning.[7] Discordance between a patient's perspective of their HRQoL and objective disability has been described as the "disability paradox,"[8] and is grounded in the assumption that disability is associated with a poor HRQoL state.[9] Thus, the use of the term, "paradox," to describe this phenomena has been questioned, particularly following brain injury.[9,10] Unlike observer-based metrics of functional recovery, patient-reported outcomes, such as HRQoL measures, provide the survivors perspective on how their disability impacts their overall health state, allowing for a more holistic view of recovery after ICH.

Observational studies of outcome after ICH have primarily assessed HRQoL of ICH survivors using the EQ-5D, a generic health status questionnaire that is widely accepted and validated in stroke.[11–15] Early studies reporting on the HRQoL of ICH survivors used a 90-day timepoint to assess HRQoL post-hemorrhagic stroke.[12,13,16] Christensen and colleagues reported that the vast majority of ICH survivors had very poor HRQoL three months post-hemorrhagic stroke. Advanced age, higher baseline National Institutes of Health Stroke Scale (NIHSS) score, higher systolic blood pressure, larger hematoma volume, deep hematoma location, and neurological decline in the first 72 hours after ICH onset were independent predictors of poor HRQoL.[16] Three months post-stroke, Sallinen and colleagues reported that HRQoL was affected by stroke severity, comorbidities and age, with a stronger influence on the report of anxiety/depression with pre-stroke feelings of sadness rather than stroke severity.[13] Delcourt and colleagues reported that high NIHSS score, larger hematoma volume and proxy responders were associated with low scores in all five EQ-5D dimensions, with NIHSS score having a strong association with poor HRQoL three months post-stroke.[12]

More recently, Shah and colleagues reported on the long-term recovery trajectories after ICH. EQ-5D visual analog scale (EQ-VAS) was significantly lower in ICH survivors with poor outcome one-year post-hemorrhagic stroke. Survivors with good and poor outcome demonstrated a significant upward trend in self-reported EQ-VAS. Of the survivors with severe disability in the acute phase after ICH, more than 40% of the survivors achieved a good functional outcome at one year.[14] Jakobsson and colleagues found that self-reported HRQoL correlated with functional outcome. Nearly half of the ICH survivors had a good neurologic outcome. Older age and large hematoma volume correlated with a poor functional outcome.[15]

Using validated trial data from Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) and Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III), we sought to describe the HRQoL state of survivors with good functional recovery and those with severe disability over the course of one year following ICH. Where available, we compared proxy responses to survivor responses.

Methods

Data Source

Data for this retrospective analysis was obtained from the CLEAR III[17] and MISTIE III[18] trials. In brief, CLEAR III was a randomized, double-blinded, prospective phase 3 trial of the combination of external ventricular drain placement (EVD) and low dose alteplase for clearance of IVH, performed at 73 hospitals in the USA, Canada, Europe, South America and Asia. Eligibility criteria included the following: age 18 to 80 years with a diagnosis of IVH; obstructive hydrocephalus; known symptom onset within 24 hours of the initial, diagnostic computed tomography (CT); and spontaneous, supratentorial ICH of ≤ 30 mL with demonstrated stability (hematoma growth of < 5 mL) on CT scan at least 6 hours after EVD placement, and a pre-morbid modified Rankin Scale (mRS) of 1 or less.[17]

Briefly, MISTIE III was a randomized, controlled, open-label, blinded endpoint, phase 3 explanatory trial of image-guided, catheter-based removal plus fibrinolysis of ICH of ≥ 30 mL, performed at 78 hospitals in the USA, Canada, Europe, Australia, and Asia. Eligibility criteria included the following: age 18 years of age or older with a diagnosis of spontaneous, non-traumatic, supratentorial ICH of ≥ 30 mL due to cerebral small-vessel disease; GCS score of ≤ 14 or National Institutes of Health Stroke Scale (NIHSS) score of 6 or higher; a pre-morbid mRS score of 0 or 1; and an ICH that demonstrated stability (hematoma growth of < 5 mL) for at least 6 hours after diagnostic CT scan.[18]

All participants were medically managed in concordance with the CLEAR III protocol[17] and MISTIE III protocol,[18] both of which followed the American Heart Association guidelines for the treatment of spontaneous ICH.[19]

Health-related Quality of Life

HRQoL was assessed using the EQ-5D instrument in the CLEAR III and MISTIE III trials at days 30, 180, and 365. The EQ-5D three-level version (EQ-5D-3L) was introduced in 1990 by the EuroQol Group,[20] and includes the short descriptive system (EQ-5D-3L) and the EQ-5D visual analog scale (EQ-VAS).[21] The EQ-5D-3L descriptive system is comprised of five dimensions, each assessing a health state: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression.[21] The dimensions were assessed on three levels: no problems, some problems, and extreme problems. Respondents were asked to check the most appropriate response to each of the five dimensions. Proxies of survivors were permitted to respond to the EQ-5D-3L dimensions in the CLEAR III and MISTIE III trials.

The EQ-VAS is a quantitative measure of health outcome and allows for respondents to self-report their health state on a vertical visual analog scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).[21] Respondents were instructed to mark their current health state on the EQ-VAS.

Proxies were not permitted to complete the EQ-VAS on the behalf of the patient in the CLEAR III and MISTIE III trials.

Statistical Analysis

A retrospective, descriptive analysis of ICH survivors (n=732) enrolled in the CLEAR III and MISTIE III trials was performed, and compared the EQ-5D-3L dimensions and EQ-VAS by dichotomized "good" (mRS 0–3) vs. "poor" (mRS 4–5) functional outcome at days 30, 180, and 365. The EQ-5D-3L dimension responses were dichotomized by "no problems" vs. "any problems."[21] The percentage of participants (survivor, proxy, and unknown respondent) reporting "no problems" vs. "any problems" by mRS was evaluated at days 30, 180, and 365. Functional outcome of the survivors was evaluated by dichotomized mRS 0-3 vs. 4-5 at days 30, 180, and 365.

Statistical analyses were performed using Stata (version 16.0, College Station, TX) and R (version 4.0.2, R Project for Statistical Computing). All analyses were two-tailed, and significance level was determined by $p<0.05$.

Standard Protocol Approvals, Registrations, and Patient Consents

The individual clinical trial sites in the CLEAR III and MISTIE III trials obtained institutional review board or ethics committee approval from their respective institutions.[17,18] This retrospective study was approved by the Johns Hopkins Medicine Institutional Review Board. CLEAR III and MISTIE III are registered with ClinicalTrials.gov, NCT00784134 and NCT01827046. All participants, or when applicable, their legal representatives or surrogates, provided written informed consent for participation in the CLEAR III and MISTIE III trials.

Data Availability Statement

Data from the CLEAR III and MISTIE III trials, including de-identified participant data, are available at the National Institute of Neurological Disorders and Stroke (NINDS) data archive

(https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets). Those seeking access must complete a NINDS data request form and receive approval.

Results

Of the 732 survivors in CLEAR III and MISTIE III, 607 survivors or their proxies provided responses to the EQ-5D-3L dimensions and 557 survivors had EQ-VAS data available at days 30, 180, and 365 (figure 1). Preliminary analyses demonstrated no significant difference between the study populations in CLEAR III and MISTIE III. The baseline demographic and clinical characteristics of the ICH survivors (n=732) are shown in table 1.

Functional Outcome

Figure 2 shows the proportion of survivors by dichotomized mRS 0-3 vs. mRS 4-5 and timepoint. Of 732 survivors, mRS was missing for 5 survivors at day 30 and 2 survivors at day 180. Of 727 survivors at day 30, 141 (19.4%) had a mRS of 0-3 vs. 586 (80.6%) had a mRS of 4-5. Of 730 survivors at day 180, 411 (56.3%) had a mRS of 0-3 vs. 319 (43.7%) had a mRS of 4-5. Of 732 survivors at day 365, 451 (61.6%) had a mRS of 0-3 vs. 281 (38.4%) had a mRS of 4-5.

EQ-5D-3L Dimensions

Figure 3/table S1 shows the EQ-5D-3L dimensions by percentage of participant responses (survivors, proxies and unknown respondents) to “any problems” by mRS 0-3 vs. mRS 4-5 and timepoint. Both mRS groups showed significant differences at day 30 ($p<0.0001$), day 180 ($p<0.0001$), and day 365 ($p<0.0001$), in all five EQ-5D-3L dimensions, where a significantly higher percentage of participants in the mRS 4-5 group reported having “any problems” compared to participants in the mRS 0-3 group.

Figure 4/table S2 shows the EQ-5D-3L dimensions by percentage of responses to “any problems” by mRS group (0-3) vs. (4-5), by respondent (survivor, proxy or unknown respondent), and timepoint. Survivors in both mRS groups showed significant differences at day 30 ($p<0.0001$, $p=0.001$ [anxiety/depression]), day 180

(p<0.0001, p=0.01 [anxiety/depression]), and day 365 (p<0.0001, p=0.001 [anxiety/depression]) in all five EQ-5D-3L dimensions, where a significantly higher percentage of survivors with mRS 4-5 reported having "any problems" compared to survivors with mRS 0-3. Survivors with mRS 0-3 reported the highest percentage of "any problems" with usual activities at day 30 (71.4%), day 180 (69.1%), and day 365 (64.5%), and the lowest percentage of "any problems" related to self-care at day 30 (32.8%), day 180 (29.6%), and day 365 (29.0%). Survivors with mRS 4-5 reported the highest percentage of "any problems" with mobility at day 30 (99.1%) and day 365 (98.3%), and usual activities (99.3%) at day 180. Survivors with mRS 4-5 reported the lowest percentage of "any problems" related to anxiety/depression at day 30 (55.9%), day 180 (56.3%), and day 365 (56.3%).

Proxies of survivors with mRS 4-5 had a significantly higher percentage of those who reported "any problems" with mobility (day 30, p<0.0001; day 180, p<0.0001; day 365, p<0.0001) and self-care (day 30, p<0.0001; day 180, p<0.0001; day 365, p<0.0001), and with usual activities at day 180 (p=0.024) and day 365 (p=0.005), compared to proxies of survivors with mRS 0-3. No significant difference was demonstrated among the proxies of both mRS groups in the EQ-5D-3L dimensions of usual activities at day 30 and anxiety/depression at all timepoints (figure 4/table S2). The EQ-5D-3L dimension respondent was unknown in 28 (4.6%) cases at day 30, 33 (5.4%) at day 180, and 26 (4.3%) at day 365.

A sensitivity analysis of the demographic and clinical characteristics of participants with EQ-5D-3L dimension data available at no timepoint, at least one timepoint and all timepoints is shown in table S3. A higher percentage of participants who had EQ-5D-3L dimension data available at all timepoints were white, had lower total blood burden, higher Glasgow Coma Scale (GCS), and higher rates of hyperlipidemia.

EQ-VAS

Figure 5 shows the median EQ-VAS of survivors by mRS 0-3 vs. mRS 4-5 and timepoint. Using the EQ-VAS (n=557) of survivors available at days 30, 180, and 365, the median (IQR) EQ-VAS of survivors with mRS 0-3 vs. mRS 4-5 was 70 (60-80) vs. 40 (20-55) at day 30; 77 (60-90) vs. 50 (35-70) at day 180; and 80

(65-90) vs. 50 (40-70) at day 365 (figure 5). The median increase for EQ-VAS between days 30 and 180 was 20 (5-40; $p<0.0001$), and 16.5 (0-35; $p<0.0001$) for days 30 to 365. Of 557 survivors with EQ-VAS available at all timepoints: 427 (76.7%) had mRS 4-5 at day 30, of which 252 (59%) survivors achieved mRS 0-3 at day 365. Of these 252 survivors, the median (IQR) was 50 (30-60) at day 30, 70 (50-80) at day 180, and 73.5 (60-80) at day 365, which approached the US population norm of 75 for age-matched persons (figure 6).[22]

The median self-reported EQ-VAS of survivors with EQ-VAS and mRS data available at any timepoint vs. those with data available at all timepoints is shown in figure S1. The median EQ-VAS of both survivor groups was nearly equal. A sensitivity analysis of the demographic and clinical characteristics of participants with EQ-VAS data available at no timepoint, at least one timepoint and all timepoints is shown in table S4. A higher percentage of participants who had EQ-VAS data available at all timepoints had lower IVH volume, lower total blood burden, higher GCS, and higher rates of hyperlipidemia.

Discussion

The findings of this retrospective, descriptive study demonstrate that the HRQoL of ICH survivors varies across the spectrum of functional recovery. Participants with poor functional outcome reported having more problems with HRQoL dimensions, specifically with mobility, than those with good functional recovery. ICH survivors with severe disability reported the lowest percentage of problems with anxiety/depression. For the survivors with good functional recovery, the highest percentage of problems reported was related to usual activities for all timepoints, with the lowest percentage of problems reported with self-care. EQ-VAS of the survivors increased within the first six months, but not significantly beyond six months to one year. Of the survivors with severe disability in the acute phase, almost 60% achieved functional independence and reported EQ-VAS that approached the EQ-VAS US population norm by one year.

Our results are consistent with recent literature reporting long-term HRQoL after ICH. Similar to the findings of Shah and colleagues,[14] our results suggest that HRQoL varies by level of functional recovery and EQ-VAS increases from the acute phase to the first six months, but not significantly beyond six months to one

year. Consistent with the findings of Jakobsson and colleagues,[15] we describe a similar pattern in survivor EQ-5D-3L dimension responses with the highest percentage of problems reported with mobility and usual activities, and the lowest percentage of problems with anxiety/depression and pain. Additionally, our study demonstrated that a significant percentage of ICH survivors achieved functional independence at one year, which is consistent with prior studies of functional recovery over time.[14,15]

Our study has several limitations. Proxy responses were limited and were not compared to all survivor responses in this analysis. Although some studies support the use of proxy responses for the EQ-5D-3L dimensions after stroke,[23,24] it has been reported that patient and proxy agreement is higher for more observable dimensions, such as mobility, and lower for less observable dimensions, such as psychosocial health, with proxy respondents having a tendency to provide more pessimistic views of HRQoL than patients.[23–27] Additionally, proxy responses were not case-matched to survivor responses, which limits the comparability of survivor and proxy observations. Lastly, to identify patterns of HRQoL states over time, we analyzed the data of survivors and their proxies with available EQ-5D data and mRS at all timepoints, thus, eliminating those without available data at all timepoints. Understanding that this may bias the sample of those able to report their HRQoL health state, we compared the median self-reported EQ-VAS of survivors with EQ-VAS and mRS data available at any timepoint versus those with data available at all timepoints. The median EQ-VAS of both survivor groups was nearly equal, as shown in figure SI.

