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THE ALBUMIN IN SUBARACHNOID HEMORRHAGE (ALISAH) MULTICENTER PILOT CLINICAL TRIAL: SAFETY AND NEUROLOGIC OUTCOMES

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Abstract

Background and Purpose—Human albumin has been shown to exert neuroprotective effects in animal models of cerebral ischemia and humans with various intracranial pathologies. We investigated the safety and tolerability of 25% human albumin (ALB) in patients with subarachnoid hemorrhage (SAH).

Methods—The ALISAH (Albumin in Subarachnoid Hemorrhage) Pilot Clinical Trial was an open-label, dose-escalation study. We intended to study 4 different dosages of ALB of increasing magnitude (0.625 g/kg: tier 1; 1.25 g/kg: tier 2; 1.875 g/kg: tier 3; and 2.5 g/kg: tier 4). Each dosage was to be given to 20 adult patients. Treatment was administered daily for 7 days. We investigated the maximum tolerated dose of ALB based on the rate of severe-to-life-threatening heart failure and anaphylactic reaction, and functional outcome at 3 months.

Results—We treated 47 adult subjects: 20 in tier 1; 20 in tier 2; and 7 in tier 3. We found that doses ranging up to 1.25 g/kg/day × 7 days were tolerated by patients without major dose-limiting complications. We also found that outcomes trended towards better responses in those subjects enrolled in tier 2 compared to tier 1 (OR: 3.0513; CI: 0.6586 – 14.1367) and to the International Intra-operative Hypothermia for Aneurysm Surgery Trial cohort (OR: 3.1462; CI: 0.9158 – 10.8089).

Conclusions—ALB in doses ranging up to 1.25 g/Kg/day × 7 days was tolerated by patients with SAH without major complications and may be neuroprotective. Based on these results,

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planning of the ALISAH II, a Phase III, randomized, placebo-controlled trial to test the efficacy of ALB is underway.

Clinical Trial Registration Information: NCT00283400 (clinicaltrials.gov) http://clinicaltrials.gov/ct2/show/NCT00283400?term=subarachnoid+hemorrhage+houston&rank=1

Keywords

subarachnoid hemorrhage; albumin; neuroprotection; outcome; delayed ischemic deficit

Subarachnoid hemorrhage (SAH) is a neurological emergency that carries high morbidity and mortality. Half of the approximately 30,000 Americans that suffer SAH every year will die and a third of survivors will be left dependent[1]. Significant advances in the diagnosis, management, and prevention of complications in patients with SAH have occurred in the past few decades. However, improvement of clinical outcome has been modest. Newer treatments with proven neuroprotective benefits on clinical outcomes are needed. Nimodipine is the only available treatment with proven marginal efficacy[2].

Administration of high doses of 25% human albumin (ALB) has been associated with improved outcomes and reduced costs in SAH patients[3]. Furthermore, several pre-clinical and clinical studies demonstrated the role of ALB as a neuroprotective treatment in cerebral ischemia[4–9]. These findings formed the rationale for the design of a phase I pilot study investigating the safety and tolerability of ALB in patients with SAH[10].

Materials and Methods

The National Institutes of Health (NIH) funded the ALISAH (Albumin in Subarachnoid Hemorrhage) pilot study, initiated in May 2006 and terminated in May 2010. The study was originally planned for 3 years but mostly due to the PI's transferring institutions and initiation of 2 non-US sites, one extra year was needed. ALISAH investigated the intravenous administration of ALB in subjects with SAH. The primary objective of this prospective dose-finding pilot study was to demonstrate the tolerability and safety of four dosages of ALB in patients with SAH. For each dosage group, 20 patients who met the eligibility criteria were to be enrolled. Maximum tolerated dosage of ALB determination was based on the rate of treatment-related severe or life-threatening heart failure[10]. Secondary objectives were to obtain preliminary estimates of the albumin treatment effect using incidence of neurological deterioration within 15 days of symptom onset, as well as, incidence of rebleeding, hydrocephalus, seizures, delayed cerebral ischemia (DCI) and vasospasm (both symptomatic and by transcranial Doppler ultrasound criteria) within 15 days after symptom onset. In addition, the Glasgow Outcome Scale (GOS), Barthel Index (BI), modified Rankin Scale (mRS), NIH Stroke Scale (NIHSS), and Stroke Impact Scale (SIS) at 3 months following onset of symptoms were collected to assess residual neurological deficits.

ALISAH was conducted at 6 North American sites (Online Table S1). The Central Coordinatingcenter(CCC) was at the Baylor College of Medicine. The Statistical and Data Managementcenter(SDMC) was at the Medical University of South Carolina in Charleston, SC. Each site obtained IRB/Ethics Committees approval, and the study was registered at www.clinicaltrials.gov prior to patient recruitment.

All patients presenting with SAH to the participating clinical sites were screened for study eligibility[10] (Online Table S2). A cardiologist or cardiology fellow performed cardiologic evaluations and a qualified neurological surgeon or intensive care unit (ICU) physicians

performed a neurological assessment upon study entry. Once informed written consent was obtained patients were enrolled into the study.

Study Intervention

Subjects were allocated in a dose escalation design into one of four dosage groups of 25% ALB: 0.625 g/kg/d × 7 days; 1.25 g/kg/d × 7 days; 1.875 g/kg/d × 7 days; and 2.5 g/kg/d × 7 days. The tolerability and safety of the previous dosage tier of ALB was evaluated by the NIH-appointed Data and Safety Monitoring Board (DSMB) prior to advancing to the next dosage. The estimated volume of infusion for a 70-kg subject ranged from 175 to 700 ml, and the delivery time was 3 h for all dosage groups. Dosage ranges of ALB were chosen based on the range administered to patients for induction of hypervolemia and hyperdynamia after SAH including our preliminary data[3,10], and dosage ranges studied in animal models of focal cerebral ischemia[7]. The duration of treatment (7 days) was chosen on the premise that it would cover the highest risk period for DCI (peak occurrence at days 8–10). As the half-life of human albumin is around 21 days with a degradation rate of 3.7% per day and a transcapillary escape rate of 4– 5% per hour[10,11], we expected that the volume repletion and other neuroprotective effects of 25% ALB would persist for 24 h or more beyond the 7 days. In addition, animal models of focal cerebral ischemia have shown significantly higher plasma oncotic pressures and serum ALB concentrations up to 3 days after treatment[5].

