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Clinical Prediction of Functional Outcome after Ischemic Stroke: The Surprising Importance of Periventricular White Matter Disease and Race

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Abstract

Background—We sought 0074o build models that address questions of interest to patients and families by predicting short- and long-term mortality and functional outcome after ischemic stroke, while allowing for risk re-stratification as comorbid events accumulate.

Methods—A cohort of 451 ischemic stroke subjects in 1999 were interviewed during hospitalization, at 3 months, and at approximately 4 years. Medical records from the acute hospitalization were abstracted. All hospitalizations for 3 months post-stroke were reviewed to ascertain medical and psychiatric comorbidities, which were categorized for analysis. Multivariable models were derived to predict mortality and functional outcome (modified Rankin Scale) at 3 months and 4 years. Comorbidities were included as modifiers of the 3 month models, and included in 4-year predictions.

Results—Post-stroke medical and psychiatric comorbidities significantly increased short term post-stroke mortality and morbidity. Severe periventricular white matter disease (PVWMD) was significantly associated with poor functional outcome at 3 months, independent of other factors, such as diabetes and age; inclusion of this imaging variable eliminated other traditional risk factors often found in stroke outcomes models. Outcome at 3 months was a significant predictor of long-term mortality and functional outcome. Black race was a predictor of 4-year mortality.

Conclusions—We propose that predictive models for stroke outcome, as well as analysis of clinical trials, should include adjustment for comorbid conditions. The effects of PVWMD on short-term functional outcomes and black race on long-term mortality are findings that require confirmation.

Keywords

Ischemic stroke; outcomes; white matter disease; race; models; predicted models

Introduction

One of the hardest questions asked at a stroke patient's bedside in the acute care setting is "What is the prognosis?" This question can be reframed as a progressive series of questions. During the stroke hospitalization, the clinician is asked, "Will I die?" and "If I don't die, will

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I be disabled?" After discharge from the acute hospitalization, e.g., during outpatient follow-up, additional questions arise: "What is my long-term life expectancy?" and ""Will my disabilities improve over time?"

Numerous predictive models exist. Some models for predicting short-term outcome are built on data that are available only during the acute hospitalization, with no adjustment made for subsequent comorbid events[1–3] that may be relevant to post-stroke outcomes.[4, 5] Other models take change over time into account with regard to post-stroke recovery, but also do not account for subsequent events.[6] Further, models for mortality and outcome in both the short and long term are rarely derived from longitudinal datasets with comprehensive measurements made at different time points.

We sought to demonstrate a method for developing predictive models that correspond to the pertinent questions asked by patients about both short- and long-term prognosis after ischemic stroke. We used data from a well-characterized cohort of patients who were assessed over a four-year period following their strokes. Our aim was to test the feasibility of a practical approach where the model for predicting post-stroke outcome changes over time, and which uses all data that are readily available at the particular points in time when questions about prognosis are asked. In our study, we collected data about post-stroke medical and psychiatric comorbidities, some of which were due to stroke and others that were not. We hypothesized that three-month outcomes are impacted by the occurrence of these comorbidities and that four-year outcomes are impacted by three-month outcomes. We present statistical models that use such a theoretical framework, and we suggest that the questions asked in the clinical setting be used to drive outcomes research so that it is directly translatable to the clinical arena.

Methods

A. Subject ascertainment and short-term follow-up

This work was undertaken as part of the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), a five-county population-based study that tracks the regional incidence of stroke and case fatality. This study was approved by the Institutional Review Boards at all participating institutions, and detailed methods have been previously described.[7–9]

As part of Phase III of the GCNKSS, a cohort of ischemic stroke patients was prospectively identified from the larger stroke population. After a potential subject was identified as having had an ischemic stroke, the subject's treating physician was contacted for permission to approach the patient for informed consent. Informed consent was obtained either from the patient, or from a proxy for patients who were unable to supply reliable information or were unresponsive, aphasic, or confused. *[The order of preference for proxy was the spouse or live-in companion, adult child, parent, sibling, or close friend of the person.]* All ischemic stroke patients during 1999 at any of the 17 hospitals in our study area were eligible for enrollment; the primary reason for not enrolling was discharge prior to contact for consent.

For each case, trained research nurses abstracted demographics, presenting symptoms, functional status prior to stroke, social, family, and medical histories, medications (including treatment with tPA as documented in the medical record), testing and laboratory results, and imaging studies. Data were recorded on case report forms. Stroke severity (retrospective NIH stroke scale score; NIHSS) was estimated from the medical record utilizing the methods of Williams,[10] which we have subsequently validated.[11]

Stroke team physicians reviewed each abstract and all available imaging studies to verify that each case was a stroke and to classify the subtype of stroke. Three-dimensional infarct volumes were measured using the modified ellipsoid method,[12] and the degree of periventricular white

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matter changes was assessed using a four-level ordinal scale (none, mild, moderate, or severe) similar to the methodology of Fazekas[13] When patients had multiple imaging studies, the first MRI scan was preferentially used for white matter grading.

This cohort was followed over time to determine both short-term functional outcome (assessed via an initial interview and a three-month interview) and long-term functional outcome (assessed via interview at four years).

Initial interview—Each consented patient or proxy underwent an initial face-to-face structured interview with a research nurse. The interview included questions about recent systemic illness, recent medications, past medical history, family history, and risk factors, including weight, eating behaviors, subjective stress ratings, and caffeine, alcohol, and tobacco use.

Three-month interview—At three months following stroke, research nurses telephoned patients or proxies and asked about vital status, post-stroke hospitalizations, medical contacts other than simple office visits, and current residence. The modified Rankin Scale (mRS) and Barthel Index (BI) were used to determine the functional status of each surviving patient.

Assessment of comorbidities—Research nurses retrospectively reviewed the hospital charts from the acute setting and all hospitalizations that had occurred in the three-month post-stroke period to document any new instance of an acute condition, new onset of a chronic condition, or exacerbation of a chronic condition, along with dates of occurrence. Thus, comorbidities were defined by documentation in the medical record. Case report forms were similar to those used by Johnston et al.[4] Post-stroke mRS was estimated at time of hospital discharge or at 30 days, if available. Because comorbidities were obtained retrospectively, it was not possible to determine whether a medical or psychological condition occurred as a direct result of the stroke. Comorbidities were classified by body system according to the National Cancer Institute's Cancer Treatment Evaluation Program's Common Terminology Criteria for Adverse Events, version 3 (http://ctep.cancer.gov/reporting/ctc.html); categories included neurologic/neurovascular, cardiopulmonary, infectious, and psychiatric. In addition, we classified *potentially* fatal conditions as "life threatening." Because data were collected retrospectively, we could not always determine whether a GI bleed, for example, was mild or life threatening. Thus, we treated any GI bleed as "life threatening." We also collapsed comorbidities arising from cardiopulmonary, infectious, vascular (deep venous thrombosis), skin (decubitus ulcer), and other body systems into a "medical comorbidity" category. Groupings were not mutually exclusive—for example, a urinary tract infection was counted in both the "infectious" and "medical" categories. *[A detailed description of the comorbidity categories appears in Table A of the appendix.]*

Four-year interview—Each surviving cohort member, or their proxy, was interviewed approximately four years post-stroke. Functional outcomes were categorized using the mRS and BI. The patient or proxy was asked to recollect whether comorbidities had occurred.

Mortality—Mortality was assessed by use of Ohio and Kentucky death records (complete through 2003). The Social Security Death Index was searched via Rootsweb for deaths not already found in the Ohio and Kentucky records. Deaths found via chart review were verified by one or more of the three aforementioned sources.

B. Statistical Analysis

Logistic regression was used to predict the probability of death and linear regression was used to predict functional outcome at three months and four years. While we collected both mRS

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and BI functional outcome data, the mRS was our primary measure of functional status, and only mRS results are presented below. For modeling three-month mortality and functional outcome, univariable analyses identified independent predictors from among clinically relevant variables that were reasonably available to physicians during the acute hospitalization following stroke admission, i.e., demographics, medical history, acute imaging results, acute treatments, stroke severity scores (retrospective NIHSS), and measures of functional independence (mRS). Only these variables were considered in building the primary model for predicting three-month outcomes. The effects of comorbidities that occurred during the three-month period were considered separately, as modifiers of the predicted outcome. Although post-stroke therapy (physical, occupational, and speech therapy) might also modify outcome, it was not included in the model due to its bi-directional effect; patients with excellent or poor post-stroke status were both unlikely to receive therapy.