Conclusion

Only a few studies have evaluated the long-term HRQoL of ICH survivors and long-term outcomes of ICH survivors with large hematoma volumes is limited.[12,14–16] Functional recovery continues to serve as the primary endpoint for clinical trials in ICH. Intervention studies for ICH should consider including patient-reported outcomes, such as HRQoL, to incorporate the patient's perspective of their health state, in addition to an observer's view of functional recovery. A patient-centered approach will provide investigators with a highly-detailed and precise understanding of the effects of investigational interventions and treatments on patients,

defined by meaningful therapeutic goals and decisions. Furthermore, future research is needed to identify the HRQoL trajectory of ICH survivors, and how coping and adaptation to a new disability state changes an individual's perspective of their health state over time.

Acknowledgements

We would like to acknowledge the patients, families and investigative teams, all of whom made CLEAR III and MISTIE III possible. NINDS program officials Scott Janis, PhD and Claudia Moy, PhD provided critical initial guidance regarding long-term outcomes and HRQoL during planning and substantial support during execution of the MISTIE III trial.

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Disclosures

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Supplemental Material

Tables S1-S4

Figure S1

References

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet*. 2009;373:1632-1644.

2. Caceres JA, Goldstein JN. Intracranial Hemorrhage. *Emerg Med Clin North Am*. 2012;30(3):771-794.

3. Frontera JA, Curtis JR, Nelson JE, et al. Integrating Palliative Care Into the Care of Neurocritically Ill Patients: A Report From the Improving Palliative Care in the ICU Project Advisory Board and the Center to Advance Palliative Care. *Crit Care Med*. 2015;43:1964-1977. doi:10.1097/CCM.0000000000001131

4. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology*. 2001;56:766-772.

5. Creutzfeldt CJ, Holloway RG. Treatment decisions after severe stroke: Uncertainty and Biases. *Stroke*. 2012;43(12):3405-3408. doi:10.1161/STROKEAHA.112.673376

6. Zahuranec DB, Morgenstern LB, Sánchez BN, Resnicow K, White DB, Hemphill JC. Do-not-resuscitate orders and predictive models after intracerebral hemorrhage. *Neurology*. 2010;75(7):626-633. doi:10.1212/WNL.0b013e3181ed9cc9

7. Wilson, Ira B. and and Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. *Jama*. 1995;273(1):59-65.

8. Albrecht GL, Devlieger PJ. The Disability Paradox: Highly Qualified of Life against All Odds. *Soc Sci Med*. 1999;48:977-988. doi:10.1016/S0277-9536(98)00411-0

9. Koch T. The illusion of paradox: Commentary on Albrecht, G.L. and Devlieger, P.J. (1998). The disability paradox: High quality of life against all odds. Social Science and Medicine 48, 977-988 (multiple letters) [1]. *Soc Sci Med*. 2000;50(6):757-759. doi:10.1016/S0277-9536(99)00385-8

10. Retel Helmrich IRA, Van Klaveren D, Andelic N, et al. Discrepancy between disability and reported well-being after traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2022;93(7):785-796. doi:10.1136/jnnp-2021-326615

11. Golicki D, Niewada M, Buczek J, et al. Validity of EQ-5D-5L in stroke. *Qual Life Res*. 2015;24(4):845-850. doi:10.1007/s11136-014-0834-1

12. Delcourt C, Zheng D, Chen X, et al. Associations with health-related quality of life after intracerebral haemorrhage: Pooled analysis of INTERACT studies. *J Neurol Neurosurg Psychiatry*. 2017;88(1):70-75. doi:10.1136/jnnp-2016-314414

13. Sallinen H, Sairanen T, Strbian D. Quality of life and depression 3 months after intracerebral hemorrhage. *Brain Behav*. 2019;9(5):1-10. doi:10.1002/brb3.1270

14. Shah VA, Thompson RE, Yenokyan G, et al. One-Year Outcome Trajectories and Factors Associated with Functional Recovery among Survivors of Intracerebral and Intraventricular Hemorrhage with Initial Severe Disability. *JAMA Neurol*. 2022;79(9):856-868. doi:10.1001/jamaneurol.2022.1991

15. Jakobsson J, Redebrandt HN, Tobieson L, et al. Long-Term Functional Outcome and Quality of Life After Surgical Evacuation of Spontaneous Supratentorial Intracerebral Hemorrhage: Results from a Swedish Nationwide Cohort. *World Neurosurg*. 2022:351-363. doi:10.1016/j.wneu.2022.11.013

16. Christensen MC, Mayer S, Ferran JM. Quality of life after intracerebral hemorrhage: results of the factor seven for acute hemorrhagic stroke (FAST) trial. *Stroke*. 2009;40(5):1677-1682. doi:10.1161/STROKEAHA.108.538967

17. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet*. 2017;389(10069):603-611. doi:10.1016/S0140-6736(16)32410-2

18. Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet*. 2019;393(10175):1021-1032. doi:10.1016/S0140-6736(19)30195-3

19. Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the management of spontaneous

intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41(9):2108-2129. doi:10.1161/STR.0b013e3181ec611b

20. Group TE. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy (New York)*. 1990;16(3):199-208. doi:10.1016/0168-8510(90)90421-9

21. Devlin N, Parkin D, Janssen B. *Methods for Analysing and Reporting EQ-5D Data*. Springer Nature; 2020. doi:10.1007/978-3-030-47622-9

22. Janssen MF, Szende A, Cabases J, Ramos-Goñi JM, Vilagut G, König HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. *Eur J Heal Econ*. 2019;20(2):205-216. doi:10.1007/s10198-018-0955-5

23. Dorman PJ, Waddell F, Slattery JM, Dennis M, Sandercock PA for the UKC in the IST. Are proxy assessments of health status after stroke with the EuroQol ques- tionnaire feasible, accurate, and unbiased? *Stroke*. 1997;28:1883–1887.

24. Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between Patient and Proxy Assessments of Health-Related Quality of Life after Stroke Using the EQ-5D and Health Utilities Index. *Stroke*. 2004;35(2):607-612. doi:10.1161/01.STR.0000110984.91157.BD

25. Slaughter KB, Meyer EG, Bambhroliya AB, et al. Direct Assessment of Health Utilities Using the Standard Gamble among Patients with Primary Intracerebral Hemorrhage. *Circ Cardiovasc Qual Outcomes*. 2019;12(9):1-10. doi:10.1161/CIRCOUTCOMES.119.005606

26. Sneeuw KCA, Aaronson NK, de Haan RJ LM. Assessing the quality of life after stroke: the value and limitations of proxy ratings. *Stroke*. 1997;28:1541–1549.

27. Hwang HF, Chen CY, Lin MR. Patient-Proxy Agreement on the Health-Related Quality of Life One Year After Traumatic Brain Injury. *Arch Phys Med Rehabil*. 2017;98(12):2540-2547. doi:10.1016/j.apmr.2017.05.013

Tables

Table 1. Demographic and clinical characteristics of ICH survivors enrolled in CLEAR III and MISTIE III.

Characteristic	Survivors (n=732)
Age of consent (years)	59.0 (50.0, 67.0)
Male, sex	433 (59%)
Race	
African-American	193 (26%)
Not reported	6 (0.8%)
Other	49 (6.7%)
White	484 (66%)
Hispanic, ethnicity	96 (13%)
Stability ICH clot volume (mL)	27.2 (7.9, 43.6)
Stability IVH clot volume (mL)	6.0 (0.2, 19.8)
Stability IVH presence	575 (79%)
Stability Total Blood Burden (mL)	37.7 (28.0, 51.9)
Stability Total Blood Burden (mL) group	
≤ 30 mL	225 (31%)
> 30 to ≤ 40 mL	179 (24%)
> 40 to ≤ 55 mL	183 (25%)
> 55 mL	145 (20%)
GCS at randomization	10.0 (8.0, 13.0), n=731
GCS at randomization (group)	n=731
GCS (13-15)	244 (33%)
GCS (9-12)	285 (39%)
GCS (3-8)	202 (28%)
Hyperlipidemia	201 (27%)
Diabetes	129 (18%)
Hypertension	689 (94%)
Deep ICH Location*	513 (70%)

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; and IVH, intraventricular hemorrhage

*Deep ICH location is defined as involvement of thalami or basal ganglia.

Figures with Figure Legends

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram depicting the phases of the CLEAR III and MISTIE III trials through data collection of the EQ-5D-3L dimensions and EQ-VAS. EQ-5D-3L indicates EQ-5D three-level version; and EQ-VAS, EQ-5D Visual Analog Scale.

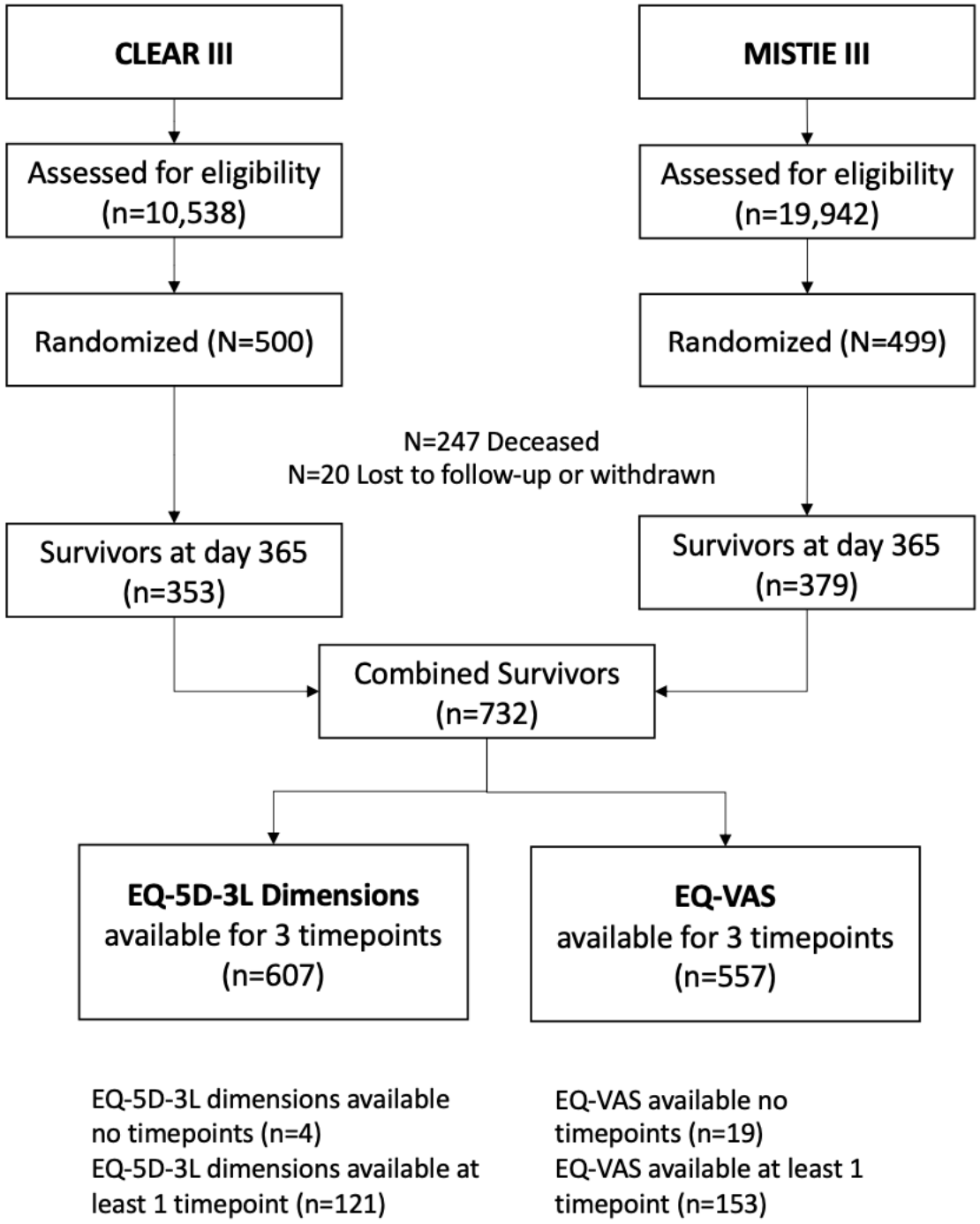


Figure 2. Number of survivors by dichotomized mRS 0-3 vs. mRS 4-5 over time. mRS indicates modified Rankin Scale.

