ARTERIAL LACTATE DRIFT RATIO IN PATIENTS WITH ANEURYSMAL SUBARACHNOID HAEMORRHAGE- A PREDICTIVE BIOMARKER OF DELAYED CEREBRAL ISCHEMIA (**ALDRID** Study)

A PROSPECTIVE OBSERVATIONAL STUDY

Dr. Arvin Ahuja

DM Neuroanaesthesia

July, 2023

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, THIRUVANANTHAPURAM, KERALA

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A PROSPECTIVE OBSERVATIONAL STUDY

A THESIS SUBMITTED BY

Dr. Arvin Ahuja

(Towards partial fulfilment of the requirements for the award of DM, Neuroanaesthesia)

To,

Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India

JULY 2023

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. Arvin Ahuja hereby certify that I have personally carried out the work depicted in this thesis titled 'Arterial Lactate Drift Ratio In patients with aneurysmal subarachnoid haemorrhage- a predictive biomarker of Delayed cerebral ischemia (ALDRID Study): a prospective observational study'.

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Dated: 25th August 2023

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APPROVAL OF THE THESIS

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Dated- 25th August 2023. *Dr. Arvin Ahuja*

Thiruvananthapuram

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ABBREVIATIONS

ABG- Arterial Blood Gas

ACA- Anterior Cerebral Artery

ACOM- Anterior Communicating Artery

ADAMTS- A Disintegrin And Metalloproteinase with a Thrombo Spondin motif

ADPKD- Adult Polycystic Kidney Disease

AHA- American Heart Association

AKI- Acute Kidney Injury

ALI- Acute Lung Injury

ANOVA- Analysis of Variance

ARDS- Acute Respiratory Distress Syndrome

ASA- American Society of Anesthesiologists

aSAH- Aneurysmal Sub-Arachnoid Hemorrhage

AUC- Area Under the Curve

AVM- Arterio-Venous Malformation

BBB- Blood Brain Barrier

BRAT- Barrow Ruptured Aneurysm Trial

CAD- Coronary Artery Disease

CAR- Cerebral Autoregulation

CBF- Cerebral Blood Flow

CD- Cluster of Differentiation

CHD- Congenital Heart Disease

CI- Confidence Interval

CKD- Chronic Kidney Disease

CLD- Chronic Liver Disease

CMD- Cerebral Microdialysis

CONSCIOUS Trial- Clazosentan in Aneurysmal Subarachnoid Hemorrhage

COPD- Chronic Obstructive Pulmonary Disease

CPP- Cerebral Perfusion Pressure

CSD- Cortical Spreading Depolarizations

CSF- Cerebrospinal Fluid

CT- Computed Tomography

DALYs- Disability Adjusted Life Years

DACA- Distal Anterior Cerebral Artery

DAVF- Dural Arterio-Venous Fistulas

DCI- Delayed Cerebral Ischemia

DeoxyHb- Deoxygenated Hemoglobin

DM- Diabetes Mellitus

DVT- Deep Venous Thrombosis

EBI- Early Brain Injury

EDH- Extra Dural Hemorrhage

EEG- Electroencephalogram

EVD- Extra Ventricular Drain

GCS- Glasgow Coma Scale

HCP- Hydrocephalus

HSA- Hemodynamically Significant Arrhythmia

HTN- Hypertension

IA- Intracranial Aneurysm

ICA- Internal Carotid Artery

ICH- Intra-cranial Hemorrhage

ICP- Intra-cranial Pressure

ICU- Intensive Care Unit

IEL- Internal Elastic Lamina

IHAST- Intraoperative Hypothermia for Aneurysm Surgery Trial

IL-Interleukin

iNOS- Inducible Nitric Oxide synthase

IP10- Interferon gamma induced Protein 10

IQR- Interquartile Range

ISAT- International Subarachnoid Aneurysm Trial

KLF- Krüppel-like transcription factors

LDH- Lactate Dehydrogenase

LDRb- Lactate Drift Ratio Baseline

LDRi- Lactate Drift Ratio Intervention

LOI- Lactate Oxygen Index

LPR- Lactate Pyruvate Ratio

MAP- Mean Arterial Pressure

MCA- Middle Cerebral Artery

MCP-1- Monocyte chemoattractant Protein-1

MeSH- Medical Subject Headings

MFG- Modified Fisher Grade CT Score

MHH- Modified Hunt and Hess Scale

MIG- Monokine Induced by Gamma interferon

MMP- Matrix Metallo Proteinases

MRI- Magnetic Resonance Imaging

mRS- Modified Rankin Score

NAD- Nicotinamide adenine dinucleotide

NF- Neurofibromatosis

NF- kB- Nuclear Factor Kappa B

NMDA- N-methyl-D-aspartate receptor

NO- Nitric Oxide

NOS- Nitric Oxide Syntase

NPE- Neurogenic Pulmonary Edema

OxyHb- Oxygenated Haemoglobin

PCOM- Posterior Communicating Artery

RANTES- Regulated upon Activation, Normal T cell Expressed and Secreted

ROC- Receiver Operating Characteristic curve

RWMA- Regional Wall Motion Abnormality

SCM- Stress Cardiomyopathy

STROBE- Strengthening the reporting of observational studies in Epidemiology

TBI- Traumatic Brain Injury

TLR- Toll like receptor

TNF- Tumour Necrosis Factor

WFNS- World Federation of Neurosurgeons

UTI- Urinary Tract Infection

VAP- Ventilator Associated Pneumoniae

VP Shunt- Ventriculo-Peritoneal Shunt

VSMC- Vascular Smooth Muscle Cell

SYNOPSIS

Background:

- DCI causes an insult to injury & worsen the outcomes exponentially in patients with aSAH.
- Biomarkers which can predict the occurrence of DCI are hence need of the hour.
- Arterial Lactate is a convenient, cost effective, readily available, bedside test which is minimally invasive, can be serially analyzed and easily interpreted.

Aims and Objectives:

- To study the temporal trends of arterial lactate drift ratios as a predictive biomarker of DCI in patients with anterior circulation aSAH.

Methodology:

- On admission baseline neurological evaluation was done & WFNS, mHunt & Hess, mFischer grade scores noted.
- Daily serial ABGs were done & arterial lactate levels noted. Lactate >2mmol/lts was considered elevated.
- Post-hoc analysis- Patients were grouped into 2 groups Group A- Patients who developed DCI Group B- Patients who did not develop DCI.
- Timeline of recordings was Tb-Baseline on admission, T0-Immediate post intervention, T1-Postop Day0, D1/2/3…V-Postop Day 1/2/3 till Day of Event ie Dv, Dd-Day of Hospital discharge. Day of Event (Dv) for Group A- day of occurrence of DCI, Dv for Group B- day of ICU Discharge.
- Lactate drift ratios (LDRb& LDRi) were computed daily till Dv & Dd.
- LDRb= $\frac{\text{Lactate on a particular day or till event (Dv), whichever is later}}{\text{Baseline lactate (Tb)}}$
- LDRi=$\frac{\text{Lactate on a particular day or till event (Dv), whichever is later}}{\text{Lactate immediate post intervention (Clipping/Coiling) (T0)}}$

Results:

- 22 patients (40.74%) developed DCI & 32 patients (59.26%) did not.

- *Baseline lactate* values were found to be elevated in 14 patients (25.92%). Of these,12 patients (85.71%) developed DCI.

- *LDRb*- The mean for Gp A on Dv was found to be 2.30±0.74 & for Gp B was 1.43±1.24. In the ROC analysis, at a cut-off point of 1.78, the AUC was 0.878(95% CI: 0.778-0.978); with a sensitivity of 81.8% & specificity of 85.5%.

- *LDRi*- The mean for Gp A on Dv was 1.97±1.54 & for Gp B was 0.79±0.28. In the ROC analysis, at a cut-off point of 1.01, the AUC was 0.858(95% CI: 0.756-0.960); with a sensitivity of 72.7% and a specificity of 68.7%.

- For both the tests (in parallel) LDRb and LDRi with a cutoff values 1.78 & 1.01 respectively, the combined sensitivity predictive of DCI was 95% and the combined specificity was 58.7%.

Conclusions:

- Elevated baseline lactate is a good prognostic marker predictive of DCI.
- Arterial lactate drift ratios LDRb & LDRi can be used together as an effective bedside screening tool for DCI.
- The tests when done in parallel have a combined sensitivity of 95% and a combined specificity of 58.7% at an upper cutoff value of LDRb= 1.78 and LDRi= 1.01.

1. Introduction

1. INTRODUCTION

Aneurysmal Sub-arachnoid haemorrhage (aSAH) is a catastrophic event which is associated with high mortality and morbidity burdens along-with increased number of Disability adjusted life years (DALYs) and productive life years lost amongst the survivors of this devastating disease. It occurs with increasing frequency in comparatively younger and working population group unlike other forms of stroke and is associated with a significant socioeconomic and psychological stress both for patient and the family alike. Even amongst survivors there is a significant residual neurocognitive decline noted in areas such as memory, executive functioning, and language precluding their return to the original premorbid functional state.

Delayed cerebral ischemia (DCI) is a clinical entity associated with new onset brain ischemia/infarct which occurs in a delayed fashion as the diseases evolves through its natural course in patients who survive the initial bleed. It causes an insult to injury which further worsens the outcomes by increasing both the mortality and morbidity of the disease manifolds. The exact underlying cause of DCI remains obscure and is considered to be multifactorial. Both early diagnosis and effective treatment protocols remain elusive, hence necessitating intensive research in this field.

Biomarkers which can precede & correctly predict the occurrence of DCI are hence need of the hour. However, none are sufficiently studied let alone their time frame kinetics during the disease evolution process (1,2) . Early diagnosis can help the treating intensivist to intervene in time and take remedial measures to limit this secondary brain injury.

Lactate: Increased blood lactate levels have been associated with significant morbidity and mortality ever since their first description in 1843 by Scherer (3) .

Lactic acidosis occurs when lactic acid production exceeds lactic acid clearance. Type A Lactic acidosis, is seen associated with shock caused by either hypovolemia/ cardiac failure/ sepsis. This occurs as a systemic phenomenon. However, Type B lactic acidosis is seen in all other conditions where there is no evidence of overt systemic hypoperfusion and includes causes like regional areas of tissue ischemia, toxins which impair cellular metabolic machinery, drugs like metformin / adrenergic agents / antiretrovirals etc, malignancy-associated lactic acidosis, alcoholism, some biochemical storage disorders, etc

In DCI following aSAH the regional increase in cerebral lactate production can be attributed to impaired tissue oxygenation, due to decreased oxygen delivery along-with decreased mitochondrial oxygen utilization secondary to underlying neuroinflammation.

Arterial Lactate is a

- convenient,

- cost effective

- readily available

- bedside test

Which is minimally invasive & can be serially analysed, but whose kinetics have so far not been studied in a prospective study model for DCI.

On the contrary Venous Lactate estimation has a limitation as the levels are affected by the site of sampling eg Jugular Venous v/s Mixed Venous v/s peripheral venous samples. CSF lactate and lactate as estimated by Cerebral micro dialysis has a limitation of being too invasive and is fraught with procedural complications like bleeding, infection, meningitis etc

Hence this study aims to investigate the arterial lactate kinetics (measured as both serial absolute values and as daily drift ratios from baseline) and its use as a predictive Biomarker for the occurrence of DCI in patients with aSAH.

1.1 HYPOTHESIS

Hypothesis- Arterial Lactate levels have a positive correlation with onset and occurrence of DCI in patients presenting with aSAH.

Null Hypothesis: In patients presenting with aSAH arterial blood lactate levels do not have any correlation with the occurrence of DCI.

1.2 AIMS AND OBJECTIVES

Primary- To study the temporal course of serial arterial blood lactate drift ratios (& the absolute values) in patients presenting with anterior circulation aSAH and to compare and contrast these trends in patients who develop DCI v/s those who do not.

Secondary- To derive upper maximum cutoff values for the lactate drift ratios which can be predictive of DCI (and be useful as an effective bedside screening tool).

2. Review of Literature

2. REVIEW OF LITERATURE

A thorough literature search for randomized clinical trials (RCT), review articles, meta-analysis, overview articles, observational studies, retrospective studies, case series, and guidelines was done systematically using the Pub-med central database employing various relevant MeSH terms (while restricting search to English language). The search terms included "aneurysmal subarachnoid hemorrhage," OR "ruptured intracranial aneurysm," AND "biomarkers," OR "lactate," AND "delayed cerebral ischemia," OR "vasospasm". It yielded below-mentioned studies done by various investigators for the topic concerned based on which this review of literature is compiled and presented. This review does not cover aneurysmal subarachnoid hemorrhage in special situations like pregnancy and childhood but rather focuses on utility of Arterial Lactate drifts as a predictive biomarker of Delayed Cerebral Ischemia in patients with aSAH.

2.1 Epidemiology & Disease Burden:

Stroke is the second leading cause of death and third most common cause of disability worldwide (4). Hemorrhagic strokes account for about 32% of all strokes globally (5). Hemorrhagic strokes can be caused by subarachnoid hemorrhage (SAH) or Intracerebral Hemorrhage (ICH). Most common cause of spontaneous (nontraumatic) subarachnoid hemorrhage is rupture of a saccular intracranial aneurysm. A saccular aneurysm is a thin-walled outpouching of the arterial wall, composed of thin or absent tunica media and absent or fragmented internal elastic lamina. Saccular aneurysms are now recognized to be acquired lesions, rather than congenital as thought previously. Other forms of aneurysms include fusiform, mycotic, blister types. Other causes of SAH include trauma, AVM ie arteriovenous malformations, subarachnoid extension of a primary ICH, vasculitides, arterial dissections, amyloid

angiopathy, bleeding diatheses, illicit drug use (cocaine and amphetamines) and DAVF ie Dural arteriovenous fistulas.

The prevalence rate of intracranial aneurysms is estimated to be around 3.2% in the general population (8.09 million , 95% uncertainty interval, 7.02–9.72 million cases) with a 1.1% annual rupture risk (6). The global incidence of aSAH is 6.1 per 100,000 person-years, with an incidence rate in low and middle income countries almost double that of high-income countries (7). aSAH occurs in a comparatively younger age group of population as compared to other forms of stroke with women having 1.24 times greater risk than men (8) and accounts for approximately 5% of strokes (9). Mortality rates range anywhere between 32% to 67%, and a third of the survivors remain dependent (10). If the patient survives but the aneurysm is not obliterated, the rate of rebleeding is about 20% in the first 2 weeks, 30% in the first month, and about 3% per year afterwards.

2.2 Etiopathogenesis:

2.2.1 Etiology & Risk Factors: Hemodynamic stress along-with turbulent blood flow leads to damage and fragmentation of the IEL (internal elastic lamina), especially at points of high shear stress like sharp angles and at the bifurcation points of major vessels (11). Patients with hyperdynamic flow patterns, are hence more predisposed to aneurysm formation. Hypertension, smoking, and connective tissue disorders are known to exacerbate the vascular damage, thereby increasing the risk of aneurysm development (11). 8% Patients with ADPKD (Adult Polycystic Kidney Disease) have an associated unruptured IA (12). Ehlers–Danlos syndrome type IV, NF1 (neurofibromatosis type 1), Marfan syndrome and coarctation of the aorta are all known to be associated with aSAH(9). About 7% to 20% patients with aSAH have familial history with affection of a first or second degree relative(13). Matrix metalloproteinases (MMP) are also associated with a predisposition to IA formation and rupture.

Specifically, MMP-2 and MMP-9 levels in the aneurysm wall are increased, MMP-2 gene expression being increasingly associated with the development and rupture of IA (14–16)

2.2.2 Pathogenesis: aSAH-associated brain injury is both multiphasic and multifactorial. Three phases can be defined in the pathogenesis of an intracranial aneurysms (IA) ie a) formation b) growth & progression and c) rupture.

IA are thought to arise as a result of disrupted balance between local hemodynamic stress and arterial wall strength. There is a continuous balance between hemodynamic stress and the integrity of the vessel wall (17). An insult happens whenever this balance is perturbed during times when the hemodynamic stress overwhelms the arterial wall strength. This hemodynamic insult propagates an inflammatory response in the vessel wall (18). There is activation of MMP which degrades the extracellular matrix. MMP activation also leads to flow-induced internal elastic lamina (IEL) fragmentation (19). Concomitantly there is apoptotic death of vascular smooth muscle cells (VSMCs)(18). Together these processes cause vessel wall weakening and fragmentation leading to dilation and IA formation. Phenotypic transformation occurs both in endothelial cells and the vascular smooth muscles cells (VSMCs) following the inciting endothelial injury . VSMC are normally mainly found in the media layer and are major producers of matrix in the vessel wall. However, following endothelial injury, VSMCs migrate into the intima and proliferate causing intimal thickening.(18,20) . These migrated VSMCs switch from a contractile phenotype to a synthetic pro-inflammatory matrix remodeling phenotype (21). Endothelial cells are also affected by the hemodynamic insult. Endothelial cells under laminar flow become aligned with the flow but endothelial cells under turbulent flow become cuboidal due to F-actin reorganization (22). Endothelial cells respond to hemodynamic stress with the up-regulation of the inflammatory mediator, prostaglandin E receptor 2 (EP2), during the formation of cerebral aneurysms. The stimulation of

EP2 in primary endothelial cells also led to the activation of the transcription factor NF-κB, a well-studied transcriptional mediator of inflammation in IA (23). As cerebral vessel walls undergo change during aneurysm development, the formation of new vessels, angiogenesis, also contributes to aneurysmal progression (24). Angiogenesis indirectly advances the inflammatory process of aneurysm progression by aiding in the delivery of inflammatory cells to vessel walls. Human and animal studies have conclusively shown that inflammatory cells and mediators are involved in IA pathogenesis. A number of these inflammatory cells and mediators are discussed below. Mast cells infiltration into vessel wall has been illustrated throughout the pathophysiological chronology of IA development by Ishibashi et al. who found that the degranulation of mast cells promoted MMP-2, MMP-9, and iNOS expression and hence affects all phases ie the formation, progression and rupture of IA (25). Both T cells & macrophage infiltration have found to be associated with human IA rupture (26). Proteinases secreted by macrophages have been found to be involved in the vascular remodelling of IA. (27) showed that in human IA, M1 & M2 macrophages occur in equal proportions; however, after rupture this balance tilts towards M1 macrophages (which are proinflammatory) which occur in higher levels as compared to M2 macrophages (which are involved in reparative process and are anti-inflammatory). There is also a concurrent increase in mast cell in the ruptured IA (27) . The role of the inflammatory mediators, chemokines has also been extensively studied in IA formation. Chemokines facilitate chemotaxis ie the process of cellular migration of inflammatory cells during the inflammatory response. (28) demonstrated that plasma concentrations of, interleukin 8 (IL-8), IL-17, RANTES (regulated upon activation, normal T cell expressed and secreted) , MIG (monokine induced by gamma interferon) , IP-10 (interferon gamma induced protein 10), eotaxin, and the monocyte chemoattractant protein-1 were significantly increased in the lumen of unruptured human IA when compared to femoral arterial plasma of the same patient. The study also found an

increase in plasma concentrations of MCP-1 (Monocyte chemoattractant Protein-1) in unruptured aneurysms (28). This reaffirms the work of (29) who observed increased MCP-1 expression in rat arterial walls. These data indicate that inflammatory cells are being actively recruited to the aneurysm wall as a result of high chemokine levels, further contributing to IA formation and eventual rupture. (28) . TNF-α (Tumour Necrosis Factor alpha) has been previously identified as a contributor to the phenotypic modulation of VSMCs in vivo following hemodynamic stress (30). The transcription factor, NF-κB (Nuclear Factor Kappa B), has also been found to be essential in the activation and recruitment of macrophages as it influences the expression of a number of pro-inflammatory genes. (17,31).

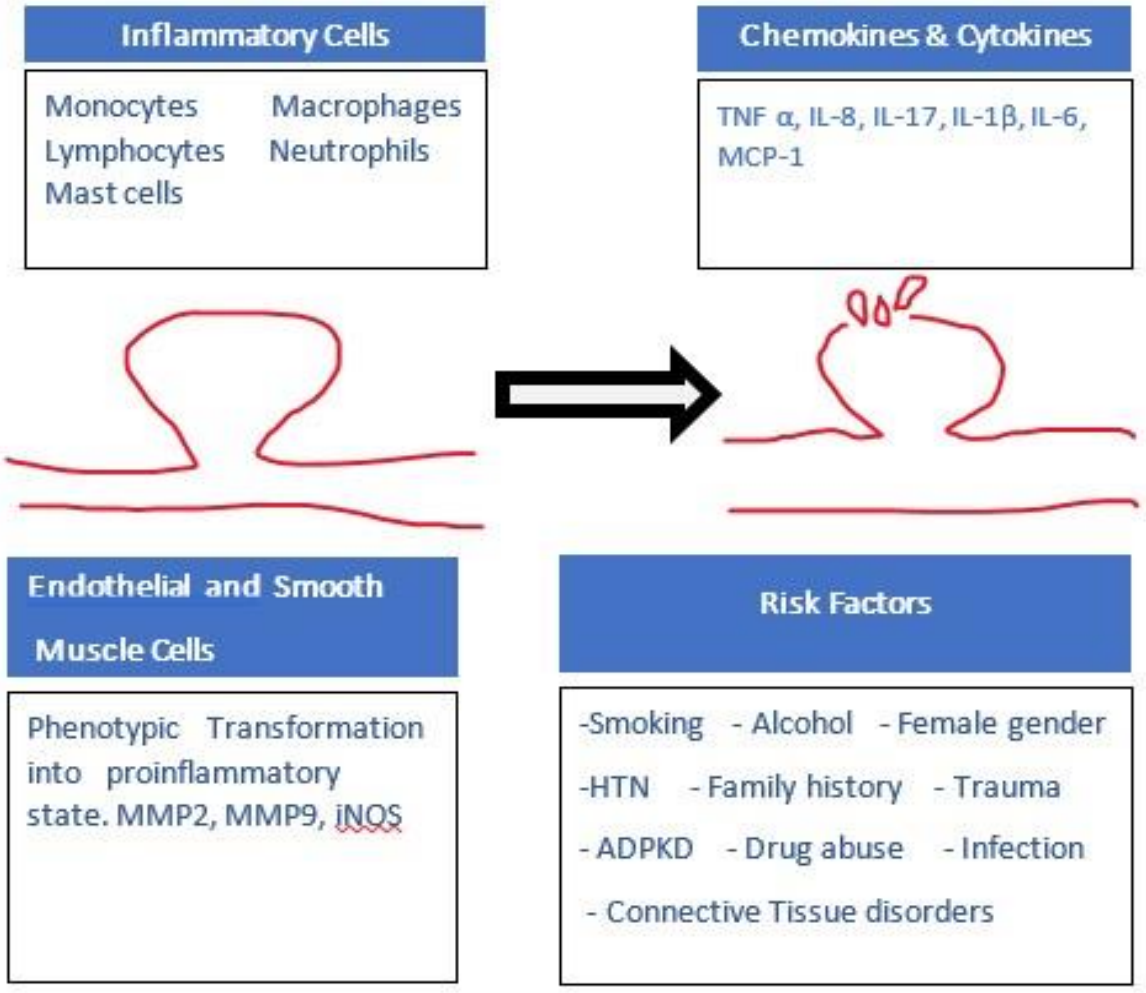


Fig1: Interplay of factors affecting IA formation, growth & rupture

Risk Factors for aneurysm rupture: include large size, symptomatic aneurysms, and located at vertebrobasilar system or on PCOM, a previous history of aSAH (with or without a residual untreated aneurysm), positive familial history (with at least one first-degree relative with an IA aneurysm), (32,33) and aneurysms associated with connective tissue disorders and ADPKD. Aneurysms in the anterior circulation appear to be more prone to rupture in patients < 55 years of age, whereas posterior communicating aneurysms ruptured more frequently in men. The rupture size is relatively smaller in patients with both arterial hypertension & smoking than in those with either risk factor alone (34) . Significant life events (eg legal /financial /personal /social stress) within past one month may increase the risk of aSAH (35) . Aneurysm size >7 mm has been shown to be a risk factor for rupture (36) . There does not appear to be an increased risk of aSAH in pregnancy, delivery, and puerperium (37,38). Diet: Increased consumption of yogurt (but not all dairy products) is associated with a higher risk of aSAH. (39). Greater vegetable consumption is associated with a lower risk of stroke and aSAH. (40). Higher coffee and tea consumption (41) and higher magnesium consumption (42) are associated with reduced risk of stroke overall but do not change the risk of aSAH

Risk factors for Aneurysm Rebleed: Factors associated with aneurysm rebleeding include longer interval time to definitive aneurysm treatment, worse neurological status on admission, initial loss of consciousness, history of previous sentinel headaches (severe headaches lasting >1 hour that do not lead to the diagnosis of aSAH), larger aneurysm size, and possibly systolic blood pressure >160 mm Hg. (43–45).

2.3 Vasospasm and DCI following aSAH:

Early case reports showed that some patients who had demonstrated clinical improvement in neurological state after aSAH, suddenly and unexpectedly deteriorated and died in the days following the initial bleed (46). The mechanism

behind this subsequent deterioration was unclear until in 1949, when post-mortem examination of 27 fatal cases of aSAH demonstrated infarction remote from the site of the ruptured aneurysm, despite apparently patent cerebral vessels (47) . This was attributed to transient spasm of the supplying blood vessels, even remote from the site of aneurysm rupture and was the first suggestion that cerebral arterial vasoconstriction was linked to delayed clinical deterioration after aSAH. This Delayed cerebral ischaemia (DCI) was hence identified as a clinical syndrome which was associated with new onset focal neurological and/or cognitive deficits, that occurred unpredictably in approximately 30% of patients, 3–14 days after and upto 21 days of the initial bleed (48) . While re-bleeding is still a major complication in the hours following the initial bleed, DCI remains the single most important cause of mortality and morbidity in patients who survive till the definitive aneurysm treatment (49) . The risk factors for developing DCI are primarily related to the severity of the initial bleed (ie high grades of modified Fisher scale), with a greater amount of cisternal and intraventricular blood on initial imaging and a poor post-resuscitation neurological examination being the strongest predictors of this unfavourable event (50).

Definition: In 2010, a consensus statement by a multidisciplinary group proposed new definitions for clinical deterioration caused by DCI and cerebral infarction after SAH (51) . They defined

DCI: as a focal (hemiparesis, aphasia, hemianopia, or neglect) or a global (2 points decrease on GCS) neurological impairment lasting for at least 1 hour and/or cerebral infarction, which is not apparent immediately after aneurysm occlusion, which is attributable to ischemia, but is not attributed to other causes (i.e. surgical complication, metabolic derangements) after appropriate clinical, imaging, and laboratory evaluation

Cerebral infarction: Presence of cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks, or proven at autopsy; that which is: not present on the CT or MR scan between 24 and 48 hours after early aneurysm occlusion, not attributable to other causes such as surgical clipping or endovascular treatment, not due to a non-ischemic lucency related to a ventricular catheter, intraparenchymal hematoma, or brain retraction injury.

2.3.1 Pathogenesis of EBI (Early Brain Injury) & DCI (Delayed Cerebral Ischemia)

EBI: The first 72 hours after ictus is the phase of early brain injury, characterized by increased ICP and transient global ischemia. Although this is before the onset of DCI, the physiological changes occurring at this time directly influence the likelihood and severity of later ischaemic complications. At the time of aSAH, the extravasating blood leaks under high pressure into the subarachnoid space. The size of defect correlates with the volume of leaked blood (52). Within minutes there is a rapid rise in ICP, with the rate of rise reflecting the severity of the initial bleed leading to the classical 'thunderclap' headache. This can be accompanied with a syncopal attack caused by a sudden reduction in cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) (53) as rising ICP starts nearing the MAP values causing a transient global ischemia. As this transient global ischemic phenomenon affects the hypothalamus there is a rapid catecholamine surge that sets in with plasma catecholamines remaining elevated for next several days post aSAH. The initial ICP crisis and global hypoperfusion trigger glial activation, endothelial dysfunction, inflammatory pathways, BBB disruption, and apoptotic cell death all together promoting formation of vasogenic and cytotoxic oedema. Marked acute cerebral vasoconstriction at this time has also been described that seems to occur independently of changes in CPP and ICP

and is likely to contribute to the cerebral ischaemia from aneurysmal rupture (54). This ischemic episode potentially triggers a vascular dysfunction even before the toxic effects of haemoglobin and its degraded products are realized. Autoregulatory failure, microthrombosis, cortical spreading depolarizations (CSDs), and neuroinflammation have all been observed during this period (55). Over time, the extravasated blood modulates these same abovementioned core factors, culminating in the clinical manifestation of delayed cerebral ischemia (56,57).

DCI: Historically, major vessel vasospasm with subsequent downstream ischemia was considered to be the sole cause of DCI following aSAH. This tenet has however been challenged recently with evidence to the contrary coming forth to light. There is a huge discrepancy between angiographic findings and the development of clinical signs. Not all patients having DCI showing large artery vasospasm on a catheter angiogram and vice versa. This further suggesting additional complex pathophysiological mechanisms at play for evolving DCI. Although large artery vasospasm still doubtlessly plays an important role in the pathogenesis of DCI, it is hence not the only contributing factor. There are large data evidence to suggest that DCI can occur secondary to microvascular failure which is independent of large artery angiographically visible vasospasm. For example, although the majority of aSAH patients develop angiographically evident vasospasm (up to 70 %), only 20–30 % go on to develop DCI (50), with cerebral infarction being reported even in the absence of a demonstrable vasospasm. Moreso, successful treatment of angiographic vasospasm does not necessarily lead to better functional outcome as was demonstrated by CONSCIOUS-2 trial which concluded that clazosentan, (an endothelin receptor antagonist), is successful in reducing angiographic vasospasm but has no significant effect on mortality, functional outcome, or the frequency of cerebral infarction (58). Finally, nimodipine which is the only pharmacological agent

shown to improve outcome in aSAH patients, has no impact on large-vessel vasospasm (59). The main thrust of this paradigm shift is general agreement that demonstration of large-vessel narrowing is hence no longer required as the only sole criterion to make a diagnosis of DCI.

Pathogenesis of DCI involves following mechanism:

A) Vascular Dysfunction, micro-thrombosis and thrombo-inflammation

B) Autoregulation failure

C) Systemic and Neuro inflammation.

D) Cortical spreading depolarizations.

2.3.2 Vascular Dysfunction, micro thrombosis and Thromboinflammation:

aSAH leads to cascading pathophysiological events culminating into an imbalance between factors involved in maintaining normal vascular endothelium homeostasis (ie vascular tone and thrombogenicity of the cerebral vascular tree). As described in EBI, soon after aSAH as the rising ICP approaches MAP, there occurs a phase of transient global ischemia. Haemoglobin and other blood products remain sequestered until the RBC membranes lyse, releasing oxyHb and other vasoactive end products. OxyHb and deoxyHb concentrations in the CSF peak around day 07 post aSAH roughly corresponding to the onset of the secondary brain injury. There is increase in endothelin-1 expression and a simultaneous decrease in NO (nitric oxide) thereby modulating the vascular tone unfavourably leading to vasospasm. Oxyhemoglobin being a potent scavenger of NO reduces its availability. Production of NO is unable to keep pace with its loss because of a) rise in asymmetric dimethylarginine which is an endogenous nitric oxide synthase (NOS) inhibitor b) a decrease in the expression of endothelial and neuronal-specific NOS isoforms. c) damage to the existing NOS enzymes by free

radicals and reactive oxygen species. This leads to "NOS uncoupling" wherein the consumption of substrates L-arginine and O2 is "uncoupled" from NO production and instead diverted to superoxide formation. Superoxide then further reduces NO bioavailability by reacting with the remaining NO to form peroxynitrite. A perfect storm of vasoconstriction, NO-depletion, and reactive oxygen species-generation hence sets in leading to vascular dysfunction.

Blood in cerebral cisterns can occlude arachnoid granulations, preventing reabsorption of CSF and thereby leading to delayed hydrocephalus a few weeks after the aSAH.

Microthrombi and thrombo-inflammation- The NO-cyclic guanosine monophosphate pathway causes inhibition of platelet aggregation, leukocyte adhesion, and smooth muscle cell proliferation in addition to maintaining vasodilatory tone. The injured endothelium exposes the prothrombotic subendothelial collagen leading to increased microthrombi and microclot formation in the small intraparenchymal arterioles, eventually culminating into DCI. In addition, there is ADAMTS13 dysregulation (an endothelial protease that normally inhibits platelet adhesion and thrombosis by downregulating von Willebrand factor and P-selectin) due to endothelial injury which further augments the DCI. Activated platelets apart from causing thrombo-inflammation also release glutamate which causes excitotoxicity and propagation of spreading depolarizations.

2.3.3 Autoregulation Failure:

Cerebral autoregulation (CAR) is impaired in both EBI and during phase of DCI/Vasospasm. During EBI the severity of impairment of CAR directly correlates with the size and volume of bleed and the clinical grade. Patients with H&H Grade I/II have normal CAR in areas of Brain that are not directly affected by SAH. However in patients with H&H grade III and more, the lower limit where

CAR fails is significantly higher (right shifted). Failure of CAR during episodes of relative hypotension can lead to cerebral ischemia.

In DCI as discussed above there is a microvascular failure which propels the ischemic cascade. There is diminished autoregulatory capacity, as measured by the transient hyperemic response, and can be predictive of the developing DCI in patient. This phenomenon has been demonstrated by various investigators in a variety of settings and using different imaging and vascular reactivity stimuli, thereby reaffirming the association between diminished autoregulatory capacity and development of DCI after SAH (60).

2.3.4 Systemic and Neuro Inflammation:

As discussed previously in section of aneurysmal growth and rupture there is evidence to suggest early activation of inflammatory pathways after aneurysmal rupture and that the extravasated blood is responsible for a cascade of reactions involving the release of pro-inflammatory and vasoactive factors. An early increase in pro-inflammatory cytokines including tumour necrosis factor-alpha, interleukin-1, and interleukin-6, interleukin-8, MCP-1 receptor antagonist has been documented in both serum and CSF of patients after SAH, and correlates with both EBI and DCI leading to poor outcome. There is also activation of resident glial cells and recruitment of peripheral cells like macrophages, lymphocytes etc which further fuel the inflammation. Early in aSAH there are increased levels of markers of both macrophage infiltration (CD163) & oxidative stress (myeloperoxidase). There is simultaneous increases in S100/ calgranulin expression, which acts through TLR-2 to recruit macrophages/monocytes and neutrophils. TLR-6 that forms heterodimers with TLR-2, is also significantly overexpressed, leading to activation of pro-inflammatory signaling pathways. Finally, Krüppel-like transcription factors (KLF) KLF-2, KLF-12, and KLF-15 are all down-regulated in the early ruptured IA subgroup. KLF-2 is known to possess anti-inflammatory functionality.

2.3.5 Cortical Spreading Depolarizations (CSD):

CSD were first discovered by Leão in 1944 while studying epilepsy and he noted its hyperemic effect on pial vasculature soon after (61,62). CSD are slowly propagating waves of almost complete membrane depolarizations in both neuronal and glial cells which propagate across the brain at rate of 2–5 mm/min and result in suppression of normal evoked and spontaneous brain EEG activity. They are initiated in a metabolically compromised brain tissue due to disturbed ion homeostasis. Because of their uniqueness in causing powerful suppression of normal brain activity, CSD have been extensively investigated in many neurological disorders including aSAH, stroke, migraine, TBI etc. Propagation of the CSD wave silences the brain EEG activity for 5–15 min, which is then followed by spontaneous return to normal function. There is a brief period of vasoconstriction before the CSD wave, a phase of vasodilation which accompanies the spreading wave front followed by a delayed tissue hypoperfusion which occurs and persists after the wave (ie spreading ischemia). Mechanisms of CSD propagation are still unclear, but it is a general agreement that it is caused by passive diffusion of extracellular K+ and glutamate in the surrounding grey matter mediated by a positive feedback loop through NMDA receptor and Ca2+ channel-dependent glutamate release and other voltage-gated channels which are crucial for CSD to self-sustain and propagate. CSD can occur as isolated events or as clusters with clusters magnifying the duration of tissue hypoxia and clustered CSDs being more important to DCI pathology than isolated depolarizations. It is thought that with each cluster CSD, there is an associated profound hypoperfusion of the cortex due to vasoconstriction with the hypo-perfused segments of the cortex not getting the chance to recover and are therefore exposed to recurrent episodes of tissue ischaemia leading to DCI.

2.4 Blood Lactate and its potential for a Biomarker

Blood lactate measurements have a long been used in clinical medicine to assess for both disease severity and response to treatment in various critical illness. Lactic acid was first discovered in sour milk in 1780 by Swedish pharmacist Carl Wilhelm Scheele and identified in blood during shock by the German physician Johann Scherer in 1843 (3). In humans, L-lactate is the dominant isomer that is synthesized and utilized. Lactate dehydrogenase is also stereospecific for the production of L-lactate. Normal individuals produce 15 to 20 mmol/kg of lactic acid per day. Hyperlactatemia is defined as Lactate levels greater than 2 mmol/L. It occurs when lactic acid production exceeds the lactic acid clearance. Both overproduction and reduced metabolism of lactate appear to be operative in most patients. Reviewing the biochemistry of lactate generation and metabolism hence becomes imperative in understanding the pathogenesis of hyperlactatemia.

Production: Glucose remains the main precursor from which lactate is generated via the glycolytic pathway. Another minor pathway is deamination of alanine which yields pyruvate. Pyruvate's fate (after glycolysis/ deamination of alanine) depends on the "redox state" of the of the cytoplasm which is reflected by the ratio of the oxidized and reduced nicotinamide adenine dinucleotide (ie, NAD^+, the oxidized form and NADH, the reduced form). This redox state in turn depends on tissue oxygenation and its impairment.

NAD^+ and NADH are involved in many cellular biochemical reactions, functioning as an electron acceptor or an electron donor respectively. One of these is the equilibrium between pyruvic acid and lactic acid, a reaction which is catalysed by the enzyme LDH ie lactate dehydrogenase. Thus, the ratio of

pyruvate and lactate is influenced by the ratio of NAD^+ and NADH, such that a reduced redox state (ie, low NAD^+/NADH ratio) is associated with a shift towards lactate. Many of the factors that reduce the ratio also increase pyruvate generation and simultaneously also impair its mitochondrial oxidation leading to accumulation of lactate. Hence, the increase in lactate production is usually caused by impaired tissue oxygenation, either from decreased oxygen delivery or a defect in mitochondrial oxygen utilization.

Metabolism and clearance: Lactate production is counterbalanced by its metabolism and utilization. Lactic acid is primarily oxidized to carbon dioxide and water (70 to 80 percent) whereas some may enter Cori's cycle to generate glucose (15 to 20 percent). Peripherally generated lactate under anaerobic conditions is returned back to liver where it is converted back to glucose via the Cori's cycle aka lactic acid cycle. A small amount of lactate is also converted to alanine. Utilization primarily occurs in liver, but the kidneys, heart, and other tissues also participate. When lactic acid accumulates in body fluids and its concentration increases, the hydrogen ions are almost completely buffered by extracellular bicarbonate. When lactate is utilized, a hydrogen ion is also consumed, and a bicarbonate molecule is generated. Thus, in a patient who has accumulated lactic acid, utilization of the lactate will restore the bicarbonate concentration.

Hence to summarize lactate concentrations might increase when there is

- Increased pyruvate production.

- Reduced entry of pyruvate into mitochondria, where it is normally oxidized to carbon dioxide and water or converted to glucose precursors.

- A shift of the cellular cytoplasmic redox state such that NADH accumulates and NAD^+ falls driving the pyruvate/lactate equilibrium toward lactate.

CLINICAL CAUSES- Clinically Hyperlactatemia causes are broadly classified into two types ie Type A and Type B

Type A Lactic acidosis, is seen associated with shock caused by either hypovolemia/ cardiac failure/ sepsis. This occurs as a systemic phenomenon. However, Type B lactic acidosis is seen in all other conditions where there is no evidence of overt systemic hypoperfusion and includes causes like regional areas of tissue ischemia, toxins which impair cellular metabolic machinery, drugs like metformin / adrenergic agents / antiretrovirals etc, malignancy-associated lactic acidosis, alcoholism, some biochemical storage disorders, etc.

2.4.1 Lactate and aSAH

There is a growing intrigue amongst investigators in examining the metabolic milieu of brain parenchyma in acute diseased states. Lactate has evoked a lot of interest as a marker of metabolic crisis and disease severity following acute neurologic injury. To the best of our knowledge in aSAH, lactic acid has largely been explored using a) jugular venous bulb levels as absolute values & as Lactate Oxygen Index (LOI) b) from cerebral microdialysis (CMD) catheters using lactate pyruvate ratios c) CSF Lactate values using EVD samples d) Peripheral Venous and Mixed Venous samples. In all the above modalities elevated cerebral lactate portends worse outcomes (2,63,64). As outlined previously the cerebral energy deficit after aSAH is multifactorial and related not only to a reduction in the blood flow, but also to organelle dysfunction, inflammation, cortical spreading ischemia, and neuronal cell death etc, all factors together inducing a metabolic adaptation toward anaerobic metabolism (65). Astrocytes and Neurons both exhibit a different metabolic and enzymatic profile with the former being predominantly lactate producer and later mostly a consumer involved in oxidation of lactate (66). In normal conditions, synaptically released glutamate triggers

glucose uptake and lactate production by astrocytes for the use by neurons, according to the astrocyte-neuron lactate shuttle model (67,68). However, under hypoxic conditions, the oxidative phosphorylation slows down in astrocytes and glycolysis is maximized, yielding an increase of lactate production that overwhelms the capacity of neurons to burn it, resulting in interstitial and CSF lactate accumulation (67,69–71).

3. Materials and Methods

3. MATERIALS AND METHODS

Study Design- This Study was an observational prospective study.

Study Setting:

***Site*:** Single centre study conducted at NS-OT, NS-ICU, IR Lab & IR-ICU under aegis of Division of Neuroanaesthesia and Neurocritical Care, Department of Anaesthesia, Sree Chitra Tirunal Institute of Medical Science and Technology, Thiruvananthapuram, Kerala. (a 253 bedded Tertiary care, referral, university level hospital and a high-volume centre for acute neurocritical care cases like stroke and aSAH.)

Study Population- Adult Patients >18 years age, both sexes included admitted in IPD during the period April 2022 till March 2023 with anterior circulation aSAH undergoing definitive management.

***Study Duration*-** Twelve Months (April 2022- March 2023)

***Ethical considerations*-** Study commenced only after obtaining Departmental and Institutional Ethical Committee (IEC) clearances & CTRI Approvals vide-

- IEC Regn No. ECR/189/Inst/KL/2013/RR-21, IEC/1801
- CTRI/2022/09/045806

- Written informed consent was taken from all participants after discussing the patient information sheet and providing a print copy of same to all in vernacular language.

Statistical Methods

Sample size calculations

With an estimated incidence of DCI as 33% { Dorsch, et al (72) }and following set parameters for Power, alpha error and beta error the calculated sample size was found to be n=38

Alpha - 0.05
Beta - 0.2
Power - 0.8

$$N1 = \left\{ z_1 - {}^{\alpha}/_{2} \times \sqrt{p \times q \times \left(1 + {}^{1}/_{k}\right)} + z_{1-\beta} \times \sqrt{p_1 \times q_1 + (p_2 \times q_2/k)} \right\}^2 \Big/ \Delta^2$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
α = probability of type I error (0.05)
β = probability of type II error (0.2)
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

Based on the above formula, the calculated sample size for each group was n=19 and a total calculated sample size was n=38 (both groups combined)

Assuming a 15% dropout, the total estimated sample size required was n= 44 (n=22 each for Group A and Group B). We had 60 admissions in our study period and hence we screened all the 60 patients for their participation in the study.

Statistical Analysis

Data collected was analyzed with professional help of a statistician. Data was entered into an excel sheet and statistical analysis was done using the statistical package for the social science system SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) with 95% CI (confidence interval) estimated. Absolute numbers, frequency and percentage (%) were used to define categorical data. Pearson's Chi-square test was used for the evaluation of nominal categorical variables. Student t-test and Mann-Whitney U tests were used for normally and non-normally distributed variables respectively to compare Group A and B parameters. A repeated measure ANOVA test was used to identify the daily trends in serial arterial lactate. The optimum cut-off value of lactate drift to predict the occurrence of DCI was analysed with the receiver operating characteristic (ROC) analysis. A p-value of <0.05 was considered statistically significant.

Inclusion Criterion-

- Consenting Adult patients / relatives (incase if patient is incapacitated to give consent) $\geq$18 years of age, both sexes included presenting with anterior circulation aSAH of less than 21 days of duration, planned for definitive treatment.

Exclusion Criterion-

- Non consenting patients, age<18 years, parent artery infarcts, patients with posterior circulation aSAH, patients with h/o uncontrolled DM, major organ failure (heart/ renal/ liver), alcohol abuse, malignancy, sepsis, congenital errors of metabolism, mitochondrial disorders, patients on vasopressors/NRTI/ metformin/ salicylates, pregnant/ nursing females

Study Protocol

- On admission baseline neurological evaluation was done & WFNS, mHunt & Hess, mFisher grade scores were recorded
- During Post-hoc analysis patients were divided into two groups
    - **Group A-** Patients who developed DCI during the course of their illness
    - **Group B-** Patients who did not develop DCI during the course of their illness
- Serial ABGs were done & arterial lactate levels and other parameters noted
- *Timeline of recordings* was
    - Tb- Baseline on admission, T0- Immediate post intervention (clipping/coiling), T1- Postop Day0
    - D1/2/3…till DV- Postop Day 1/2/3 till Day of Event ie Dv
    - Day of Event (Dv) for Group A was the day of DCI,
    - Day of Event (Dv) for Group B was the day of ICU Discharge
    - Dd- Day of Hospital discharge.

- Patients were followed up from the time of admission till the time of hospital discharge and the end point of observations was the day of hospital discharge.
- Absolute Lactate >2mmol/lts was considered as elevated
- *Lactate drift ratios (LDRb & LDRi)* were calculated on daily basis till Dv.

$$\text{LDRb} = \frac{\text{Lactate on a particular day or till event (Dv), whichever is later}}{\text{Baseline lactate (Tb)}}$$

$$\text{LDRi} = \frac{\text{Lactate on a particular day or till event (Dv) whichever is later}}{\text{Lactate immediate post intervention (clipping/coiling) (T0)}}$$

- DCI was defined by the 2010 consensus statement as (51)

a focal (hemiparesis, aphasia, hemianopia, or neglect) or a global (2 points decrease on GCS) neurological impairment lasting for at least 1 hour and/or cerebral infarction, which is not apparent immediately after aneurysm occlusion, which is attributable to ischemia, but is not attributed to other causes (i.e. surgical complication, metabolic derangements) after appropriate clinical, imaging, and laboratory evaluation

or a Cerebral infarction: on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks, or proven at autopsy; that which is: not present on the CT or MR scan between 24 and 48 hours after early aneurysm occlusion, not attributable to other causes such as surgical clipping or endovascular treatment, not due to a non-ischemic lucency related to a ventricular catheter, intraparenchymal hematoma, or brain retraction injury

- Perop and postop care was standardized for all the patients as per institution protocols with similar targets for hemodynamics/ ventilation/ fluid therapy/ transfusion triggers/ Weaning/ Discharge.

4. Observations & Results (Section A, Section B)

4. OBSERVATIONS AND RESULTS

A total of 60 patients with the diagnosis of anterior circulation aSAH were identified during the study period who underwent definitive management in the form of either surgical clipping or endovascular coiling (including balloon/stent assisted coiling). Of these, 6 patients were excluded from the study for the following reasons: uncontrolled DM (02 patients), chronic kidney disease (02 patients), chronic liver disease (01 patient) and sepsis (01 patient). The remaining 54 patient's data was analysed. Among 54 patients, 22 patients (40.74%) had a DCI occurrence and were categorised into Group A. 32 patients (59.26%) did not develop DCI and were categorised into group B. Post-hoc analysis was performed to study lactate kinetics during the disease evolution process.

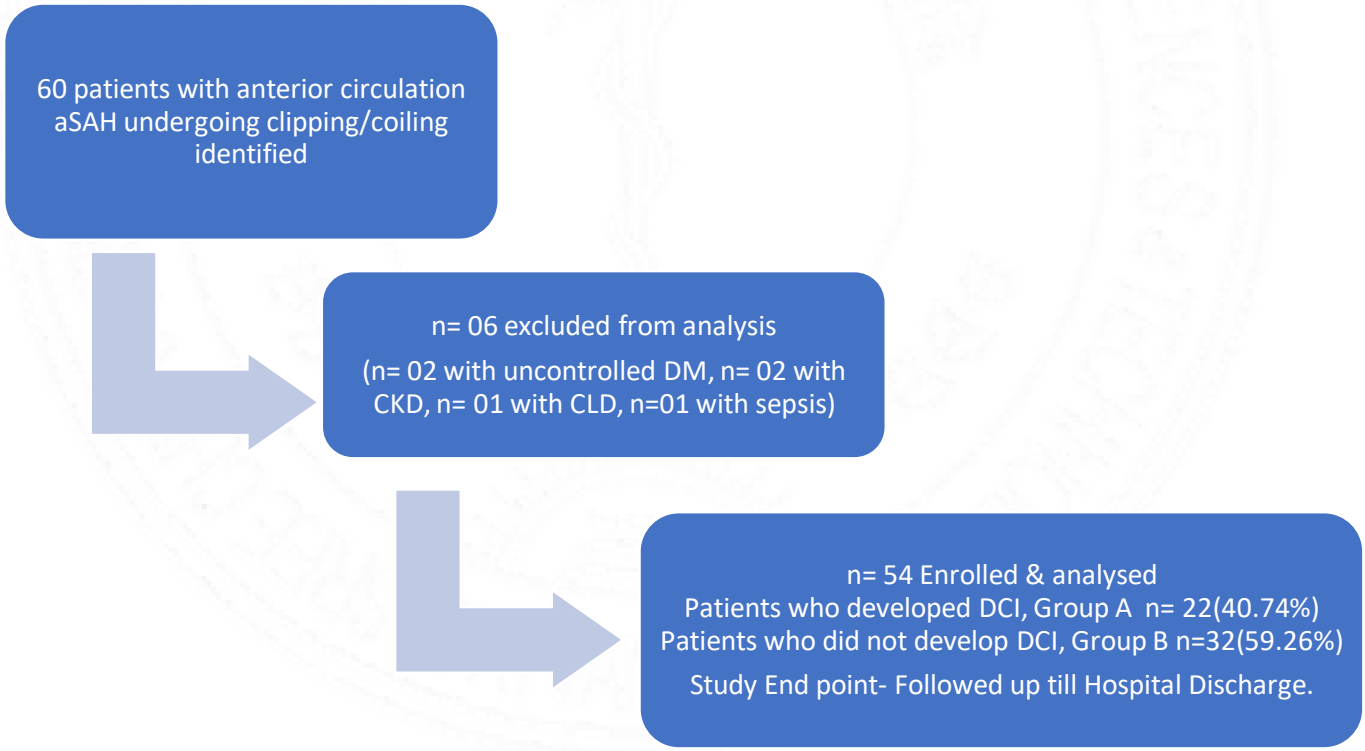


Fig 2: STROBE Flow chart – participants screening and enrolment process.

Section- 4A

Demographics, Aneurysm Morphology

Baseline patient characteristics,

Medical, Surgical Complications

and Patient Outcomes.

4.1) Demographic Data

Table 1: Demographic details of study population.

Variables	Group A (n=22)	Group B (n=32)	p-value
Age in years (Mean ± SD)	50.18 ± 11.54	53 ± 10.81	0.364
Gender n (%)	Male = 6 (27.3) Female = 16 (72.7)	Male = 14 (43.8) Female = 18 (56.2)	0.218

Age means compared by t-Test for independent sample, Gender proportions compared with Chi-square test

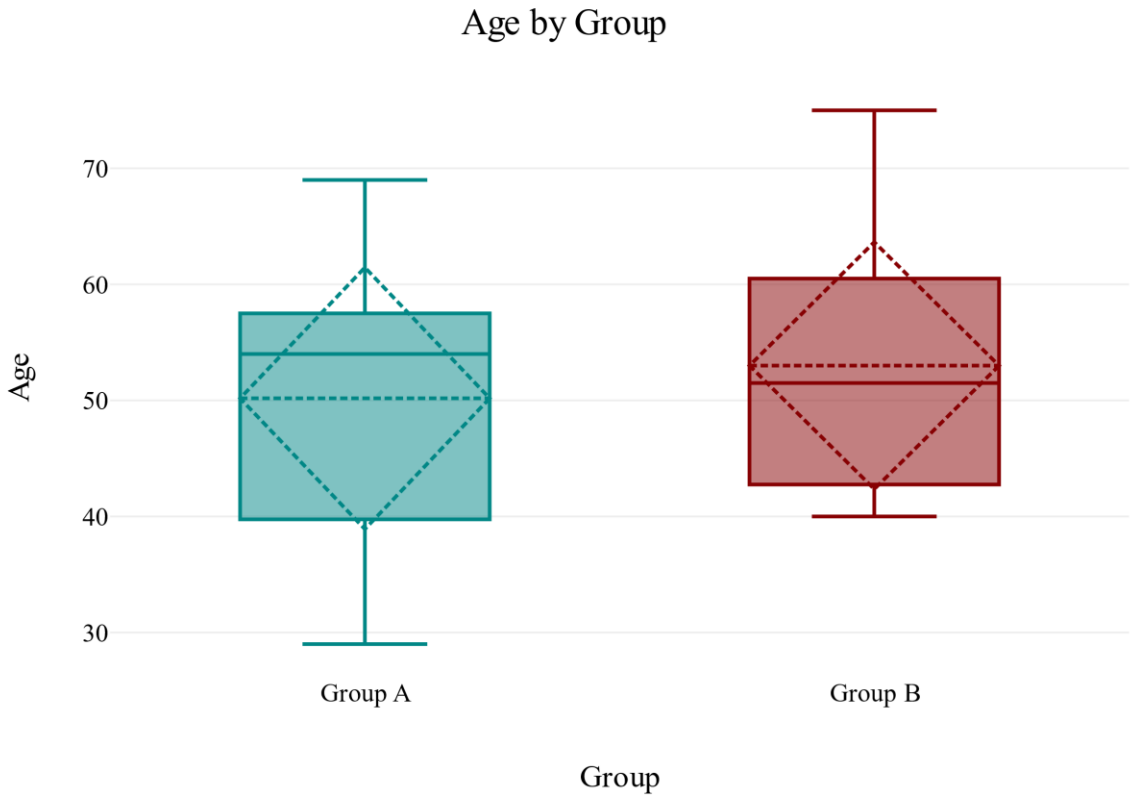


Figure 3: Age distribution of study population.

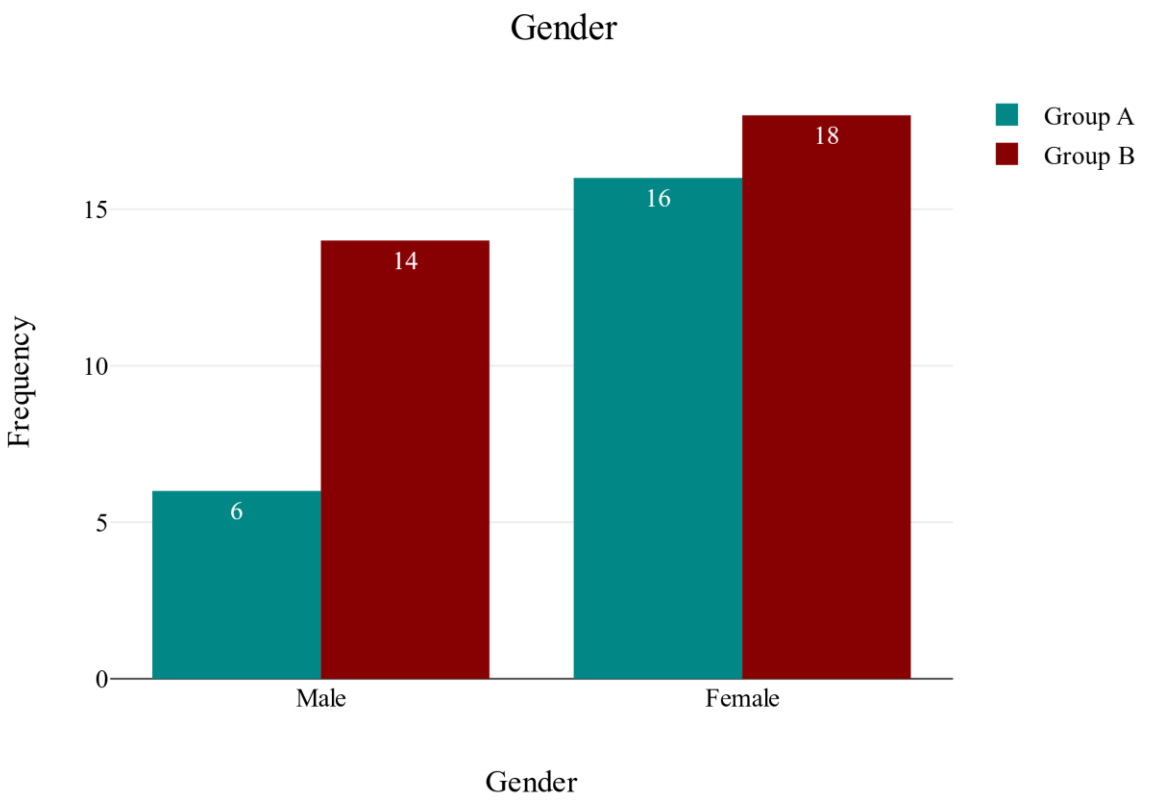


Figure 4: Gender distribution of study population.

Table 1 & figure 3 compares mean age of patients in both the groups. In Group A the mean age of patients was 50.18 ± 11.54 years & in Group B the mean age of patients was 53 ± 10.81 years. Age was comparable in both groups (p= 0.364). In table 1 & figure 4, the gender distribution across both the groups is detailed. A total of n=20 patients (37.03%) were males & n=34 patients (62.96%) were females. Within the groups, in Group A, 06 patients (27.3%) were males & 16 patients (72.7%) were females. In Group B, 14 patients (43.8%) were males & 18 patients (56.2%) were females. Gender distribution between both the groups was comparable (p=0.218).

4.2) Location of Aneurysm

Table 2: Location of Aneurysms.

Location	Group A (n=22) N (%)	Group B (n=32) N (%)	p-value
ICA	8 (36.4)	12 (37.5)	0.935
MCA	4 (18.2)	6 (18.8)	0.956
ACA	4 (18.2)	6 (18.8)	0.956
ACOM	6 (27.3)	8 (25)	0.851

Means compared using Chi-square test

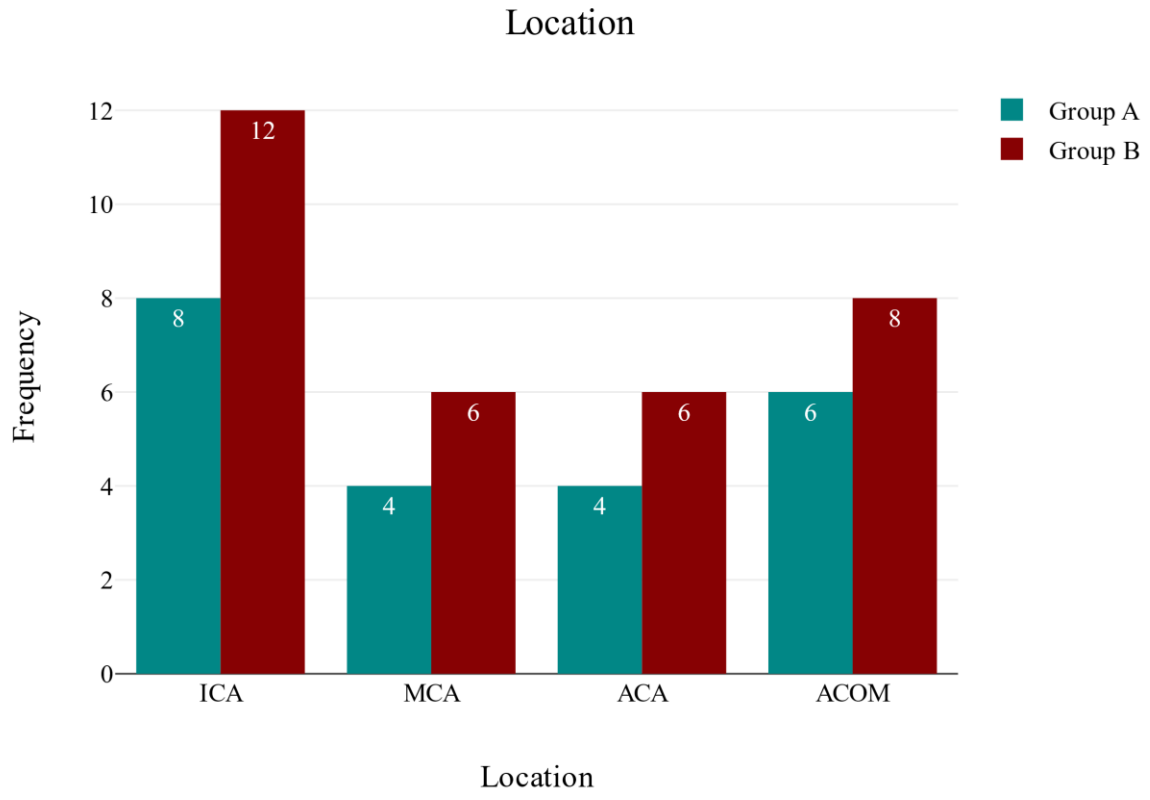


Figure 5: Location of aneurysms across both the groups

Table 2 & Figure 5 compares the frequency distribution of aneurysms based upon their location. Majority of the aneurysms in both groups were on ICA all segments combined (Gp A n=08, 36.4% Gp B n=12, 37.5%, p=0.935). The second most common vessel involved was ACOM (Gp A n=06, 27.3%, Gp B

n=08, 25%, p=0.851). According to frequency the next most common sites involved were MCA and ACA with equal distributions in both groups (Gp A n=04 each on MCA and ACA, 18.2% Gp B n= 06 each on MCA and ACA, 18.8% p=0.965). For the frequency of aneurysms as per their site distribution, both the groups were comparable with p >0.05 for all the location mean values compared.

4.3) Associated Comorbidities

Table 3: Associated comorbidities of patients in both study groups.

Conditions	**Group A (n=22) N (%)**	**Group B (n=32) N (%)**	**p-value**
HTN	14 (63.6)	18 (56.3)	0.587
DM	4 (18.2)	4 (12.5)	0.564
Hypothyroidism	6 (27.3)	2 (6.3)	0.033*
CAD	0 (0)	2 (6.3)	0.232
COPD	0 (0)	2 (6.3)	0.232
CHD	2 (9.1)	0 (0)	0.082
Thrombocytosis	2 (9.1)	0 (0)	0.082
Asthma	0 (0)	2 (6.3)	0.232
Hepatitis B	0 (0)	2 (6.3)	0.232

***** p<0.05, statistically significant, Means compared using Chi-square test

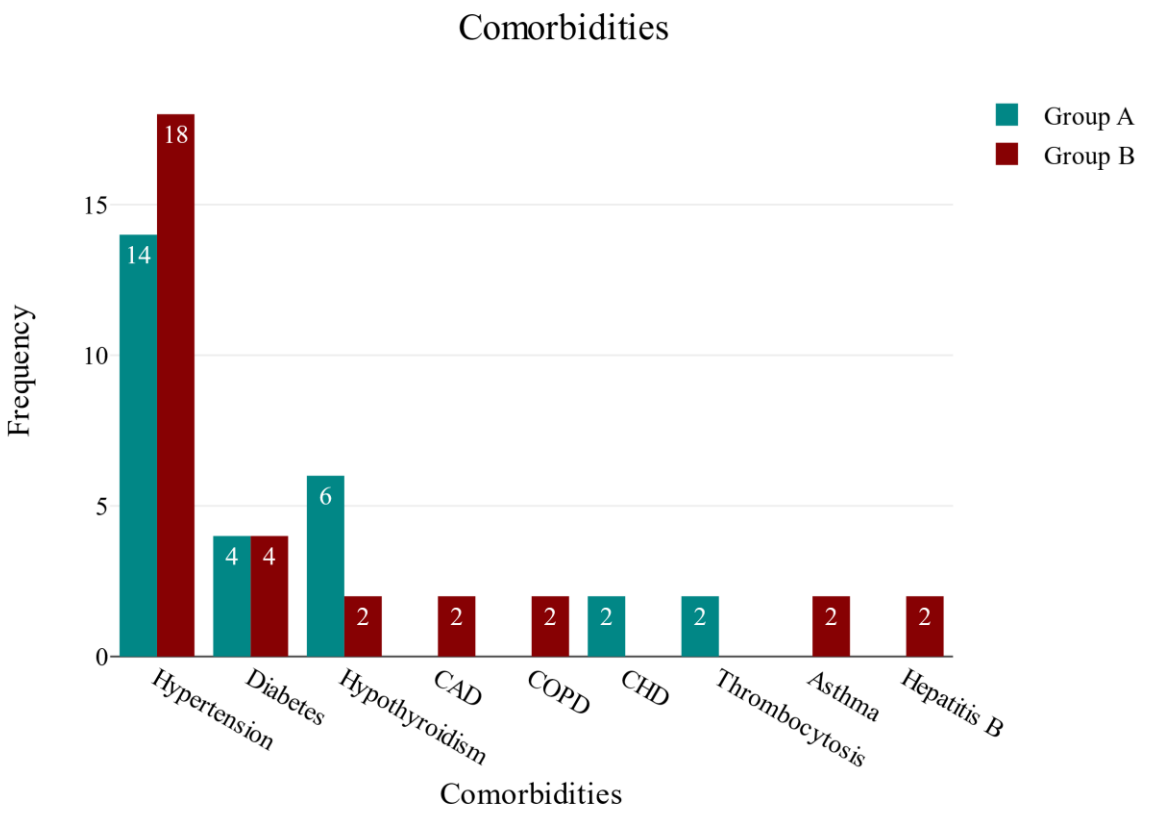


Figure 6: Associated comorbidities of patients in both the study groups.

Table 3 and Figure 6 depict the frequency distribution of associated comorbidities in both the study groups. The most common associated comorbidity was essential hypertension (Gp A n=14, 63.6%, Gp B n=18, 56.3% p=0.587). The next most common associated comorbidity in Gp A was hypothyroidism (n=6, 27.3%). As compared to Gp A, the incidence of hypothyroidism in Gp B was n=2, 6.3% and this difference was statistically significant with a p-value = 0.033. Rest all comorbidities were comparable across both the groups as follows: Diabetes mellitus (Gp A n=4, 18.2% Gp B n=4, 12.5% p=0.564), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), asthma & hepatitis B infection, (each as follows, Gp A n=0, 0% Gp B n=2, 6.3% p=0.232), Congenital Heart Disease (CHD) and Thrombocytosis (each as follows, Gp A n=2, 9.1%, Gp B n=0, 0% p=0.082).

4.4) Addictions

Table 4: Associated addictions in both the groups.

Addiction	Group A (n=22) N (%)	Group B (n=32) N (%)	p-value
Tobacco	6 (27.3)	7 (21.9)	0.651
Alcohol	4 (18.2)	6 (18.8)	0.956

Means compared using Chi-square test

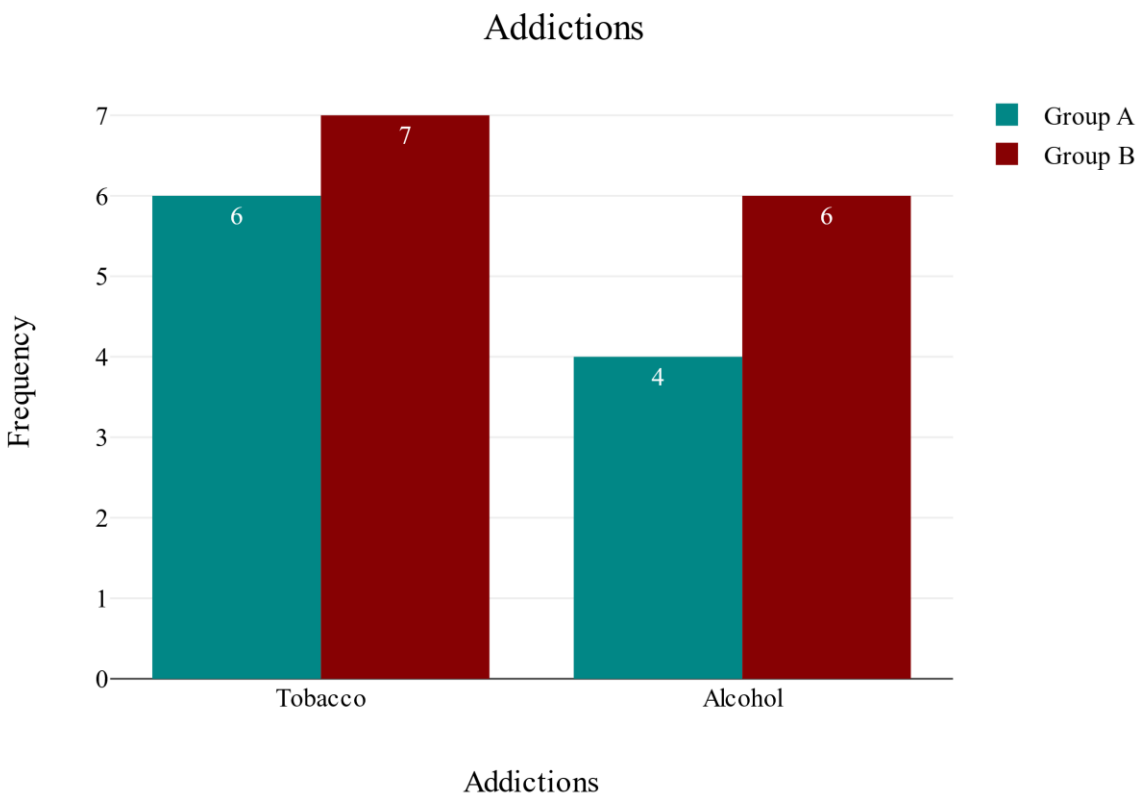


Figure 7: Associated Addictions.

Table 4 and Figure 7 depict the frequency distribution of associated addictions in both the groups. Tobacco abuse (in all forms) was the most common associated addiction seen in n=13 patients (24.07%) (Gp A n=6, 27.3% Gp B n=7, 21.9%

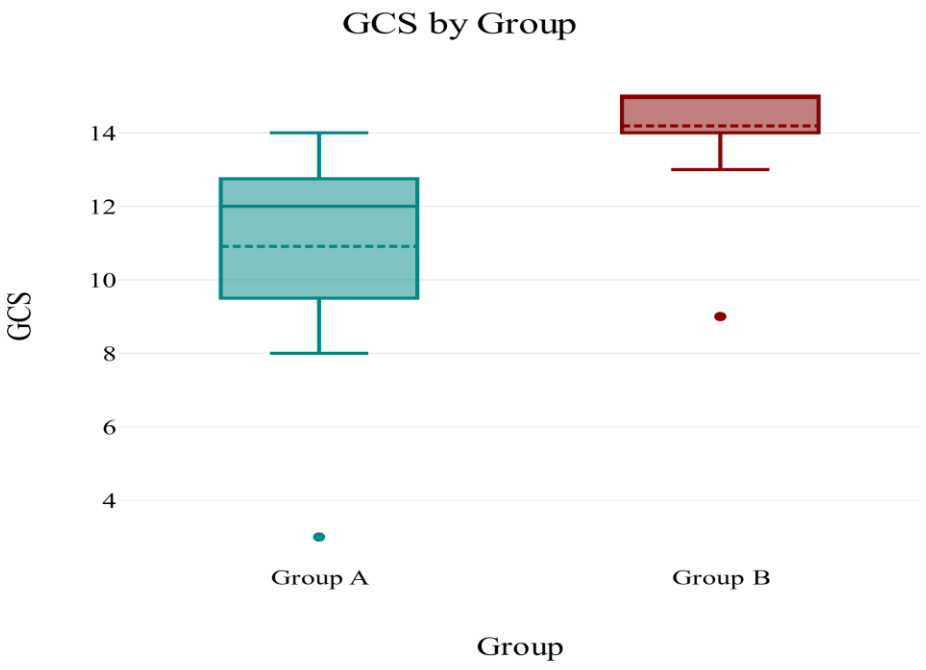
p=0.651). A total of n=10 patients (18.51%) had history of alcohol abuse (Gp A n=4, 18.2% Gp B n=6, 18.8% p=0.956). The association of addictions was comparable in both the groups.

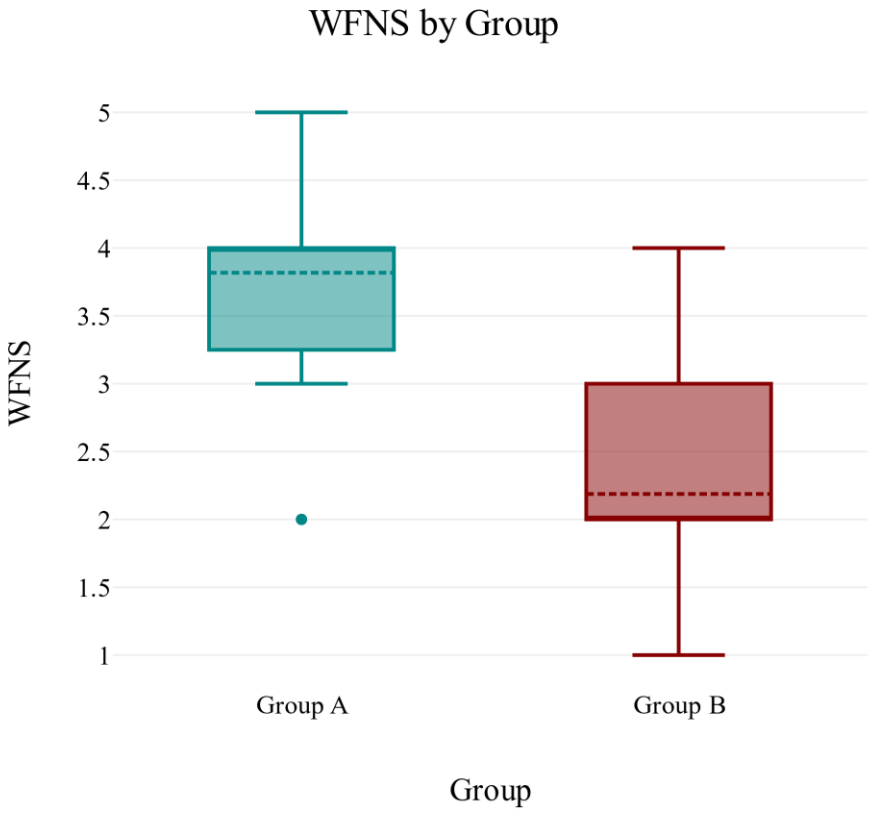
4.5) Baseline Health Status

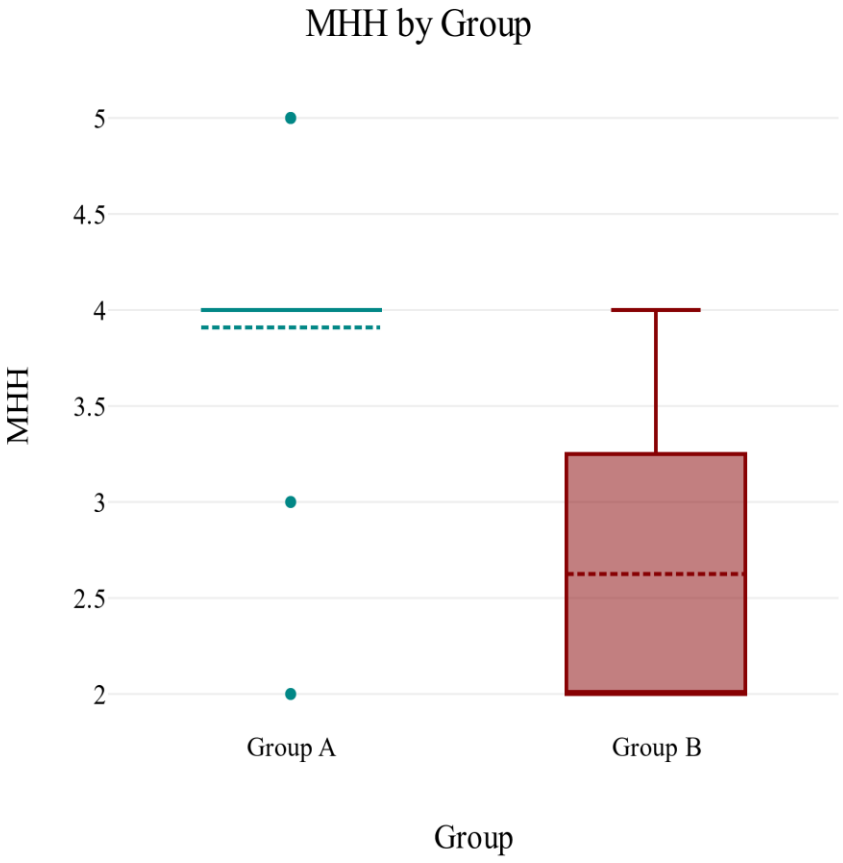
Table 5: Baseline health status of patients across groups.

Evaluation Scores	Group A (n=22) Med (IQR)	Group B (n=32) Med (IQR)	p-value
GCS	12 (10-13)	15 (14-15)	<0.001*
WFNS	4 (3-4)	2 (2-3)	<0.001*
MHH	4 (4-4)	2 (2-3)	<0.001*
MFG	3 (2-4)	2 (2-3)	<0.001*

***** p<0.05, statistically significant, Medians compared using Mann Whitney U-Test




WFNS by Group
WFNS
5
4.5
4
3.5
3
2.5
2
1.5
1
Group A
Group B
Group


MHH by Group
MHH
5
4.5
4
3.5
3
2.5
2
Group A
Group B
Group

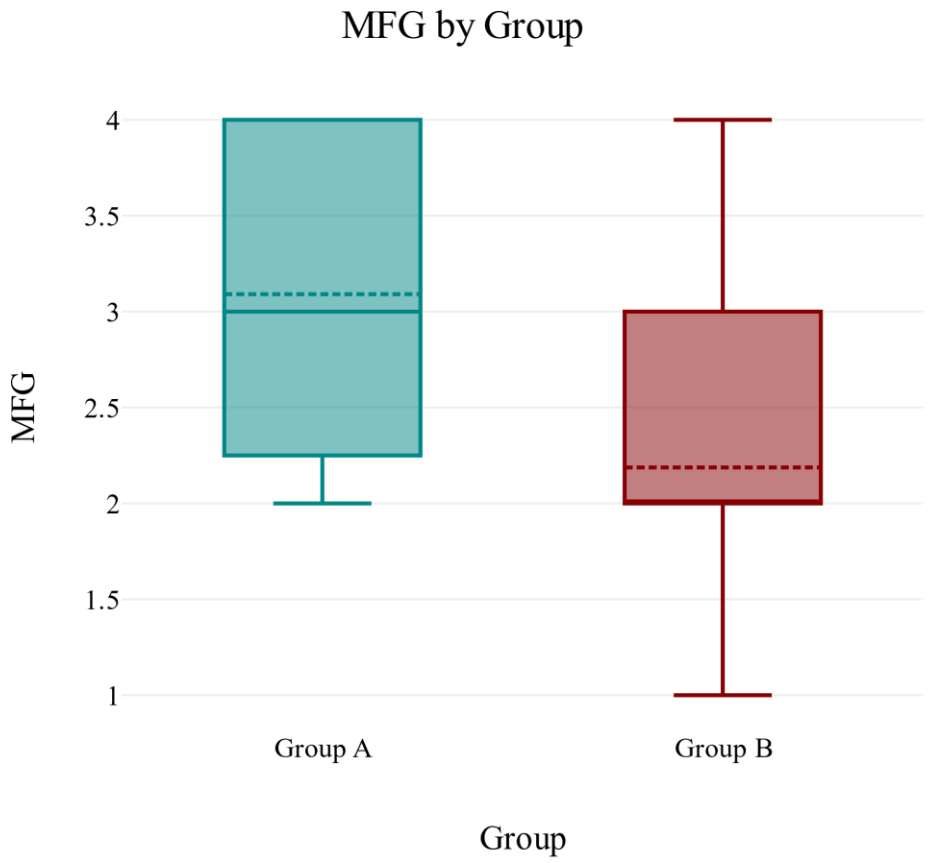


Figure 8: Box plots showing the baseline health status of patients in both the groups.

Table 5 and Figure 8 (box plots) depict the baseline health status of patients in both the groups. Patients in Gp A had a median GCS of 12 (with an IQR of 10-13), a median WFNS of 4 (with an IQR of 3-4), a median MHH of 4 (with an IQR of 4-4) and a median MFG of 3 (with an IQR of 2-4).

Patients in Gp B had a median GCS of 15 (with an IQR of 14-15), a median WFNS of 2 (with an IQR of 2-3), a median MHH of 2 (with an IQR of 2-3) and a median MFG of 2(with an IQR of 2-3). All the above medians when compared were statistically significant with a $p<0.001$.

Table 06: Patient distribution as per WFNS Grades, Good and Poor grades

WFNS	Group A (n=22) N (%)	Group B (n=32) N (%)	p-value
Good Grade (I-II)	02 (09.09)	22 (68.75)	<0.001#
Poor Grade (III-V)	20 (90.91)	10 (31.25)	<0.001#

p<0.05, statistically significant by Chi-square Test

Table 07: Patient distribution as per MFG CT Scores, Good and Poor grades

MFG	Group A (n=22) N (%)	Group B (n=32) N (%)	p-value
Good Grade (I-II)	06 (27.27)	22 (68.75)	0.003#
Poor Grade (III-IV)	16 (72.73)	10 (31.25)	0.003#

p<0.05 statistically significant by Chi-square test.

Patients within the groups were further rearranged and classified as Good Grade WFNS (Scores I-II), Poor Grade WFNS (Scores III-V), Good Grade MFG (CT Grades I-II) and Poor Grade MFG (CT Grades III-IV). Tables 06 and 07 shows the frequency distribution of patients after rearranging for these scores as mentioned above. In Gp A 02 patients (9.09%) had a good grade WFNS Score and 06 patients (27.27%) had a good CT MFG score. The remaining patients in Gp A had poor WFNS and poor CT grade scores.

In Gp B 22 patients (68.75%) had a good grade WFNS Score and 22 patients (68.75%) had a good CT MFG score. The remaining patients in Gp B had poor WFNS and poor CT grade scores.

4.6) Modality of treatment

Table 8: Modality of definitive treatment.

Modality of treatment	Group A (n=22) N (%)	Group B (n=32) N (%)	p-value
Clipping	12 (54.5)	13 (40.6)	0.313
Coiling	10 (45.5)	19 (59.4)	0.313

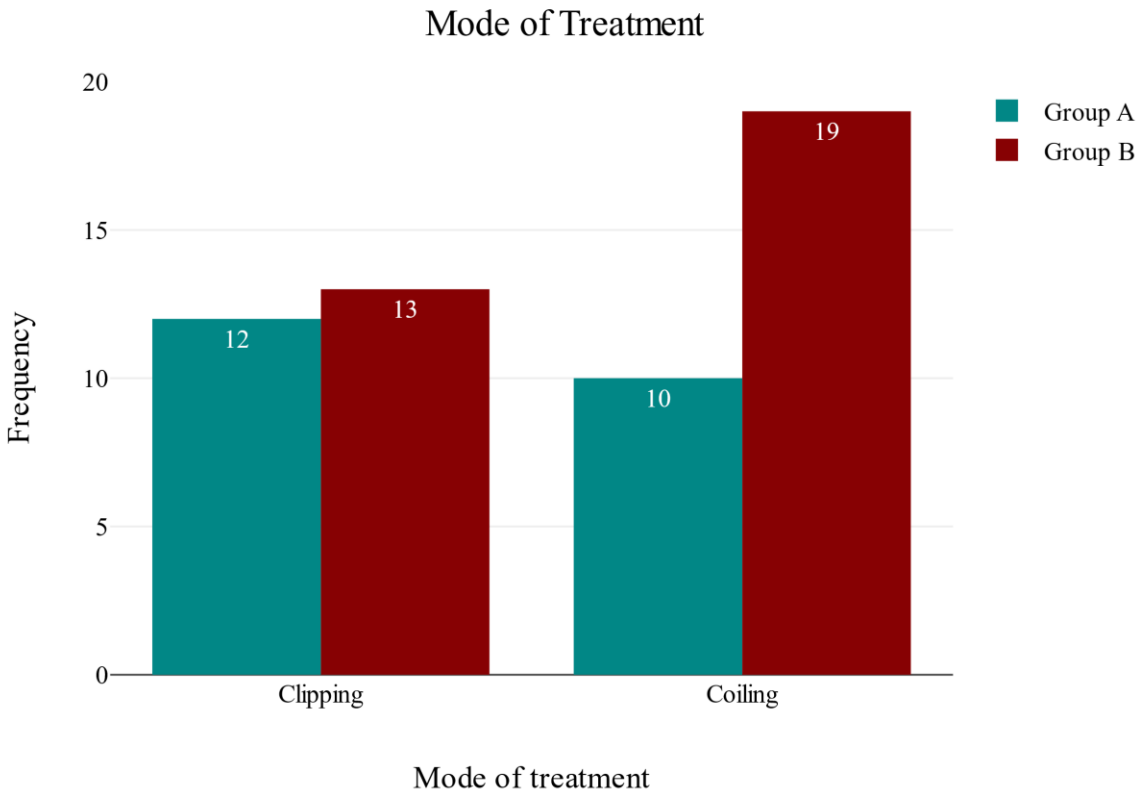


Figure 9: Modality of treatment in both the groups.

Table 8 and figure 9 depict the frequency distribution of the treatment modalities compared in both the groups (Surgical Clipping v/s Endovascular coiling). A total of 25 patients (46.29%) underwent surgical clipping and 29 patients (53.37%) underwent endovascular coiling. Within the groups, in Gp A, 12 patients (54.5%) and in Gp B, 13 patients (40.6%) underwent surgical clipping. Further, in Gp A, 10 patients (45.5%) and in Gp B, 19 patients (59.4%)

underwent endovascular intervention. The means for 'modality of treatment' were statistically non-significant when compared with a p value =0.313.

4.7) Interval Days

Table 9: Interval days from aSAH to definitive treatment.

Interval days from bleed to treatment	Group A (n=22) Mean ± SD	Group B (n=32) Mean ± SD	p-value
Clipping	3.5 ± 1.31	5.77 ± 1.54	<0.0001*
Coiling	3.6 ± 1.58	6.68 ± 2.21	<0.0001*

*p<0.05, statistically significant by t-Test for independent sample

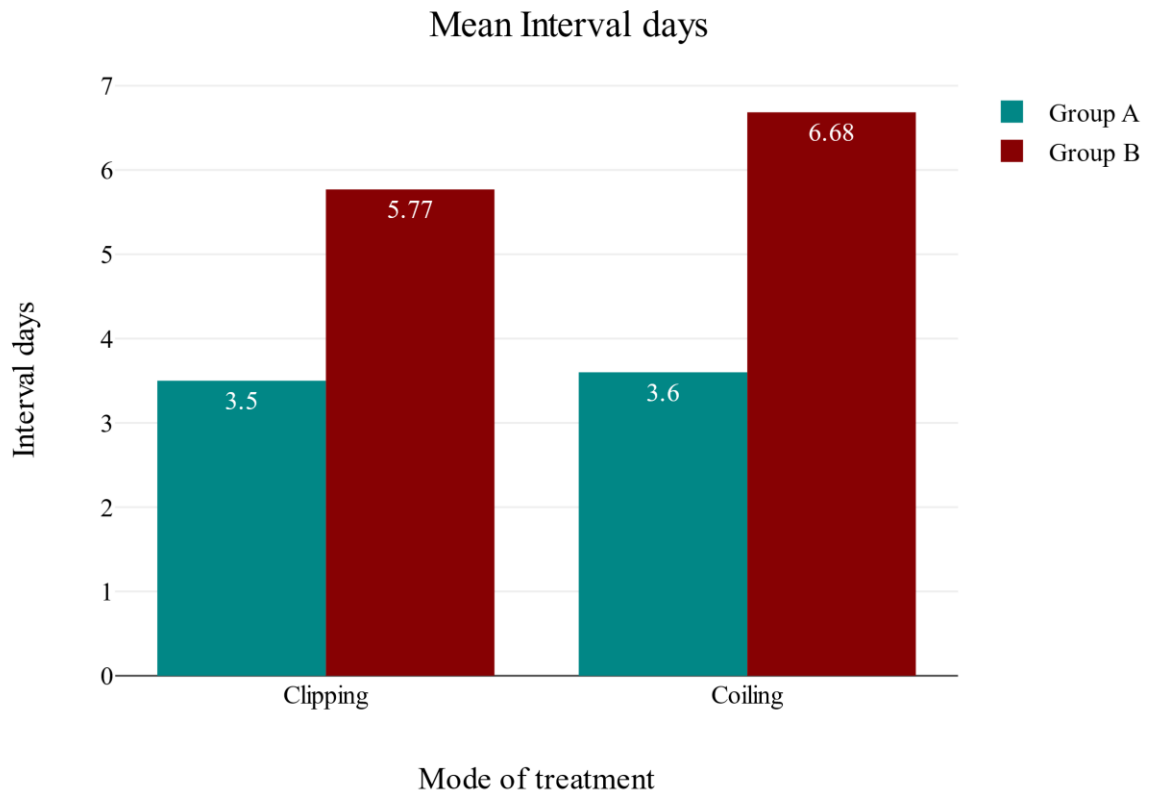


Fig 10: Interval Days from day of aSAH to the day of definitive treatment.

Table 9 and figure 10 compare the interval days from the day of bleed (aSAH) to the day of definitive treatment in both the groups separated for their modality of treatment. For patients undergoing surgical clipping the mean interval days to treatment was 3.5 $\pm$ 1.31 days in Gp A v/s 5.77 $\pm$ 1.54 days in Gp B. This difference was statistically significant with p value < 0.0001. Similarly, for patients undergoing endovascular intervention the mean interval days to treatment was 3.6 $\pm$ 1.58 in Gp A v/s 6.68 $\pm$ 2.21 days in Gp B. This difference was again statistically significant with a p value < 0.001.

4.8) Medical Complications:

The mean day of occurrence of DCI inn Group A was 10 $\pm$ 1.93. Other medical complications noted in both the groups were as follows:

Table 10: Associated medical complications.

Medical complications	Group A (n=22) N (%)	Group B (n=32) N (%)	p-value
Seizure	10 (45.5)	12 (37.5)	0.559
SCM/HSA	5 (22.7)	2 (6.3)	0.077
VAP/ARDS	6 (27.3)	2 (6.3)	0.033*
Anemia	10 (45.5)	8 (25)	0.117
UTI	6 (27.3)	2 (6.3)	0.033*
AKI	3 (13.6)	0 (0)	0.032*
DVT	3 (13.6)	1 (3.1)	0.147

*****p<0.05, Statistically significant by Chi-square test.

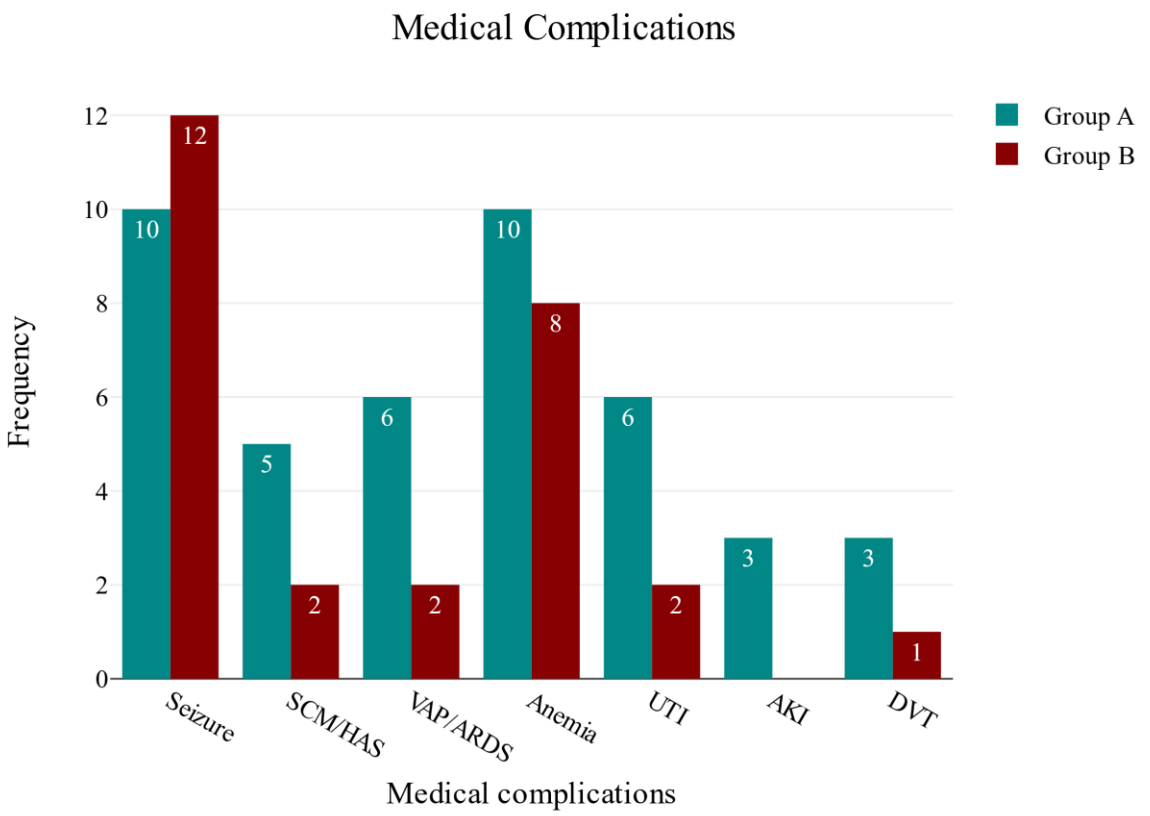


Figure 11: Medical complications during disease evolution

Table 10 and figure 11 show the medical complications which occurred in patients in both the groups during their hospital stay. The most common medical complication in both the groups was seizures (Gp A n=10, 45.5% Gp B n=12, 37.5% p=0.559). The next most common medical complication affecting both groups was anaemia (Gp A n=10, 45.5% Gp B n=8, 25% p=0.117). Urinary tract infection, UTI (Gp A n=06, 27.3% Gp B n=02, 6.3% p=0.033), Ventilator associated pneumonia/Acute respiratory distress syndrome, ARDS (Gp A n=06, 27.3% Gp B n=02, 6.3% p=0.033), Stress cardiomyopathy, SCM/ Hemodynamically significant arrhythmias, HSA (Gp A n=5, 22.7% Gp B n=2, 6.3% p=0.077), Acute Kidney Injury, AKI (Gp A n=3, 13.6% Gp B n=0, 0% p=0.032), Deep venous thrombosis, DVT (Gp A n=3, 13.6% Gp B n=1, 3.1% p=0.150) were the other medical complications noted.

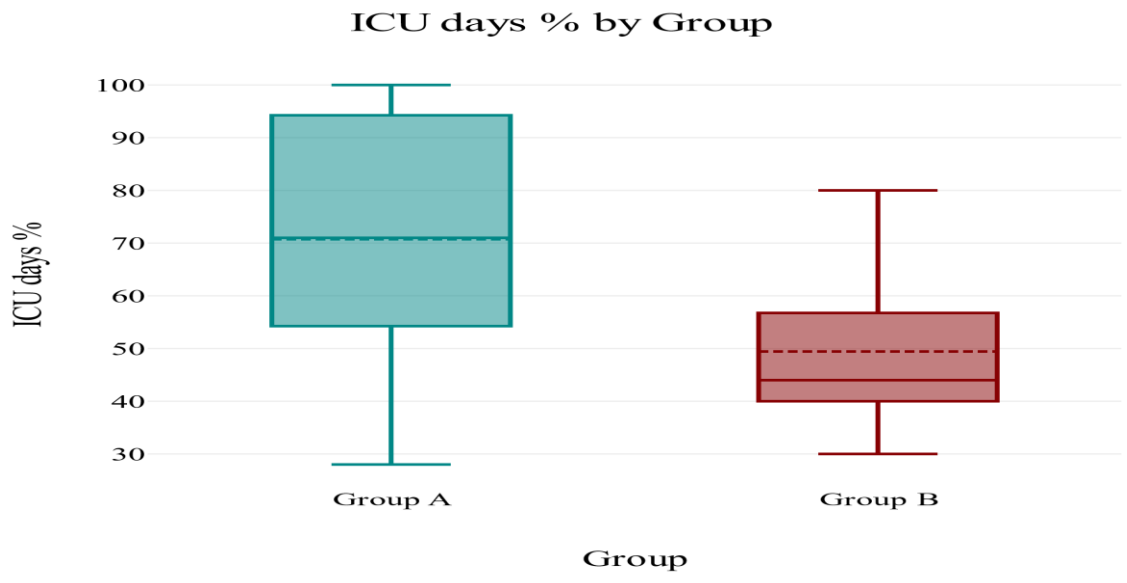
The frequency of occurrence of VAP/ ARDS (p=0.033), UTI (p=0.033), AKI (p= 0.032) was statistically significant with more patients in Gp A developing these complications vis a vis Gp B. The frequency of occurrence of other medical complications was statistically comparable across both the groups.

4.9) ICU and Ventilator Days

Table 11: ICU & Ventilator days (as percentage of total hospitalisation days)

Days	Group A (n=22) Mean ± SD	Group B (n=32) Mean ± SD	p-value
ICU	70.73 ± 23.59	49.44 ± 14.06	0.001*
Ventilator	48 ± 30.61	24.63 ± 10.47	0.002*

*p<0.05, Statistically significant by t-Test for independent sample



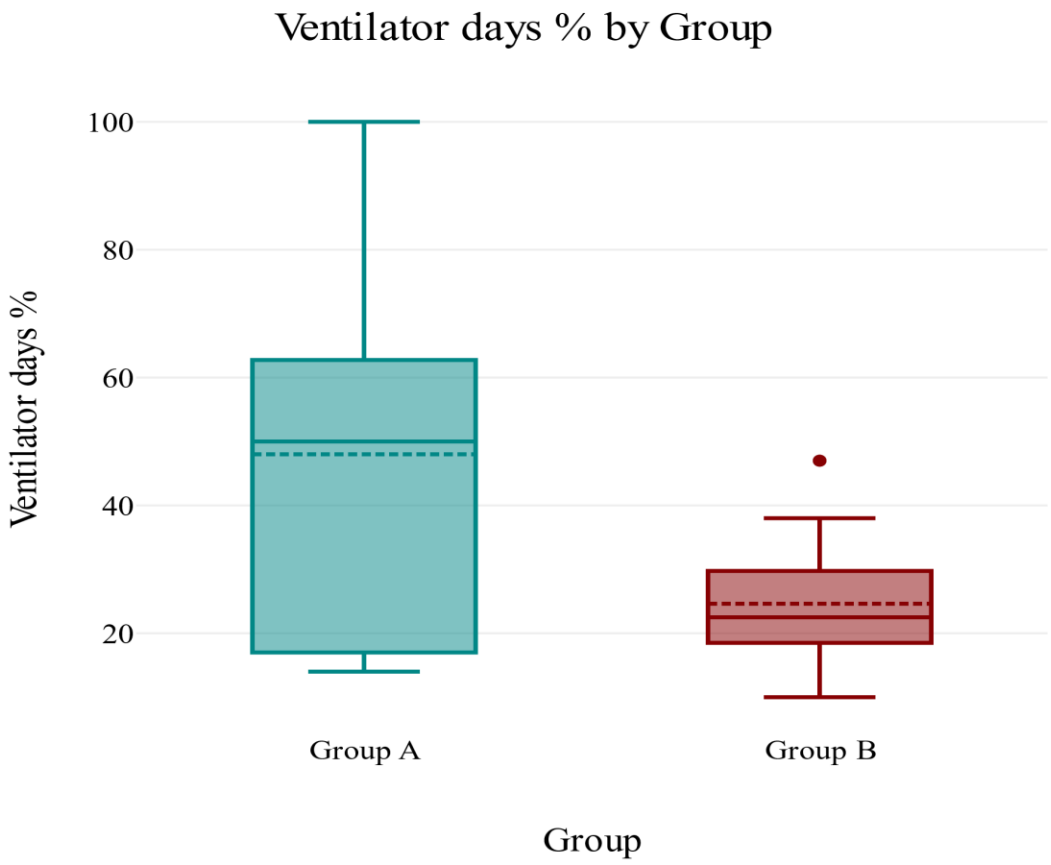


Figure 12: ICU & Ventilator days (as percentage of total hospitalisation days)

Table 11 and figure 12 depicts the mean of total number of ICU and Ventilator days in both the groups (presented as % of the total hospitalisation days). The average mean of %ICU Days for Gp A was n= 70.73 $\pm$ 23.59 % & for Gp B was n= 49.44 $\pm$ 14.06 %, p=0.001. The average mean of %Ventilator Days for Gp A was n= 48 $\pm$ 30.61 % & for Gp B was n= 24.63 $\pm$ 10.47 % , p=0.002). These both average means were statistically significant with patients in Gp A having higher number of mean %ICU and %Ventilator days as compared to patients of Gp B.

4.10) Surgical Complications

Table 12: Peri-op Surgical Complications.

Surgical complications	Group A (n=22) N (%)	Group B (n=32) N (%)	p-value
Perioperative Rupture/ Massive transfusion	6 (27.3)	4 (12.5)	0.173
HCP	6 (27.3)	6 (18.8)	0.459
Meningitis	10 (45.5)	4 (12.5)	0.007*
EDH	5 (22.7)	0 (0)	0.005*

* p<0.05, Statistically Significant by Chi-squre test.

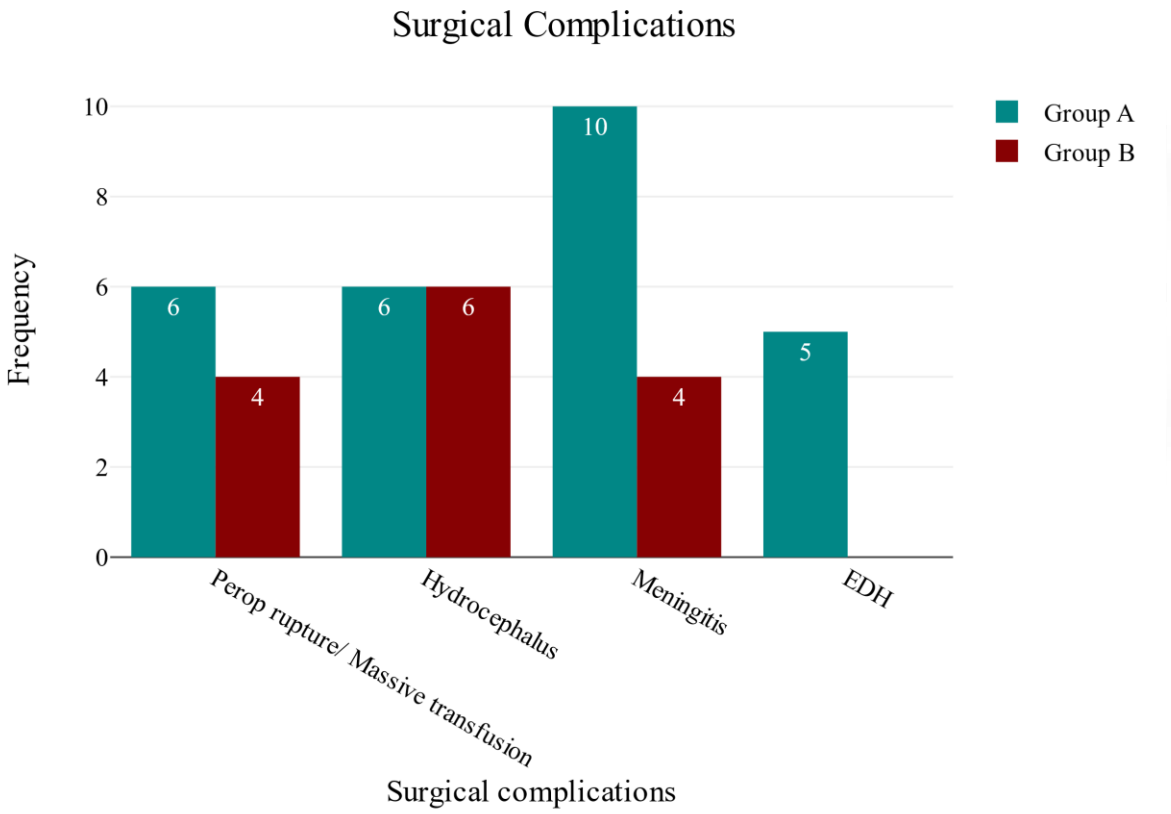


Fig 13: Peri-op Surgical Complications

Table 12 & Figure 13 shows the peri-operative surgical complications occurring in both the groups. Meningitis was the most common surgical

complication occurring in Gp A, with n=10 (45.5%) patients affected. In Gp B meningitis was noted in n=04 (12.5%) patients. This difference was statistically significant with a p=0.007.

The most common surgical complication noted in Gp B was hydrocephalus (HCP) impacting n=06 (18.8%) patients, whereas it occurred in n=06 (27.3%) patients in Gp A. The difference was not statistically significant with p=0.459.

Other perioperative surgical complications included Perop aneurysm rupture/ massive transfusion, noted in 06 patients (27.3%) in Gp A and in 04 patients (12.5%) in Gp B, p=0.173 and Extra Dural Hematoma (EDH), Gp A n=5 (22.7%), Gp B n=0 (0%), p=0.005.

4.11) Patient Outcomes at Hospital Discharge.

Table 13: Patient outcomes measured by modified Rankin Scale (mRS) score

Patient outcome at hospital discharge	Group A (n=22) Med (IQR)	Group B (n=32) Med (IQR)	p-value
mRS	4 (3-5)	2 (2-4)	0.005*

* p<0.05, statistically significant by Mann Whitney U-Test

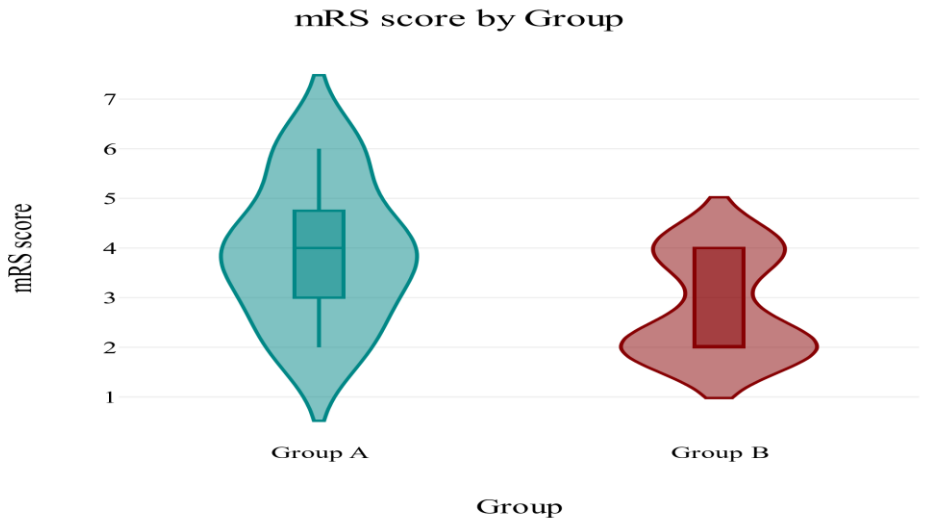


Figure 14: Patient outcomes as measured by modified Rankin scores (mRS)

Table 13 and figure 14 shows the mRS scores at discharge. Patients in Gp A had a median mRS Score of 4 with an IQR of 3-5. Patients in Gp B had a median mRS Score of 2 with an IQR of 2-4. The difference in these medians were statistically significant with a p value= 0.005.

Table 14: Patient outcomes compared (for regrouped mRS scores)

mRS Score	**Group A (n=22) N (%)**	**Group B (n=32) N (%)**	**Total**	**p-value**
Favourable Outcomes (mRS Score 0-3)	08 (36.36)	20 (62.50)	28 (51.85)	0.005*
Unfavourable Outcomes (mRS Score 4-6)	14 (63.64)	12 (37.5)	26 (48.15)	

*p<0.05, statistically significant by Chi-square test.

Table 14 shows the patient outcomes after rearranging for mRS Scores at discharge as Favourable outcomes (mRS Score 0-3) and Unfavourable outcomes (mRS Scores 4-6). A total of n=28 patients (51.85%) had favourable outcomes and n=26 (48.15%) patients had unfavourable outcomes.

Within the groups, in Gp A n=08 patients (36.36%) had a favourable outcome and n=14 patients (63.64%) had an unfavourable outcome. In Gp B n=20 patients (51.85%) had a favourable outcome and n=12 (37.5%) had an unfavourable outcome.

Section- 4B

Lactate Kinetics and DCI

4.12) Comparison of Absolute Serial Lactate in Each Group.

Table 15: Absolute Serial lactate levels in both groups

Time	Group A (n=22) Mean ± SD	Group B (n=32) Mean ± SD	p-value
Tb	1.75 ± 0.49	1.28 ± 0.66	0.006*
T0	2.76 ± 1.65	1.91 ± 0.77	0.032*
T1	4.34 ± 1.64	2.84 ± 1.66	0.002*
D1	3.21 ± 1.65	1.79 ± 0.59	0.001*
D2	2.76 ± 1.51	1.58 ± 0.55	0.002*
D3	2.52 ± 1.40	1.47 ± 0.42	0.002*
Dv	3.91 ± 1.37	1.45 ± 0.66	< 0.001*
Dd	3.00 ± 1.62	1.21 ± 0.53	< 0.001*

* p<0.05 Statistically significant by t-Test for independent sample.

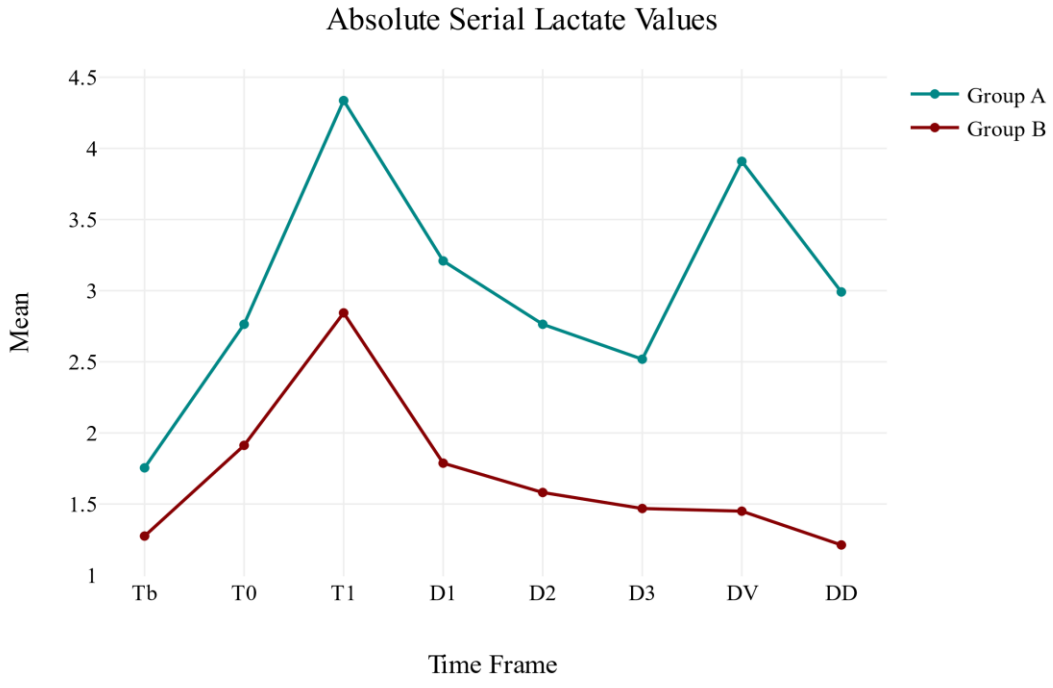


Figure 15: Graphical representation of absolute serial lactate levels.

Table 15 and figure 15 details about the means of absolute serial lactate levels observed at various timelines for both Gp A and Gp B patients.

Key to timeline- Tb-baseline lactate levels on admission. T0- Lactate levels immediate post intervention (clipping/coiling), T1- Lactate levels on Postop Day0, D1/2/3….till Dv - Lactate levels on Postop Day 1/2/3 till Day of Event ie Dv. Lactate on Day of Event (Dv) for Group A was the lactate on the day of DCI, Day of Event (Dv) for Group B was the lactate on the day of ICU Discharge, Dd- Lactate levels on the day of hospital discharge.

For the ease of presentation, values till D3 are depicted followed by Dv and Dd. The mean of absolute lactate values for patients in GpA were consistently higher on each defined time points as compared to corresponding values for Gp B patients and the difference in means was statistically significant at all time points with p value <0.05.

Line graphs were plotted with the means of absolute lactate values in both groups on y axis and defined time points on x axis. An uptrend followed by a crest point was observed in both the groups from point Tb to T1. This was followed by a downtrend and a near plateau phase on subsequent post intervention days. However, a second crest point was noted on day of DCI in Gp A patients whereas the values plateaued off in patients who did not develop DCI (ie Gp B patients).

Baseline lactate values were found to be elevated in n=14 patients (25.92%). Of these 14 patients, n=12 patients (85.71%) developed DCI and were grouped in Gp A.

4.13) