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Ocular fundus abnormalities as a prognostic marker in acute subarachnoid hemorrhage: The FOTO-ICU Study

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Ocular fundus abnormalities as a prognostic marker in acute subarachnoid hemorrhage: The FOTO-ICU Study

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Abstract

Ocular fundus abnormalities as a prognostic marker in acute subarachnoid hemorrhage: The FOTO-ICU Study
By Philip Stephen Garza

Ocular fundus abnormalities, especially intraocular hemorrhage, are common among patients with acute subarachnoid hemorrhage (SAH) and may represent a clinically useful prognostic marker. We enrolled patients admitted to our neurointensive care unit (Neuro ICU) between 9/2014-4/2015 with a working diagnosis of SAH into a prospective cohort study. Handheld ocular fundus photography was performed once patients were deemed appropriate for pupillary dilation, and photographs were reviewed for intraocular hemorrhage and other neurologically-relevant fundus abnormalities. Multivariable logistic and Cox models were used to evaluate associations between fundus abnormalities and poor outcome (defined as inpatient death, care withdrawal, or discharge Glasgow Outcome Score < 4) and ICU and hospital lengths-of-stay, controlling for APACHE II score, respiratory failure at ICU admission, Hunt & Hess score, aneurysmal etiology, age, and sex. 79 consecutively enrolled patients had confirmed acute SAH. Twenty-eight of these 79 (28/79 [35.4%]) had an ocular fundus abnormality, and 20/79 (25.3%) had intraocular hemorrhage. In univariate analyses, poor outcomes were more likely in patients with fundus abnormalities vs. without (15/28 [53.6%] vs. 15/51 [29.4%], p=0.03), whereas median length of ICU stay was longer in patients with intraocular hemorrhage than without (18 days [IQR 12-25] vs. 11 [IQR 7-17], p=0.03). Logistic regression modeling with fundus abnormality as predictor of interest showed that male sex (OR 5.33 [95% CI 1.09-26.0], p=0.04), higher APACHE II (OR, per 1-point increase, 1.43 [95% CI 1.09-1.87, p=0.01], and aneurysmal etiology (OR 5.95 [95% CI 1.06-33.2], p=0.04), but not fundus abnormalities (OR 1.46 [95% CI 0.37-5.82], p=0.59), were associated with poor outcome. The results were similar using intraocular hemorrhage as the predictor (OR 1.13 [95% CI 0.23-5.53], p=0.88). Cox models stratified on respiratory failure at ICU admission identified aneurysmal SAH etiology, but not fundus abnormalities, as a strong independent predictor of length-of-stay (HRs for ICU and hospital discharge, aneurysmal vs. nonaneurysmal = 0.3 [95% CI 0.2-0.6], p<0.001). Therefore, although ocular fundus abnormalities are associated with markers of disease severity in SAH, they do not add value to patients' acute management beyond other risk factors already in clinical use.

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INTRODUCTION

Patients with acute subarachnoid hemorrhage (SAH), a neurological emergency caused by bleeding into the subarachnoid layer of the meninges, are usually critically ill. In the days immediately following the hemorrhage, these patients may be minimally responsive, require mechanical ventilation, and develop complications that can cause further brain damage or even death. As a result, despite recent advances in intensive care for patients with critical neurological and neurosurgical illness, as many as half of SAH patients die, with about half of the remaining survivors left with severe, permanent neurological disability.

The mainstay of treatment for acute SAH is supportive therapy aimed at mitigating complications such as cerebral vasospasm, intracranial hypertension (elevated intracranial pressure), and systemic physiological derangements. Therefore, it is important to identify the subset of patients most in need of aggressive supportive care. However, the use of disease scoring systems and invasive neuromonitoring techniques for this purpose has failed to substantially improve clinical outcomes in SAH.

In contrast, ocular fundus abnormalities are physical examination signs that frequently occur in SAH and do not require invasive testing to detect. For example, intraocular hemorrhage occurs in up to 1 in 5 acute SAH patients and has been associated with increased mortality in previous studies. Until recently, however, the ocular fundus examination required use of the direct ophthalmoscope, which is very difficult to use in critically ill patients. Now, handheld ocular fundus cameras are commercially available and allow acquisition of high-quality, wide-angle digital images of the ocular fundus regardless of the patient population.

We sought to determine if ocular fundus abnormalities, as detected using handheld fundus photography, could predict poor clinical outcome, ICU length-of-stay, and hospital length-of-stay among patients with acute SAH independent of other methods currently in clinical use. We enrolled consecutive patients admitted to our neurointensive care unit (Neuro ICU) with acute SAH in a prospective cohort study in which all patients received fundus photography upon enrollment and were followed until hospital discharge or death. We hypothesized that those patients with neurologically-relevant ocular fundus abnormalities would be more likely to have a poor outcome and longer ICU and hospital lengths-of-stay compared to patients without ocular fundus abnormalities. As illustrated in FIGURE 1, this finding could characterize ocular fundus abnormalities as a new prognostic marker for elevated intracranial pressure and other currently unmeasurable mediators of poor outcome and an extended hospital course.

BACKGROUND

In recent decades, Neuro ICUs specialized in the treatment of critical neurological illness have become increasingly common in the United States, and evidence from large observational studies has shown that patients with severe neurological disease who are treated in Neuro ICUs have lower mortality rates and better functional outcomes than those treated in general medical or surgical ICUs (1). However, outcomes have not improved for patients with SAH, a neurological emergency that involves bleeding into the subarachnoid layer of the meninges, most commonly due to a ruptured cerebrovascular aneurysm (2). In the United States, over 30,000 patients are diagnosed with acute SAH each year, and as many as half of these patients die due to complications such as delayed cerebral ischemia and secondary stroke (occurring in 40-60% of SAH cases), intracranial hypertension (occurring in ~54% of cases), rebleeding (occurring in 8-23% of cases), and hydrocephalus (occurring in ~15% of cases) (3–5). Even among the patients who survive, half will be completely dependent on others for their basic needs due to severe, permanent neurological disability (2).

To improve SAH outcomes, clinicians have attempted to identify those patients most in need of aggressive supportive care. Qualitative, SAH-specific severity scores such as the Hunt & Hess scale have been used for this purpose for decades (BOX 1) (6). However, these scoring

BOX 1. HUNT & HESS SAH SEVERITY SCALE.

Grade I – Asymptomatic, or minimal headache and slight nuchal rigidity

Grade II – Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy

Grade III – Drowsiness, confusion, or mild focal deficit

Grade IV – Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances

Grade V – Deep coma, decerebrate rigidity, moribund appearance

systems are subjective, requiring the clinician to assign the patient an ordinal score based on how well their symptoms match a standardized description. Therefore, the score does not necessarily reflect the actual degree of nervous system injury (7).

More recently, quantitative neuromonitoring techniques such as intracranial pressure (ICP) measurement have been used in an attempt to prevent death and disability due to intracranial hypertension (i.e., elevated ICP). ICP measurement has allowed for better medical and surgical control of intracranial hypertension, but requires the surgical placement of a transcranial catheter or probe, which exposes patients to risks such as further intracranial bleeding, infection, or direct damage to brain structures (8). Most importantly, neither ICP monitoring nor the use of severity scoring systems has demonstrably improved SAH patient outcomes (7,9). For these reasons, noninvasive biomarkers for predicting the risk of death and secondary brain injury in SAH have long been desired, but those studied to-date have not demonstrated reproducible clinical success (10,11).

In contrast to severity scores and ICP measurements, ocular fundus abnormalities are objective physical examination signs that can be detected at the bedside using noninvasive techniques. A subset of these signs, especially intraocular hemorrhage (called Terson syndrome in the context of SAH), are common among patients with SAH and may be related to patient outcomes. For example, papilledema occurs in over 40% of patients with SAH and is usually the only sign of elevated ICP observable on physical examination (12). Our meta-analysis of the literature showed that as many as one in five SAH patients have intraocular hemorrhage and that the death rate is over three times higher among SAH patients with intraocular hemorrhage than among those without it.

Additionally, surviving patients who have intraocular hemorrhage are often left with severe visual impairment or blindness due to dense vitreous hemorrhage, which may lead to irreversible complications if it is not identified and treated early enough. This emphasizes the importance of the ocular fundus examination for identifying SAH patients most at risk for poor outcomes and in need of ophthalmic follow-up.

However, a major technical barrier has prevented the detection of ocular fundus abnormalities in SAH patients. Until recently, direct ophthalmoscopy was the only practical way for non-ophthalmologists to detect ocular fundus abnormalities, but this technique affords a very restricted view of the fundus (~5 degrees) and is especially difficult to perform on ICU patients due to obstruction by life support and monitoring devices (13). This has changed within the past several years, as handheld ocular fundus cameras have become commercially available. These compact, point-and-shoot cameras allow non-ophthalmologists and even non-physicians to acquire high-resolution, wide-angle (>30 degrees) digital images of the fundus within minutes, regardless of the patient population of interest. Therefore, this technology has the potential to eliminate a longstanding technical barrier to the detection of ocular fundus abnormalities in SAH patients and facilitate the characterization of fundus abnormalities as a prognostic marker in acute SAH.

Our team pioneered the use of fundus photography in the emergency department, and we are now applying this technology to the assessment and management of patients with SAH in the Neuro ICU. In the FOTO-ED (Fundus photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department) study, we enrolled over 700 acute care patients and showed that fundus photography could be reliably completed within minutes

and with minimal patient discomfort (14,15). Building on this experience, we designed and implemented the present study, FOTO-ICU (Fundus Photography and Ophthalmic Technologies Observational Study in the Intensive Care Unit). In FOTO-ICU, we sought to characterize ocular fundus abnormalities as a new prognostic marker with the potential to improve clinicians' ability to target supportive care to SAH patients at highest risk for poor outcomes. We ultimately hope that the use of this marker will allow more patients to survive SAH with minimal neurological impairment, as well as remove a barrier to the detection of potentially blinding eye disease.

METHODS

Research Goal

The goal of the present study was to investigate ocular fundus abnormalities in general, and intraocular hemorrhage in particular, as markers of disease severity in SAH. We sought to determine if ocular fundus abnormalities can provide prognostic information about patients who are acutely ill with SAH that cannot otherwise be obtained using current clinical tools (e.g., invasive ICP monitoring and clinical scoring systems). If fundus abnormalities are better able to identify the SAH patients who are most likely to die or otherwise have poor clinical outcomes, then perhaps clinical interventions can be targeted at these patients to improve their outcomes.

Our research question is shown in BOX 2. To answer this question, we developed the following Specific Aims:

BOX 2. RESEARCH QUESTION.

Among patients admitted to the Neuro ICU for acute SAH, do neurologically-relevant ocular fundus abnormalities, as identified using bedside fundus photography, predict poor clinical outcome, ICU length-of-stay, and hospital length-of-stay independent of other known risk factors already in clinical use?

- Aim #1: To estimate measures of association between neurologically-relevant ocular fundus abnormalities, as identified using fundus photography, and (1) poor outcome, (2) ICU length-of-stay, and (3) hospital length-of-stay among patients with acute SAH, controlling for known risk factors.
- Aim #2: To develop a predictive model for poor outcome among patients with acute SAH using the presence of neurologically-relevant ocular fundus abnormalities, as identified using fundus photography, as well as other known risk factors.

For Aim #1, we hypothesized that, among patients with acute SAH, those with neurologically-relevant ocular fundus abnormalities would be more likely to have a poor outcome and longer ICU and hospital lengths-of-stay compared to patients without ocular fundus abnormalities.

Study Design & Population

FOTO-ICU (Fundus Photography and Ophthalmic Technologies Observational Study in the Intensive Care Unit) was a prospective cohort study conducted in the Emory University Hospital Neuro ICU between September 22, 2014 and April 10, 2015. To be eligible for the study, patients had to be admitted to the Neuro ICU with a primary working diagnosis of acute SAH. Patients who were <18 years old, had a known history of chronic ocular fundus abnormalities or a medical condition associated with chronically elevated intracranial pressure (e.g., an intracranial mass), or who declined to participate were excluded from the study. Eligible patients who lacked decision-making capacity per the treating ICU physician were enrolled in the study under a waiver of informed consent granted by the Emory University IRB, and consent was obtained if the patient regained decision-making capacity later in the hospital stay.

Measurements

Our exposures of interest (i.e., independent variables) were any neurologically relevant ocular fundus abnormality and, more specifically, intraocular hemorrhage. Patients were assessed for exposure using handheld ocular fundus photography (Pictor Plus, Volk Optical Inc., Mentor, OH), which was performed at the bedside as soon as the patient was clinically stable and deemed appropriate for pharmacologic pupil dilation with 1% tropicamide and 2.5% phenylephrine by the treating ICU physician. Once the

eyes were fully dilated (30-60 min. after administration of dilating agents), fundus photographs were obtained. Photography was repeated until the best possible images of the optic disc, macula, and superior and inferior vascular arcades were acquired.

Fundus photographs were later graded for neurologically-relevant abnormalities by two masked neuro-ophthalmologists. We defined a neurologically relevant fundus abnormality as papilledema (optic disc edema), cotton wool spots, hypertensive retinopathy, retinal vascular abnormalities, intraocular hemorrhage, or any combination thereof. When intraocular hemorrhage was present, the graders also noted the subtype of hemorrhage(s) seen in the photograph (i.e., nerve fiber layer, deep retinal, subhyaloid, and/or vitreous hemorrhages). Any disagreement between the graders was adjudicated by a third neuro-ophthalmologist.

Our outcomes of interest were poor clinical outcome (binary; 1 if the patient had a poor outcome, 0 otherwise) and ICU and hospital lengths-of-stay (continuous in days). A patient was deemed to have a poor clinical outcome if he or she died or had his or her care withdrawn during the hospitalization, or if he or she was discharged from the hospital with a Glasgow Outcome Score (GOS) < 4 (BOX 3), signifying an inability to live independently. ICU and hospital lengths-of-stay were measured in days from the date of ICU admission to the date of ICU discharge and the date of hospital discharge, respectively. If a patient was

BOX 3. GLASGOW OUTCOME SCORE (GOS).

1 point – Patient died

2 points – Patient was in a vegetative state (unresponsive and unable to interact with the environment) at last follow-up

3 points – Patient was severely disabled (able to follow commands but unable to live independently) at last follow-up

4 points – Patient was moderately disabled (able to live independently but unable to return to work or school) at last follow-up

5 points – Patient had a good recovery and was able to return to work or school as of last follow-up

readmitted to the ICU after being transferred out of the ICU earlier in the hospital stay, the length of time (in days) from the ICU readmission date to the second ICU discharge date was added to the ICU length-of-stay. All outcome variables were obtained from unmasked review of the electronic medical record, where the required clinical information had been recorded as part of standard care.

Covariates of interest included Hunt & Hess score > 3 (binary; 1 if the Hunt & Hess score was > 3, 0 otherwise), aneurysmal etiology of the SAH (binary; 1 if the SAH was determined to have been caused by a ruptured intracranial aneurysm during the hospital stay, 0 otherwise), APACHE II score at ICU admission (ordinal, ranging from 0 to 71), respiratory failure at ICU admission (binary; 1 if patient required invasive mechanical ventilation at admission, 0 otherwise), age (continuous in years), and sex (binary; 1 if male, 0 if female). Covariates were obtained by unmasked review of the electronic medical record, where the required clinical information had been recorded as part of standard care.

FIGURE 2 shows the data collection timeline for the study. Assessment of patient exposure status by fundus photography (green star) and covariates by medical record review (yellow star) occurred at the time of the study examination, which was also the time of study enrollment. The sole exception was the aneurysmal SAH etiology covariate, which was updated based on clinical or imaging data acquired any time between study enrollment and hospital discharge or death. Red stars indicate that ICU and hospital length-of-stay were assessed by record review at the time of ICU and hospital discharge, respectively. Poor outcome was also assessed by record review at the time of hospital discharge or inpatient death. Notably, the timepoints that appear within the grey box were

not observed. For example, many SAH patients ultimately admitted to our Neuro ICU first presented to an outside hospital's emergency department or ICU, but were then transferred to Emory once they were found to have SAH. Therefore, we expect that some patients with SAH who would have been appropriate for inclusion in the study may have not been transferred to Emory or may have died between the time of SAH onset (the "true" time zero) and arrival at our Neuro ICU. Additionally, some SAH patients admitted to the Neuro ICU for acute SAH may have died before they could be enrolled and the first study examination performed (study time zero), although we expect the number of such patients to be small since screening and enrollment were performed daily. Even so, it is likely that the unobserved timepoints represent a degree of left truncation between the time of SAH onset and the study examination.

Sample Size & Power

Sample size was calculated for a log-rank test with ICU length of stay as the primary endpoint. Using a 7-day median ICU stay in the non-intraocular hemorrhage group and a 14-day median ICU stay in the intraocular hemorrhage group, a sample size of 39 patients per group was required to achieve a power of 0.8 at an alpha of 0.05. Assuming a 25% prevalence of intraocular hemorrhage in acute SAH, we needed to enroll at least 156 patients in order to enroll a sufficient number of patients with intraocular hemorrhage.

Analytic Plan

All analyses used SAS 9.4 (SAS Institute Inc., Cary, NC). Frequencies and 95% confidence intervals were calculated for the exposures of interest (ocular fundus abnormalities and intraocular hemorrhage), the relevant outcome variable (poor

outcome), and the relevant covariates of interest (Hunt & Hess score > 3, aneurysmal SAH etiology, respiratory failure at admission, and sex). The frequencies and 95% confidence intervals for intraocular hemorrhage subtypes, cotton wool spots, and papilledema were also calculated. Means and medians were calculated for age, APACHE II score, ICU length-of-stay, and hospital length-of-stay. To evaluate the distributions of these variables, histograms were created and Kolmogorov-Smirnov tests for goodness-of-fit to the normal distribution were performed.

All inferential analyses used a two-tailed significance cutoff of 0.05. Univariate inferential analyses used the Chi-square test of independence, Fisher's exact test, the Wilcoxon rank-sum test, or the independent samples t-test, as appropriate, to compare poor outcome, ICU length-of-stay, hospital length-of-stay, APACHE II score, respiratory failure, Hunt & Hess > 3, aneurysmal SAH etiology, age, and sex between patients with and without ocular fundus abnormalities and intraocular hemorrhage.

Logistic regression modeling for poor outcome used the following initial main effects models, where p = Probability(poor outcome), OFA = ocular fundus abnormalities, and IOH = intraocular hemorrhage:

Logistic Model #1

$$log(\frac{p}{1-p}) = \beta_0 + \beta_1(OFA) + \beta_2(APACHE) + \beta_3(HuntHess > 3) + \beta_4(RespiratoryFailure) + \beta_5(Aneurysm) + \beta_6(Sex) + \beta_7(Age)$$

Logistic Model #2

$$log(\frac{p}{1-p}) = \beta_0 + \beta_1(IOH) + \beta_2(APACHE) + \beta_3(HuntHess > 3) + \beta_4(RespiratoryFailure) + \beta_5(Aneurysm) + \beta_6(Sex) + \beta_7(Age)$$

All pairwise interaction terms were tested and included if they were found to be statistically significant, and APACHE II score and age were checked for nonlinearity. To satisfy Aim #1, we calculated point estimates and 95% confidence intervals for $e^{\hat{\beta}_1}$ using the final fitted models to estimate odds ratios for poor outcome among patients with versus without ocular fundus abnormalities (Model #1) and for poor outcome among patients with versus without intraocular hemorrhage (Model #2). To satisfy Aim #2, we performed automated forward, backward, and stepwise model selection on Logistic Model #1 with significance cutoffs of 0.05 and 0.1. Receiver operating curves were created for each selected model, and the selected model with the highest area-under-the-curve (AUC) was chosen for further development. Predictors that were felt to be clinically relevant and easily obtainable in the clinical setting were added back to this model to maximize the AUC. At this point, a final model was reached, and a calibration plot and the Hosmer-Lemeshow test were used to evaluate its fit to the training dataset. Leave-one-out cross-validation was then performed to assess the model's likely performance outside of the training dataset. Boxplots were created using both the training dataset and the cross-validation procedure to evaluate the model's discriminatory performance. Using cutpoints defined to maximize the model's sensitivity for poor outcome, we calculated sensitivity and specificity estimates based on the training dataset and the cross-validation procedure.

Survival analyses used Kaplan-Meier survival curves and log-rank tests to compare ICU and hospital lengths-of-stay between patients with and without ocular fundus abnormalities and intraocular hemorrhage. Cox proportional hazards modeling for ICU and hospital length-of-stay used the following initial models, where h(t) = the hazard

of ICU or hospital discharge, OFA = ocular fundus abnormalities, and IOH = intraocular hemorrhage:

Cox Model #1

$h(t) = h_0(t)e^x$, where

$x = \beta_1(OFA)+\beta_2(APACHE)+\beta_3(HuntHess > 3)+\beta_4(RespiratoryFailure)+\beta_5(Aneurysm) + \beta_6(Sex) + \beta_7(Age)$

Cox Model #2

$h(t) = h_0(t)e^y$, where

$y = \beta_1(IOH)+\beta_2(APACHE)+\beta_3(HuntHess > 3)+\beta_4(RespiratoryFailure)+\beta_5(Aneurysm) + \beta_6(Sex) + \beta_7(Age)$

Log-log curves were used to evaluate the proportional hazards assumption for each predictor variable, and subsequent analyses were stratified on any variables for which the log-log curves were found to be substantially non-parallel. To address the potential complication of death as a competing risk, and because few enrolled patients died, we excluded patients who died from all time-to-event analyses and performed sensitivity analyses to evaluate the potential bias induced by excluding these patients (and effectively selecting for survivors). To satisfy Aim #1, we calculated point estimates and 95% confidence intervals for $e^{\hat{\beta}_1}$ using the final fitted models to estimate hazard ratios for ICU and hospital discharge among patients with versus without ocular fundus abnormalities (Model #1) and among patients with versus without intraocular hemorrhage (Model #2).