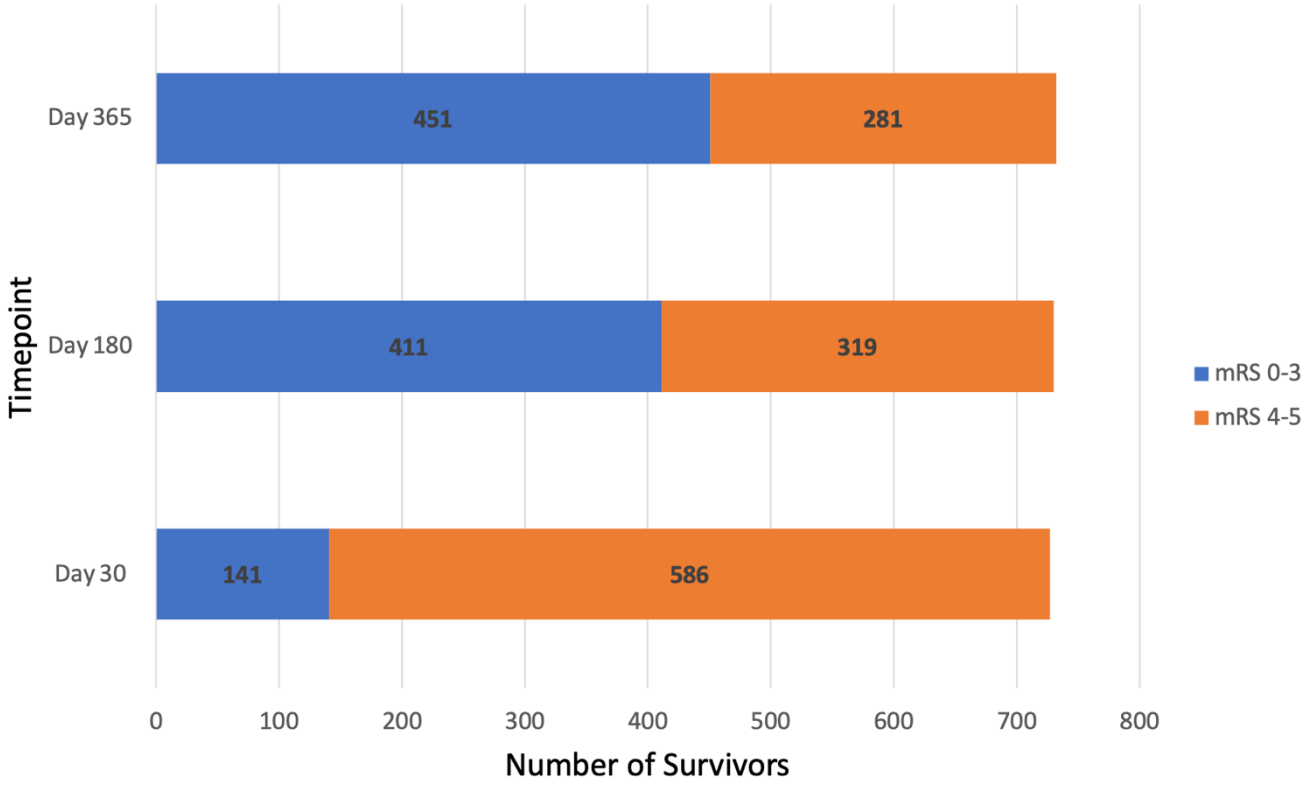


Figure 3. Percentage of participants reporting “any problems” with the EQ-5D-3L dimensions by dichotomized mRS 0-3 vs. mRS 4-5 and timepoint. mRS indicates modified Rankin Scale.

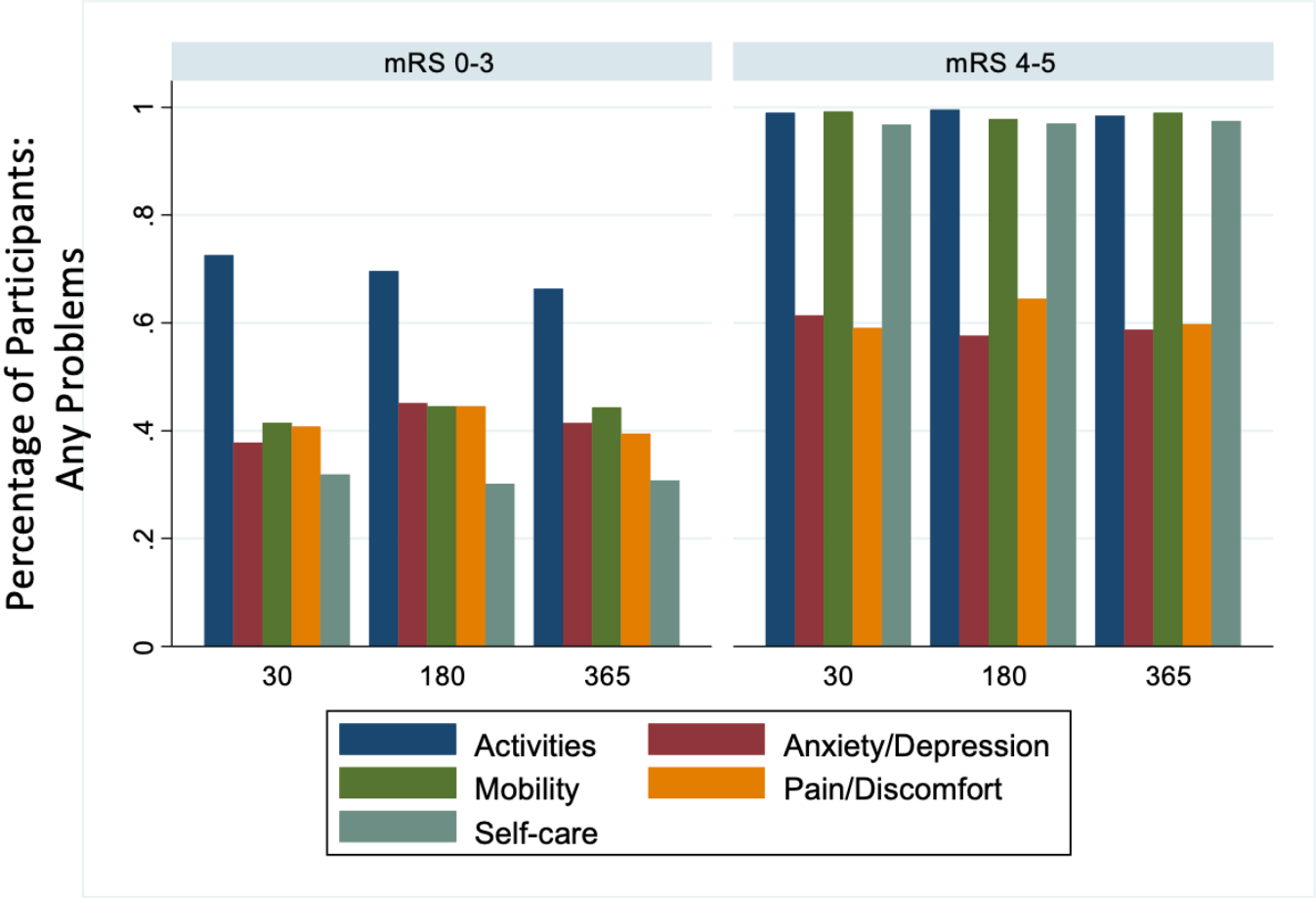


Figure 4. Percentage of unknown respondents, survivors and proxies reporting “any problems” with the EQ-5D-3L dimensions by dichotomized mRS 0-3 vs. mRS 4-5 and timepoint. EQ-5D-3L indicates EQ-5D three-level version; and mRS, modified Rankin Scale.

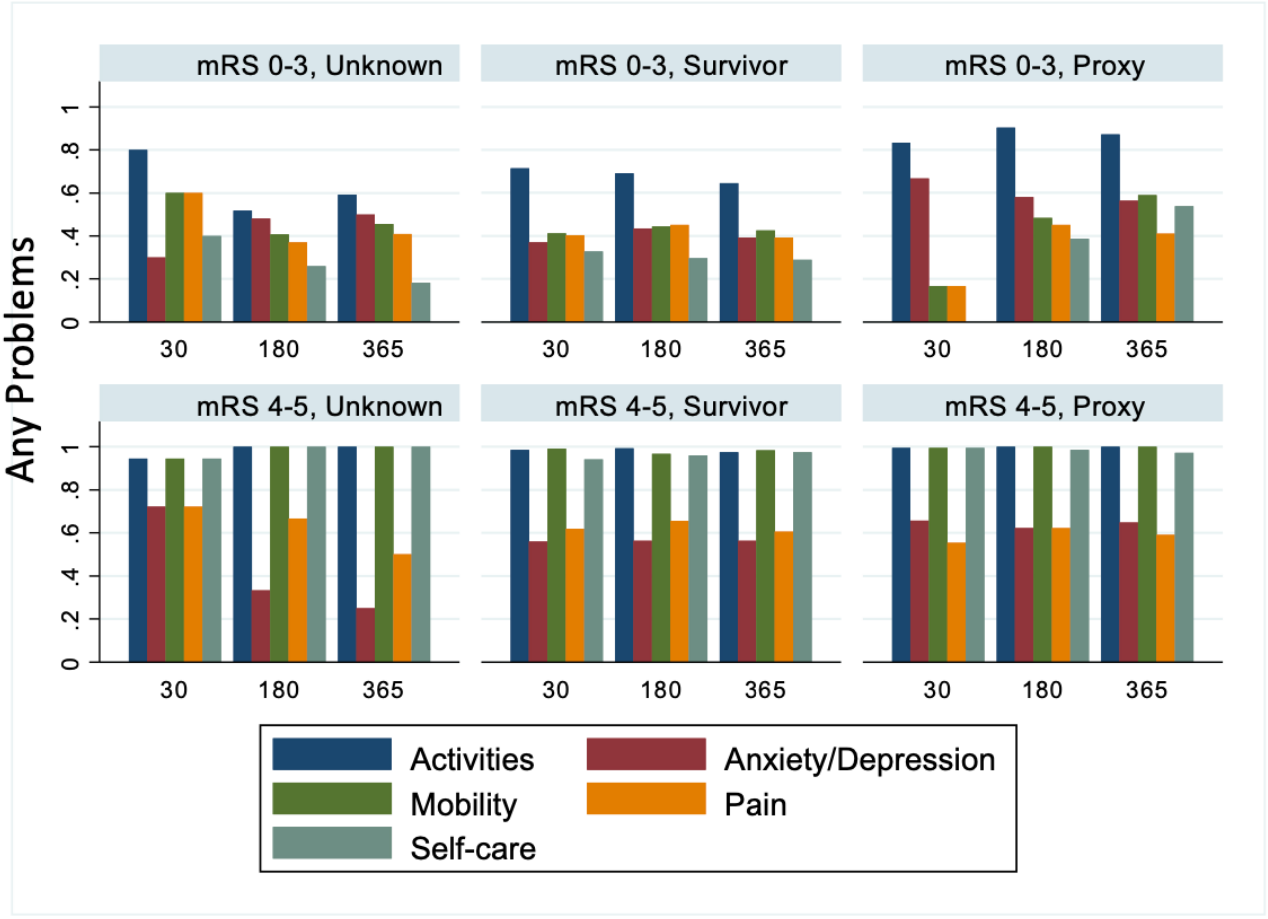


Figure 5. EQ-VAS by mRS 0-3 vs. mRS 4-5 and timepoint. EQ-VAS indicates EQ-5D Visual Analog Scale; and mRS, modified Rankin Scale.

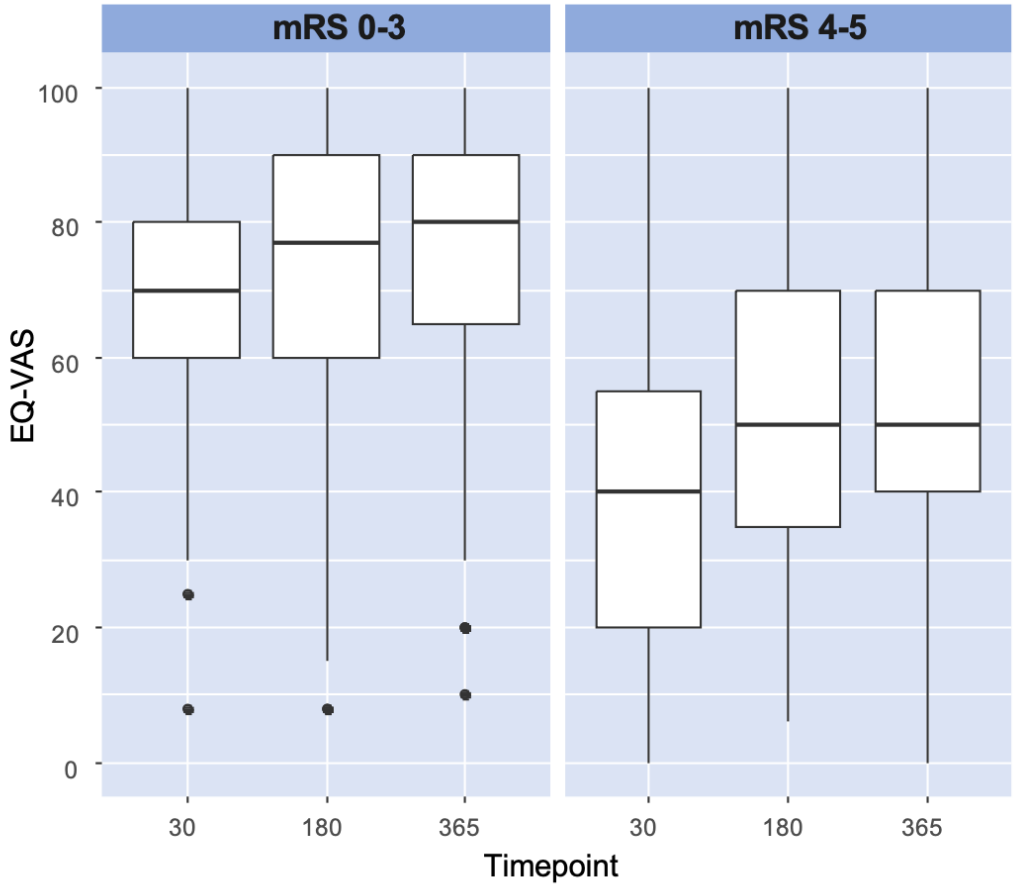
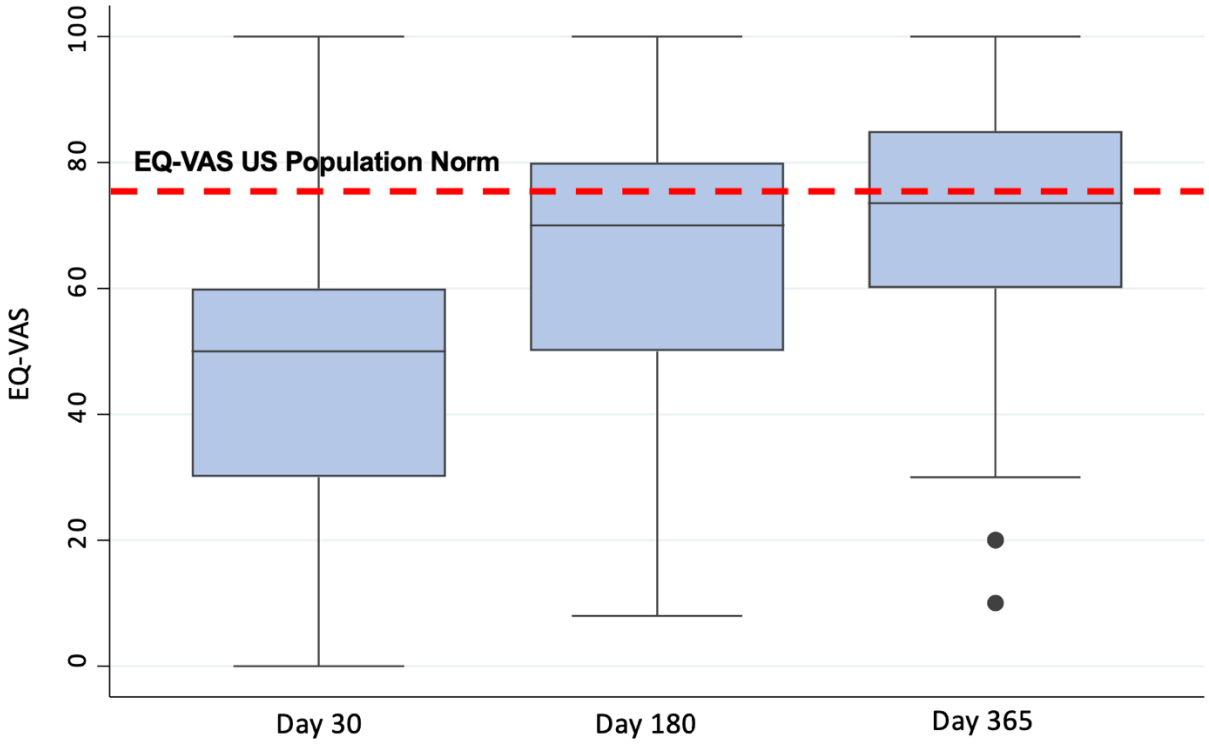