For modeling four-year outcomes, variables available at baseline and in the short term (three months following stroke) were considered, based on our theoretical framework that long-term survival and functional status are likely to be related to short-term recovery. Consideration of the variables available to the clinician at three months is akin to the questions patients ask at their three-month follow-up visit regarding long-term prognosis. Significant predictors were then combined into a single model, and non-significant terms were removed using a manual backwards stepwise procedure.

For all modeling, colinearity of predictor variables was evaluated to minimize the likelihood of inappropriate inferences. At each stage of model development, the primary criterion for removal was a significance level less than 0.05. The impact of a variable's removal was gauged by inspection of the regression parameter estimates to ensure that interactions and spurious relationships were not evident. In addition, because removing a variable based solely on significance level might result in a large change in model accuracy, non-significant variables were not removed if the C-statistic (for logistic regression) or the R^2 (for linear regression) changed more than 0.1. Analyses were conducted using SPSS version 14.0 (SPSS Inc., Chicago, IL).

[The functional outcome we modeled was the mRS, a six-level ordinal variable. We elected to use linear regression for simplicity of interpreting our results. While using the mRS as a primary outcome variable in linear regression is inconsistent with the requirement that the dependent variable be continuous, the alternatives have significant disadvantages. Binary logistic regression would be simple to interpret, yet this would require dichotomization of the mRS at some arbitrary cut point. Appropriate selection of the cut point would be highly dependent on the individual concerns of the patient and the patient's care-givers, and might variably be set as the point at which any disability is apparent (an mRS of 2 or above) or the point at which complete independence is lost (an mRS of 3 or greater). Considering a single binary cut point, therefore, does not satisfy our goal of answering the questions that patients might have. More appropriate would be multinomial logistic regression (or ordinal regression). With this approach, odds ratios are computed that indicate the effect of the predictor variable on the odds of having a certain mRS score compared to a reference mRS score. Odds ratios would be computed for each level of the mRS compared to the selected reference, which would result in a complex of parameter estimates. This would not satisfy our requirement of offering a straightforward explanation to patients of how they might fair following their stroke. Based on the assumption that the mRS is a coarse measure of an underlying continuous distribution of functionality, the underlying distribution is appropriately modeled using the linear regression technique.]

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Results

A cohort of 451 ischemic stroke patients agreed to participate in the longitudinal study. At baseline, there were 341 subject interviews and 110 proxy interviews. Functional outcome was measured for 406 of 415 surviving patients at three months, and for 154 of 301 surviving patients at four years. Figure 1 documents the inclusion and exclusion of patients in the samples used for the development of each predictive model. The characteristics of the four samples are given in Table 1. Due to the large number of patients excluded from the 4-year functional status model, these are also described in Table 1 to ascertain follow-up bias. Final multivariable models for functional outcome are presented in Table 2 and Table 3 and for mortality in online Table 2 and Table 3. *[For each model, univariable analyses are presented in the appendix, including model-building steps.]*

Three-Month Outcomes

The description of univariable and multivariable analyses for predicting mortality at 3 months is available online. When combined into a multivariable model, age and post-stroke Rankin were significant independent predictors of three-month mortality (Table 2, model C-statistic 0.803, SE 0.038). Comorbidities, with the exception of psychiatric comorbidities, that occurred in the three months after stroke tended to increase the odds of three-month mortality.

Among patients who survived to three months post-stroke, univariable predictors of worse functional status included older age, not being partnered, not being a smoker, having diabetes, having a prior stroke, having PVWMD, having worse pre-stroke and post-stroke functional status, greater stroke severity, and not being treated with thrombolytics. Additionally, male gender, white race, and increasing lesion volume had a tendency towards decreasing three-month functional status *[(appendix, Table B)]*. In multivariable modeling, age, diabetes, severe PVWMD, pre-and post-stroke functional status, and stroke severity were related to three-month mRS (Table 3, $R^2 = 0.484$). Medical, infectious, and neurovascular complications that occurred within the three months after stroke significantly worsened three-month functional outcome. *[Steps for the three-month models are shown in appendix Table C and appendix Table D]*.

Long-term outcomes

The description of univariable and multivariable analyses for predicting mortality at 3 months is available online. The final multivariable model (Online Table 2) included age, non-white race, and three-month functional status as the primary predictors of four-year mortality (C-statistic 0.740; SE 0.026).

Among patients who survived to four years, univariable predictors of worse functional status included older age at stroke, having diabetes, having had a prior stroke, poor functional status at pre-stroke, post-stroke, and three months, greater stroke severity, and having psychiatric, infectious, or neurovascular comorbidities. Being treated with thrombolytics improved four-year functional status. PVWMD and increased lesion volume tended to worsen functional outcome but were not significant *[(appendix, Table E)]*. In the final multivariable model (Table 3), functional status (pre-stroke, post-stroke, and at three months), a history of a prior stroke, and the occurrence of infectious complications within three months after stroke all independently worsened four-year mRS (R^2=0.508). *[Steps for the four-year models are shown in appendix Table F and appendix Table G.]*

Discussion

We have shown that statistical modeling driven by the clinical questions asked at different time points during a patient's post-stroke treatment and follow-up can be used to develop clinically

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useful models that are not static. Mortality and functional status outcomes benefit from different considerations, and in prognosticating long-term outcome, short-term recovery cannot be ignored. Our results suggest several unique findings. Our short-term model for functional outcomes reveals that severe PVWMD was associated with poor outcome. Furthermore, non-white race significantly predicts four-year mortality. We are currently in the process of finalizing data collection on a similar cohort of patients to which we will apply our models to assess not only the feasibility of this practical way of thinking but also the validity of the models themselves. As such, we discuss here the hypotheses generated by our exploration and the potential impact of revising the manner in which outcomes research in stroke is designed so that clinically practical questions are asked and answered.

With regard to the modeling, we feel that it is insufficient to look at one model that combines morbidity and mortality endpoints as they confound each other. Separating these outcomes is necessary for understanding which factors truly impact each endpoint, and our results suggest that different variables are relevant to each endpoint. Although this approach requires building two models for each time point, this process corresponds naturally to the clinical questions that patients and families will ask after a stroke has occurred. It is also best to consider how initial risk is modified by subsequent factors like treatment and comorbidities, which allows for progressive risk re-stratification as subsequent events occur in the post-stroke setting. We have demonstrated that a range of comorbidities occurring in the post stroke setting, whether due to the stroke or not, impact mortality and functional outcome for stroke survivors in both the short and long term. Our data add to the growing body of literature showing that medical comorbidities significantly and independently influence post-stroke outcome, including not only those caused by the stroke, such as aspiration pneumonia or DVT, but also those that were present before the stroke, those made worse by the stroke, and/or those intermittent chronic conditions with exacerbations after the stroke.[4, 5] This further emphasizes the importance of diligent post-stroke medical care to prevent or limit the development of these comorbidities, and implies that future clinical trials and studies of post-stroke outcome must take comorbid conditions into account. Future work must also consider whether it is overall medical illness that limits post-stroke recovery, or alternatively whether medications taken for these various conditions can inhibit recovery. Regardless, our findings reinforce the need for intense medical vigilance in the post-stroke setting, so as to limit the impact of preventable comordibities on recovery.

Our results suggest several unique findings. Our short-term model for functional outcomes reveals that severe PVWMD was associated with poor outcome in our cohort. Previous work has shown that imaging findings such as stroke volume can significantly impact prediction of post-stroke outcomes.[3, 14] While it is well known that PVWMD is associated with post-stroke mortality and risk for stroke and cardiac events,[15–19] the association of PVWMD with poor post-stroke outcome has been reported only once before. In that report, as in our model, risk factors traditionally associated with poor outcome in univariable modeling became insignificant when PVWMD was included in multivariable models.[20] Given that these traditional risk factors are associated with the development of PVWMD[21–22], we propose a new conceptual model for stroke recovery (Figure 2). As shown, severity of stroke is one incontrovertible determinant of outcome. However, it is conceivable that recovery is limited for those patients with severe PVWMD due to structural damage to the white matter tracts, limiting the physiologic process of neuroplasticity. Notably, PVWMD grade was independent of stroke severity (stroke severity did not differ between those with and without severe PVWMD; $p = 0.816$ using Mann-Whitney U test). The limited neuroplasticity may be related to the effects of chronic white matter ischemia on growth factor production, stem cells, or other neurobiologic factors. As such, traditional risk factors contribute to poor outcome by leading to increased PVWMD. Furthermore, PVWMD has been associated with higher incidence of cognitive decline and dementia,[23–25] and those with greater incidence of cognitive decline will

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likely have less capacity for motor learning and functional recovery after stroke, leading to poor functional outcomes.