RESULTS

Cohort Characteristics

FIGURE 3 provides an overview of study recruitment procedures and participant exposure status. Eighty-two Neuro ICU patients admitted with a working diagnosis of SAH were screened for inclusion in the study. Imaging or other clinical tests ruled out SAH as the primary diagnosis in two (2) patients, leaving 80 study-eligible patients. Of these, one (1) patient declined to participate. The remaining 79 patients comprised our study cohort, all of whom were consecutively enrolled and had a confirmed primary diagnosis of SAH.

Mean age of the overall cohort was 54.1 years (SD 12.8). Median APACHE II score was 7 (IQR 5 – 11), and 14/79 (17.7%) patients had APACHE II scores > 12. 29/79 (36.7%) patients were male; 53/70 (67.1%) had aneurysmal SAH; 16/79 (20.3%) had respiratory failure at ICU admission; and 13/79 (16.5%) had Hunt & Hess scores > 3. Twenty-eight of 79 (28/79 [35.4%, 95% CI 25.0 – 47.0%]) had a neurologically-relevant ocular fundus abnormality, and 20/79 (25.3% [95% CI 16.2 – 36.4%]) had intraocular hemorrhage. Nerve fiber layer hemorrhages were seen in 15/79 (19.0% [95% CI 11.0 – 29.4%]); deep retinal hemorrhages were seen in 14/79 (17.7% [95% CI 10.0 – 27.9%]); subhyaloid hemorrhage was seen in 4/79 (5.1% [95% CI 1.4 – 12.5%]); and vitreous hemorrhage was seen in 4/79 (5.1% [95% CI 1.4 – 12.5%]). Eight of 79 (8/79) patients had fundus abnormalities other than intraocular hemorrhage: 7/79 (8.9% [95% CI 3.6 – 17.4%]) had cotton wool spots and 1/79 (1.3% [95% CI 0.0 – 6.9%]) had papilledema. Median ICU length-of-stay was 13 days (IQR 8 – 20), and median hospital length-of-stay

was 15 days (IQR 10 – 22). Five of 79 (5/79 [6.33%]) patients died during the hospitalization, and 30/79 (38.0%) had a poor clinical outcome.

Univariate Results

TABLE 1A compares demographic and clinical characteristics of SAH patients with and without ocular fundus abnormalities. Compared to patients without fundus abnormalities, patients with fundus abnormalities were more likely to have APACHE II scores > 12 (9/28 [32.1%] vs. 5/51 [9.8%]; p = 0.02) and Hunt & Hess scores > 3 (9/28 [32.1%] vs. 4/51 [7.8%]; p = 0.01). Patients with fundus abnormalities were also more likely to have respiratory failure at ICU admission (11/28 [39.3%] vs. 5/51 [9.8%]; p = 0.002). Aneurysmal SAH etiology and sex did not differ significantly between patients with and without fundus abnormalities (aneurysmal etiology: 53/79 [67.1%] vs. 21/28 [75.0%], p = 0.27; male sex: 11/28 [39.3%] vs. 18/51 [35.3%], p = 0.72), but there was a trend toward significance for higher mean age among patients with fundus abnormalities (fundus abnormality vs. no fundus abnormality: 57.1 [SD 8.77] vs. 52.5 years [SD 14.3], p = 0.08).

TABLE 1B compares demographic and clinical characteristics of SAH patients with and without intraocular hemorrhage. Compared to patients without intraocular hemorrhage, patients with intraocular hemorrhage were more likely to have APACHE II scores > 12 (7/20 [35.0%] vs. 7/59 [11.9%]; p = 0.01) and Hunt & Hess scores > 3 (8/20 [40.0%] vs. 5/59 [8.5%]; p = 0.003). Patients with intraocular hemorrhage were also more likely to have respiratory failure at ICU admission (9/20 [45.0%] vs. 7/59 [11.9%]; p = 0.003). Aneurysmal SAH etiology, age, and sex did not differ significantly between patients with and without intraocular hemorrhage (aneurysmal etiology: 15/20 [75.0%]

vs. 38/59 [64.4%], p = 0.38; mean age: 56.4 [SD 8.11] vs. 53.4 years [SD 14.0], p = 0.25; male sex: 7/20 [35.0%] vs. 22/59 [37.3%], p = 0.85).

Patients with ocular fundus abnormalities were more likely to have a poor clinical outcome (15/28 [53.6%]) than patients without fundus abnormalities (15/51 [29.4%]; χ^2 = 4.48, df = 1, p = 0.03). For intraocular hemorrhage, there was a similar but nonsignificant trend (poor outcome, intraocular hemorrhage vs. no intraocular hemorrhage: 11/20 [55.0%] vs. 19/59 [32.2%]; χ^2 = 3.30, df = 1, p = 0.07). Median ICU length-of-stay was longer among patients with fundus abnormalities (17 days [IQR 10.5 – 24]) than among those without fundus abnormalities (11 days [IQR 7 – 17]; Wilcoxon rank-sum test statistic = 1342, p = 0.03). Median ICU and hospital lengths-of-stay were longer among patients with intraocular hemorrhage (ICU length-of-stay: 18 days [IQR 12 – 25]; hospital length-of-stay: 19.5 days [IQR 16.5 – 29.0]) than among those without intraocular hemorrhage (ICU length of stay: 11 days [IQR 7 – 17], Wilcoxon rank-sum test statistic = 1035, p < 0.01; hospital length-of-stay: 14 days [IQR 9 – 20], Wilcoxon rank-sum test statistic = 1027, p = 0.01).

Logistic Regression Modeling

For the logistic regression models for poor outcome, all possible pairwise interaction terms, as well as quadratic and cubic terms for the APACHE II and age variables, were found to be nonsignificant by the likelihood-ratio test. Therefore, we proceeded with the analyses using the initial main effects models stated above (Logistic Models #1 and #2).

In the logistic regression model using ocular fundus abnormality as the ocular exposure of interest (Logistic Model #1), male sex, higher APACHE II score, and

aneurysmal SAH etiology were independently associated with poor clinical outcome (TABLE 2A). Fifteen of 29 (15/29 [51.7%, 95% CI 32.5 – 70.6%]) male patients had a poor outcome, compared to 15/50 (30.0% [95% CI 17.9 – 44.6%]) female patients (OR, male vs. female = 5.33 [95% CI 1.09 – 26.0], p = 0.04). Each 1-point increase in APACHE II score was associated with an odds ratio (OR) of 1.43 (95% CI 1.09 – 1.87, p = 0.01) for poor outcome. Twenty-six of 53 (26/53 [49.1%, 95% CI 35.1 – 63.2%]) patients with aneurysmal SAH etiology had a poor outcome, compared to 4/26 (15.4% [95% CI 4.4 – 34.9%]) patients with nonaneurysmal SAH (OR, aneurysmal vs. nonaneurysmal = 5.95 [95% CI 1.06 – 33.2], p = 0.04). Controlling for covariates, ocular fundus abnormalities were not independently associated with poor outcome (OR for poor outcome, fundus abnormality vs. no fundus abnormality = 1.46 [95% CI 0.37 – 5.82], p = 0.59).

As shown in TABLE 2B, the results were similar for the logistic regression model for poor outcome using intraocular hemorrhage as the ocular exposure of interest (Logistic Model #2): male sex (OR, male vs. female = 5.28 [95% CI 1.07 – 26.1], p = 0.04), higher APACHE II score (OR per 1-point increase = 1.42 [95% CI 1.08 – 1.86], p = 0.01), and aneurysmal SAH etiology (OR, aneurysmal vs. nonaneurysmal = 6.04 [95% CI 1.05 – 34.9], p = 0.04) were independently associated with poor clinical outcome. Intraocular hemorrhage was not independently associated with poor outcome (OR for poor outcome, intraocular hemorrhage vs. no intraocular hemorrhage = 1.13 [95% CI 0.23 – 5.53], p = 0.88).

To develop an optimized model for predicting poor outcome among patients with acute SAH, we applied automated forward, backward, and stepwise model selection to

Logistic Model #1. Using a significance cutoff of 0.05, only the APACHE II variable remained in the model as a predictor, regardless of the selection procedure used; the resultant single-predictor model had an AUC (c-index) of 0.878. Using a significance cutoff of 0.1, all automated selection procedures yielded a three-predictor model containing the APACHE II, sex, and aneurysmal SAH etiology variables; this model had an AUC of 0.905. Adding back the age, Hunt & Hess > 3, and respiratory failure variables as predictors resulted in a six-predictor model with an AUC of 0.911. This AUC was identical to that of the initial, seven-predictor model (Logistic Model #1), without requiring inclusion of the ocular fundus abnormality predictor. Therefore, the six-predictor model was chosen as the final, optimized model for predicting poor outcome in acute SAH. FIGURE 4 shows the ROCs of the candidate logistic regression models for poor outcome and compares their corresponding AUCs.

The final, six-predictor model was evaluated for fit to the training dataset. The calibration plot shown in FIGURE 5 shows an approximately one-to-one relationship between predicted and observed proportions across the range of possible values. Likewise, the Hosmer-Lemeshow test failed to reach statistical significance ($\chi^2 = 4.66$, df = 8, p = 0.79). Together, these results suggest that the model fit the training dataset well.

FIGURE 6 shows boxplots for the final model based on both the training dataset and the leave-one-out cross-validation procedure. The lack of substantial overlap between the boxplots suggests that the model has good discriminatory performance for poor outcome within the training dataset. The overlap increases for the cross-validation procedure, but the boxplots remain mostly separated, suggesting that the model is likely

to have good discriminatory performance outside the training dataset (i.e., in a validation cohort) as well.

A cutpoint of $\hat{p} = 0.14$ was chosen to maximize the model's sensitivity for poor clinical outcome. Based on the training dataset, the use of this cutpoint yields a sensitivity of 100% and a specificity of 51.0% for poor outcome; based on the cross-validation procedure, the sensitivity and specificity decrease to 96.7% and 49.0%, respectively. The estimated AUC likewise decreases from 0.911 based on the training dataset to 0.827 based on the cross-validation procedure.