Figure 6. EQ-VAS of survivors (n=252) with mRS 4-5 at day 30 who achieved mRS 0-3 by day 365. EQ-VAS indicates EQ-5D Visual Analog Scale; and mRS, modified Rankin Scale.



Supplemental Material

Tables

Table S1. EQ-5D-3L dimensions by mRS 0-3 vs. mRS 4-5 over time.

	Day 30			**Day 180**			**Day 365**		
	mRS 0-3	mRS 4-5		mRS 0-3	mRS 4-5		mRS 0-3	mRS 4-5	
n	135	471		375	231		413	194	
	Any Problems (%)		*p*-value	Any Problems (%)		*p*-value	Any Problems (%)		*p*-value
Usual Activities	72.6%	98.9%	**<0.0001**	69.6%	99.6%	**<0.0001**	66.3%	98.5%	**<0.0001**
Anxiety/Depression	37.8%	61.4%	**<0.0001**	45.1%	57.6%	**0.003**	41.4%	58.8%	**<0.0001**
Mobility	41.5%	99.2%	**<0.0001**	45.1%	97.8%	**<0.0001**	44.3%	99.0%	**<0.0001**
Pain	40.7%	59.0%	**<0.0001**	44.5%	97.8%	**<0.0001**	39.5%	59.8%	**<0.0001**
Self-care	31.9%	96.8%	**<0.0001**	30.1%	97.0%	**<0.0001**	30.8%	97.4%	**<0.0001**

mRS indicates modified Rankin Scale.

Table S2. EQ-5D-3L dimensions by respondent and mRS 0-3 vs. mRS 4-5 over time.

	Day 30			**Day 180**			**Day 365**		
mRS Group	**mRS 0-3**	**mRS 4-5**	***p*-value**	**mRS 0-3**	**mRS 4-5**	***p*-value**	**mRS 0-3**	**mRS 4-5**	***p*-value**
Survivor Respondent									
	Any Problems (%)			Any Problems (%)			Any Problems (%)		
N	119	220	*p* value	317	317	*p* value	352	119	*p* value
Usual Activities	71.4%	98.6%	**<0.0001**	69.1%	99.3%	**<0.0001**	64.5%	97.5%	**<0.0001**
Anxiety/Depression	37.0%	55.9%	**0.001**	43.5%	56.3%	**0.01**	39.2%	56.3%	**0.001**
Mobility	41.2%	99.1%	**<0.0001**	44.5%	96.7%	**<0.0001**	42.6%	98.3%	**<0.0001**
Pain	40.3%	61.8%	**<0.0001**	45.1%	65.6%	**<0.0001**	39.2%	60.5%	**<0.0001**
Self-care	32.8%	94.1%	**<0.0001**	29.6%	96.0%	**<0.0001**	29.0%	97.5%	**<0.0001**
Proxy Respondent									
	Any Problems (%)			Any Problems (%)			Any Problems (%)		
N	6	233	*p* value	31	74	*p* value	39	71	*p* value
Usual Activities	83.3%	99.6%	0.05	90.3%	100.0%	**0.024**	87.2%	100.0%	**0.005**
Anxiety/Depression	66.7%	65.7%	>0.9	58.1%	62.3%	0.695	56.4%	64.8%	0.387
Mobility	16.7%	99.6%	**<0.0001**	48.4%	100.0%	**<0.0001**	59.0%	100.0%	**<0.0001**
Pain	16.7%	55.4%	0.095	45.2%	62.2%	0.108	41.0%	59.2%	0.068
Self-care	0.0%	99.6%	**<0.0001**	38.7%	98.6%	**<0.0001**	53.8%	97.2%	**<0.0001**
Unknown Respondent									
	Any Problems (%)			Any Problems (%)			Any Problems (%)		
N	10	18	*p* value	27	6	*p* value	22	4	*p* value
Usual Activities	80.0%	94.4%	0.284	51.9%	100.0%	0.060	59.0%	100.0%	0.263
Anxiety/Depression	30.0%	72.2%	0.05	48.1%	33.3%	0.665	50.0%	25.0%	0.598
Mobility	60.0%	94.4%	**0.023**	40.7%	100.0%	**0.018**	45.5%	100.0%	0.100
Pain	60.0%	72.2%	0.677	37.0%	66.7%	0.363	40.9%	50.0%	0.735
Self-care	40.0%	94.4%	**0.003**	25.9%	100.0%	**0.002**	18.2%	100.0%	**0.005**

mRS indicates modified Rankin Scale.

Table S3. Sensitivity analysis of the demographic and clinical characteristics of participants with EQ-5D-3L dimensions available at no timepoints, at least one timepoint, and all timepoints.

Characteristic	EQ-5D-3L available at no timepoints (n=4)	EQ-5D-3L available at least 1 timepoint (n=121)	EQ-5D-3L available all timepoints (n=607)	*p* value
Male, sex	4 (100%)	66 (55%)	363 (60%)	0.14
Race				**0.011**
African-American	**2 (50%)**	**48 (40%)**	**143 (24%)**	
Not reported	**0 (0%)**	**1 (0.8%)**	**5 (0.8%)**	
Other	**0 (0%)**	**5 (4.1%)**	**44 (7.2%)**	
White	**2 (50%)**	**67 (55%)**	**415 (68%)**	
Hispanic, ethnicity	1 (25%)	17 (14%)	78 (13%)	0.5
Age of consent (years)	61.0 (53.0, 66.8)	58.0 (53.0, 65.0)	59.0 (50.0, 67.0)	>0.9
Stability ICH volume (mL)	54.5 (43.4, 68.4)	23.1 (9.2, 38.9)	27.6 (7.1, 43.6)	0.057
Stability IVH volume (mL)	7.3 (1.7, 13.2)	11.6 (1.1, 21.7)	5.2 (0.1, 19.2)	0.1
Stability IVH presence (yes)	3 (75%)	103 (85%)	469 (77%)	0.11
Stability Total Blood Burden (mL)	**61.8 (52.7, 74.0)**	**39.9 (30.8, 51.9)**	**37.4 (27.3, 51.6)**	**0.034**
Stability Total Blood Burden (group)				0.1
≤ 30 mL	0 (0%)	29 (24%)	196 (32%)	
> 30 to ≤ 40 mL	1 (25%)	32 (26%)	146 (24%)	
> 40 to ≤ 55 mL	0 (0%)	33 (27%)	150 (25%)	
> 55 mL	3 (75%)	27 (22%)	115 (19%)	
GCS at randomization	**7.0 (7.0, 7.8)**	**9.0 (7.0, 11.0)**	**11.0 (9.0, 13.0)**	**<0.001**
Missing	**0**	**0**	**1**	
GCS at randomization (group)				**<0.001**
GCS (13-15)	**0 (0%)**	**21 (17%)**	**223 (37%)**	
GCS (9-12)	**1 (25%)**	**48 (40%)**	**236 (39%)**	
GCS (3-8)	**3 (75%)**	**52 (43%)**	**147 (24%)**	
Missing	**0**	**0**	**1**	
Hyperlipidemia	**1 (25%)**	**19 (16%)**	**181 (30%)**	**0.003**
Diabetes	0 (0%)	20 (17%)	109 (18%)	>0.9
Hypertension	3 (75%)	114 (94%)	572 (94%)	0.3
ICH Location				0.2
Deep*	3 (75%)	93 (77%)	417 (69%)	
Lobar	1 (25%)	28 (23%)	190 (31%)	

EQ-5D-3L indicates EQ-5D three-level version; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; and IVH, intraventricular hemorrhage.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

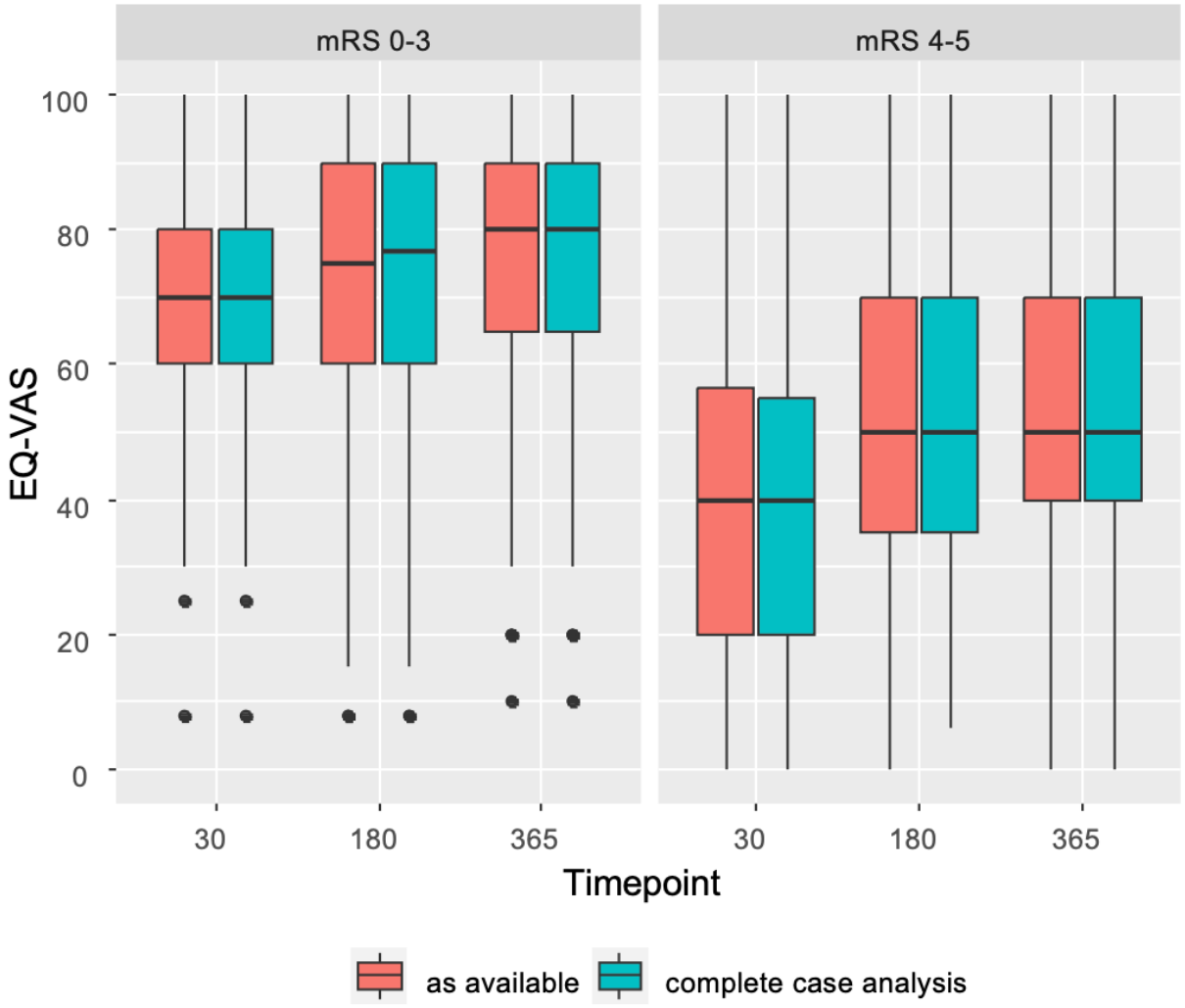
Table S4. Sensitivity analysis of the demographic and clinical characteristics of participants with EQ-VAS available at no timepoints, at least one timepoint, and all timepoints.

Characteristic	**EQ-VAS available at no timepoints (n=19)**	**EQ-VAS available at least 1 timepoint (n=153)**	**EQ-VAS available all timepoints (n=557**	***p*-value**
Male, sex	10 (53%)	90 (59%)	332 (60%)	0.800
Race				0.064
African-American	11 (58%)	45 (29%)	136 (24%)	
Not reported	0 (0%)	2 (1.3%)	4 (0.7%)	
Other	0 (0%)	10 (6.5%)	39 (7.0%)	
White	8 (42%)	96 (63%)	378 (68%)	
Hispanic, ethnicity	2 (11%)	24 (16%)	70 (13%)	0.600
Age of consent (years)	59.0 (56.0, 65.5)	59.0 (53.0, 67.0)	59.0 (50.0, 67.0)	0.700
Stability ICH volume (mL)	25.0 (11.3, 51.0)	23.1 (9.1, 39.4)	27.9 (7.1, 43.6)	0.700
Stability IVH volume (mL)	**11.6 (2.8, 20.9)**	**12.2 (0.3, 21.9)**	**4.5 (0.1, 18.2)**	**0.016**
Stability IVH presence (yes)	17 (89%)	127 (83%)	428 (77%)	0.140
Stability Total Blood Burden (mL)	**46.4 (35.9, 60.4)**	**39.4 (30.2, 54.6)**	**37.4 (27.0, 49.6)**	**0.028**
Stability Total Blood Burden (group)				
≤ 30 mL	3 (16%)	37 (24%)	182 (33%)	
> 30 to ≤ 40 mL	4 (21%)	45 (29%)	130 (23%)	
> 40 to ≤ 55 mL	5 (26%)	33 (22%)	145 (26%)	
> 55 mL	7 (37%)	38 (25%)	100 (18%)	
GCS at randomization	**8.0 (7.0, 10.0)**	**9.0 (7.0, 11.0)**	**11.0 (9.0, 14.0)**	**<0.001**
Missing	0	0	1	
GCS at randomization (group)				**<0.001**
GCS (13-15)	**1 (5.3%)**	**32 (21%)**	**209 (38%)**	
GCS (9-12)	**6 (32%)**	**65 (42%)**	**213 (38%)**	
GCS (3-8)	**12 (63%)**	**56 (37%)**	**134 (24%)**	
Missing	**0**	**0**	**1**	
Hyperlipidemia	**1 (5.3%)**	**32 (21%)**	**168 (30%)**	**0.007**
Diabetes	0 (0%)	27 (18%)	101 (18%)	0.100
Hypertension	16 (84%)	145 (95%)	525 (94%)	0.200
ICH Location				0.100
Deep*	15 (79%)	117 (76%)	380 (68%)	
Lobar	4 (21%)	36 (24%)	177 (32%)	

EQ-VAS indicates EQ-5D Visual Analog Scale; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; and IVH, intraventricular hemorrhage.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

Figure S1. EQ-VAS of survivors with EQ-VAS and mRS available at any timepoint (as available) by mRS 0-3 vs. mRS 4-5 and timepoint compared to EQ-VAS of survivors with EQ-VAS and mRS available at all timepoints (complete case analysis) by mRS 0-3 vs. mRS 4-5 and timepoint. EQ-VAS indicates EQ-5D Visual Analog Scale; and mRS, modified Rankin Scale.



CHAPTER 4:

Patient Disposition and Health-Related Quality of Life in MISTIE III: Opportunities to Improve Decision Making with Intracerebral Hemorrhage Patients

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Abstract

Background: Prognostication occurs early and often in patients with intracerebral hemorrhage (ICH). Recovery is prolonged and unpredictable, resulting in challenges to estimating health-related quality of life (HRQoL). Patient disposition and HRQoL for ICH survivors with similar baseline disease severity are compared to ICH patients who had withdrawal of life-sustaining treatment (WLST).

Methods: Using data from the Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III) trial, a modified severity index compared ICH survivors to patients who had WLST. Patient disposition and EQ-5D visual analog scale (EQ-VAS) of matched survivors were evaluated at days 30, 180, and 365. The mean EQ-VAS at day 365 was compared to the mean EQ-VAS US population norm for age-matched individuals. The rationale for WLST was examined.

Results: Of 379 survivors at one year, 90 were matched to patients who had WLST (n=61). Of 90 matched survivors, 11.1%, 65.6%, and 73.3% returned home by days 30, 180, and 365. The mean (SD) EQ-VAS of matched survivors at days 30, 180, and 365 was 41.9 (24), 62.2 (20.8), and 65.6 (21.8). At day 365, matched survivors living at home (n=66) had mean (SD) EQ-VAS of 70.6 (18.9) as compared to the mean EQ-VAS US population norm of 75. The rationale for WLST was an anticipated dependent state for 38 (62%) of the 61 WLST patients.

Conclusions: ICH survivors with comparable baseline disease severity to those who underwent WLST demonstrated improvement in HRQoL over time. The majority returned home by one year. The EQ-VAS of matched survivors living at home approached the EQ-VAS US population norm for age-matched persons at one year. This study challenges the current practice of early pessimistic prognostication in concert with goals of care decision making, as early estimates of potential recovery do not appear to match the potential for acceptable HRQoL outcomes.

Trial Registration: URL: https://clinicaltrials.gov/ct2/show/NCT01827046; Unique Identifier: NCT01827046

Non-Standard Abbreviations and Acronyms

EQ-5D visual analog scale (EQ-VAS)

Glasgow Coma Scale (GCS)

Health-related quality of life (HRQoL)

Intensive care unit (ICU)

Intracerebral hemorrhage (ICH)

Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III)

modified Severity Index (mSI)

National Institutes of Health Stroke Scale (NIHSS)

Principal investigator (PI)

Withdrawal of life-sustaining treatment (WLST)

Introduction

Recovery in intracerebral hemorrhage (ICH) is prolonged and unpredictable, resulting in considerable challenges in estimating long-term health-related quality of life (HRQoL) for survivors of ICH.[1–4] Intensive care unit (ICU) clinicians who support goals of care decision making, to continue, limit or withdraw life-sustaining treatment, for critically ill patients with ICH rarely participate in recovery care or long-term follow-up of these patients. Thus, limited opportunities are provided for ICU health care professionals to evaluate the recovery trajectory of patients with ICH following the acute phase of injury. Surrogate decision makers of incapacitated patients with ICH face making early consequential goals of care decisions based on prognostic estimates provided by ICU clinicians. Although well-established, population-based demographic and clinical characteristics have been described to influence a poor prognostic estimate,[3–5] concerns regarding a "self-fulfilling prophecy" affecting mortality estimates following current prognostication algorithms exist in ICH.[2,3] Importantly, prognostication following this and other forms of devastating brain injury is limited mostly to disability prognostication and does not generally involve HRQoL domains.[6]

Using trial data from Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III),[7] this study aimed to describe patient disposition and HRQoL for ICH survivors with similar baseline demographic and clinical characteristics to ICH patients who had withdrawal of life-sustaining treatment (WLST) performed in the acute phase of injury.

Methods

Data Source

Data was obtained from the MISTIE III trial.[7] Briefly, MISTIE III was a randomized, controlled, open-label, blinded endpoint, phase 3 explanatory trial of image-guided, catheter-based removal plus fibrinolysis of ICH of ≥ 30 mL, performed at 78 hospitals in the USA, Canada, Europe, Australia, and Asia. Eligible patients were aged 18 years or older with a spontaneous, non-traumatic, supratentorial ICH of 30 mL or more due to cerebral small-vessel disease, with a Glasgow Coma Scale (GCS) of 14 or less or National Institutes of Health

Stroke Scale (NIHSS) score of 6 or higher, a modified Rankin Scale (mRS) of 0 or 1 before the bleed, and an ICH that remained stable (hematoma growth of < 5 mL) for at least 6 hours after diagnostic computed tomography (CT).[7]

Patients who were not expected to survive the acute phase or with expressed care limitations at ICU presentation were excluded from MISTIE III. Discussions between clinicians and surrogate decision makers involving prognosis and goals of care decisions were conducted according to each institution's policies, and in conjunction with their respective institutional codes of medical ethics. The medical management of all enrolled patients was in concordance with the MISTIE III protocol,[7] which followed the American Heart Association guidelines for the treatment of spontaneous ICH.[8]

Severity Index Analysis

A severity index has been previously described in the MISTIE III results.[7] Briefly, the severity index analysis used well-described, validated, demographic and clinical characteristics of disease severity[4,9] (age, GCS, ICH volume, intraventricular hemorrhage [IVH] volume, ICH location [deep or lobar], the presence of diabetes, and white matter disease [Fazekas total score]) to compose a multivariable logistic regression model of good outcome (defined as a mRS of 0–3) at day 365.[10] The presence of 3 or more comorbidities was considered with the severity index as these factors have been described to influence do-not-resuscitate status in critically ill patients with ICH.[11] The inclusion of this clinical characteristic resulted in a modification to the previously published severity index.[7] Based on the coefficients of this modified Severity Index (mSI) model, a severity score was created.[10]

A two-level matching process was used to match survivors with ICH patients who had WLST, based on mSI at baseline.[12] First-level matching involved matching all survivors with the exact total mSI of each WLST patient. Patients with missing EQ-5D visual analogue scale (EQ-VAS) data at any timepoint were eliminated. Survivors with EQ-VAS data at all timepoints were then matched by exact mSI coefficients to patients who had

WLST (second-level matching). Case examples of the first- and second-level matching process are provided (table S1). Patient disposition and EQ-VAS of the matched survivors were examined at days 30, 180, and 365.

Patient Disposition and HRQoL Outcomes

At days 30, 180, and 365, study coordinators performed in-person study visits to obtain patient disposition and HRQoL outcomes of all survivors. Patient disposition was defined by physical location at days 30, 180, and 365, and categorized as acute care hospital, acute rehabilitation facility, long-term care facility, or home.

The EQ-5D instrument was used to assess HRQoL at days 30, 180, and 365. The EQ-5D instrument was introduced in 1990 by the EuroQol Group,[13] and includes a short descriptive system and a visual analog scale.[14] The EQ-5D visual analog scale (EQ-VAS) is a quantitative measure of health outcome and allows for respondents to self-report their health state on a vertical visual analog scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).[14]

Patients were instructed to mark their current health state on the EQ-VAS. Proxies were not permitted to complete the EQ-VAS on the behalf of the patient. The mean EQ-VAS of the matched survivors was reviewed at days 30, 180, and 365. The mean EQ-VAS US population norm for age-matched persons (45 to over 75 years of age)[15] was used to compare the mean EQ-VAS of matched survivor groups at day 365. Norms for minimally important difference for the EQ-VAS have been established in chronic disease.[16]

Medically Attributed Rationale for WLST

Rationale for level of care determination was assessed via standardized questions after family conferences. Respondents were instructed to indicate the rationale for the decision to pursue WLST. Respondents included attending physicians, site principal investigators (PIs), and others (i.e., residents/fellows, palliative care, nurse practitioners). Responses were categorized as: (a) prior statement by the patient; (b) living will; (c) dependent outcome anticipated; (d) dependent outcome anticipated, living will, prior statement by

patient; (e) dependent outcome anticipated, prior statement by patient; and (f) unknown. A data manager (RA) reviewed the MISTIE III case report forms of patients who had WLST to identify the medically attributed rationale for the decision to withdraw life-sustaining treatment.

Statistical Analysis

A matched cohort analysis was performed utilizing EQ-VAS of matched survivors at days 30, 180, and 365. The relation between mSI status and outcomes in survivors and deceased participants was assessed using multivariable logistic regression. A model was created using well-established demographic (age in years) and clinical characteristics (GCS, deep ICH location [defined as involvement of thalami or basal ganglia], stability ICH ≥ 45 mL and IVH volume > 0.4 mL, and the presence [yes or no] of 3 or more comorbidities [renal failure, diabetes, hypertension, cardiovascular disease, hyperlipidemia, and tobacco use]). Hematoma volumes were measured using volumetric software OsiriX MD (version 9.0.1). Age in years was captured at time of consent. GCS, ICH location, and the presence of 3 or more comorbidities were captured at time of randomization. ICH and IVH volume were captured following the stability CT scan obtained at least 6 hours after diagnostic CT showing clot stability (defined as hematoma growth of < 5 mL) as measured by ABC/2 method.[17] Based on the coefficients of the model, a total mSI score was created.

Statistical analyses were performed using Stata (version 16.0, College Station, TX) and R (version 4.0.2, R Project for Statistical Computing). All analyses were two-tailed, and significance level was determined by $p<0.05$.

Standard Protocol Approvals, Registrations, and Patient Consents

Each of the 78 hospitals included in the MISTIE III trial obtained institutional review board or ethics committee approval from their respective institutions.[7] This study was approved by the Johns Hopkins Medicine Institutional Review Board. MISTIE III is registered with ClinicalTrials.gov, NCT01827046. Written informed consent for participation in the MISTIE III trial was obtained from all participants (or legal representatives or surrogates when applicable).

Data Availability Statement

The MISTIE III trial data, including de-identified participant data, is available at the National Institute of Neurological Disorders and Stroke (NINDS) data archive (https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets). Those seeking access must complete a NINDS data request form and receive approval.

Results

MISTIE III enrolled 506 patients, 61 of whom had WLST. Of the 379 survivors, 90 survivors were matched by total mSI and mSI coefficients to patients who had WLST in a 1 to 1.5 matching ratio. Figure 1 shows the number of survivors matched by total mSI (n=298) and mSI coefficient (n=90) to WLST patients. A total of 68 survivors with missing EQ-VAS data at one or more timepoints were excluded from the final analysis. Patients who were deceased of causes other than WLST (n=49), patients who had WLST (n=61), and matched survivors (n=90) had similar baseline demographic and clinical characteristics, with the exception of deep ICH location. There were small differences in age, ICH/IVH volume, and comorbidity severity that would appear to favor the matched survivor group (table 1). The survivors who were excluded (n=68) from the final analysis as a result of missing EQ-VAS data were compared to matched survivors (n=90). In comparison to excluded survivors, the matched survivors were older, had a higher percentage of greater than 3 or more comorbidities, and a lower percentage of deep hemorrhages as shown in table S2.