The association of severe PVWMD with poor post-stroke outcome must be explored in future studies, and more sophisticated quantitation of PVWMD burden should be undertaken. Figure 3 demonstrates that while some effect of lesser grades of PVWMD is evident, this does not impact on outcomes nearly as much as severe PVWMD. If severe PVWMD (or white matter disease burden above a more sophisticated, quantitative threshold) is indeed proven to be associated with inability to recover after stroke, this will have important implications for future clinical trials studying stroke recovery. Inclusion of patients with severe PVWMD in a trial would potentially dilute the effect seen in the intervention arm if they are significantly less likely to recover. Alternatively, some therapies may be specifically targeted towards those patients with severe PVWMD who are otherwise unlikely or unable to recover. Interventions such as constraint induced therapy, epidural cortical stimulation, and others are already being tested to enhance post-stroke recovery,[26,27] and considering PVWMD as a modifier of the intervention might have significant implications particularly for studies that employ motor learning. The association between PVWMD and outcomes must be studied further in order to improve inclusion and exclusion criteria for future studies, thus allowing faster and more-cost efficient clinical trials to test recovery interventions. Finally, as PVWMD has been associated with cognitive decline,[23–25] cognitive testing would be prudent in future recovery studies since motor learning may be impaired in those with highest PVWMD burden.

It is not surprising that outcomes at three months are highly significant predictors of outcomes at four years, although this approach is not commonly considered. It is surprising, however, that non-white race significantly predicts four-year mortality. In our study, there were two Hispanic patients and one Asian patient in the non-white group, the remaining 146 were black. Thus, it might be concluded that this finding is driven by a difference between blacks and whites, although this may be a unique finding within the particular cohort being studied. Mortality data from the CDC have shown that stroke mortality is higher for blacks than whites, but we have shown in other studies that this is primarily due to higher stroke incidence in blacks as compared to whites.[8] Previous analyses of long-term mortality in our population have not shown race to be a significant predictor of mortality at 30 days, 90 days, or 1 year, after adjusting for age.[8, 28] Some might interpret the effect of race presented here as a surrogate for the effects of socioeconomic status (SES), which we have previously shown to be related to stroke incidence.[29] The current study did not include the collection of detailed socioeconomic data. We did capture insurance status, and, in an attempt to use this as a surrogate for SES, we included this among our predictor variables. However, in univariable models this was not found to be associated with outcomes. The finding that race may play a significant role in long-term post-stroke mortality must be confirmed in subsequent studies, and highlights the need to explore the interrelation of race, health culture and SES, and their impact on long-term outcomes. Other factors could also be relevant such as racial differences in risk factor control or management of chronic diseases.

[There were several findings that cannot be easily explained, such as the apparent beneficial effect of having smoked or having high cholesterol, which were found only in univariable analyses. This finding may be related to unique characteristics of the cohort willing to participate in the study both in the short and long term or survival bias.]

We collected a convenience sample of stroke patients, which is associated with survival bias and bias arising from early discharge, although other undetected biases might also occur. These biases are an expected component of our approach and modify our models to being applicable only to patients who survive the first few days following stroke and who remain hospitalized acutely. Testing and validation of the models are necessary, and this is currently underway.

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Another limitation of our models is non-uniform collection of post-stroke mRS data (ranging from hospital discharge to 30 days post-stroke). Comorbidities were retrospectively determined by documentation in the medical record, and there may be biases due to underdocumentation of some conditions, especially depression and anxiety. There was significant loss to follow-up between 3 months and 4 years, and the resulting biases shown in Table 1 may confound the results for long-term functional outcome. Available imaging review was often for CT scans, not MRI's. We did not consider "silent cerebral infarctions" (SCI's) for this analysis. In the dataset currently being assembled for testing our models, we will be able to investigate the impact of SCI's further. Finally, the overlap in categories of comorbidities makes use of models for prediction cumbersome, and further refinement of our methodology for handling these comorbidities is necessary.

In summary, we present an approach to modeling outcomes following stroke that is driven by the questions asked by patients and is relevant to the various time points when a clinician must attempt to answer them; this approach is also responsive to subsequent events that impact the outcomes. We contend that this is an improvement upon traditional statistical modeling, and that incorporating such an approach in clinical trials as well as observational research will enhance the global adoption of new treatments, both acute and longer term, through improved contextualization of outcomes. In the course of our analyses, we have discovered several important relationships that warrant further investigation, including the associations of severe PVWMD with poor functional outcome, and of black race with long-term post-stroke mortality.

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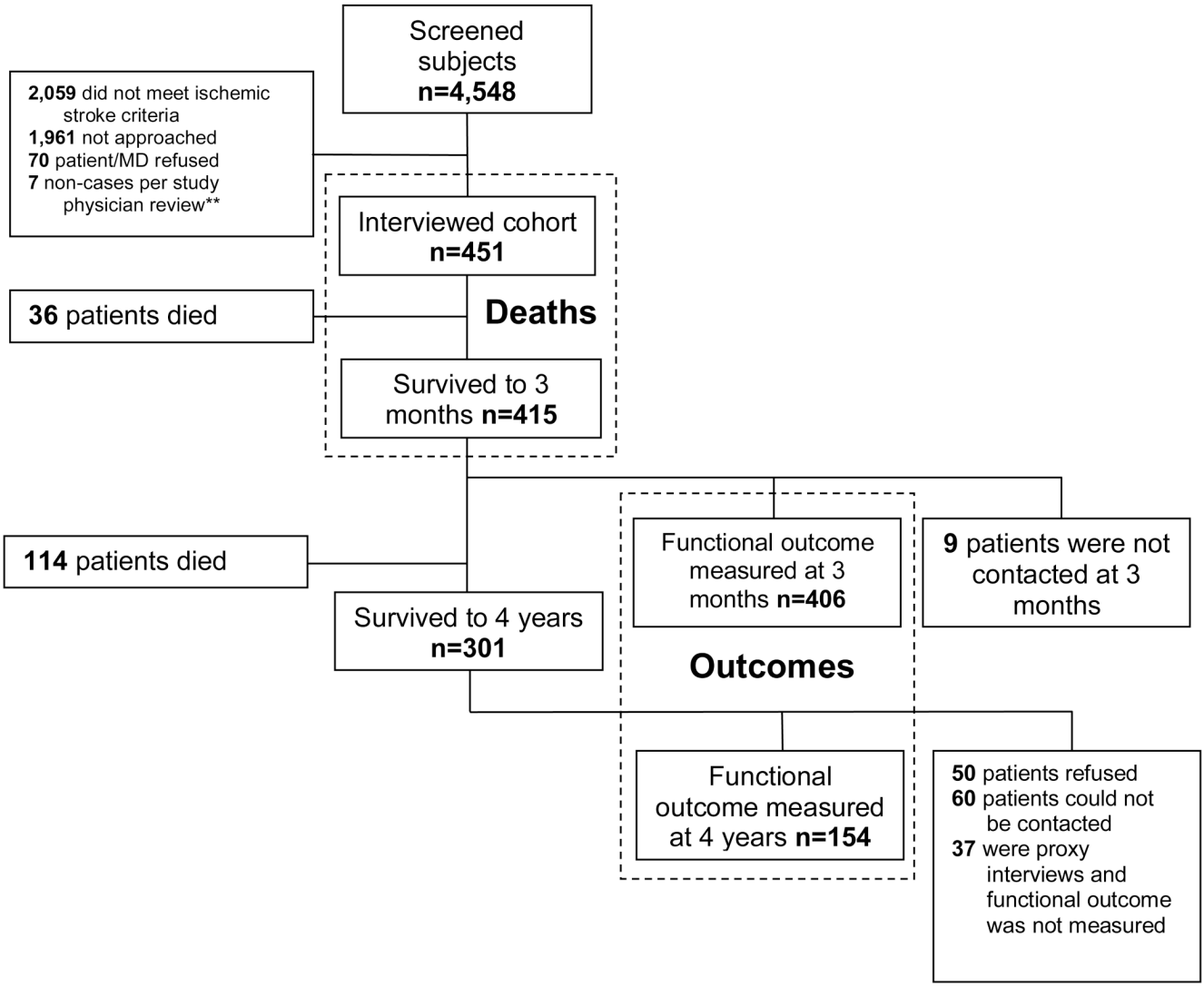

Figure 1.