Time-to-Event Analyses

Kaplan-Meier survival curves for ICU and hospital length-of-stay are shown in FIGURE 7. Kaplan-Meier analysis did not support a statistically significant difference in ICU or hospital length-of-stay between patients with and without ocular fundus abnormalities (for ICU length-of-stay, p = 0.11 by the log-rank test; for hospital length-of-stay, p = 0.27). However, ICU length-of-stay was longer for patients with intraocular hemorrhage than for those without intraocular hemorrhage (p = 0.028 by the log-rank test), and a similar trend was found for hospital length-of-stay (p = 0.057).

Log-log survival curves for ICU and hospital length-of-stay among patients with and without respiratory failure at ICU admission were substantially non-parallel (FIGURE 8), indicating a likely violation of the proportional hazards assumption for the respiratory failure variable. Therefore, we stratified all Cox proportional hazards regression analyses on respiratory failure at ICU admission.

The results of the Cox proportional hazards regression analysis are shown in TABLES 3A through 3D. For Cox Model #1 (TABLES 3A & 3B), which used ocular fundus

abnormality as the ocular exposure of interest, only aneurysmal SAH etiology was independently associated with ICU length-of-stay (HR for ICU discharge, aneurysmal vs. nonaneurysmal SAH etiology = 0.31 [95% CI 0.17 – 0.57], $p < 0.001$) and hospital length-of-stay (HR for hospital discharge, aneurysmal vs. nonaneurysmal = 0.30 [95% CI 0.16 – 0.55], $p < 0.001$), although male sex (HR for ICU discharge, male vs. female sex = 0.60 [95% CI 0.34 – 1.03], $p = 0.07$) and Hunt & Hess score > 3 (HR for hospital discharge, Hunt & Hess score > 3 vs. ≤ 3 = 0.21 [95% CI 0.04 – 1.05], $p = 0.06$) approached significance for the ICU and hospital length-of-stay analyses, respectively. For Cox Model #2 (TABLES 3C & 3D), which used intraocular hemorrhage as the ocular exposure of interest, aneurysmal SAH etiology was also independently associated with ICU length-of stay (HR for ICU discharge, aneurysmal vs. nonaneurysmal SAH etiology = 0.30 [95% CI 0.16 – 0.55], $p < 0.001$) and hospital length-of-stay (HR for hospital discharge, aneurysmal vs. nonaneurysmal = 0.29 [95% CI 0.15 – 0.55], $p < 0.001$). In addition, male sex was independently associated with ICU length-of-stay (HR for ICU discharge, male vs. female sex = 0.56 [95% CI 0.32 – 0.97], $p = 0.04$).

All of the aforementioned time-to-event analyses excluded the five patients who died to address the potential problem of death as a competing risk. However, sensitivity analyses including these patients produced equivalent results, suggesting that any bias induced by selecting for survivors was small.

DISCUSSION AND CONCLUSIONS

We found that ocular fundus abnormalities were common among critically ill patients with acute SAH, occurring in 35.4% of our study cohort. Intraocular hemorrhage was the fundus abnormality seen most often, occurring in 25.3% of the cohort. Our meta-analysis of the previous literature on intraocular hemorrhage in acute SAH found a prevalence of 16.2% across prospective studies, so the one-in-four prevalence that we observed in the present study represents a substantially higher prevalence compared to the existing literature. This may reflect the increased sensitivity of handheld fundus photography for detecting intraocular hemorrhage compared to direct or indirect ophthalmoscopy, the examination modalities used in all previous studies on this topic. In contrast to ophthalmoscopy, fundus photography provides a wide-angle digital image that can be interpreted outside of the ICU setting by experts. Therefore, it is likely to be less examiner- and setting-dependent and may provide a more accurate assessment of exposure status than ophthalmoscopy. Ultimately, we believe that the use of fundus photography together with a prospective study design and consecutive patient enrollment provided a more accurate estimate of the prevalence of fundus abnormalities in acute SAH than was possible in previous studies.

The results of our univariate analyses were similar to those of previous studies, which found that patients with intraocular hemorrhage were more likely to have GOS < 4 and Hunt & Hess scores > 3 (markers of poor outcome and severe SAH, respectively). We likewise found that ocular fundus abnormalities and intraocular hemorrhage were individually associated with poor clinical outcome and Hunt & Hess scores > 3. Patients with fundus abnormalities and intraocular hemorrhage also had higher APACHE II

scores and were more likely to have respiratory failure at ICU admission, suggesting that these patients had more severe disease overall. The finding of higher APACHE II scores in patients with fundus abnormalities supports the previously demonstrated association between intraocular hemorrhage and higher Glasgow Coma Scores (GCS), since the GCS is a major component of the APACHE scoring system (16). Finally, our finding of an association between intraocular hemorrhage and longer ICU length-of-stay in the univariate Kaplan-Meier analysis represents a novel contribution to the literature. To our knowledge, ours is the first study to investigate and demonstrate such an association in this patient population.

Although fundus abnormalities were associated with markers of disease severity and clinical outcome in the univariate context, the results of our multivariable logistic regression analyses did not support an independent association between fundus abnormalities or intraocular hemorrhage and poor outcome. In partial satisfaction of Aim #1, we calculated adjusted odds ratios (ORs) for poor clinical outcome, comparing patients with and without fundus abnormalities and intraocular hemorrhage. The point estimates for these odds ratios were >1 (i.e., in the expected direction per our hypothesis that patients with fundus abnormalities would be more likely to have poor outcomes), but they were not statistically significant. Considered together with the significant univariate association between fundus abnormalities and poor outcome, this result likely means that fundus abnormalities are indeed a marker for SAH severity as illustrated in FIGURE 1, but they do not add prognostic information beyond the clinical markers already used in the care of patients who are critically ill with SAH. In other words, fundus abnormalities did

not sufficiently account for the contribution of unmeasured and unknown mediators (FIGURE 1, in blue) on poor outcome to be useful as an independent clinical marker.

However, APACHE II score was a strong independent predictor of poor clinical outcome in our cohort, with an estimated odds ratio (OR) of over 1.4 per one-point increase in the APACHE score. Given that the APACHE II score ranges from 0 to 71, this is a remarkably large odds ratio for a single point increase, and automated model selection procedures using a stringent significance cutoff (0.05) yielded a well-performing model (AUC = 0.878) that used APACHE II score as the sole predictor of poor outcome. This result adds to other recently published work supporting use of the APACHE scoring system as a tool for predicting outcomes in patients critically ill with SAH (17).

As we demonstrate with our final, six-predictor model, the predictive ability of APACHE II for poor outcome in SAH is maximized in combination with the other significant independent predictors identified in our logistic regression analyses (male sex and aneurysmal SAH etiology), as well as additional variables that are either readily available at ICU admission (e.g., age and sex) or are routinely ascertained as part of the standard clinical workup for SAH (Hunt & Hess score and aneurysmal etiology). The resultant model performed well overall (AUC = 0.911 based on the training dataset) and had excellent sensitivity for poor clinical outcome at the chosen cutpoint based on both the training dataset (100%) and cross-validation procedure (96.7%). Even though the specificity of the model was poor (~50%), such a high-sensitivity clinical prediction rule may nevertheless prove useful when Neuro ICU beds are scarce and it becomes necessary to triage those patients least likely to have poor outcomes to less intensive care settings.

One observation potentially affecting our logistic regression models is that the adjusted odds ratios (ORs) for poor outcome comparing patients with versus without respiratory failure at ICU admission are <1 (TABLE 2A and 2B). These odds ratios are not in the expected direction given that, in the univariate context, patients with respiratory failure were more likely to have poor outcomes than those without respiratory failure. We believe this occurred due to the inclusion of both the APACHE II score and respiratory failure as predictors in the models. Even though APACHE II does not explicitly account for respiratory failure, its GCS component is substantially influenced by the patient's ability or inability to speak, which is in turn affected by respiratory failure. Therefore, APACHE II and respiratory failure may be substantially collinear. This is supported by the observation that removing APACHE II from the logistic models corrects the adjusted odds ratios for respiratory failure (i.e., the estimated odds ratios are >1, as expected). Importantly, we performed additional analyses with the respiratory failure predictor excluded and found that the change did not affect any of the findings discussed above. Even so, we recommend that future studies using multivariable techniques and including APACHE II or GCS as predictor variables do not also include a respiratory failure predictor due to the potential problem of collinearity.

Cox proportional hazards regression analysis did not support an independent association between fundus abnormalities or intraocular hemorrhage and ICU or hospital length-of-stay. As for the measures of association we calculated for poor clinical outcome, the HR point estimates for ICU and hospital discharge comparing patients with and without intraocular hemorrhage were in the expected direction (0.67 and 0.74, respectively) per our hypothesis that patients with fundus abnormalities would have

longer lengths-of-stay. However, these estimates were not statistically significant. In the context of the significant association between intraocular hemorrhage and ICU length-of-stay in the univariate Kaplan-Meier analysis, it appears that intraocular hemorrhage is indeed a marker for longer ICU length-of-stay, but as for poor clinical outcome, does not outperform other markers already in clinical use, specifically aneurysmal SAH etiology.

Indeed, aneurysmal SAH etiology was strongly independently associated with longer ICU and hospital length-of-stay in all of our Cox analyses; male sex was the only other predictor variable to reach statistical significance, particularly in the analysis for ICU length-of-stay using intraocular hemorrhage as the predictor of interest. One potential explanation for longer length-of-stay among patients with aneurysmal SAH is that these patients have an identifiable vascular lesion that can be treated endovascularly (i.e., by coil embolization) or surgically (i.e., by aneurysm clipping). These procedures are often performed during the same admission as the acute SAH, adding post-procedure recovery time to the inpatient stay, most of which is spent in the Neuro ICU. Although we did not record aneurysm treatment status, we did find in an exploratory analysis that aneurysmal etiology was not associated with non-ICU length-of-stay, lending support to post-procedure recovery time as the explanation for the association between aneurysmal etiology and longer length-of-stay in acute SAH. However, further investigation will be necessary to clarify the nature of this association.

Compared to previous studies on ocular fundus abnormalities and intraocular hemorrhage in acute SAH, our study had several important strengths. As discussed previously, the use of fundus photography to detect fundus abnormalities likely reduced misclassification of exposure status relative to previous studies on this topic. We also

used robust outcome variables (poor outcome and ICU and hospital lengths-of-stay) that were recorded in the medical record as part of standard care and were therefore subject to minimal misclassification bias. Additionally, to our knowledge, our study was the first on this topic to use an IRB-approved waiver of informed consent to enroll patients who lacked capacity. This helped ensure the integrity of our consecutive enrollment procedure and likely reduced selection bias by preventing the systematic exclusion of incapacitated patients, who would be expected to have worse outcomes associated with a higher prevalence of ocular fundus abnormalities. Finally, our study was the first of its kind to use multivariable modeling to evaluate the association between ocular fundus abnormalities and SAH outcomes, which provides a new understanding of a relationship that has been recognized for decades but never studied outside of the univariate context.