Modified Severity Index

The multivariable logistic regression model for the mSI is shown in table 2. The maximum total mSI and mean mSI (SD) for patients who had WLST (n=61) and matched survivors (n=90) was 6.5, 2.9 (1.5) and 5.2, 3.2 (1.3), respectively. For every unit increase in mSI score, there was a 2.70-fold increase in odds of having a good outcome (mRS 0–3) at day 365 (p<0.0001). The total mSI range, mean, and SD are included in table S3. The mean (SD) mSI scores of patients by patient disposition and timepoint are shown in table S4.

Patient Disposition

At day 30, 30 (33.3%) of the 90 matched survivors were in an acute care hospital. No matched survivors were in an acute care hospital at days 180 and 365. At days 30, 180, and 365, respectively, 41 (45.5%), 8 (8.9%), and 3 (3.3%) of the 90 matched survivors were in an acute rehabilitation facility. At days 30, 180, and 365, 9 (10%), 23 (25.6%), and 21 (23.3%) of the 90 matched survivors were in a long-term care facility. Ten (11.1%) of the 90 matched survivors were home by day 30. At days 180 and 365, 59 (65.6%) and 66 (73.3%) of 90 matched survivors were home.

EQ-VAS

The mean (SD) EQ-VAS of matched survivors (n=90) at days 30, 180, and 365 was 41.9 (24), 62.2 (20.8), and 65.6 (21.8). The mean (SD) EQ-VAS increased for matched survivors (n=90) from days 30 to 365 by 24 (24), $p<0.0001$, with the highest EQ-VAS mean (SD) increase between days 30 to 180 (20 [23]). The mean EQ-VAS US population norm for age-matched persons (45 years to over 75 years of age) is 75.[15] Matched survivors living at home at day 365 (n=66) demonstrated the highest mean (SD) EQ-VAS of 70.6 (18.9) (figure 2). The mean EQ-VAS of survivors with EQ-VAS data available at day 365 (n=347), matched survivors at day 365 (n=90), and matched survivors living at home at day 365 (n=66), as compared to the mean EQ-VAS US population norm for age-matched persons (75),[15] is shown in a violin plot (figure 3). The mean EQ-VAS of matched survivors by patient disposition and timepoint are shown in table S4.

Medically Attributed Rationale for WLST

The medically attributed rationale for the decision to withdraw life-sustaining treatment for the 61 patients who had WLST included responses from: 32 (52.4%) attending physicians, 5 (8.2%) site PIs, and 14 (22.9%) others (i.e., residents/fellows, palliative care, nurse practitioners). WLST decisions were attributed to dependent outcome anticipated in 38 (62%), living will in 7 (11.5%), and prior statement by patient in 30 (48.4%) (table 3).

Discussion

This study demonstrated that ICH survivors with comparable baseline disease severity to ICH patients who had WLST demonstrated improvement in EQ-VAS over time, and the majority returned home by one year. The EQ-VAS of matched survivors, specifically those living at home at one year, approached the EQ-VAS US population norm for age-matched persons.[15] The results of this study provide ICH patient-specific assessments of HRQoL over a year's recovery. This analysis illuminates several challenges in prognosticating HRQoL outcomes for critically ill patients with ICH and further emphasize that early prognostication of pessimistic outcomes in this population does not appear to match the potential for acceptable HRQoL outcomes.

When caring for critically ill ICH patients, discussions between clinicians and surrogate decision makers often involve making consequential decisions about the extent of intensive treatments. Robust prognostication is a fundamental component of such discussions. Prognostication following devastating brain injury has been recently identified as an area of critical importance in comatose states, including ICH.[6,18] Important components of prognostication for critically ill patients with ICH involve the perception(s) of severity of disease on outcomes and the use of prognostication models. However, current survival and functional prognostication models for ICH have failed to consider WLST as a primary determinant in the modeling process, thus overestimating poor outcomes.[6] Consequently, literature-derived, preconceived notions about futility of care may be relayed to surrogate decision makers in goals of care discussions prompting WLST, and the utilization of perceived outcome in patient populations in which WLST is performed may lead to self-fulfilling prophecies.[2,3] As a result, caution has been advised against the provision of early care limitations following ICH and other forms of brain injury in the acute phase.[18–21] This data provides longitudinal HRQoL information from survivors over the trajectory of acute to recovery phases.

ICH prognostication models focus primarily on observed survival and health professional measured functional outcomes at pre-defined time points, with limited emphasis on patient-reported HRQoL outcomes.[4,6,9] Of the 61 patients enrolled in MISTIE III who had WLST, an anticipated future with disability was the most commonly documented rationale for the decision to pursue WLST as prognosticated by the

treating team. The results of this retrospective study demonstrated that of the 90 survivors with similar baseline demographic and clinical characteristics, 73.3% returned home by one year and reported a HRQoL state comparable to that of age-matched individuals who had never experienced an ICH. This finding highlights an important health care delivery aspect of current prognostication practices which rest primarily on the decision-maker's understanding of the patient's likelihood to achieve an acceptable level of functional independence. While professionally determined functional outcomes are commonly used as measures of efficacy for therapeutic interventions in stroke and other forms of brain injury, current prognostication addresses the question of whether or not the patient will recover to the extent of being able to function independently again.[6] Functional outcome alone ignores a person's ability to adjust to a new life of disability, and fails to account for the dynamic process involved in a person's capacity to reframe their values and perceptions of quality of life in a new health state.[6,22,23] These factors are included in personal HRQol determinations. Thus, an observer's measure of functional outcome fails to capture the complex nature of a person's self-reported HRQoL in a new state of disability. Such discrepancies between functional outcome and HRQoL have been described in patients with ischemic stroke.[24,25] HRQoL clearly provides important utility information from the lived experience of ICH survivors. Information such as this can provide a more precise link between acute care and neurorehabilitation and reintegration into society for patients with ICH.[26]

This study has several limitations. First, matching survivors to patients who had WLST by severity index has weaknesses in small populations, where multiple independent factors determine prognosis. It is possible that small imbalances in clinical severity may be sufficient to change long-term outcomes and HRQoL assessments affecting comparative equivalence of the two groups. However, the matching process in this study was robust, and given the relatively low rate of WLST in this study, the matched survivor cohort appears to be a clinically high severity group. Importantly, our process considered the individual disease severity factors of patients rather than population means in making prognostic inference. Another limitation is that patient wishes and living will status were captured only when patients had WLST. It was established that all MISTIE III participants initially agreed to intervention and medical support, but prior patient wishes and living will status

for the survivors was not obtained. Additionally, the detailed nature of discussions between clinicians and surrogate decision makers was not captured for this study; therefore, little is known regarding the prognostic information that was relayed to surrogate decision makers by the treating team, the role this information played, or the exact, prior patient wishes expressed to surrogate decision makers and how this information was utilized to make goals of care decisions. Lastly, it was recognized that the matching process did not include the clinical course of events of individual matched survivors and patients that had WLST.

The results of this study have demonstrated that an unacceptable patient perspective gap exists in correlating the long-term HRQoL outcomes of critically ill patients with ICH in the current practice of identifying poor ICH outcomes in concert with goals of care decisions that employ WLST. Prospective, longitudinal studies evaluating the long-term HRQoL outcomes of patients following ICH are urgently needed. Additionally, there is a significant need to develop prognostic processes that incorporate patient-reported HRQoL outcomes into WLST decision making. An informed, shared decision-making framework that allows for the use of ICH survivor-based HRQoL data has potential to improve the optimization of patient, family, and caregiver experiences in dealing with health uncertainties and increase the quality of consequential decisions.

Conclusion

ICH survivors with comparable demographic and clinical severity characteristics to ICH patients who underwent WLST demonstrated substantial improvement in HRQoL over time. The majority returned home by one year. If goals of care discussions between ICU clinicians and surrogate decision makers were to include HRQoL outcomes, including returning home, these results suggest that prognostication in ICH would be improved to better inform the goals of care decision-making process for critically ill patients with ICH.

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Supplemental Material

Tables S1-S4

References

1. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo Hi, Hanley DF. Spontaneous Intracerebral Hemorrhage. *N Engl J Med*. 2001;344(19):1450-1460.
2. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology*. 2001;56:766-772.
3. Zahuranec DB, Brown DL, Lisabeth LD, et al. Early care limitations independently predict mortality after intracerebral hemorrhage. *Neurology*. 2007;68(20):1651-1657. doi:10.1212/01.wnl.0000261906.93238.72
4. Hemphill, JC, Bonovich, DC, Besmertis, L, Manley, GT, Johnston S. The ICH Score: A Simple, Reliable Grading Scale for Intracerebral Hemorrhage. *Stroke*. 2001;32:891-897.
5. Broderick JP. Haemostatic treatment for intracerebral haemorrhage. *Lancet*. 2018;391(10135):2081-2082. doi:10.1016/S0140-6736(18)31040-7
6. Frontera JA, Curtis JR, Nelson JE, et al. Integrating Palliative Care Into the Care of Neurocritically Ill Patients: A Report From the Improving Palliative Care in the ICU Project Advisory Board and the Center to Advance Palliative Care. *Crit Care Med*. 2015;43:1964-1977. doi:10.1097/CCM.0000000000001131
7. Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet*. 2019;393(10175):1021-1032. doi:10.1016/S0140-6736(19)30195-3
8. Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41(9):2108-2129. doi:10.1161/STR.0b013e3181ec611b
9. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: The FUNC score. *Stroke*. 2008;39(8):2304-2309. doi:10.1161/STROKEAHA.107.512202

10. Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial [Supplementary appendix]. *Lancet*. 2019;393(10175):1021-1032.

11. Hemphill JC, Newman J, Zhao S, Johnston SC. Hospital usage of early do-not-resuscitate orders and outcome after intracerebral hemorrhage. *Stroke*. 2004;35(5):1130-1134. doi:10.1161/01.STR.0000125858.71051.ca

12. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55. doi:10.1017/CBO9780511810725.016

13. Group TE. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy (New York)*. 1990;16(3):199-208. doi:10.1016/0168-8510(90)90421-9

14. Devlin N, Parkin D, Janssen B. *Methods for Analysing and Reporting EQ-5D Data*. Springer Nature; 2020. doi:10.1007/978-3-030-47622-9

15. Janssen MF, Szende A, Cabases J, Ramos-Goñi JM, Vilagut G, König HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. *Eur J Heal Econ*. 2019;20(2):205-216. doi:10.1007/s10198-018-0955-5

16. Simon AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;273(1):2-9. doi:10.1186/1477-7525-5-70

17. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage: A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24(7):987-993. doi:10.1161/01.STR.24.7.987

18. Souter MJ, Blissitt PA, Blosser S, et al. Recommendations for the Critical Care Management of Devastating Brain Injury: Prognostication, Psychosocial, and Ethical Management: A Position Statement for Healthcare Professionals from the Neurocritical Care Society. *Neurocrit Care*. 2015;23(1):4-13. doi:10.1007/s12028-015-0137-6

19. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart

Association/American Stroke Association. *Stroke*. 2015;46(7):2032-2060. doi:10.1161/STR.0000000000000069

20. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014;9(7):840-855. doi:10.1111/ijs.12309
21. Cronberg T, Greer DM, Lilja G, Moulaert V, Swindell P, Rossetti AO. Brain injury after cardiac arrest: from prognostication of comatose patients to rehabilitation. *Lancet Neurol*. 2020;19(7):611-622. doi:10.1016/S1474-4422(20)30117-4
22. Creutzfeldt CJ, Holloway RG. Treatment decisions after severe stroke: Uncertainty and Biases. *Stroke*. 2012;43(12):3405-3408. doi:10.1161/STROKEAHA.112.673376
23. Carhuapoma L, Kapadia A, Glick HA, Hanley DF. What is the Price of the Potential for a Meaningful Recovery following Intracerebral Hemorrhage? *J stroke Cerebrovasc Dis*. 2021;30(10).
24. Vahedi K, Benoist L, Kurtz A, et al. Quality of life after decompressive craniectomy for malignant middle cerebral artery infarction [1]. *J Neurol Neurosurg Psychiatry*. 2005;76(8):1181-1182. doi:10.1136/jnnp.2004.058537
25. Polding LC, Tate WJ, Mlynash M, et al. Quality of Life in Physical, Social, and Cognitive Domains Improves with Endovascular Therapy in the DEFUSE 3 Trial. *Stroke*. 2021;52(4):1185-1191. doi:10.1161/STROKEAHA.120.031490
26. Menon DK, Bryant C. Time for change in acquired brain injury. *Lancet Neurol*. 2019;18(1):28. doi:10.1016/S1474-4422(18)30463-0

Tables

Table 1. Baseline demographic and clinical characteristics of deceased patients (from causes other than WLST), WLST patients, and second-level matched survivors.

Characteristics	Deceased, no WLST (n=49)	WLST patients (n=61)	Matched survivors (n=90)	*p* value
Age at consent, y				
< 56	10 (20.4%)	9 (14.8%)	18 (20.0%)	0.678
56–66	16 (32.6%)	15 (24.6%)	24 (26.7%)	
≥ 67	23 (46.9%)	37 (60.7%)	48 (53.3%)	
GCS at randomization				
3–8	16 (32.6%)	23 (37.7%)	18 (20.0%)	0.099
9–12	25 (51.0%)	27 (44.3%)	46 (51.1%)	
13–15	8 (16.3%)	11 (18.0%)	26 (28.9%)	
Stability ICH ≥ 45 mL	33 (67.3%)	50 (82.0%)	62 (68.9%)	0.136
Stability IVH > 0.4 mL	32 (65.3%)	37 (60.7%)	52 (57.8%)	0.686
≥ 3 comorbidities	22 (44.9%)	29 (47.5%)	30 (33.3%)	0.168
Deep ICH location*	34 (69.4%)	32 (52.5%)	43 (47.8%)	**0.047**

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; and WLST, withdrawal of life-sustaining treatment.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

Table 2. Multivariable logistic regression model of mSI.