Patient Management during Acute Period

All subjects had vital signs monitored hourly and were assessed by ICU nursing staff and/or site investigators for any new episode of neurological or cardiovascular deterioration. In addition, subjects had daily laboratory evaluations, assessment of neurologic function (GCS, NIHSS), transcranial Doppler ultrasound, complete cardiac examinations, evaluation of intravascular volume status, and monitoring of vital signs (including weight) for 15 days, or until hospital discharge if prior to that.

All subjects were treated with maintenance fluids of 0.9% normal saline (NS) at 80–125 ml/h (total 2–3 liters per day) with the goal central venous pressure (CVP) between 5–8 mmHg. In the event that subjects required further fluid administration beyond their maintenance to maintain the desired CVP, they received 250–500 ml intermittent intravenous boluses of NS as needed. Extra ALB administration was not allowed, and the initial fluid balance goal was set at < +2000 ml/day.

Neurological deterioration after treatment was defined as a decline in more than 2 points in the GCS[10,12]. Investigators determined causes for such deterioration. Acute left heart failure was defined as pulmonary edema occurring during the 7 days and up to 48 hours of treatment administration[10,13–15]. All neurological and cardiovascular complications were managed according to a pre-specified management protocol.

Post-Discharge Follow Up

Patients returned to the clinic 90-days after enrollment. During this follow-up visit subjects underwent a head computed tomography (CT), and were assessed using the GOS, mRS, NIHSS, BI, and the SIS. Information on adverse events and concomitant medications since the time of discharge was also collected. Following the 90-day evaluation, subjects were discharged from the study.

Data Management

Data management was handled by the SDMC at the Medical University of South Carolina (MUSC).The SDMC developed the Case Report Forms with input from the CCC. The

clinical site staff entered data electronically into the database via the WebDCU™ System, a user-friendly menu-driven system with built-in warnings and rules to facilitate the data collection process and ensure sufficient quality control.

Statistical Considerations and Safety Monitoring

Sample size consideration for this phase I dose escalation study was based on the feasibility of recruiting patients in a three-year study period at five sites[10]. The recruitment yield would be a maximum of 80 patients or 20 patients per dosage group. Statistical analyses were mainly descriptive.

Serious adverse events (SAEs) were defined as those resulting in: death from any cause, a life-threatening adverse experience, prolongation of hospitalization, persistent or significant disability, or an important medical event requiring medical or surgical intervention to prevent one of the previously mentioned outcomes. Safety guidelines for escalation to the next ALB dosage level were based on the rate of cardiovascular SAEs defined as severe or life-threatening heart failure considered to be related (probably, possibly, and definitely) to ALB treatment[10,16]. Upon completion of each ALB dosage level, if 2 or more subjects out of 20 experienced one of these events, then the independent Medical Safety Monitor (MSM) and DSMB could suggest termination of escalation to the next dosage level with the maximum tolerated dosage designated as the one dosage level below the current level[10]..

In addition we analyzed the functional clinical outcome and embarked upon comparisons between the safe dosage tiers (tiers 1 and 2) and data from the International Intra-operative Hypothermia for Aneurysm Surgery Trial (IHAST)[17]. Historical data from the latter was chosen because the inclusion criteria were very similar to ALISAH allowing for more comparable populations than seen in other studies. Since ALISAH was an open-label study without concurrent controls, two analytical approaches to evaluate for potential treatment effects were adopted. First, statistical comparisons were made between subjects receiving the two dosage tiers deemed to be safe based on the safety analyses (tier 1: 0.625 and tier 2: 1.25 g/kg/d × 7 days). Second, data from ALB tiers 1 and 2 were compared to the entire IHAST cohort, IHAST normothermia, and IHAST hypothermia groups. Data from ALB tier 3 were not included due to very small numbers of observations and the safety issues present in that tier. The analyses conducted here were not pre-specified but rather were conducted in a purely exploratory, post-hoc fashion. Favorable outcome was defined as a score of 0 to 1 on the GOS, reflecting good recovery at 3 months. GOS is the most commonly-used outcome measure in SAH clinical trials. For these exploratory comparisons, relative risks were generated using the generalized linear model with log link.

Results

A total of 383 subjects were screened and 47 (12.3%) enrolled in the ALISAH study. The most common reasons for exclusion were unavailable written-informed consent (17%); no aneurysm found on cerebral angiography (14%); aneurysm treatment >72 hours from symptom onset (12%); stupor or coma (11%); age >80 years (7%); ALB administration prior to screening (7%); symptoms not related to SAH (6%); and unreliable time of onset (5%). The majority of subjects were female (72.3%), Caucasian (87%), and median age was 51 years (Table 1). Most subjects were current smokers and all were fully independent prior to symptom onset. Ruptured aneurysms were mostly located in the anterior circulation and were treated within 24 hours of symptom onset.

We enrolled 20 subjects in dosage tier 1, 20 subjects in dosage tier 2, and 7 subjects in dosage tier 3. Two subjects died while in the study: 1 in tier 1 and 1 in tier 3. The former died of septic shock secondary to gram-negative ventriculitis 2 weeks after symptom onset

and was adjudicated as not related to ALB. The latter developed pulmonary edema possibly related to ALB, and aspiration pneumonia with ARDS which was the presumed cause of death.

Most subjects completed ALB treatment. In the first dosage tier 3 subjects did not complete ALB infusion: 1 withdrew consent after developing DCI on day 6; 1 skipped 1 day of treatment due to mild pulmonary edema on day 3; and 1 developed mild pulmonary edema on day 3 of treatment and medication was held. The latter was reported as a protocol violation since the clinical site did not consult with the primary coordinating center. In the second dosage tier 4 subjects did not complete ALB infusion: 1 withdrew consent after 5 days of treatment; 1 skipped 1 day of treatment due to neurological deterioration on day 2; 1 developed serious respiratory insufficiency possibly related to ALB after the first day of treatment; and 1 patient developed SAE with respiratory failure unlikely related to ALB on day 3 of treatment.

Physiologic and Laboratory Data

Daily serum albumin concentrations increased from baseline in all dosage tiers during the treatment period (Figure 1A). The changes were more prominent for tier 2 and were sustained up to 15 days after enrollment (online Table S3).

Daily maximum mean arterial blood pressures also increased from baseline for all treatment tiers during the treatment period (Figure 1B). These values tended to decrease to baseline after treatment was completed (online Table S4). Baseline blood pressures were higher for subjects in tier 2 compared to the other tiers. This was not related to prior known history of hypertension. We observed no differences in serum osmolality, serum creatinine, daily fluid balance, and daily weight from baseline in all the dosage tiers (Online Tables S5, S6, S7, and S8). In addition, there was no difference in CVP values. However due to concerns with higher values of fluid intake potentially leading to higher incidence of cardiac complications, the DSMB recommended reducing the fluid balance value to <+1000 ml/day after 22 subjects had been enrolled.

Adverse Events

There were 171 AEs in 32 subjects. The only expected and observed AEs related to ALB were those related to volume overload leading to acute heart failure or pulmonary edema. There were 17 SAEs reported in 7 subjects (15%) but only 3 adjudicated as related to ALB (Table 2). In the second dosage tier 1 subject experienced pulmonary edema which was possibly related to ALB. In the third dosage tier 2 subjects experienced pulmonary edema with 1 possibly and 1 definitely related to ALB. Because of the 2 SAEs related to ALB in dosage tier 3, the study was terminated after 47 patients had been enrolled and completed treatment.

Functional Outcomes

The summary functional outcome scores for all the tiers and historical IHAST treatment groups are presented in Table 3. We also present the distribution of GOS, mRs, and BI scores at 3 months in Figure 2. There was a consistent dose response relationship in that those subjects in tier 2 did better overall than those in tier 1 on all functional outcome measures, and those in tier 3 did worse overall. In addition, the overall incidence of DCI secondary to symptomatic vasospasm was low (17%). However, the proportion was lower for subjects in tier 2 (15%) compared to those in tier 3 (20%). We also reviewed head CT scans at 90 days to investigate new cerebral infarctions that were not present at the baseline study. We found a total of 7 new cerebral infarctions (3 in dosage tier 1, 3 in dosage tier 2, and 1 in dosage tier 3).

Subjects in ALB dosage tiers 1 and 2 were compared with subjects in the IHAST study (Total N= 1000; hypothermia group = 499; normothermia group = 501)[17]. Subjects in tier 2 had better outcomes compared to those of tier 1 suggesting a dose response (Table 4). In addition, when compared to IHAST subjects, outcomes for tier 2 subjects were better.

Discussion

We have shown that large doses of ALB up to 1.25 g/Kg/day × 7 days are safe in patients with aneurysmal SAH. The safety stopping rule of at least 2 events of severe-to-life-threatening heart failure in dosage tiers 1 and 2 was not met. Dosages higher than 1.25 g/Kg/day were associated with significant cardiovascular complications including 2 SAEs related to ALB. The latter resulted in early termination of the study. It is important to note that in all instances pulmonary edema was easily treated and resolved. We have also demonstrated that our treatment protocol was feasible and successfully implemented in several international centers. Our data are supported by findings from ALB studies in patients with acute ischemic stroke[8,9].

The main physiologic effects of ALB treatment were elevation in the serum albumin concentration and mean arterial blood pressure. The latter improved to baseline values after treatment completion. Serum albumin values remained elevated 7 days after treatment suggesting that any potential beneficial effects of ALB may remain throughout the critical period of DCI risk. We observed no changes in serum osmolality or renal function. In addition, we found that fluid intake increased in direct relationship to higher dosage tiers. However, there was no correlation between higher fluid intake or fluid balances and cardiovascular complications. This suggests that factors other than pure intravascular volume augmentation may play a role. We speculate that diastolic cardiac dysfunction may be a contributing factor rather than systolic abnormalities due to the fact that left ventricular ejection fractions were within normal limits in all our subjects. Note, however that the sample size was small and therefore our findings will have to be validated in a larger cohort of SAH subjects.

The data also suggest that high dosage of ALB up to 1.25 g/Kg/d × 7 days are not only safe but also may be neuroprotective. This is supported by data from ischemic stroke subjects treated with ALB[8,9,18] and retrospective data from SAH patients[3]. ALB has several potential mechanisms that could explain its neuroprotective effects. The increase in serum albumin concentrations is expected to increase the serum oncotic pressure which in turn will mobilize interstitial fluid and improve organ function including the brain[19]. ALB also possesses antioxidant and scavenger properties in part by its potential to replete thiol stores[20–22], and it can modulate apoptosis[23]. In addition, ALB administration may also improve microcirculatory blood flow, increase organ blood flow, decrease leukocyte rolling and adherence, and reduce the inflammatory response[24].

The potential reduction DCI secondary to symptomatic vasospasm may be explained by the interaction of ALB with the albumin-specific binding sites of the microvasculature endothelium.[25–27]. By binding to the endothelial glycocalyx, albumin maintains the normal permeability of microvessel walls[26, 28, 29]. It has also been suggested that albumin may be a factor in mediating the effect of blood coagulation on vascular tone and capillary permeability[30]. Moreover, serum albumin reacts with nitric oxide to form a stable S-nitrosothiol that has endothelium-derived relaxing factor-like properties[31].