A couple of limitations may have affected our ability to detect a significant independent association between ocular fundus abnormalities and outcomes in acute SAH. First, we were unable to screen or enroll patients who did not survive to study enrollment, which could only occur after the patient was admitted to the Neuro ICU and cleared for a dilated eye examination by the neurocritical care team. It is likely that some patients with high-grade SAH died during the unobserved time between SAH onset and study enrollment, which represents a period of left truncation (FIGURE 2, gray shaded area). If these patients were also the most likely to have ocular fundus abnormalities, this would result in bias in the negative direction. The limitation of follow-up time to the current inpatient stay represented another possible source of bias in the negative direction, since some patients with fundus abnormalities may have died only after hospital discharge, when this outcome could not be observed. Similarly, by excluding the

five patients who died from our time-to-event analyses to address the potential problem of death as a competing risk, we selected for survivors, which may have induced a small amount of bias, likely in the negative direction. Lastly, we did not achieve the total enrollment target (156 patients) specified by our power calculations. Even so, we were able to detect significant univariate associations between ocular fundus abnormalities and our outcome variables. We believe these associations did not persist in the multivariable context because covariates such as the APACHE II score and aneurysmal SAH etiology were far more powerful predictors of the outcomes of interest, rather than because the study was under-powered.

Our results suggest that handheld fundus photography is a viable alternative to traditional examination modalities in critically ill patients for whom pharmacologic pupillary dilation is safe. Therefore, future studies could deploy handheld fundus photography in different critically ill populations and outside the Neuro ICU setting. For example, patients critically ill with metabolic encephalopathy (e.g., due to liver cirrhosis) are usually admitted to the medical ICU, but they may have ocular fundus abnormalities such as papilledema due to cerebral edema and elevated intracranial pressure. Handheld fundus photography may allow for characterization of fundus abnormalities as new clinical markers in this population. It would also be worthwhile to develop and validate quantitative exposure variables based on handheld fundus imaging (e.g., percent of fundus surface area obscured by intraocular hemorrhage), which may have greater power for detecting clinically important differences between patients with varying degrees of fundus abnormalities. Finally, even though our study did not support fundus abnormalities as an independent predictor of clinical outcomes in the population of acute

SAH patients whose eyes could be dilated safely, ocular fundus findings may yet prove useful as a clinical marker among patients who are undergoing initial work-up and stabilization in the hyper-acute setting. For patient safety, future studies targeted at this population would likely require an improved handheld fundus camera design that does not require pharmacologic pupillary dilation.

In the meantime, for acute SAH patients who survive the hyper-acute period of their illness, we conclude that systematic ophthalmologic examination in the ICU can be deferred until the patient is discharged or has visual complaints. In current practice, ophthalmologists are often asked to evaluate SAH patients in the ICU setting for possible ocular fundus abnormalities, whether or not they are conscious and can express visual complaints. However, our results suggest that the presence of ocular fundus abnormalities is unlikely to contribute useful information to the acute management of SAH patients beyond that contributed by other clinical variables. That said, ocular fundus abnormalities, especially intraocular hemorrhage, are very common in acute SAH and can lead to long-term visual complications in SAH survivors. Therefore, it is advisable for these patients to receive a comprehensive ophthalmological examination in the outpatient setting, after ICU and hospital discharge.

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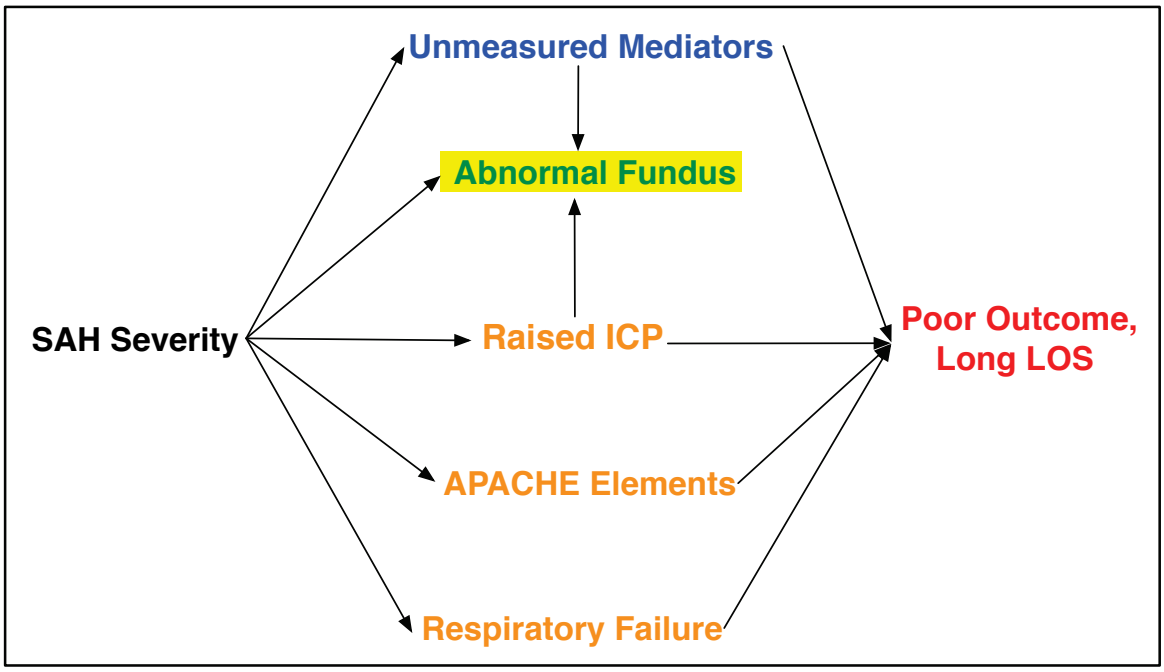
TABLES AND FIGURES

FIGURE 1. Hypothesized causal diagram in which ocular fundus abnormalities (highlighted in yellow) are a marker for SAH severity, raised intracranial pressure (ICP), and unmeasurable mediators of poor outcome and extended length-of-stay (LOS) in acute SAH. Notice that fundus abnormalities themselves are not hypothesized to mediate clinical outcomes in SAH but would still be expected to be independently associated with poor outcome and LOS in a model that does not control for unmeasurable mediators and ICP (because they are unavailable).



Abbreviations: ICP = intracranial pressure; LOS = length-of-stay; SAH = subarachnoid hemorrhage.

FIGURE 2. Data collection timeline. Timepoints within the area shaded gray were not observed, representing left truncation between the time of SAH onset ("true" time zero) and the study examination (study time zero).

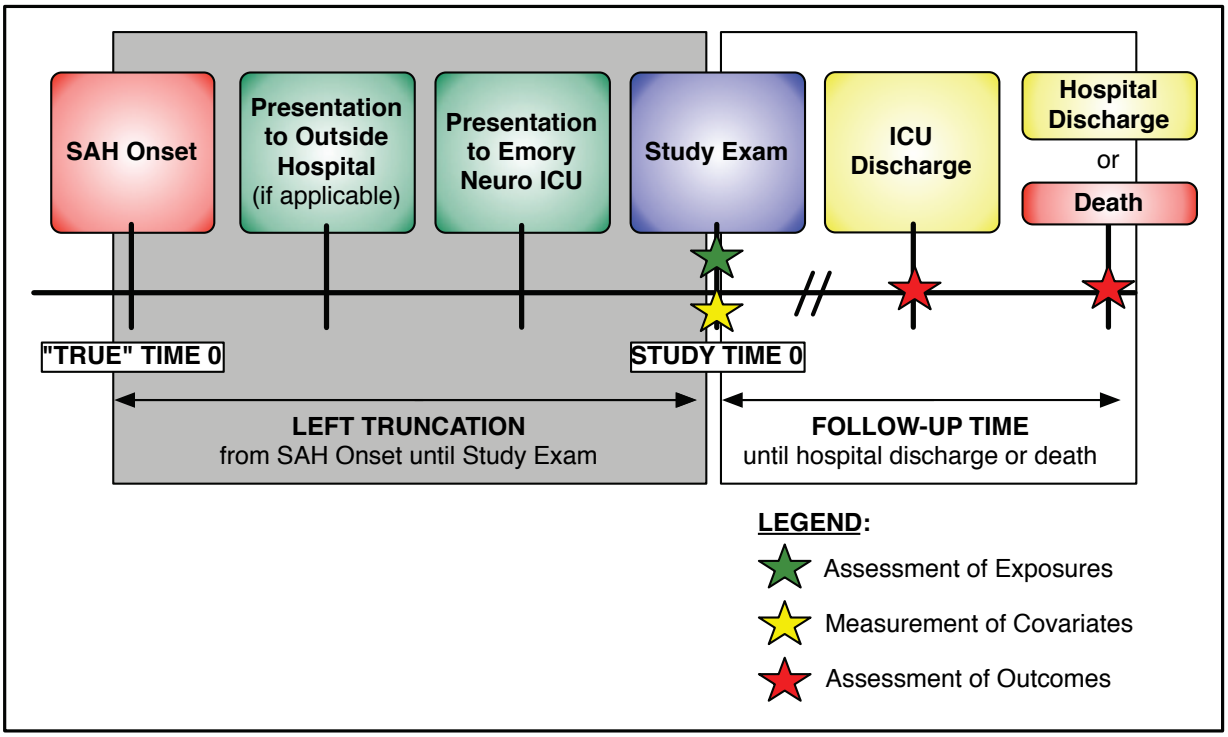


FIGURE 3. Overview of study recruitment procedures and participant exposure status.