Patients included and excluded in each analysis. Derivation of samples used for modeling the probability of death at three months and four years, and to predict functional outcome at three months and four years is shown.

Footnote: **For 2,059 patients with potential ischemic stroke by admission diagnosis, prospective screening revealed that 1,605 did not have strokes and 454 had TIAs; 1,961 potential ischemic strokes were not able to be approached for consent prior to hospital discharge; there were 70 refusals—2 treating physicians refused to allow contact with their patients, and 68 ischemic stroke patients declined to participate. Thus, a total of 458 patients were interviewed, but 7 cases subsequently determined not to be strokes by study physician review were not included in the final cohort.

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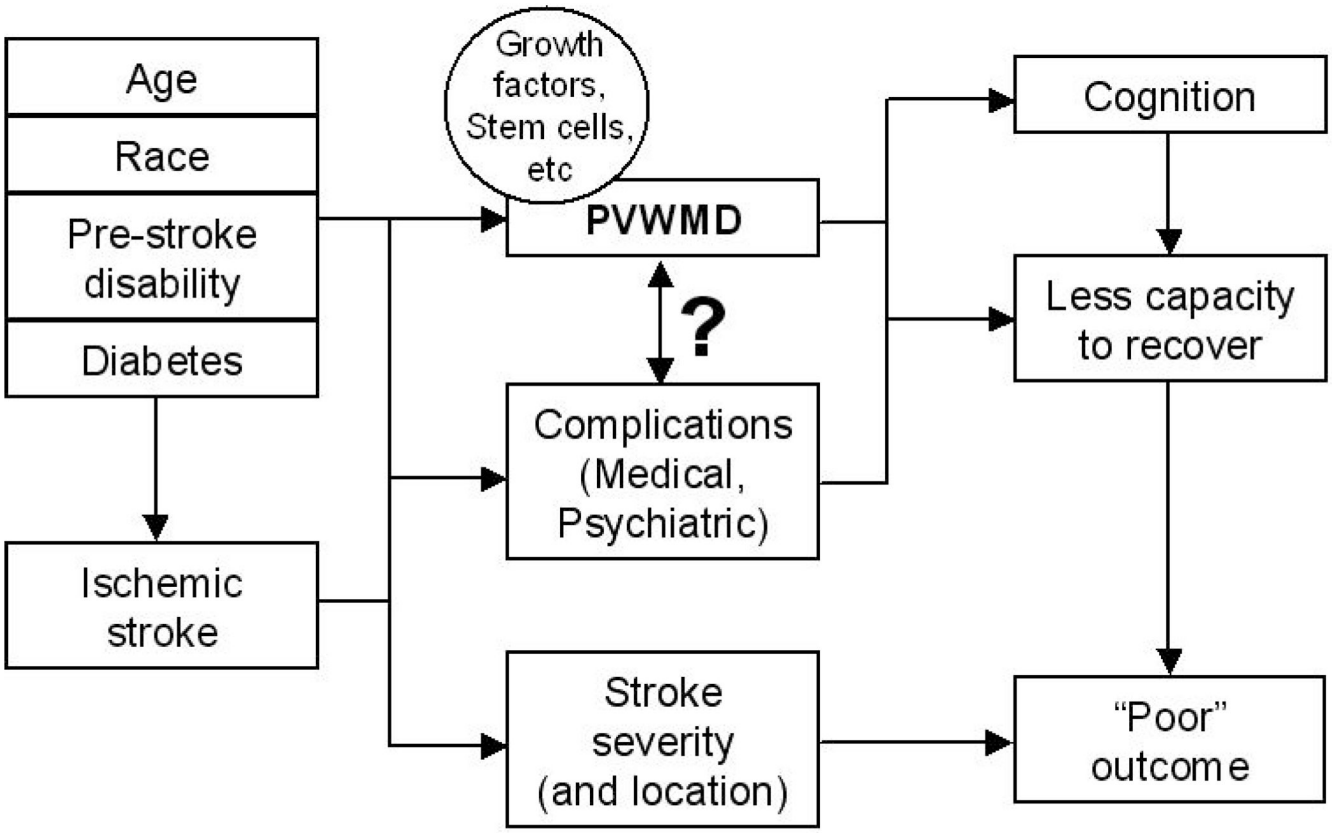

Figure 2.
Theoretical model describing potential mechanisms altering functional outcome post-stroke

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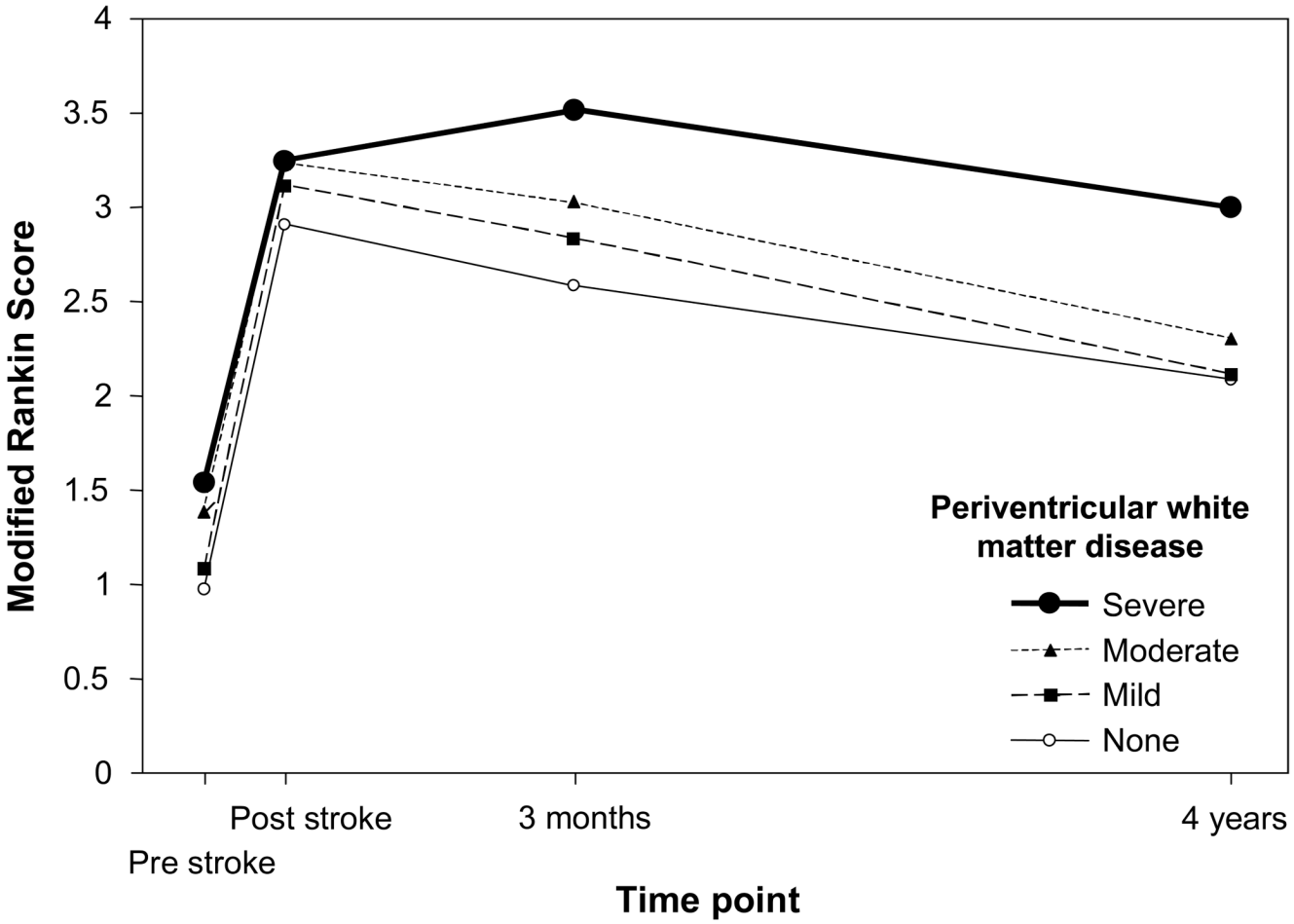

Figure 3.
Relationship between periventricular white matter disease and functional outcome following stroke.