Our study has several limitations. ALISAH is an early phase design and we do not have concurrent controls. In addition, the study was neither randomized, nor powered to test for efficacy effects. Therefore, caution is advised in the interpretation of our data and

comparison with the IHAST study. Moreover, we did not obtain head CT scans following aneurysmal treatment. This limits our ability to determine whether the cerebral infarctions found at 90 days were due to treatment modalities or ischemic complications from SAH. Lastly, the severity of radiological infarctions cannot be ascertained since we did not measure infarction volume.

Conclusion

The ALISAH Pilot Study has demonstrated that large ALB dosages up to 1.25 g/Kg/d × 7 days are safe and the treatment protocol is feasible. These dosages have been found to be neuroprotective in animal models of cerebral ischemia. Pulmonary edema, the main systemic complication related to ALB, was easily managed in the ICU setting. Despite the limited sample size, the ALISAH data also provide preliminary evidence that high-dose ALB may be neuroprotective after aneurysmal SAH. Based on these encouraging results, initial planning of ALISAH II, a large Phase III multicenter, randomized, placebo-controlled clinical trial to evaluate the efficacy of ALB in subjects with SAH is underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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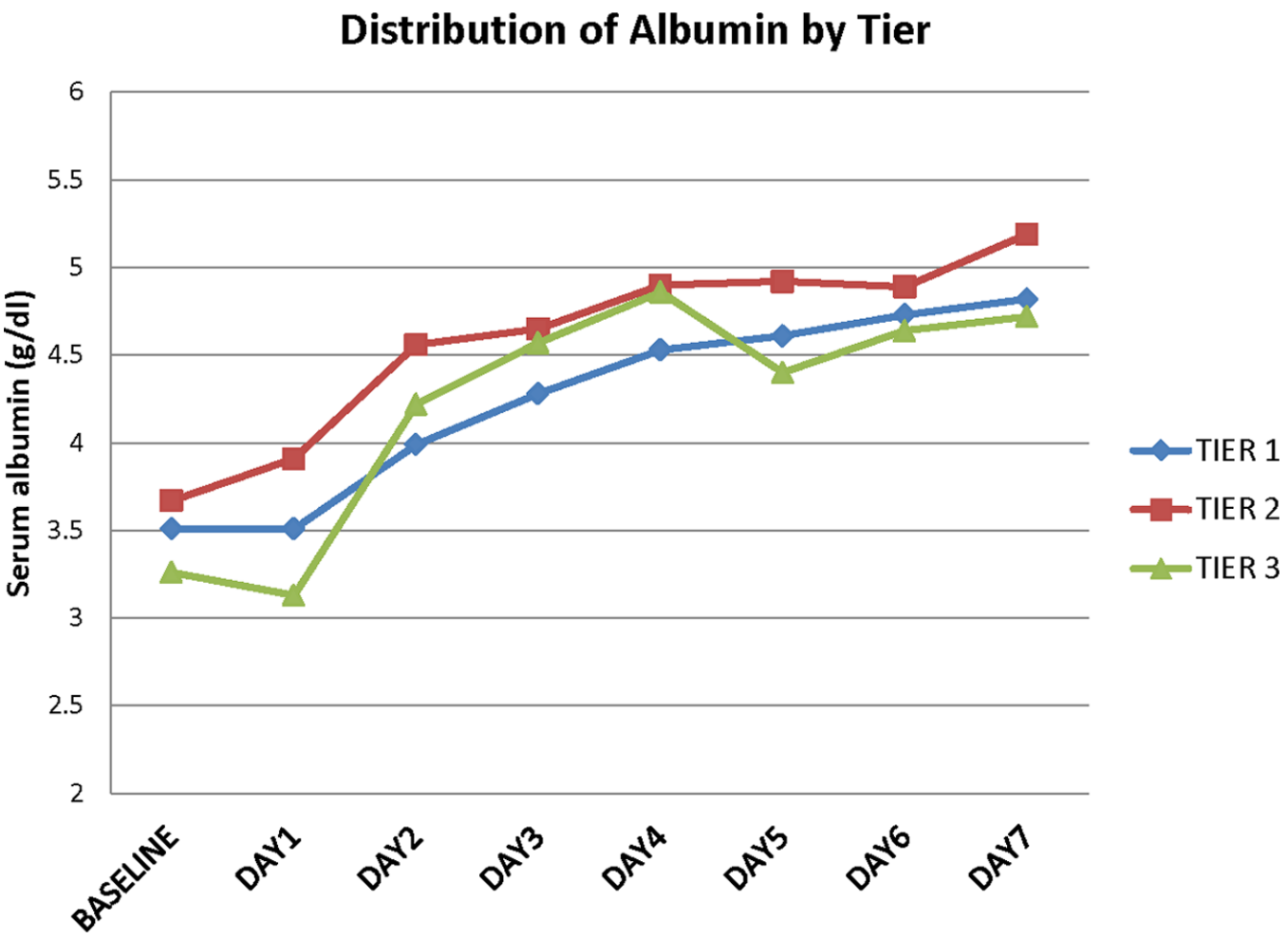


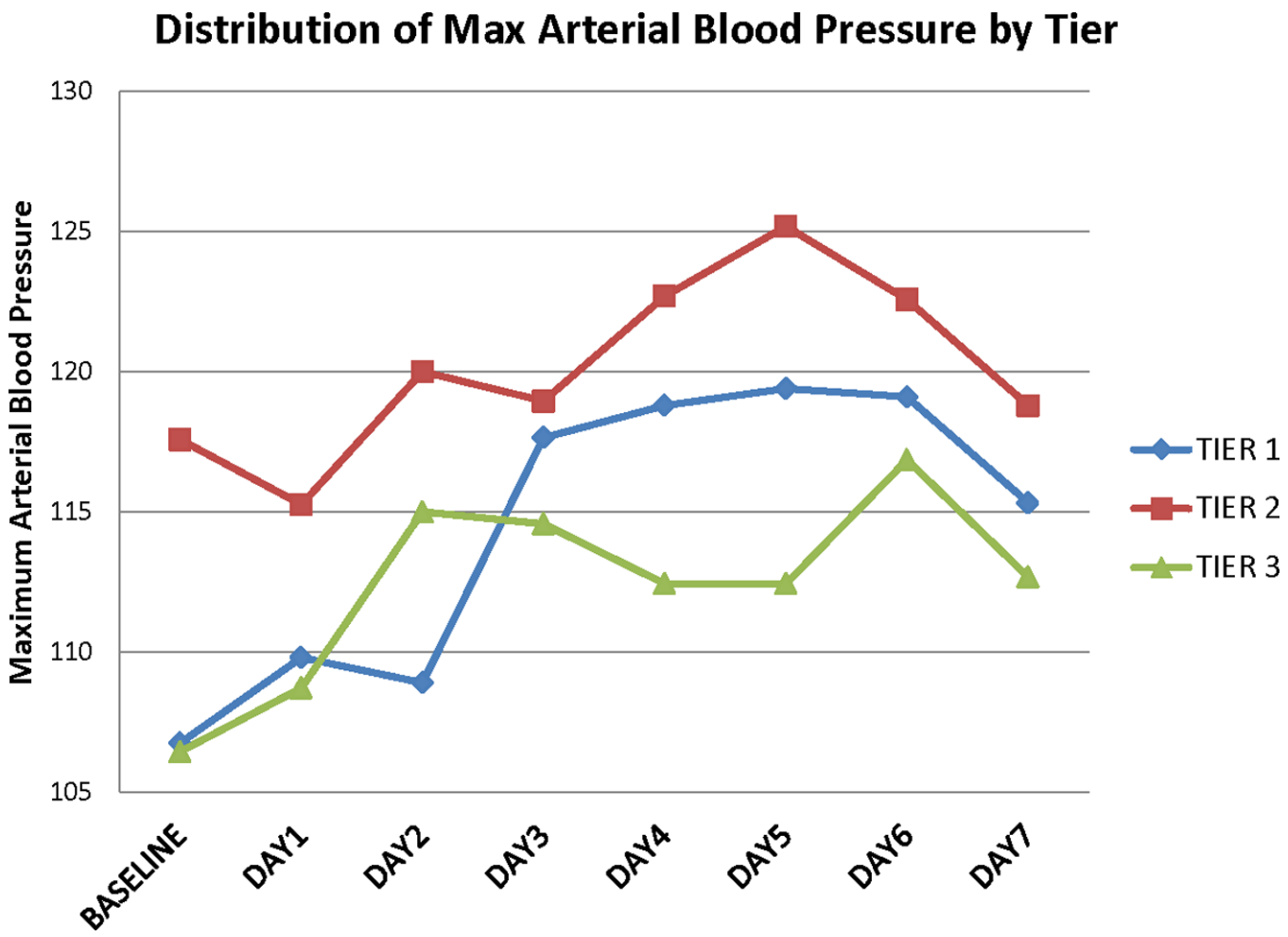
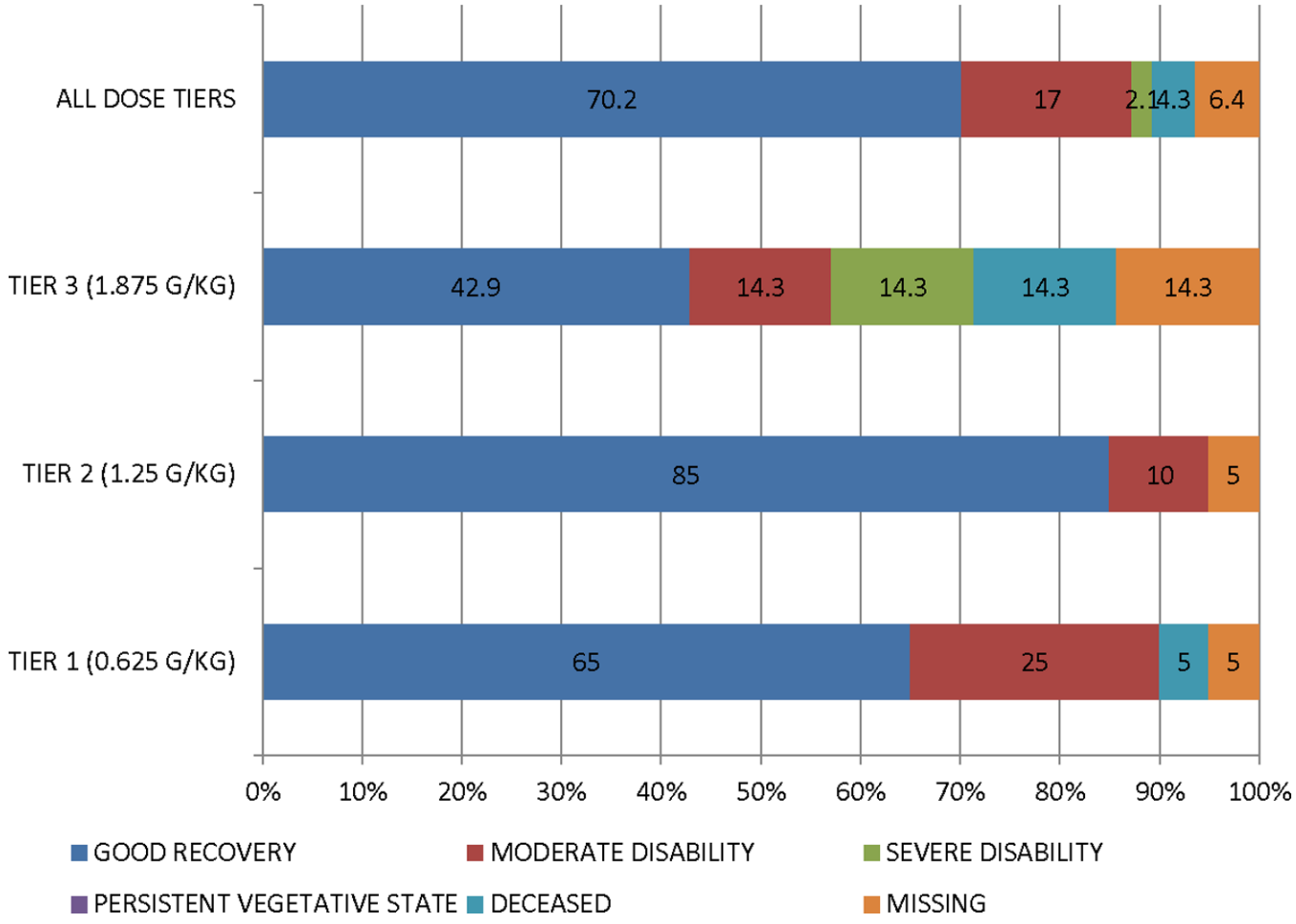
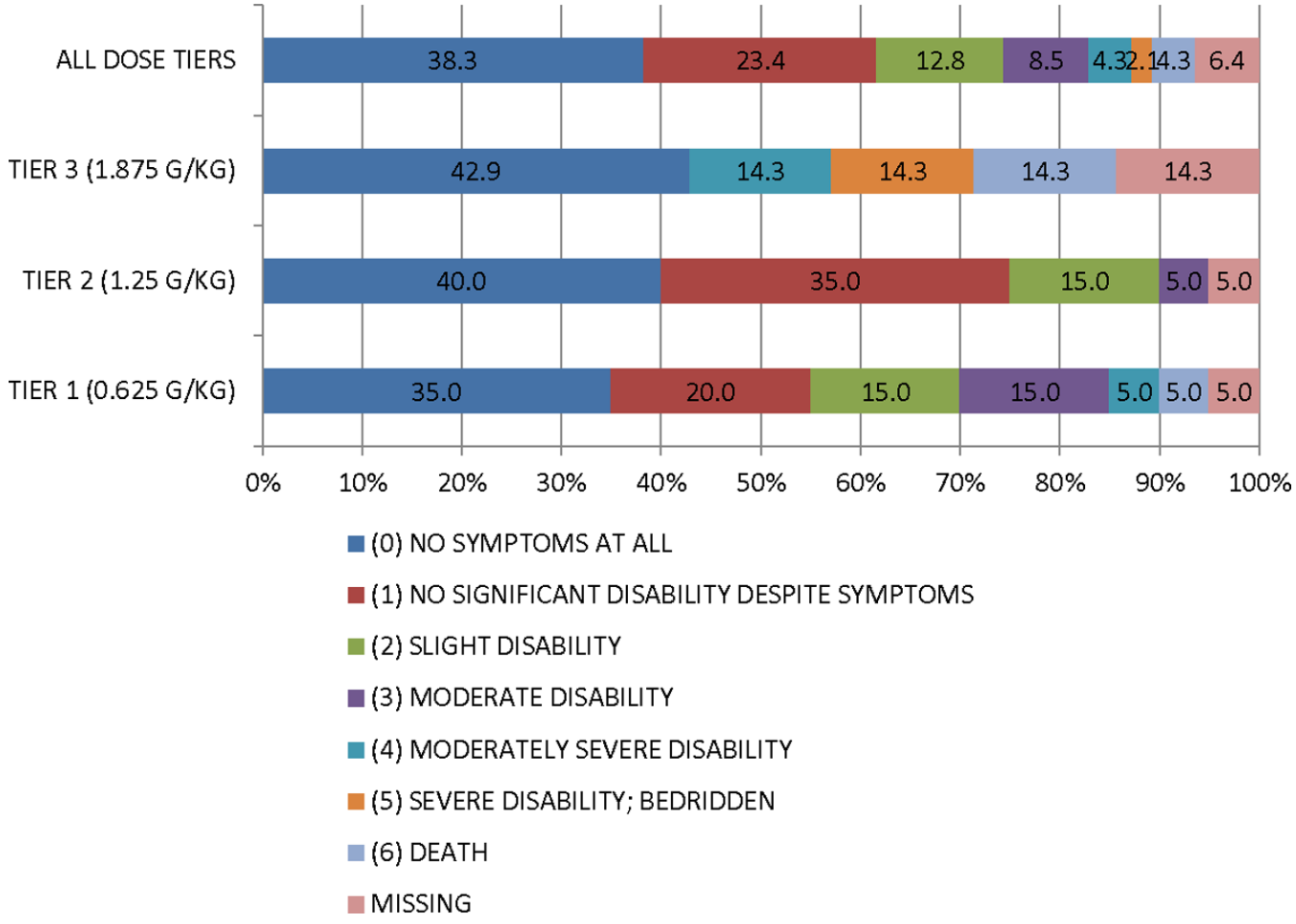


Figure 1. Laboratory and physiologic variables during the treatment period
A. Serum albumin concentrations
B. Maximum mean arterial blood pressure





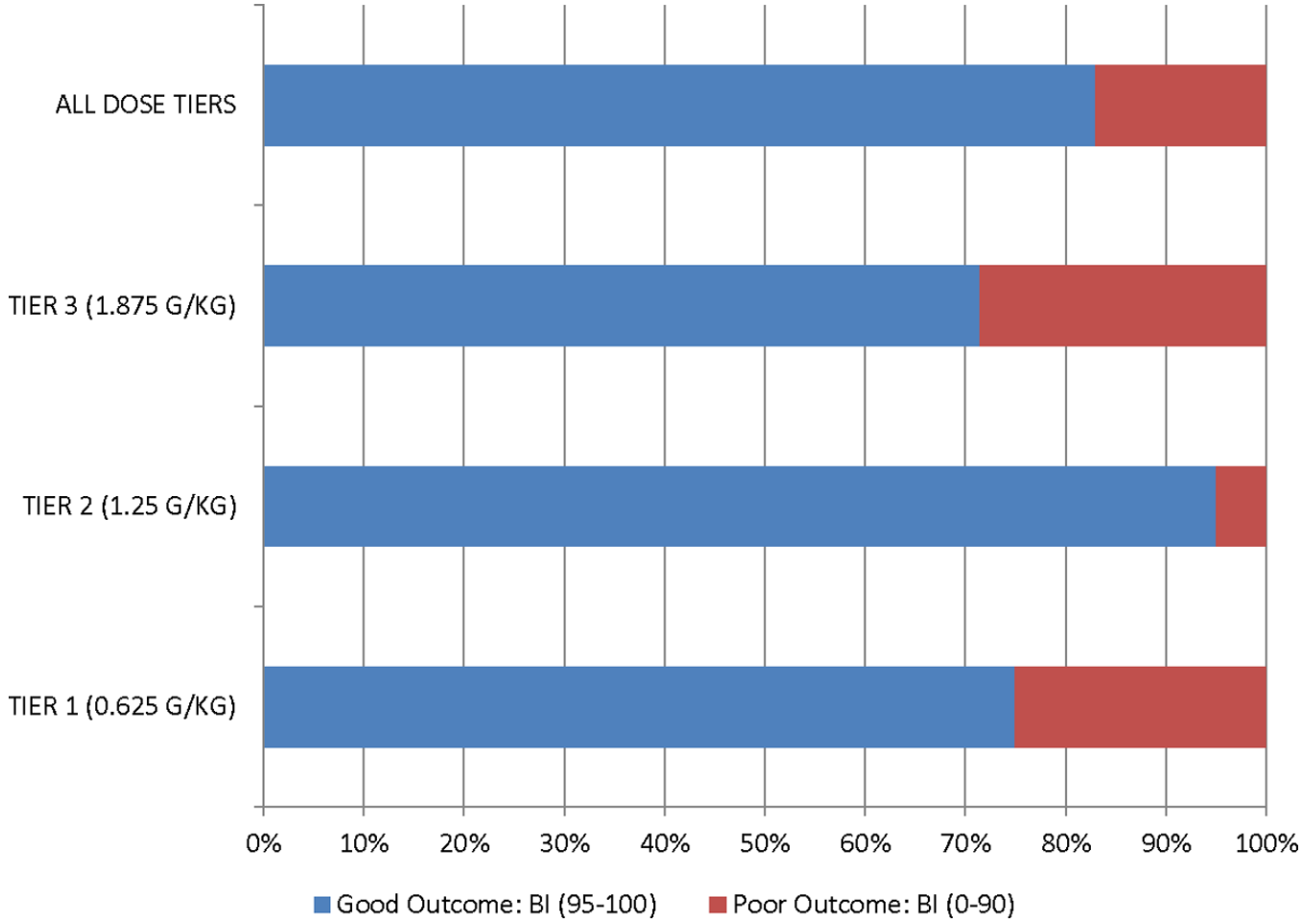


Figure 2. Distribution of functional outcomes at 90 days by treatment tier

A. Glasgow Outcome Scale

B. Modified Rankin Scale

C. Barthel Index

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Table 1

Demographic and Baseline Characteristics by ALB Dosage Group.

	TIER 1 (0.625 G/KG)	TIER 2 (1.25 G/KG)	TIER 3 (1.875 G/KG)	All Groups
N	20	20	7	47
Age				
Median (Min – Max)	51 (25 – 79)	51 (33 – 77)	55 (38 – 75)	51 (25 – 79)
Gender				
FEMALE	15 (75.0%)	13 (65.0%)	6 (85.7%)	34 (72.3%)
Race				
WHITE	18 (90.0%)	18 (90.0%)	5 (71.4%)	41 (87.2%)
Ethnicity				
HISPANIC OR LATINO	2 (10.0%)	1 (5.0%)	1 (14.3%)	4 (8.5%)
NOT HISPANIC/NOT LATINO	17 (85.0%)	14 (70.0%)	3 (42.9%)	34 (72.3%)
UNKNOWN	1 (5.0%)	5 (25.0%)	3 (42.9%)	9 (19.1%)
Smoking Status				
NEVER SMOKED	5 (25.0%)	8 (40.0%)	2 (28.6%)	15 (31.9%)
PAST SMOKER	0 (0.0%)	1 (5.0%)	2 (28.6%)	3 (6.4%)
CURRENT SMOKER	15 (75.0%)	11 (55.0%)	3 (42.9%)	29 (61.7%)
Alcohol Use				
NONE	6 (30.0%)	7 (35.0%)	3 (42.9%)	16 (34.0%)
< 3 DRINKS/DAY AVERAGE	12 (60.0%)	12 (60.0%)	4 (57.1%)	28 (59.6%)
>= 3 DRINKS/DAY AVERAGE	1 (5.0%)	1 (5.0%)	0 (0.0%)	2 (4.3%)
UNKNOWN	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Recreational Drug Use				
NONE	17 (85.0%)	16 (80.0%)	7 (100.0%)	40 (85.1%)
PAST USER	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (2.1%)
CURRENT USER	2 (10.0%)	2 (10.0%)	0 (0.0%)	4 (8.5%)
UNKNOWN	1 (5.0%)	1 (5.0%)	0 (0.0%)	2 (4.3%)
History of Hypertension (YES)	8 (40.0%)	9 (45.0%)	3 (42.9%)	20 (42.6%)

	TIER 1 (0.625 G/KG)	TIER 2 (1.25 G/KG)	TIER 3 (1.875 G/KG)	All Groups
Symptom Onset to Aneurysm Treatment (days)				
Median (Min – Max)	1 (0 – 2)	1 (0 – 2)	1 (0 – 2)	1 (0 – 2)
Premorbid mRS				
NO SYMPTOMS AT ALL	20 (100.0%)	19 (95.0%)	7 (100.0%)	46 (97.9%)
NO SIGNIFICANT DISABILITY DESPITE SYMPTOMS	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (2.1%)
World Federation of Neurological Surgeons Scale				
GLASGOW COMA SCALE SCORE 15	9 (45.0%)	9 (45.0%)	3 (42.9%)	21 (44.7%)
GLASGOW SCORE 14 OR 13 W/O MOTOR DEFICIT	6 (30.0%)	11 (55.0%)	3 (42.9%)	20 (42.6%)
GLASGOW SCORE 14 OR 13 W/MOTOR DEFICIT	5 (25.0%)	0 (0.0%)	1 (14.3%)	6 (12.8%)
GLASGOW SCORE 12 TO 7 WITH OR W/O MOTOR DEFICIT	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GLASGOW SCORE 6 TO 3 W/ OR W/O MOTOR DEFICIT	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline Glasgow Coma Scale				
MODIFIED FISHER SCALE				
GRADE 2	2 (10%)	3 (15%)	1 (14.2%)	6 (12.8%)
GRADE 3	5 (25%)	4 (20%)	3 (42.9%)	12(25.5%)
GRADE 4	13 (65%)	13 (65%)	3 (42.9%)	29 (61.7%)
Median (Min – Max)	14 (13 – 15)	14 (13 – 15)	15 (13 – 15)	14 (6 – 15)
Baseline NIHSS				
Median (Min – Max)	2 (0 – 16)	2 (0 – 14)	2 (0 – 14)	2 (0 – 16)
Location of Aneurysm				
MCA	3 (15.0%)	2 (10.0%)	0 (0.0%)	5 (10.6%)
ICA	3 (15.0%)	0 (0.0%)	1 (14.3%)	4 (8.5%)
ACA	0 (0.0%)	2 (10.0%)	1 (14.3%)	3 (6.4%)
ACOM	4 (20.0%)	5 (25.0%)	0 (0.0%)	9 (19.1%)
MULTIPLE ANEURYSMS	6 (30.0%)	5 (25.0%)	1 (14.3%)	12 (25.5%)
PCOM	4 (20.0%)	2 (10.0%)	3 (42.9%)	9 (19.1%)
BASILAR	0 (0.0%)	2 (10.0%)	0 (0.0%)	2 (4.3%)
PICA	0 (0.0%)	2 (10.0%)	0 (0.0%)	2 (4.3%)

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	TIER 1 (0.625 G/KG)	TIER 2 (1.25 G/KG)	TIER 3 (1.875 G/KG)	All Groups
MISSING	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (2.1%)
Treatment of Aneurysm				
Surgical clipping	6 (30.0%)	4 (20.0%)	3 (42.9%)	13 (27.7%)
Endovascular coiling	14 (70.0%	16 (80.0%	4 (57.1%	34 (72.3%)

Abbreviations: mRs: modified Rankin Scale; SD: standard deviation; Min: minimum; Max: maximum; MCA: middle cerebral artery; ICA: internal carotid artery; ACA: anterior cerebral artery; ACOM: anterior communicating artery; PCOM: posterior communicating artery; PICA: posterior inferior cerebellar artery.

Table 2

Cardiovascular and Respiratory Serious Adverse Events

ALB Dosage Tier	Serious Adverse Event	Relationship to ALB*
1	- Hypotension due to sepsis	- Not related
	- Pulmonary embolism	- Not related
	- Rebleeding	- Not related
	- Gram-negative ventriculitis	- Not related
	- Symptomatic vasospasm (4 subjects)	- Not related
2	- Pulmonary edema (2 subjects)	- Possible 1; Unlikely 1
	- Symptomatic vasospasm (3 subjects)	- Not related
3	- Pulmonary edema (2 subjects)	- Definite 1; Possible 1
	- Pulmonary edema	- Not related
	- ARDS	- Not related
	- Symptomatic vasospasm	- Not related

Abbreviations: ALB: 25% human albumin; ARDS: Acute Respiratory Distress Syndrome.

*After adjudication by Medical Safety Monitor and review by Data and Safety Monitoring Board.

Table 3

Outcome summary by treatment group for ALISAH and IHAST

STUDY AND TREATMENT GROUPS	mRs ≤ 1	mRs ≤ 2	Barthel Index 95–100	Glasgow Outcome Scale 0 – 1
-ALISAH				
TIER 1 (0.625 G/KG)	11 (55%)	15 (70%)	15 (75%)	13 (65%)
TIER 2 (1.25 G/KG)	15 (75%)	18 (90%)	19 (95%)	17 (85%)
TIER 3 (1.875 G/KG)	3 (43%)	3 (43%)	5 (71%)	3 (43%)
-IHAST				
HYPOTHERMIA	333 (67%)	-	416 (89%)	329 (66%)
NORMOTHERMIA	318 (63%)	-	403 (86%)	314 (63%)

Abbreviations: mRs: modified Rankin Scale score; BI: Barthel Index; GOS: Glasgow Outcome Scale.

Table 4

Glasgow Outcome Scale comparisons between dosage tiers and IHAST data.

Comparison	Odds Ratio for GOS=1	95% Confidence interval
ALISAH Tier 2 vs ALISAH Tier 1	3.0513	0.6586, 14.1367
ALISAH Tier 2 vs IHAST all	3.1462	0.9158, 10.8089
ALISAH Tier 1 vs IHAST all	1.0311	0.4077, 2.6079
ALISAH Tier 3 vs IHAST all	0.4164	0.0927, 1.8709
ALISAH Tier 2 vs IHAST normothermia	3.3747	0.9760, 11.6694
ALISAH Tier 2 vs IHAST hypothermia	2.9281	0.8463, 10.1310

Abbreviations: GOS: Glasgow Outcome Scale; ALISAH: Albumin in Subarachnoid Hemorrhage; IHAST: Intraoperative Hypothermia for Aneurysm Surgery Trial.