	Coefficient	95% CI	*p* Value
Age at consent, y			
≤ 55	2.20	1.54–2.87	**< 0.0001**
56–66	1.28	0.70–1.86	**< 0.0001**
≥ 67		*Reference*	
GCS at randomization			
3–8		*Reference*	
9–12	0.56	0.02–1.10	**0.041**
13–15	0.79	0.21–1.40	**0.008**
Stability ICH < 45 mL*	0.87	0.43–1.32	**< 0.0001**
Stability IVH < 0.4 mL†	0.70	0.25–1.13	**0.002**
< 3 comorbidities‡	0.76	0.29–1.23	**0.001**
ICH lobar location§	2.01	1.47–2.55	**< 0.0001**

CI indicates confidence interval; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; and mSI, modified severity index.
*Reference stability ICH ≥ 45 mL.
†Reference stability IVH ≥ 0.4 mL.
‡Reference ≥ 3 comorbidities.
§Reference deep ICH location (involvement of thalami or basal ganglia).

Table 3. Rationale for the decision to withdraw life-sustaining treatment in MISTIE III.

Response Option	**Number (%)**
Prior statement by patient	12 (19.7%)
Living will	2 (3.3%)
Dependent outcome anticipated	18 (29.5%)
Dependent outcome anticipated, living will	2 (3.3%)
Dependent outcome anticipated, living will, prior statement by patient	3 (4.9%)
Dependent outcome anticipated, prior statement by patient	15 (24.6%)
Unknown	9 (14.8%)

Rationale data were obtained from MISTIE III case report forms.

Figures with Figure Legends

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram depicting the phases of the MISTIE III trial through EQ-VAS data collection and the matching of survivors with WLST patients by total mSI and coefficients. EQ-VAS indicates EQ-5D Visual Analog Scale; mSI, modified severity index; and WLST, withdrawal of life-sustaining treatment.

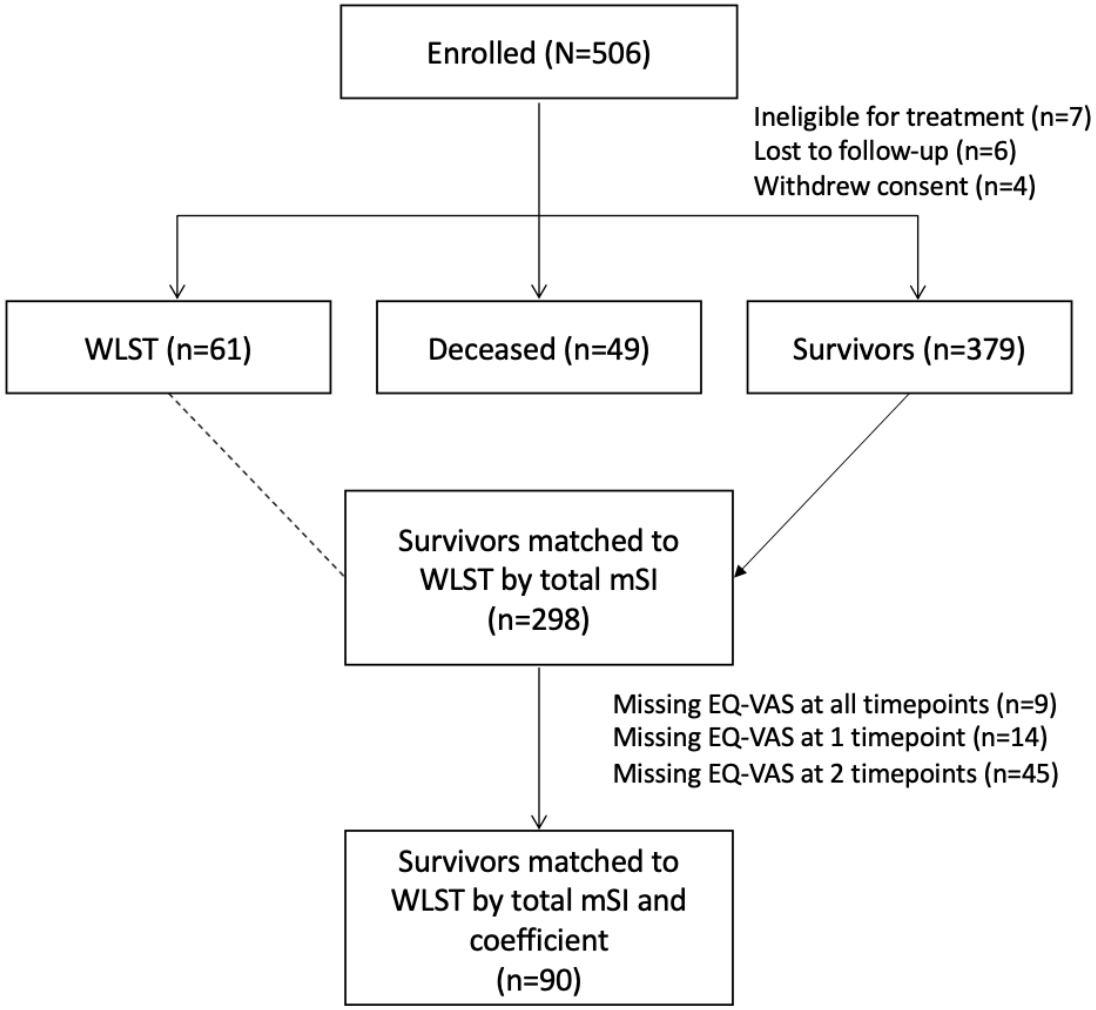


Figure 2. Patient disposition and mean EQ-VAS of matched survivors at days 30, 180, and 365. EQ-VAS indicates EQ-5D Visual Analog Scale; and LTCF, long-term care facility.

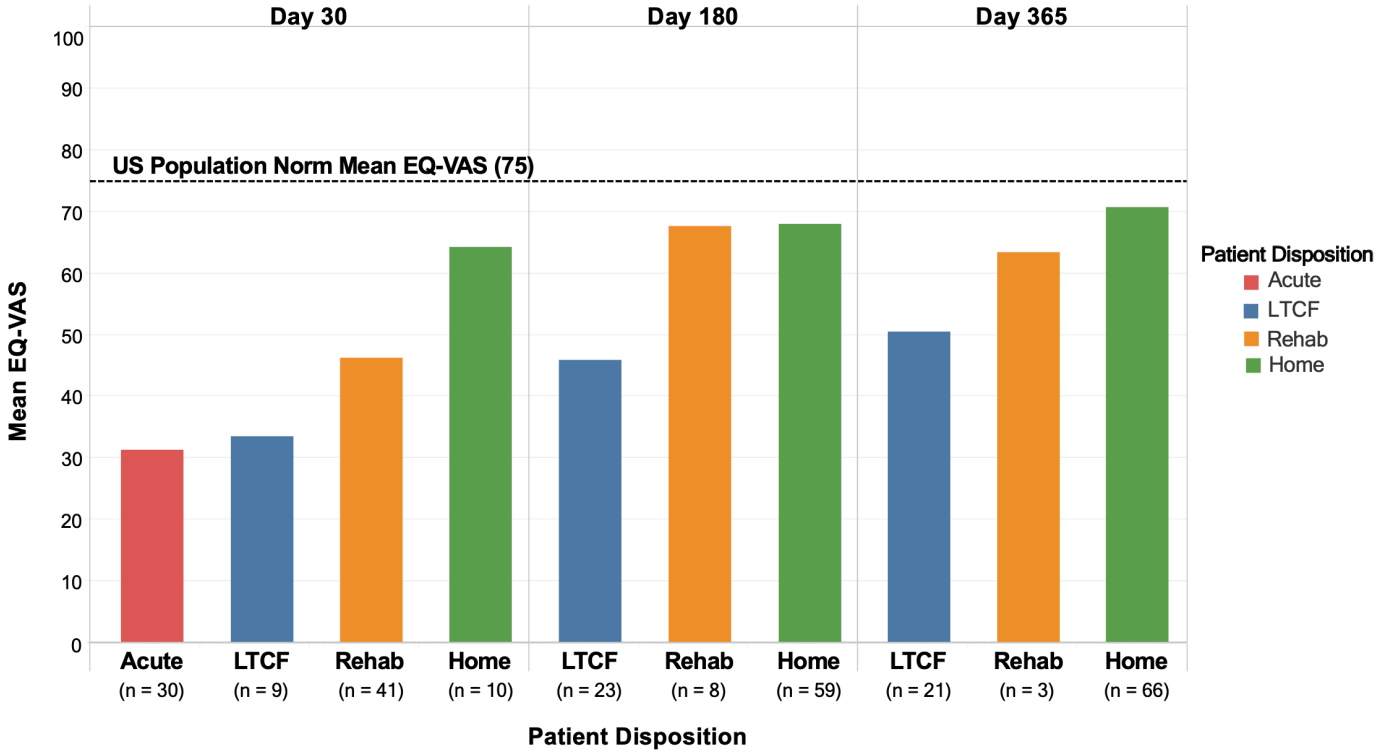
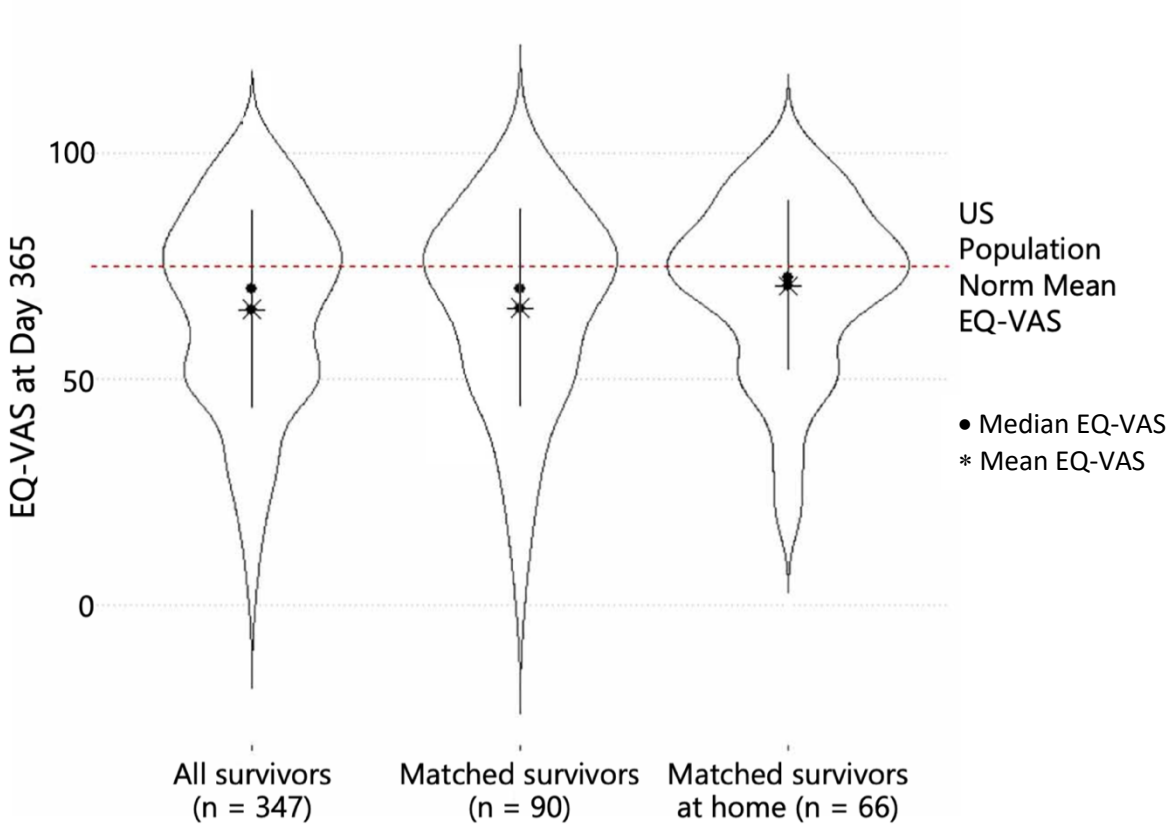


Figure 3. Violin plot of mean EQ-VAS distribution at day 365 for all survivors, matched survivors, and matched survivors living at home. The mean EQ-VAS of all survivors, matched survivors and matched survivors living at home at day 365 is compared to the mean EQ-VAS US population norm for age-matched persons. EQ-VAS indicates EQ-5D Visual Analog Scale.



Supplemental Material

Table S1. First-level matching (total mSI only; Case A) and second-level matching (total mSI and coefficients; Case B) of WLST patients to survivors.

	Case A: First-level matching by total mSI		**Case B: Second-level matching by total mSI and coefficients**	
Characteristic (mSI coefficient)	**WLST**	**Survivor**	**WLST**	**Survivor**
Total mSI	2.2	2.2	3.4	3.4
Age at consent, years	**56–66 (1.28)**	**≥ 67 (0)**	≥ 67 (0)	≥ 67 (0)
GCS at randomization	**3–8 (0)**	**9–12 (0.56)**	9–12 (0.56)	9–12 (0.56)
Stability ICH < 45 mL	stability ICH < 45 mL (0.87)	stability ICH < 45 mL (0.87)	stability ICH ≥ 45 mL (0)	stability ICH ≥ 45 mL (0)
Stability IVH < 0.4 mL	**stability IVH ≥ 0.4 mL (0)**	**stability IVH < 0.4 mL (0.7)**	stability IVH ≥ 0.4 mL (0)	stability IVH ≥ 0.4 mL (0)
< 3 comorbidities	≥ 3 comorbidities (0)	≥ 3 comorbidities (0)	< 3 comorbidities (0.76)	< 3 comorbidities (0.76)
ICH lobar location	deep ICH location (0)	deep ICH location (0)	lobar ICH location (2)	lobar ICH location (2)

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mSI, modified severity index; and WLST, withdrawal of life-sustaining treatment.

Case A demonstrates a mismatch between the survivor and WLST patient in age, GCS at randomization, and stability IVH. Case B demonstrates equal total mSI and coefficients for all characteristics between the survivor and WLST patient.

The mSI coefficients may not equal total mSI due to rounding.

Table S2. Baseline demographic and clinical characteristics of second-level matched survivors and excluded survivors.

Characteristics	Matched Survivors (n=90)	Excluded Survivors (n=68)	*p* value
Age at consent, years, median (IQR)	68.0 (58.2, 75.0)	59.0 (53.0, 70.0)	**0.002**
GCS at randomization, median (IQR)	10.5 (9.0, 13.0)	10.0 (8.0, 12.0)	0.14
Stability ICH ≥ 45 mL, n (%)	62 (69%)	31 (54.4%)	0.063
Stability IVH > 0.4 mL, n (%)	54 (60%)	33 (48.5%)	0.15
≥ 3 comorbidities, n (%)	30 (33%)	10 (15%)	**0.008**
Deep ICH location*, n (%)	43 (48%)	50 (74%)	**0.001**
ICH Hemisphere, n (%)			0.053
Left	43 (48%)	43 (63%)	
Right	47 (52%)	25 (37%)	

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; and WLST, withdrawal of life-sustaining treatment.

*Deep ICH location is defined as involvement of thalami or basal ganglia.

Table S3. mSI minimum, maximum, mean, and standard deviation (SD) for WLST patients and matched survivors.

	n	Minimum	Maximum	Mean	SD
WLST patients	61	0	6.5	2.9	1.5
Matched survivors	90	0	5.2	3.5	1.3

mSI indicates modified severity index; and WLST, withdrawal of life-sustaining treatment.

Table S4. Patient disposition, mean EQ-VAS, and mean mSI scores of matched survivors at days 30, 180, and 365.

	Day 30			Day 180			Day 365		
Patient Disposition	**n**	**Mean (SD) EQ-VAS**	**Mean (SD) mSI score**	**n**	**Mean (SD) EQ-VAS**	**Mean (SD) mSI score**	**n**	**Mean (SD) EQ-VAS**	**Mean (SD) mSI score**
Acute care hospital	30	31.2 (22.3)	2.9 (1.3)	0			0		
Long-term care facility	9	33.4 (21.1)	3.4 (1.3)	23	45.9 (19.4)	2.3 (1.3)	21	50.5 (24.9)	2.1 (1.2)
Rehabilitation facility	41	46.2 (21.6)	3.6 (1.2)	8	67.5 (24.2)	3.2 (1.7)	3	66.3 (15.3)	3.1 (2.3)
Home	10	64.2 (22.5)	4.6 (0.7)	59	67.9 (17.6)	4.0 (0.9)	66	70.6 (18.9)	3.9 (0.9)
Total	90	41.9 (24.0)	3.5 (1.3)	90	62.2 (20.8)	3.5 (1.3)	90	65.6 (21.8)	3.5 (1.3)

LTCF indicates long-term care facility; mSI, modified severity index; and WLST, withdrawal of life-sustaining treatment.

CHAPTER 5:

Conclusion

Evidence Before this Dissertation Research

Goals of care decisions, to maintain, limit or withdraw life-sustaining treatment, occur early and often for incapacitated patients with severe intracerebral hemorrhage (ICH). This consequential decision-making process relies on an informed, shared decision-making model in which surrogate decision makers and clinicians align the patient's preferences and values with the clinical team's opinions, beliefs and expectations of the potential for a meaningful recovery. Considerable challenges exist in prognosticating outcomes for ICH patients that may impact this decision-making process.[1,2] Current prediction models in ICH focus mostly on mortality and observer-measured functional outcomes, while not utilizing patient-reported health-related quality of life (HRQoL).[2–4] Furthermore, while the existing prognostic models have performed well at the population level, concerns have been raised surrounding their use for individual patients.[2,5,6] Additionally, many existing outcome models in ICH have been formulated with the implicit and unstated assumption that withdrawal of life-sustaining treatment (WLST), the most common cause of immediate death in ICH,[1,7] is part of the natural history of the most severely injured patients with ICH. Therefore, the dependence on mortality data and prognostic models may create a "self-fulfilling prophecy" and maintain high mortality rates in ICH.[1,2] Consequently, the practice of utilizing established demographic and clinical predictors of morbidity and mortality in ICH has been challenged.[1,5,7–9]

Becker and colleagues demonstrated that preconceived notions about futility of care may lead to WLST, creating a "self-fulfilling prophecy" in ICH. The investigators identified that WLST was performed more frequently in patients with lower GCS and larger hematoma volumes; yet, a high proportion of patients with low GCS and larger hematoma volumes not only survived, but achieved functional independence.[1] More recently, Shah and colleagues reported on the long-term recovery trajectories after ICH. Of the survivors with severe disability in the acute phase after ICH, more than 40% achieved a good functional outcome at one year.[8] HRQoL was significantly lower in ICH survivors with poor functional outcome one-year post-hemorrhagic

stroke; however, survivors with good and poor functional outcome demonstrated a significant upward trend in HRQoL over time. Jakobsson and colleagues found that nearly half of the ICH survivors had a good neurologic outcome, and self-reported HRQoL correlated with functional outcome.[10] Significant recovery of patients with other forms of devastating brain injury that occurs over an extended period of time has also been reported. McCrea and colleagues reported that more than half of patients with severe traumatic brain injury achieved a good functional outcome at one year, with nearly 20% of survivors reporting no disability at one year.[11]

Despite an increase in research demonstrating that critically ill ICH patients predetermined to have a poor prognosis not only survive, but achieve functional independence,[8,10] few studies have examined the long-term HRQoL of ICH survivors. Discrepancies between functional outcome and patient-reported HRQoL have been described in patients with acute neurologic injury,[12–14] which raises the question of whether the standard metric of recovery after ICH, functional outcome, holistically encompasses the health state of ICH survivors. Thus, the paucity of literature surrounding the long-term HRQoL of ICH survivors creates an unacceptable gap in essential knowledge that may impact prognostication during the acute phase of injury and goals of care decisions for severely injured ICH patients.

Synthesis of Results

This dissertation study has examined the predictors of WLST, and described the long-term recovery trajectories of ICH survivors, including those with similar baseline disease severity to ICH patients who had WLST. Using longitudinal, validated data from two, NIH-sponsored clinical trials, CLEAR III[15] and MISTIE III,[16] the results of this research have demonstrated the following:

(1) The same disease severity predictors of poor outcome, first described in the late 1980s, continue to influence the decision to withdraw life-sustaining treatment in the critically ill ICH patient population;

(2) More than half of ICH survivors achieve functional independence by one year, and the majority return home by one year;

(3) The HRQoL of ICH survivors varies with level of functional recovery with improvement in self-reported HRQoL within the first six months after ICH;

(4) Of the ICH survivors with initial severe disability (clinical and demographic characteristics similar to those who had WLST), self-reported HRQoL, specifically for those living at home, approached the US population norm of HRQoL for age-matched persons at one year.

Added Value of Dissertation Research

The findings of this research suggest that biases in the early prediction of outcomes appear to influence the decision to withdraw life-sustaining treatment; yet, the early prognostication of pessimistic outcomes does not appear to match the potential for acceptable HRQoL as reported by ICH survivors. Specifically, this study questions the current practice of early identification of poor ICH outcomes in concert with goals of care decision making as it lacks sufficient precision for this highly consequential decision. Importantly, this dissertation research has significant implications on goals of care decisions for the most vulnerable of patients with ICH, specifically those who are unable to speak for themselves. Accordingly, this study has significant ethical and moral implications which raises a critical question: Should all critically ill patients with ICH be treated aggressively unless explicitly stated prior to diagnosis? Only the ICH survivors with the lived experience can answer this question. The voice of survivors should be considered in ICH outcomes research.

The National Institute of Nursing Research (NINR) has developed a Strategic Plan "that boldly communicates the discipline's imperative to ensure that all people have the opportunity and ability to achieve optimal health, well-being, and quality of life."[17] This research directly aligns with NINR's research framework "that encourages research that informs practice and policy, and improves health and quality of life for all people, their families and communities, and the society in which they live."[17] Considering that nurses have been instrumental in acknowledging that health must be considered within the greater context of people's lives, nurse scientists are uniquely positioned to leverage the voice of the vulnerable in multidisciplinary research.

Outcomes research that aims to incorporate HRQoL survivor data in the goals of care decision-making process for patients with severe ICH, and spans from the acute phase to neurorehabilitation and reintegration into society, is greatly needed.

Future Directions for Research

Future studies investigating the long-term HRQoL trajectories of survivors of ICH, including those with initial severe disability, and how adapting to a new disability state changes an individual's perspective of their health over time, are critically needed. Additionally, there is an unmet need to understand factors, specifically those in relation to prognostication, affecting the deliberation process in goals of care decision making, to ensure high-quality decisions. Research that explores decisional conflict and decision regret among the surrogate decision makers of critically ill patients with ICH is needed to understand the psychological impact of making consequential decisions for patients with severe ICH. Lastly, the development of innovative decision-making interventions that include ICH survivor-reported outcomes and surrogate data to help optimize goals of care decision making are urgently needed.

Summary

In conclusion, this dissertation research has highlighted the need to understand recovery from the perspective of those living the life lived, the ICH survivors. The avoidance of early pessimistic predictions may allow for a better understanding of the natural history of ICH and, thus, improve the ability to prognosticate their recovery. An informed, shared decision-making framework, one that includes the use of ICH survivor-based HRQoL data and the normalization of uncertainty in the prognostication process, has the potential to improve future predictions of recovery after ICH, and provide valuable information that may optimize surrogate decision maker experiences in making high-quality, consequential decisions.

References

1. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology*. 2001;56:766-772.
2. Frontera JA, Curtis JR, Nelson JE, et al. Integrating Palliative Care Into the Care of Neurocritically Ill Patients: A Report From the Improving Palliative Care in the ICU Project Advisory Board and the Center to Advance Palliative Care. *Crit Care Med*. 2015;43:1964-1977. doi:10.1097/CCM.0000000000001131
3. Hemphill, JC, Bonovich, DC, Besmertis, L, Manley, GT, Johnston S. The ICH Score: A Simple, Reliable Grading Scale for Intracerebral Hemorrhage. *Stroke*. 2001;32:891-897.
4. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: The FUNC score. *Stroke*. 2008;39(8):2304-2309. doi:10.1161/STROKEAHA.107.512202
5. Zahuranec DB, Morgenstern LB, Sánchez BN, Resnicow K, White DB, Hemphill JC. Do-not-resuscitate orders and predictive models after intracerebral hemorrhage. *Neurology*. 2010;75(7):626-633. doi:10.1212/WNL.0b013e3181ed9cc9
6. Hemphill JC. Do-not-resuscitate orders, unintended consequences, and the ripple effect. *Crit Care*. 2007;11(2):11-12. doi:10.1186/cc5687
7. Zahuranec DB, Brown DL, Lisabeth LD, et al. Early care limitations independently predict mortality after intracerebral hemorrhage. *Neurology*. 2007;68(20):1651-1657. doi:10.1212/01.wnl.0000261906.93238.72
8. Shah VA, Thompson RE, Yenokyan G, et al. One-Year Outcome Trajectories and Factors Associated with Functional Recovery among Survivors of Intracerebral and Intraventricular Hemorrhage with Initial Severe Disability. *JAMA Neurol*. 2022;79(9):856-868. doi:10.1001/jamaneurol.2022.1991
9. Morgenstern LB, Zahuranec DB, Sánchez BN, et al. Full medical support for intracerebral hemorrhage. *Neurology*. 2015;84(17):1739-1744. doi:10.1212/WNL.0000000000001525
10. Jakobsson J, Redebrandt HN, Tobieson L, et al. Long-Term Functional Outcome and Quality of Life

After Surgical Evacuation of Spontaneous Supratentorial Intracerebral Hemorrhage: Results from a Swedish Nationwide Cohort. *World Neurosurg*. 2022:351-363. doi:10.1016/j.wneu.2022.11.013

11. McCrea MA, Giacino JT, Barber J, et al. Functional Outcomes over the First Year after Moderate to Severe Traumatic Brain Injury in the Prospective, Longitudinal TRACK-TBI Study. *JAMA Neurol*. 2021;78(8):982-992. doi:10.1001/jamaneurol.2021.2043
12. Vahedi K, Benoist L, Kurtz A, et al. Quality of life after decompressive craniectomy for malignant middle cerebral artery infarction [1]. *J Neurol Neurosurg Psychiatry*. 2005;76(8):1181-1182. doi:10.1136/jnnp.2004.058537
13. Polding LC, Tate WJ, Mlynash M, et al. Quality of Life in Physical, Social, and Cognitive Domains Improves with Endovascular Therapy in the DEFUSE 3 Trial. *Stroke*. 2021;52(4):1185-1191. doi:10.1161/STROKEAHA.120.031490
14. Retel Helmrich IRA, Van Klaveren D, Andelic N, et al. Discrepancy between disability and reported well-being after traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2022;93(7):785-796. doi:10.1136/jnnp-2021-326615
15. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet*. 2017;389(10069):603-611. doi:10.1016/S0140-6736(16)32410-2
16. Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet*. 2019;393(10175):1021-1032. doi:10.1016/S0140-6736(19)30195-3
17. National Institute of Nursing Research. The National Institute of Nursing Research 2022-2026 Strategic Plan. https://www.ninr.nih.gov/aboutninr/ninr-mission-and-strategic-plan. Accessed February 25, 2023.