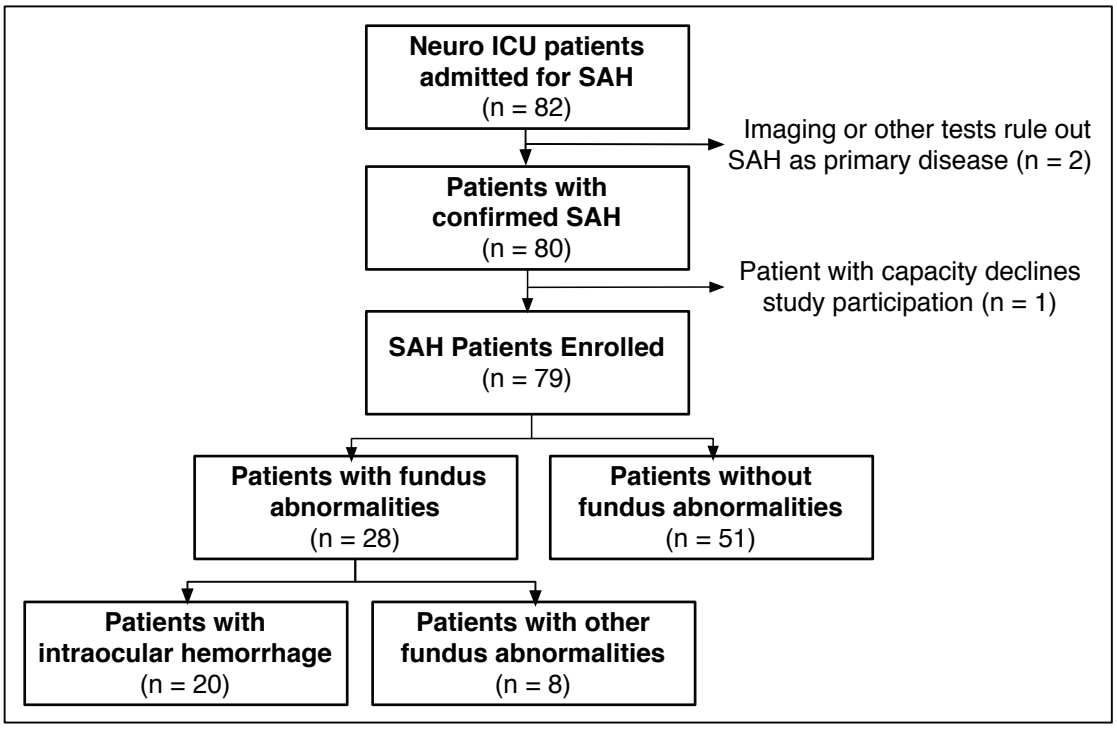


TABLE 1A. Clinical and demographic characteristics for 79 SAH patients, 28 with and 51 without neurologically relevant ocular fundus abnormalities (OFA).

Characteristic	All Patients (n = 79)	OFA (n = 28)	No OFA (n = 51)	p
APACHE II Score[a]				
0 - 6	32 (40.5%)	7 (25%)	25 (49%)	0.02[b]
7 - 12	33 (41.8%)	12 (42.9%)	21 (41.2%)	
13 - 22	14 (17.7%)	9 (32.1%)	5 (9.8%)	
Respiratory Failure[a]				
No	63 (79.8%)	17 (60.7%)	46 (90.2%)	0.002[b]
Yes	16 (20.3%)	11 (39.3%)	5 (9.8%)	
Hunt & Hess Score				
≤ 3	66 (83.5%)	19 (67.9%)	47 (92.2%)	0.01[c]
> 3	13 (16.5%)	9 (32.1%)	4 (7.8%)	
SAH Etiology				
Nonaneurysmal	26 (32.9%)	7 (25.0%)	19 (37.3%)	0.27[b]
Aneurysmal	53 (67.1%)	21 (75.0%)	32 (62.7%)	
Age (years ± SD)	54.1 ± 12.8	57.1 ± 8.77	52.5 ± 14.3	0.08[d]
Sex				
Female	50 (63.3%)	17 (60.7%)	33 (64.7%)	0.72[b]
Male	29 (36.7%)	11 (39.3%)	18 (35.3%)	

Abbreviations: OFA = ocular fundus abnormality; SAH = subarachnoid hemorrhage.

[a]At time of admission to the Neuro ICU.

[b]By Chi-square test of independence.

[c]By Fisher's exact test.

[d]By independent-samples t test assuming unequal variances.

TABLE 1B. Clinical and demographic characteristics for 79 SAH patients, 20 with and 59 without intraocular hemorrhage (IOH).

Characteristic	All Patients (n = 79)	IOH (n = 20)	No IOH (n = 59)	p
APACHE II Score[a]				
0 - 6	32 (40.5%)	3 (15.0%)	29 (49.2%)	0.01[b]
7 - 12	33 (41.8%)	10 (50.0%)	23 (39%)	
13 - 22	14 (17.7%)	7 (35.0%)	7 (11.9%)	
Respiratory Failure[a]				
No	63 (79.8%)	11 (55.0%)	52 (88.1%)	0.003[c]
Yes	16 (20.3%)	9 (45.0%)	7 (11.9%)	
Hunt & Hess Score				
≤ 3	66 (83.5%)	12 (60.0%)	54 (91.5%)	0.003[c]
> 3	13 (16.5%)	8 (40%)	5 (8.5%)	
SAH Etiology				
Nonaneurysmal	26 (32.9%)	5 (25.0%)	21 (35.6%)	0.38[c]
Aneurysmal	53 (67.1%)	15 (75.0%)	38 (64.4%)	
Age (years ± SD)	54.1 ± 12.8	56.4 ± 8.11	53.4 ± 14.0	0.25[d]
Sex				
Female	50 (63.3%)	13 (65.0%)	37 (62.7%)	0.85[c]
Male	29 (36.7%)	7 (35.0%)	22 (37.3%)	

Abbreviations: IOH = intraocular hemorrhage; SAH = subarachnoid hemorrhage.

[a]At time of admission to the Neuro ICU.

[b]By Fisher's exact test.

[c]By Chi-square test of independence.

[d]By independent-samples t test assuming unequal variances.

TABLE 2A. Multivariable logistic regression analysis of the risk for poor outcome among 79 SAH patients, with ocular fundus abnormality (OFA) as the ocular predictor of interest.

Variable	Poor Outcome		Odds Ratio (95% CI)	p
	No./Total	% (95% CI)		
OFA				
No	15/51	29.4 (17.5-43.8)	1 [Reference]	0.59
Yes	15/28	53.6 (33.9-72.5)	1.46 (0.37-5.82)	
Age (per 1 year increase)	–	–	1.03 (0.97-1.11)	0.33
Sex				
Female	15/50	30 (17.9-44.6)	1 [Reference]	0.04
Male	15/29	51.7 (32.5-70.6)	5.33 (1.09-26.0)	
APACHE II Score[a] (per 1 point increase)	–	–	1.43 (1.09-1.87)	0.01
Hunt & Hess Score				
≤ 3	18/66	27.3 (17.0-39.6)	1 [Reference]	0.22
> 3	12/13	92.3 (64.0-99.8)	9.85 (0.26-375.1)	
SAH Etiology				
Nonaneurysmal	4/26	15.4 (4.4-34.9)	1 [Reference]	0.04
Aneurysmal	26/53	49.1 (35.1-63.2)	5.95 (1.06-33.2)	
Respiratory Failure[a]				
No	16/63	25.4 (15.3-37.9)	1 [Reference]	0.43
Yes	14/16	87.5 (61.7-98.5)	0.27 (0.01-7.12)	

Abbreviations: OFA = ocular fundus abnormality; SAH = subarachnoid hemorrhage.

[a]At time of admission to the Neuro ICU.

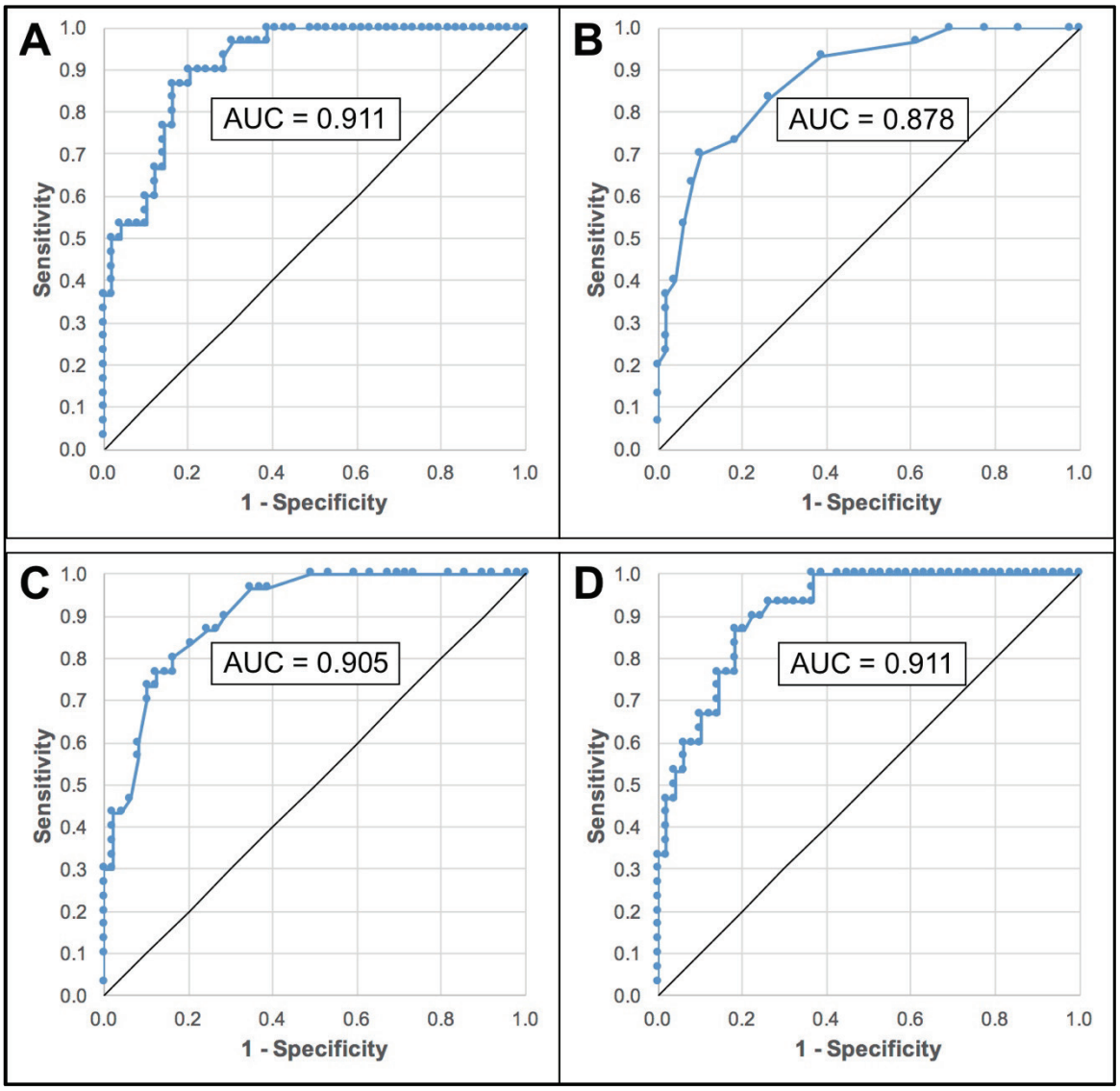
TABLE 2B. Multivariable logistic regression analysis of the risk for poor outcome among 79 SAH patients, with intraocular hemorrhage (IOH) as the ocular predictor of interest.

Variable	Poor Outcome		Odds Ratio (95% CI)	p
	No./Total	% (95% CI)		
IOH				
No	19/59	32.2 (20.6-45.6)	1 [Reference]	0.88
Yes	11/20	55.0 (31.5-76.9)	1.13 (0.23-5.53)	
Age (per 1 year increase)	–	–	1.04 (0.97-1.11)	0.26
Sex				
Female	15/50	30 (17.9-44.6)	1 [Reference]	0.04
Male	15/29	51.7 (32.5-70.6)	5.28 (1.07-26.1)	
APACHE II Score[a] (per 1 point increase)	–	–	1.42 (1.08-1.86)	0.01
Hunt & Hess Score				
≤ 3	18/66	27.3 (17.0-39.6)	1 [Reference]	0.23
> 3	12/13	92.3 (64.0-99.8)	10.0 (0.23-430.3)	
SAH Etiology				
Nonaneurysmal	4/26	15.4 (4.4-34.9)	1 [Reference]	0.04
Aneurysmal	26/53	49.1 (35.1-63.2)	6.04 (1.05-34.9)	
Respiratory Failure[a]				
No	16/63	25.4 (15.3-37.9)	1 [Reference]	0.48
Yes	14/16	87.5 (61.7-98.5)	0.31 (0.01-7.85)	

Abbreviations: IOH = intraocular hemorrhage; SAH = subarachnoid hemorrhage.

[a]At time of admission to the Neuro ICU.

FIGURE 4. Receiver operating curves (ROCs) for candidate logistic regression models predicting poor outcome. (A) ROC for the initial seven-predictor main effects model using ocular fundus abnormality as the exposure of interest, AUC = 0.911. (B) ROC for selected model using APACHE II score as the only predictor, AUC = 0.878. (C) ROC for selected model using APACHE II score, sex, and aneurysmal etiology as the predictors, AUC = 0.905. (D) ROC for the final, six-predictor model excluding the ocular fundus abnormality predictor, AUC = 0.911.



Abbreviations: AUC = area under the curve; ROC = receiver operating curve.

FIGURE 5. Calibration plot for the final, six-predictor logistic regression model for poor outcome based on the training dataset. The points cluster around the 45-degree line, indicating an approximately one-to-one relationship between predicted and observed proportions across the range of possible values. This suggests that the model fits the training dataset well.

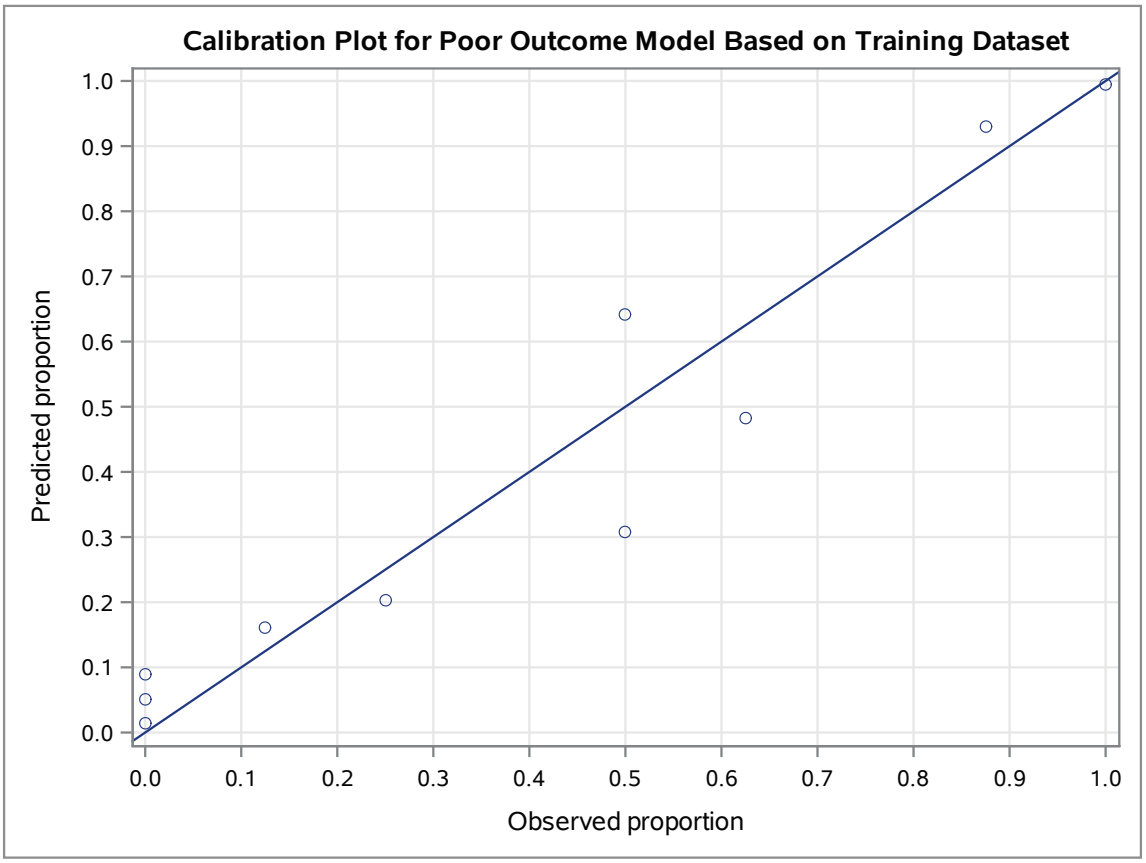


FIGURE 6. Boxplots for the final, six-predictor logistic regression model for poor outcome based on (A) the training dataset and (B) the leave-one-out cross-validation procedure. The lack of substantial overlap between the boxplots suggests that the model has good discriminatory performance both within and outside the training dataset.

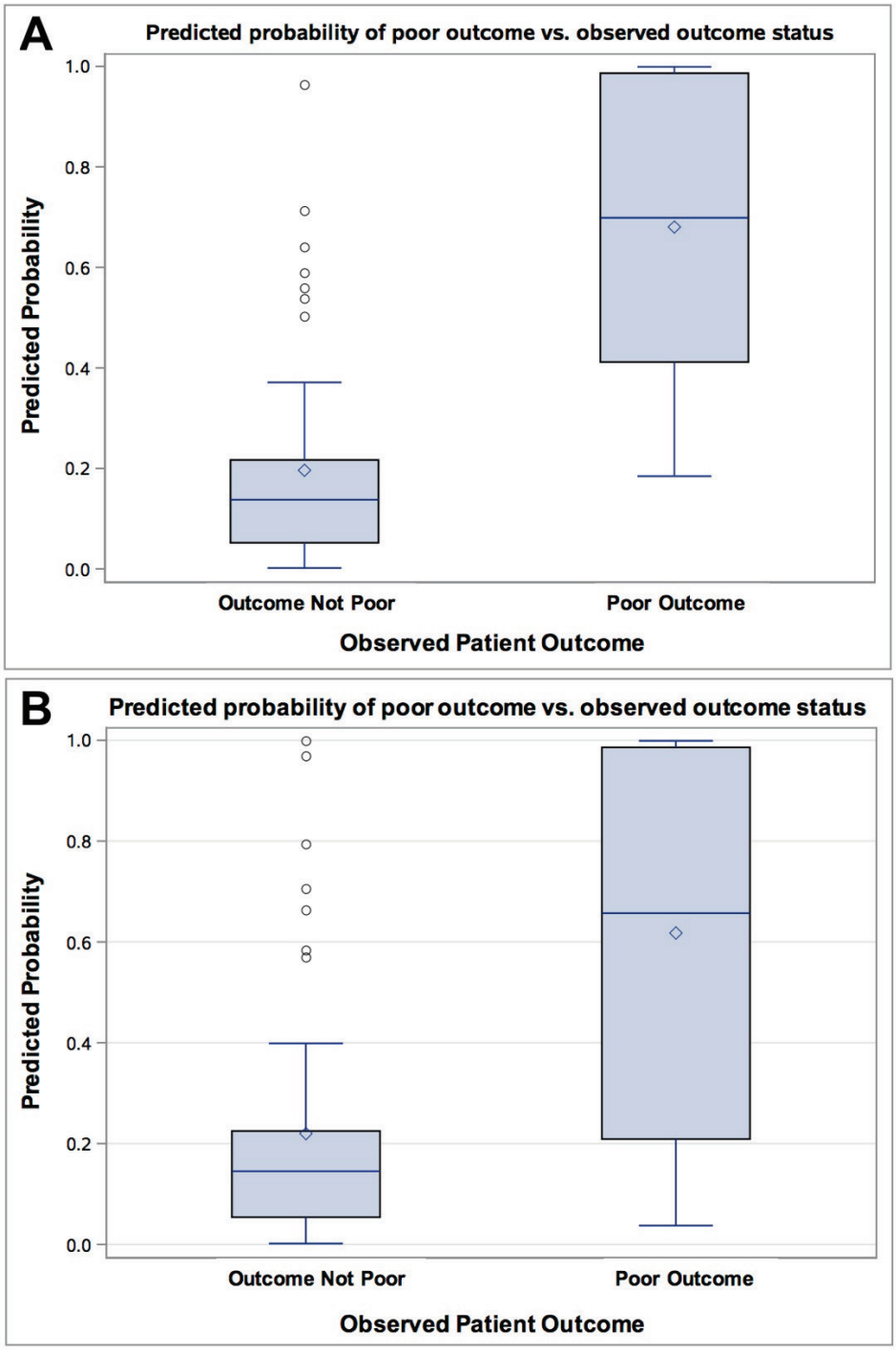


FIGURE 7. Kaplan-Meier survival curves for: (A) ICU length-of-stay among patients with and without ocular fundus abnormalities (OFA), p = 0.11; (B) hospital length-of-stay among patients with and without OFA, p = 0.27; (C) ICU length-of-stay among patients with and without intraocular hemorrhage (IOH), p = 0.028; and (D) hospital length-of-stay among patients with and without IOH, p = 0.057.

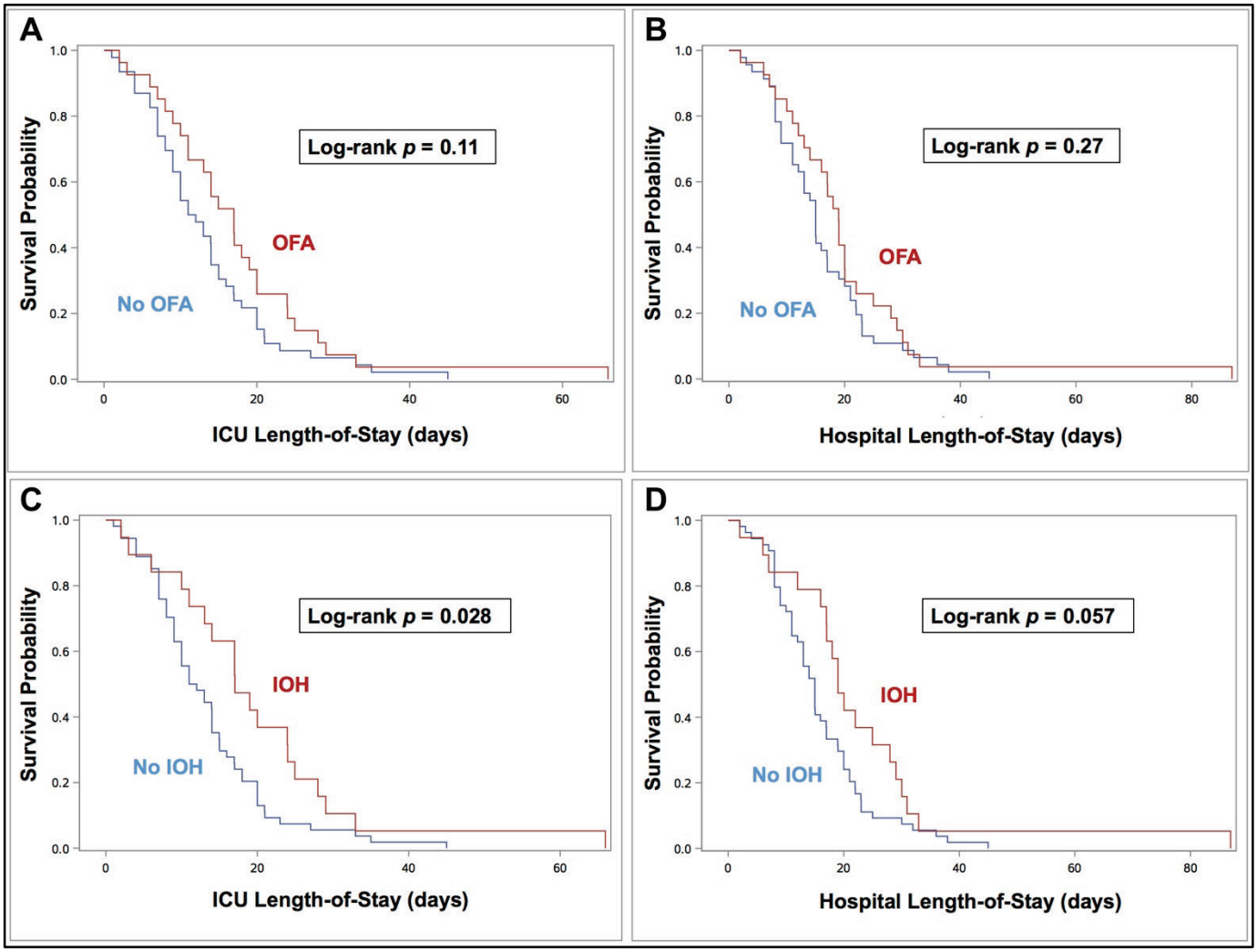


FIGURE 8. Log-log survival curves for (A) ICU length-of-stay and (B) hospital length-of-stay among patients with and without respiratory failure at ICU admission. The lines are substantially non-parallel, indicating a likely violation of the proportional hazards assumption for the respiratory failure variable.

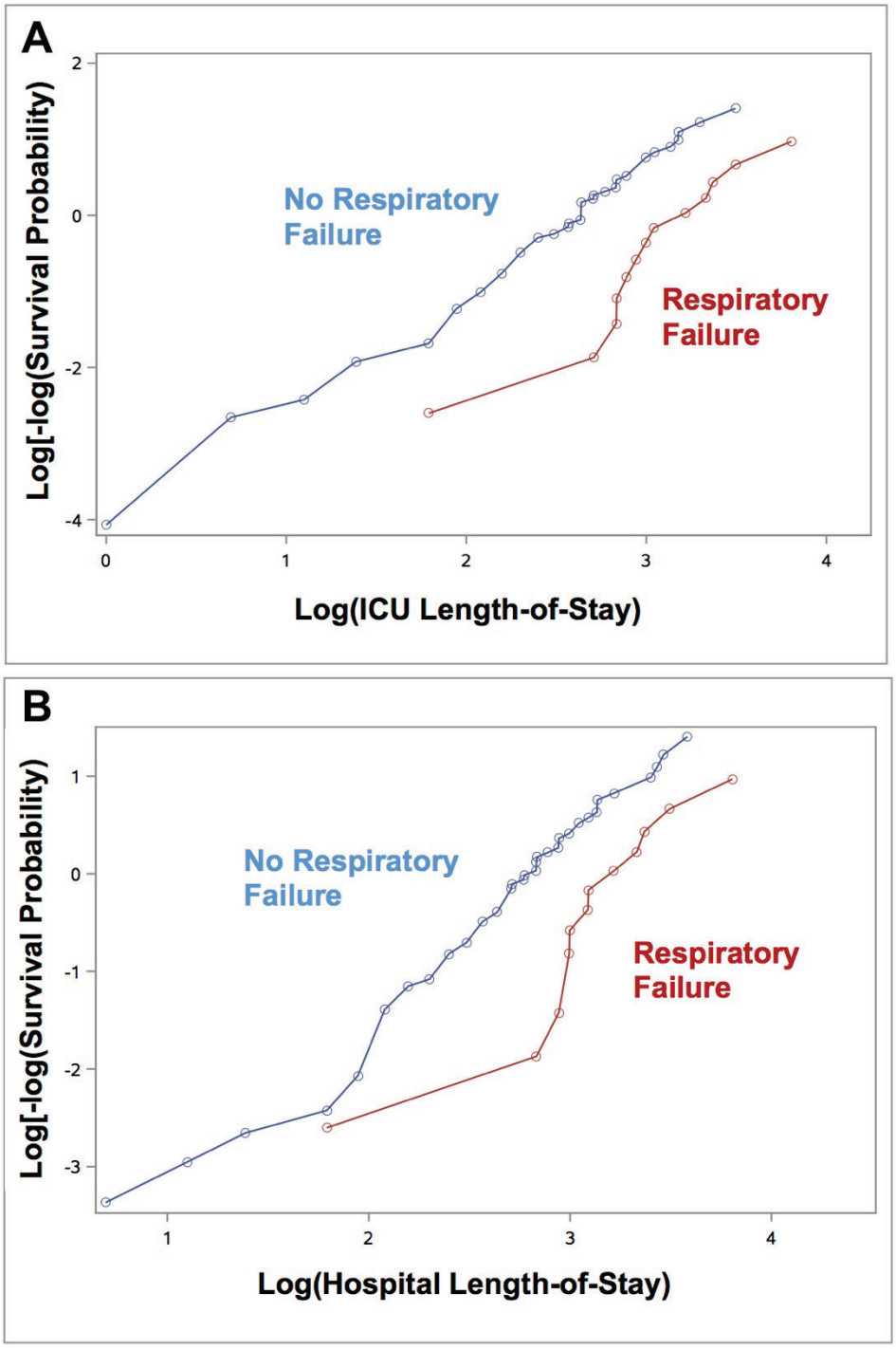


TABLE 3A. Proportional hazards regression analysis for ICU discharge among 73 SAH patients, stratified by respiratory failure at ICU admission, with ocular fundus abnormality (OFA) as the ocular predictor of interest.

Variable	Hazard Ratio	95% CI	p
OFA (vs. No OFA)	0.95	0.54 – 1.69	0.87
Age (per 1 year increase)	1.00	0.97 – 1.02	0.82
Male Sex (vs. Female Sex)	0.60	0.34 – 1.03	0.07
APACHE II Score[a] (per 1 point increase)	0.99	0.89 – 1.10	0.81
Hunt & Hess Score > 3 (vs. Hunt & Hess Score $\leq$ 3)	0.33	0.07 – 1.51	0.15
Aneurysmal SAH Etiology (vs. Nonaneurysmal Etiology)	0.31	0.17 – 0.57	<0.001

Abbreviations: OFA = ocular fundus abnormality; SAH = subarachnoid hemorrhage.

[a]At time of admission to the Neuro ICU.

TABLE 3B. Proportional hazards regression analysis for hospital discharge among 73 SAH patients, stratified by respiratory failure at ICU admission, with ocular fundus abnormality (OFA) as the ocular predictor of interest.

Variable	Hazard Ratio	95% CI	p
OFA (vs. No OFA)	1.08	0.62 – 1.88	0.79
Age (per 1 year increase)	0.99	0.97 – 1.02	0.63
Male Sex (vs. Female Sex)	0.68	0.40 – 1.15	0.15
APACHE II Score[a] (per 1 point increase)	0.99	0.89 – 1.10	0.82
Hunt & Hess Score > 3 (vs. Hunt & Hess Score $\leq$ 3)	0.21	0.04 – 1.05	0.06
Aneurysmal SAH Etiology (vs. Nonaneurysmal Etiology)	0.30	0.16 – 0.55	<0.001

Abbreviations: OFA = ocular fundus abnormality; SAH = subarachnoid hemorrhage.

[a]At time of admission to the Neuro ICU.

TABLE 3C. Proportional hazards regression analysis for ICU discharge among 73 SAH patients, stratified by respiratory failure at ICU admission, with intraocular hemorrhage (IOH) as the ocular predictor of interest.

Variable	Hazard Ratio	95% CI	p
IOH (vs. No IOH)	0.67	0.36 – 1.28	0.23
Age (per 1 year increase)	1.00	0.97 – 1.02	0.83
Male Sex (vs. Female Sex)	0.56	0.32 – 0.97	0.04
APACHE II Score[a] (per 1 point increase)	1.00	0.90 – 1.11	0.94
Hunt & Hess Score > 3 (vs. Hunt & Hess Score $\leq$ 3)	0.39	0.08 – 1.84	0.23
Aneurysmal SAH Etiology (vs. Nonaneurysmal Etiology)	0.30	0.16 – 0.55	<0.001

Abbreviations: IOH = intraocular hemorrhage; SAH = subarachnoid hemorrhage.

[a]At time of admission to the Neuro ICU.

TABLE 3D. Proportional hazards regression analysis for hospital discharge among 73 SAH patients, stratified by respiratory failure at ICU admission, with intraocular hemorrhage (IOH) as the ocular predictor of interest.

Variable	Hazard Ratio	95% CI	p
IOH (vs. No IOH)	0.74	0.40 – 1.39	0.35
Age (per 1 year increase)	1.00	0.97 – 1.02	0.72
Male Sex (vs. Female Sex)	0.64	0.37 – 1.09	0.10
APACHE II Score[a] (per 1 point increase)	0.99	0.90 – 1.10	0.89
Hunt & Hess Score > 3 (vs. Hunt & Hess Score $\leq$ 3)	0.26	0.05 – 1.29	0.10
Aneurysmal SAH Etiology (vs. Nonaneurysmal Etiology)	0.29	0.15 – 0.55	<0.001

Abbreviations: IOH = intraocular hemorrhage; SAH = subarachnoid hemorrhage.

[a]At time of admission to the Neuro ICU.