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Table 1

Characteristics of patients included in this study (counts and percents, unless otherwise noted)

	Ischemic stroke cohort n=451		Survivors at 3 months n=415		Survivors with 3-month Rankin n=406		Survivors at 4 years n=301		Survivors with 4-year Rankin n=154		Survivors without 4-year Rankin N=147	
Age (mean ± SD in years)	69.7	(13.7)	68.9	(13.7)	69.0	(13.8)	66.9	(14.3)	65.4	(13.3)	68.5	(15.1)
Male	187	(41.5)	174.0	(41.9)	169	(41.6)	123	(40.9)	65	(42.2)	58	(39.5)
Female	264	(58.5)	241.0	(58.1)	237	(58.4)	178	(59.1)	89	(57.8)	89	(60.5)
White	302	(67.0)	275.0	(66.3)	272	(67.0)	212	(70.4)	114	(74.0)	49	(33.3)
Non-white	149	(33.0)	140.0	(33.7)	134	(33.0)	89	(29.6)	40	(26.0)	98	(66.7)
Insured at stroke	413	(92.4)	379.0	(92.2)	374	(93.0)	275	(92.0)	143	(92.9)	132	(91.0)
Partnered at stroke	193	(46.5)	179	(46.9)	175	(46.8)	140	(50.4)	83	(57.2)	57	(42.9)
Smoker	205	(45.5)	190	(45.8)	183	(45.1)	153	(50.8)	81	(52.6)	72	(49.0)
Diabetes	183	(40.6)	171	(41.2)	166	(40.9)	116	(38.5)	61	(39.6)	55	(37.4)
Hypertension	320	(71.0)	293	(70.6)	285	(70.2)	212	(70.4)	108	(70.1)	104	(70.7)
Hyperlipidemia	138	(30.6)	127	(30.6)	126	(31.0)	103	(34.2)	60	(39.0)	43	(29.3)
History of coronary artery disease	132	(33.5)	121	(33.2)	118	(33.1)	83	(31.8)	37	(28.2)	46	(35.4)
Prior stroke	130	(28.8)	124	(29.9)	123	(30.3)	80	(26.6)	43	(27.9)	37	(25.2)
No PVWMD	140	(35.3)	130	(35.8)	129	(36.2)	103	(38.9)	58	(42.6)	45	(34.9)
Mild PVWMD	117	(29.5)	108	(29.8)	107	(30.1)	78	(29.4)	36	(26.5)	42	(32.6)
Moderate PVWMD	94	(23.7)	87	(24.0)	83	(23.3)	56	(21.1)	33	(24.3)	23	(17.8)
Severe PVWMD	46	(11.6)	38	(10.5)	37	(10.4)	28	(10.6)	9	(6.6)	19	(14.7)
Pre-stroke Rankin (mean ± SD)	1.2	(1.6)	1.2	(1.6)	1.2	(1.6)	0.9	(1.5)	0.7	(1.2)	1.2	(1.7)
Post-stroke Rankin (mean ± SD)	3.2	(1.3)	3.1	(1.3)	3.1	(1.3)	2.9	(1.3)	2.8	(1.3)	3.1	(1.3)
3-month Rankin (mean ± SD)					2.9	(1.5)	2.6	(1.5)	2.4	(1.4)	2.8	(1.5)
4-year Rankin (mean ± SD)									2.2	(1.5)		
Lesion volume (mean ± SD)	20.4	(61.2)	17.2	(57.9)	17.3	(58.10	19.9	(65.4)	22.1	(72.8)	17.6	(56.7)
Estimated NIHSS (mean ± SD)	7.6	(6.0)	7.2	(5.7)	7.3	(5.7)	7.3	(5.9)	7.2	(5.5)	7.5	(6.3)
Thrombolytic therapy	39	(8.7)	35	(8.5)	35	(8.6)	29	(9.7)	18	(11.8)	11	(7.5)
Post stroke therapy	373	(88.2)	348	(89.5)	342	(89.8)	250	(88.0)	128	(88.3)	122	(87.8)
Life threatening complications	198	(43.9)	167	(40.2)	162	(39.9)	119	(39.5)	59	(38.3)	60	(40.8)
Medical complications	244	(54.1)	213	(51.3)	209	(51.5)	146	(48.5)	65	(42.2)	81	(55.1)
Psychiatric complications	142	(31.5)	130	(31.3)	127	(31.3)	88	(29.2)	43	(27.9)	45	(30.6)
Infectious complications	154	(34.1)	129	(31.1)	128	(31.5)	84	(27.9)	36	(23.4)	48	(32.7)
Cardiopulmonary complications	132	(29.3)	111	(26.7)	107	(26.4)	77	(25.6)	37	(24.0)	40	(27.2)
Neurovascular complications	70	(15.5)	55	(13.3)	54	(13.3)	40	(13.3)	19	(12.3)	21	(14.3)

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Online Table 1

Final multivariable model predicting the odds of death at 3 months, and the effect of complications when added to the model

[Online Table 1 Legend: Univariable logistic regression suggested that age, periventricular white matter disease (PVWMD), and pre-stroke functional status were significant predictors of death within three months after stroke. Post-stroke functional status (mRS at discharge or 30 days), stroke severity (as measured by the NIH Stroke Scale), and lesion volume were also predictors of death (Appendix, Table H). When combined into a multivariable model, age and post-stroke Rankin were significant independent predictors of three-month mortality (model C-statistic 0.803, SE 0.038). Comorbidities, with the exception of psychiatric comorbidities, that occurred in the three months after stroke tended to increase the odds of three-month mortality; this association was greatest for life-threatening comorbidities (OR 4.88; 95%CI 1.73–13.80) and least for cardiopulmonary comorbidities (OR 2.38; 95%CI 1.02–5.55). To interpret the models as presented, the initial odds of death would be predicted by the subject's age and post-stroke mRS. If the subject also developed an infectious comorbidity, a revised predictive model for odds of death would contain age, post-stroke mRS, and infectious complications, with an improvement in performance of the model, as measured by an increase in C-statistic, from 0.803 to 0.823.]

	Odds Ratio	***95% CI (Odds Ratio)***	***p***	***C-statistic (SE)***
Age	*1.06*	*1.01 1.10*	*0.008*	*0.803 (0.038)*
Post-stroke Rankin	*3.78*	*1.84 7.77*	*<0.001*	
Impact of individual complications on multivariable model				
Life threatening complications	*4.88*	*(1.73 – 13.80)*	*0.003*	*0.837 (0.039)*
Medical complications	*3.56*	*(1.16 – 10.89)*	*0.026*	*0.823 (0.037)*
Psychiatric complications	*0.75*	*(0.31 – 1.82)*	*0.528*	*0.803 (0.038)*
Infectious complications	*2.99*	*(1.20 – 7.44)*	*0.018*	*0.823 (0.040)*
Cardiopulmonary complications	*2.38*	*(1.02 – 5.55)*	*0.045*	*0.816 (0.039)*
Neurovascular complications	*4.25*	*(1.64 – 11.02)*	*0.003*	*0.816 (0.039)*

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Table 2

Final multivariable model for predicting 3-month functional outcome (mRS), including the effect of complications when added to the model.

	β	95% CI (β)	p	R^2
Age	0.01	(0.00 – 0.02)	0.008	0.484
Diabetes	0.27	(0.02 – 0.51)	0.031	
Severe PVWMD	0.47	(0.07 – 0.87)	0.021	
Pre-stroke Rankin	0.20	(0.12 – 0.28)	<0.001	
Post-stroke Rankin	0.56	(0.46 – 0.67)	<0.001	
Estimated NIHSS	0.03	(0.00 – 0.05)	0.016	
Impact of complications				
Life threatening complications	0.20	(−0.06 – 0.45)	0.127	0.488
Medical complications	0.31	(0.06 – 0.56)	0.014	0.494
Psychiatric complications	0.17	(−0.10 – 0.44)	0.211	0.487
Infectious complications	0.53	(0.27 – 0.79)	<0.001	0.509
Cardiopulmonary complications	0.03	(−0.25 – 0.31)	0.821	0.484
Neurovascular complications	0.52	(0.17 – 0.88)	0.004	0.498

Footnote: It should be noted that these models are not recommended for use in clinical settings at this time, as they have not been validated. However, an example is presented for ease of understanding the model construct.

A 72 yo man with diabetes and severe white matter disease, who has a pre-stroke mRS of 1, and an immediate post-stroke mRS (upon hospitalization) of 3, with an NIHSS of 15. His initial predicted 3 month mRS from the model would be 3.5 (the constant of −0.33 is not shown).

He develops a urinary tract infection and depression. The urinary tract infection, in week 2 after the stroke, adds between 0.3 to 0.5 to his mRS (counted as either infectious or medical comorbidity respectively). The depression is diagnosed at 4 weeks post-stroke. This further adds 0.17 to his predicted 3 mo mRS. Thus, his predicted mRS at 3 months would be estimated to be between 3.97 and 4.17.

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Online Table 2

Final multivariable model for predicting the odds of death at 4 years

[Online Table 2 Legend: Among patients who survived to three months, the odds of death within four years in univariable analyses were increased by older age, non-white race, not being partnered, not being a smoker, not having hyperlipidemia, having had a prior stroke, worse pre-stroke, post-stroke, and three-month functional status, or having had a medical or infectious comorbidity within the first three months after stroke. Being treated with thrombolytics decreased the odds of death (appendix, Table I). The final multivariable model included age, non-white race, and three-month functional status as the primary predictors of four-year mortality (C-statistic 0.740; SE 0.026).]

	Odds Ratio	*95% CI for Odds Ratio*	*p*	*C-statistic (SE)*
Age	*1.05*	*1.02 – 1.07*	*<0.001*	
Non-white vs. white	*2.20*	*1.32 – 3.66*	*0.002*	*0.740 (0.026)*
3-month Rankin	*1.46*	*1.21 – 1.76*	*<0.001*	

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Table 3

Final multivariable model predicting 4-year functional outcome (mRS).

	β	95% CI (β)	p	R^2
Prior stroke	0.58	(0.18 – 0.98)	0.005	
Pre-stroke Rankin	0.18	(0.02 – 0.34)	0.029	
Post-stroke Rankin	0.32	(0.15 – 0.48)	<0.001	0.508
3-month Rankin	0.29	(0.13 – 0.45)	0.001	
Infectious complications	0.76	(0.36 – 1.16)	<0.001	

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Table A

Comorbidity groups……

Neurovascular complications	brain edema, hemorrhagic conversion of ischemic infarct, herniation, ICH/SAH, ischemic stroke, transient ischemic attack
Cardiopulmonary complications	angina/chest pain, cardiac arrest, cardiac dysrythmia, congestive heart failure, hypotension/shock, hypoxia, myocardial infarction, pulmonary edema/pleural effusion, pulmonary embolus, shortness of breath/exacerbation of chronic obstructive pulmonary disease
Infectious complications	cellulitis, infection/fever not otherwise specified, pneumonia, sepsis, urinary tract infection.
Psychiatric complications	Anxiety/agitation, confusion/agitation, depression, hallucinations.
Life threatening complications	angina, brain edema, cardiac arrest, cardiac dysrhythmia, congestive heart failure, gastrointestinal (GI) bleeding, hemorrhagic conversion of ischemic infarct, herniation, hypotension/shock, hypoxia, intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH), ischemic stroke, myocardial infarction, pneumonia, pulmonary edema/pleural effusion, pulmonary embolus, sepsis, shortness of breath/exacerbation of chronic obstructive pulmonary disease.
Medical complications	angina/chest pain, cardiac arrest, cardiac dysrythmia, cellulitis, congestive heart failure, decubitus ulcer, deep venous thrombosis, dehydration, falls resulting in injury, GI bleeding, hyperglycemia, hypoglycemia, hypotension/shock, infection/fever not otherwise specified, myocardial infarction, pneumonia, pulmonary edema/pleural effusion hypoxia, pulmonary embolus, renal insufficiency, sepsis, shortness of breath/exacerbation of chronic obstructive pulmonary disease, urinary tract infection.

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Table B

Univariable models predicting the 3 month outcome. The final multivariable model and the effect of complications on this final model are also shown.

	β	95% CI (β)	P-value
Univariable models			
Age	0.04	(0.03 – 0.05)	<0.001
Female v Male	−0.29	(−0.59 – 0.01)	0.057
Non-white v white	−0.27	(−0.58 – 0.04)	0.091
Insured	−0.02	(−0.60 – 0.56)	0.947
Partnered	−0.40	(−0.71 – −0.09)	0.011
Smoker	−0.67	(−0.96 – −0.38)	<0.001
Diabetes	0.36	(0.06 – 0.66)	0.019
Hypertension	0.18	(−0.14 – 0.50)	0.270
Hyperlipidemia	−0.22	(−0.54 – 0.10)	0.183
History of CAD	0.11	(−0.23 – 0.45)	0.529
Prior stroke	0.50	(0.18 – 0.82)	0.002
Severe PVWMD	0.73	(0.22 – 1.25)	0.005
Pre-stroke Rankin	0.43	(0.35 – 0.51)	<0.001
Post-stroke Rankin	0.76	(0.67 – 0.84)	<0.001
Lesion volume	0.00	(0.00 – 0.01)	0.093
Estimated NIHSS	0.06	(0.04 – 0.09)	0.000
Thrombolytics	−0.56	(−1.08 – −0.04)	0.037

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Table C

Factors influencing the probability of death. Each stage of the modeling process is shown. The variable removed at each step is indicated by an asterisk (*).

		Odds Ratio	95% CI (Odds Ratio)	P-value	C-statistic (SE)
Initial model (maximum correlation coefficient 0.385)					
n=263	Age	1.08	(1.01 – 1.15)	0.023	0.856 (0.046)
	Severe PVWMD	0.61	(0.07 – 5.47)	0.657	
	Pre-stroke Rankin	0.82	(0.58 – 1.17)	0.274	
	Post-stroke Rankin	8.27	(2.36 – 29.02)	0.001	
	Lesion Volume	1.00	(1.00 – 1.01)	0.389	
	Estimated NIHSS*	1.01	(0.91 – 1.12)	0.893	
Step 2					
n=281	Age	1.07	(1.01 – 1.13)	0.030	0.838 (0.046)
	Severe PVWMD*	1.05	(0.20 – 5.53)	0.958	
	Pre-stroke Rankin	0.81	(0.58 – 1.14)	0.230	
	Post-stroke Rankin	7.03	(2.32 – 21.30)	0.001	
	Lesion Volume	1.00	(1.00 – 1.01)	0.237	
Step 3					
n=282	Age	1.07	(1.01 – 1.13)	0.028	0.838 (0.046)
	Pre-stroke Rankin	0.81	(0.58 – 1.14)	0.230	
	Post-stroke Rankin	7.07	(2.34 – 21.36)	0.001	
	Lesion Volume*	1.00	(1.00 – 1.01)	0.238	
Step 4					
n=441	Age	1.06	(1.02 – 1.11)	0.007	0.801 (0.038)
	Pre-stroke Rankin*	0.95	(0.75 – 1.20)	0.654	
	Post-stroke Rankin	3.90	(1.87 – 8.13)	<0.001	
Final model					
n=441	Age	1.06	(1.01 – 1.10)	0.008	0.803 (0.038)
	Post-stroke Rankin	3.78	(1.84 – 7.77)	<0.001	

Note: when excluding imaging data due to the high number of missing cases (imaging available on 263), the same model resulted.

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Table D

Factors influencing 3 month outcomes. Each stage of the modeling process is shown. The variable removed at each step is indicated by an asterisk (*).

			β	95% CI (β)	P-value	R^2
Initial model (maximum correlation coefficient −0.412)						
n=305	Age		0.01	(0.00 – 0.02)	0.047	
	Partnered	−0.04		(−0.30 – 0.22)	0.747	
	Smoker		−0.17	(−0.44 – 0.10)	0.222	
	Diabetes		0.22	(−0.04 – 0.48)	0.101	
	Prior stroke*		−0.03	(−0.31 – 0.26)	0.862	0.486
	Severe PVWMD		0.49	(0.07 – 0.91)	0.021	
	Pre-stroke Rankin		0.22	(0.13 – 0.31)	<0.001	
	Post-stroke Rankin		0.54	(0.42 – 0.66)	<0.001	
	Estimated NIHSS		0.04	(0.01 – 0.06)	0.010	
	Thrombolytics		−0.34	(−0.86 – 0.19)	0.214	
Step 2						
n=305	Age		0.01	(0.00 – 0.02)	0.044	
	Partnered*		−0.04	(−0.30 – 0.22)	0.752	
	Smoker		−0.17	(−0.44 – 0.10)	0.215	
	Diabetes		0.22	(−0.04 – 0.48)	0.103	
	Severe PVWMD		0.49	(0.07 – 0.91)	0.021	0.486
	Pre-stroke Rankin		0.22	(0.13 – 0.30)	<0.001	
	Post-stroke Rankin		0.53	(0.41 – 0.65)	<0.001	
	Estimated NIHSS		0.04	(0.01 – 0.06)	0.010	
	Thrombolytics		−0.33	(−0.86 – 0.19)	0.216	
Step 3						
n=331	Age		0.01	(0.00 – 0.02)	0.042	
	Smoker*		−0.18	(−0.43 – 0.07)	0.160	
	Diabetes		0.25	(0.01 – 0.49)	0.043	
	Severe PVWMD		0.47	(0.07 – 0.87)	0.022	0.492
	Pre-stroke Rankin		0.19	(0.11 – 0.28)	<0.001	
	Post-stroke Rankin		0.54	(0.43 – 0.65)	<0.001	
	Estimated NIHSS		0.04	(0.01 – 0.06)	0.006	
	Thrombolytics		−0.37	(−0.86 – 0.13)	0.144	
Step 4						
n=331	Age		0.01	(0.00 – 0.02)	0.015	
	Diabetes		0.27	(0.02 – 0.51)	0.032	
	Severe PVWMD		0.46	(0.06 – 0.86)	0.025	
	Pre-stroke Rankin		0.20	(0.11 – 0.28)	<0.001	0.489
	Post-stroke Rankin		0.55	(0.43 – 0.66)	<0.001	
	Estimated NIHSS		0.04	(0.01 – 0.06)	0.004	
	Thrombolytics*		−0.40	(−0.89 – 0.10)	0.115	
Final model						
n=332	Age		0.01	(0.00 – 0.02)	0.008	
	Diabetes		0.27	(0.02 – 0.51)	0.031	
	Severe PVWMD		0.47	(0.07 – 0.87)	0.021	0.484
	Pre-stroke Rankin		0.20	(0.12 – 0.28)	<0.001	
	Post-stroke Rankin		0.56	(0.46 – 0.67)	<0.001	
	Estimated NIHSS		0.03	(0.00 – 0.05)	0.016	

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Note: repeating these analyses without imaging data (excluding pvwmd) results in the same final model and an R^2 of 0.485 – one might assume knowing pvwmd status on all cases would have improved this R^2

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Table E

Univariable models predicting the 4-year outcome. The final multivariable model is also shown.

	β	95% CI (β)	P-value
Univariable models			
Age	0.02	(0.01 – 0.04)	0.013
Female v Male	−0.16	(−0.63 – 0.31)	0.509
Non-white v white	0.05	(−0.48 – 0.59)	0.844
Insured	−0.04	(−0.94 – 0.87)	0.939
Partnered	−0.38	(−0.86 – 0.11)	0.124
Smoker	−0.06	(−0.53 – 0.41)	0.795
Diabetes	0.57	(0.10 – 1.04)	0.018
Hypertension	0.21	(−0.30 – 0.72)	0.410
Hyperlipidemia	−0.02	(−0.50 – 0.46)	0.923
History of CAD	−0.01	(−0.57 – 0.54)	0.966
Prior stroke	0.96	(0.47 – 1.46)	0.000
Severe PVWMD	0.88	(−0.12 – 1.89)	0.085
Pre-stroke Rankin	0.53	(0.35 – 0.70)	0.000
Post-stroke Rankin	0.59	(0.44 – 0.75)	0.000
3-month Rankin	0.61	(0.48 – 0.74)	0.000
Lesion volume	0.00	(0.00 – 0.01)	0.076
Estimated NIHSS	0.06	(0.02 – 0.10)	0.009
Thrombolytics	−0.73	(−1.45 – −0.02)	0.045
Life threatening complications	0.26	(−0.22 – 0.74)	0.289
Medical complications	0.32	(−0.15 – 0.79)	0.178
Psychiatric complications	0.57	(0.06 – 1.09)	0.028
Infectious complications	1.03	(0.50 – 1.55)	0.000
Cardiopulmonary complications	−0.25	(−0.79 – 0.30)	0.372
Neurovascular complications	0.90	(0.20 – 1.59)	0.012

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Table F

Factors predicting death at 4 years. Each stage of the modeling process is shown. The variable removed at each step is indicated by an asterisk (*).

	(Odds ratio)	95% CI (Odds ratio)	P-value	C-statistic
Initial model (maximum correlation coefficient 0.654)				
n=374Age	1.04	(1.02 – 1.07)	<0.001	
Non-white v white	2.31	(1.31 – 4.06)	0.004	
Partnered*	1.01	(0.59 – 1.71)	0.978	
Smoker	0.70	(0.41 – 1.21)	0.204	
Hyperlipidemia	0.72	(0.41 – 1.26)	0.249	
Prior stroke	1.29	(0.74 – 2.24)	0.366	0.768 (0.026)
Pre-stroke Rankin	1.16	(0.98 – 1.38)	0.091	
Post-stroke Rankin	1.12	(0.84 – 1.49)	0.437	
3 Month Rankin	1.17	(0.92 – 1.49)	0.197	
Medical complications	0.96	(0.49 – 1.89)	0.905	
Infectious complications	0.92	(0.45 – 1.85)	0.810	
Step 2				
n=406Age	1.04	(1.02 – 1.06)	0.001	
Non-white v white	2.01	(1.19 – 3.41)	0.009	
Smoker	0.64	(0.39 – 1.08)	0.095	
Hyperlipidemia	0.71	(0.41 – 1.22)	0.214	
Prior stroke	1.34	(0.79 – 2.26)	0.280	0.769 (0.025)
Pre-stroke Rankin	1.12	(0.96 – 1.32)	0.152	
Post-stroke Rankin	1.21	(0.92 – 1.60)	0.176	
3 Month Rankin	1.19	(0.94 – 1.51)	0.151	
Medical complications*	0.91	(0.47 – 1.74)	0.774	
Infectious complications	0.86	(0.44 – 1.68)	0.659	
Step 3				0.769 (0.026)
n=406Age	1.04	(1.02 – 1.06)	0.001	
Non-white v white	2.01	(1.19 – 3.41)	0.009	
Smoker	0.65	(0.39 – 1.08)	0.096	
Hyperlipidemia	0.71	(0.41 – 1.22)	0.218	
Prior stroke*	1.33	(0.79 – 2.26)	0.285	
Pre-stroke Rankin	1.13	(0.96 – 1.32)	0.147	
Post-stroke Rankin	1.21	(0.92 – 1.60)	0.172	
3 Month Rankin	1.19	(0.94 – 1.51)	0.150	
Infectious complications*	0.81	(0.48 – 1.35)	0.413	
Step 4				0.768 (0.025)
n=406Age	1.04	(1.01 – 1.06)	0.001	
Non-white v white	2.03	(1.20 – 3.44)	0.008	
Smoker	0.65	(0.39 – 1.08)	0.096	
Hyperlipidemia	0.71	(0.41 – 1.22)	0.218	
Prior stroke*	1.33	(0.79 – 2.25)	0.289	
Pre-stroke Rankin	1.12	(0.96 – 1.32)	0.156	
Post-stroke Rankin	1.23	(0.93 – 1.62)	0.147	
3 Month Rankin	1.21	(0.96 – 1.53)	0.106	
Step 5				
n=406Age	1.04	(1.01 – 1.06)	0.001	
Non-white v white	2.06	(1.22 – 3.48)	0.007	
Smoker	0.66	(0.40 – 1.11)	0.115	0.765 (0.026)
Hyperlipidemia	0.71	(0.41 – 1.23)	0.225	
Pre-stroke Rankin	1.15	(0.98 – 1.34)	0.084	

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	(Odds ratio)	95% CI (Odds ratio)	P-value	C-statistic
Post-stroke Rankin	1.24	(0.94 – 1.63)	0.131	
3 Month Rankin	1.21	(0.96 – 1.53)	0.107	
Step 6				0.763 (0.026)
n=406Age	1.04	(1.02 – 1.06)	0.001	
Non-white v white	2.18	(1.30 – 3.65)	0.003	
Smoker	0.66	(0.39 – 1.09)	0.103	
Pre-stroke Rankin	1.14	(0.98 – 1.33)	0.099	
Post-stroke Rankin*	1.23	(0.93 – 1.62)	0.142	
3 Month Rankin	1.23	(0.97 – 1.55)	0.086	
Step 7				0.756 (0.026)
n=406Age	1.04	(1.02 – 1.06)	0.001	
Non-white v white	2.21	(1.32 – 3.70)	0.002	
Smoker*	0.66	(0.40 – 1.10)	0.110	
Pre-stroke Rankin	1.15	(0.99 – 1.35)	0.065	
3 Month Rankin	1.34	(1.10 – 1.64)	0.004	
Step 8				
n=406Age	1.04	(1.02 – 1.07)	<0.001	
Non-white v white	2.23	(1.34 – 3.72)	0.002	0.749 (0.026)
Pre-stroke Rankin*	1.15	(0.99 – 1.34)	0.066	
3 Month Rankin	1.36	(1.11 – 1.66)	0.002	
Final model				0.740 (0.026)
n=406Age	1.05	(1.02 – 1.07)	<0.001	
Non-white v white	2.20	(1.32 – 3.66)	0.002	
3 Month Rankin	1.46	(1.21 – 1.76)	<0.001	

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Table G

Factors influencing 4 year outcomes. Each stage of the modeling process is shown. The variable removed at each step is indicated by an asterisk (*).

		β	95% CI (β)	P-value	R^2
Initial Model (maximum correlation coefficient 0.632)					
n=138	Age	0.01	(−0.01 – 0.02)	0.345	
	Diabetes	0.22	(−0.15 – 0.60)	0.239	
	Prior stroke	0.52	(0.09 – 0.96)	0.018	
	Pre-stroke Rankin	0.21	(0.03 – 0.38)	0.019	
	Post-stroke Rankin	0.23	(0.04 – 0.43)	0.021	0.520
	3-month Rankin	0.25	(0.07 – 0.42)	0.005	
	Estimated NIHSS	0.04	(0.00 – 0.09)	0.055	
	Thrombolytics	−0.62	(−1.30 – 0.07)	0.078	
	Psychiatric complications	−0.20	(−0.62– 0.23)	0.366	
	Infectious complications	0.67	(0.24 – 1.10)	0.002	
	Neurovascular complications*	0.15	(−0.46 – 0.76)	0.622	
Step 2					
n=138	Age	0.01	(−0.01 – 0.02)	0.343	
	Diabetes	0.24	(−0.13 – 0.61)	0.195	
	Prior stroke	0.53	(0.09 – 0.96)	0.017	
	Pre-stroke Rankin	0.21	(0.03 – 0.38)	0.020	
	Post-stroke Rankin	0.23	(0.04 – 0.43)	0.020	0.519
	3-month Rankin	0.25	(0.08 – 0.42)	0.004	
	Estimated NIHSS	0.05	(0.00 – 0.09)	0.039	
	Thrombolytics	−0.58	(−1.26 – 0.09)	0.088	
	Psychiatric complications*	−0.20	(−0.62– 0.23)	0.360	
	Infectious complications	0.69	(0.26 – 1.11)	0.002	
Step 3					
n=138	Age*	0.01	(−0.01 – 0.02)	0.302	
	Diabetes	0.26	(−0.11 – 0.62)	0.163	
	Prior stroke	0.50	(0.07 – 0.93)	0.022	
	Pre-stroke Rankin	0.21	(0.04 – 0.38)	0.018	0.516
	Post-stroke Rankin	0.21	(0.02 – 0.39)	0.031	
	3-month Rankin	0.25	(0.08 – 0.42)	0.004	
	Estimated NIHSS	0.05	(0.00 – 0.09)	0.039	
	Thrombolytics	−0.61	(−1.28– 0.06)	0.076	
	Infectious complications	0.67	(0.25 – 1.09)	0.002	
Step 4					
n=138	Diabetes*	0.25	(−0.11 – 0.62)	0.176	
	Prior stroke	0.50	(0.07 – 0.93)	0.023	
	Pre-stroke Rankin	0.21	(0.04 – 0.39)	0.015	
	Post-stroke Rankin	0.23	(0.05 – 0.41)	0.013	0.512
	3-month Rankin	0.25	(0.08 – 0.42)	0.004	
	Estimated NIHSS	0.04	(0.00 – 0.09)	0.045	
	Thrombolytics	−0.63	(−1.30– 0.04)	0.064	
	Infectious complications	0.67	(0.25 – 1.10)	0.002	
Step 5					
n=138	Prior stroke	0.55	(0.12 – 0.97)	0.012	
	Pre-stroke Rankin	0.20	(0.03 – 0.38)	0.021	
	Post-stroke Rankin	0.24	(0.06 – 0.42)	0.010	0.505
	3-month Rankin	0.26	(0.09 – 0.43)	0.004	
	Estimated NIHSS	0.04	(0.00 – 0.08)	0.059	

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		β	95% CI (β)	P-value	R^2
	Thrombolytics*	−0.61	(−1.28– 0.06)	0.073	
	Infectious complications	0.69	(0.26 – 1.11)	0.002	
Step 6					
n=139	Prior stroke	0.56	(0.13 – 0.99)	0.011	
	Pre-stroke Rankin	0.20	(0.03 – 0.38)	0.025	
	Post-stroke Rankin	0.29	(0.11 – 0.47)	0.002	0.484
	3-month Rankin	0.26	(0.09 – 0.44)	0.003	
	Estimated NIHSS*	0.02	(−0.02 – 0.06)	0.305	
	Infectious complications	0.70	(0.27 – 1.13)	0.002	
Final model					
n=151	Prior stroke	0.58	(0.18 – 0.98)	0.005	
	Pre-stroke Rankin	0.18	(0.02 – 0.34)	0.029	0.508
	Post-stroke Rankin	0.32	(0.15 – 0.48)	<0.001	
	3-month Rankin	0.29	(0.13 – 0.45)	0.001	
	Infectious complications	0.76	(0.36– 1.16)	<0.001	

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Table H

Univariable models predicting the odds of death at 3 months. The final multivariable model and the effect of complications on this final model are also shown.

	Odds Ratio	95% CI (Odds Ratio)	P-value
Univariable models			
Age	1.08	(1.04 – 1.12)	<0.001
Female v Male	1.28	(0.63 – 2.59)	0.498
Non-white v white	0.66	(0.30 – 1.43)	0.288
Insured	0.70	(0.16 – 3.03)	0.630
Partnered	0.84	(0.41 – 1.72)	0.625
Smoker	0.85	(0.42 – 1.69)	0.635
Diabetes	0.71	(0.35 – 1.47)	0.358
Hypertension	1.25	(0.57 – 2.73)	0.578
Hyperlipidemia	1.00	(0.48 – 2.09)	0.995
History of CAD	1.16	(0.54 – 2.52)	0.703
Prior stroke	0.47	(0.19 – 1.16)	0.100
Severe PVWMD	2.63	(1.11 – 6.22)	0.028
Pre-stroke Rankin	1.28	(1.05 – 1.56)	0.013
Post-stroke Rankin	3.91	(2.00 – 7.63)	<0.001
Lesion volume	1.01	(1.00 – 1.01)	0.019
Estimated NIHSS	1.11	(1.06 – 1.16)	<0.001
Thrombolytics	1.35	(0.45 – 4.05)	0.588

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Table I

Univariable models predicting the odds of death at 4 years. The final multivariable model is also shown.

	Odds Ratio	95% CI (Odds Ratio)	P-value
Univariable models			
Age	1.05	(1.03 – 1.07)	<0.001
Female v Male	0.90	(0.59 – 1.39)	0.643
Non-white v white	1.83	(1.18 – 2.85)	0.007
Insured	0.83	(0.36 – 1.89)	0.651
Partnered	0.57	(0.36 – 0.90)	0.016
Smoker	0.47	(0.30 – 0.73)	0.001
Diabetes	1.40	(0.91 – 2.15)	0.125
Hypertension	1.06	(0.66 – 1.69)	0.815
Hyperlipidemia	0.58	(0.35 – 0.94)	0.028
History of CAD	1.30	(0.81 – 2.08)	0.280
Prior stroke	1.58	(1.01 – 2.49)	0.046
Severe PVWMD	1.05	(0.50 – 2.20)	0.902
Pre-stroke Rankin	1.38	(1.21 – 1.57)	<0.001
Post-stroke Rankin	1.75	(1.42 – 2.16)	<0.001
3-month Rankin	1.66	(1.39 – 1.98)	<0.001
Lesion volume	1.00	(0.99 – 1.00)	0.256
Estimated NIHSS	1.00	(0.96 – 1.04)	0.919
Thrombolytics	0.49	(0.20 – 1.21)	0.120
Life threatening complications	0.82	(0.53 – 1.26)	0.363
Medical complications	0.62	(0.41 – 0.96)	0.032
Psychiatric complications	0.70	(0.45 – 1.09)	0.117
Infectious complications	0.56	(0.36 – 0.87)	0.010
Cardiopulmonary complications	0.70	(0.44 – 1.11)	0.131
Neurovascular complications	0.98	(0.52 – 1.83)	0.942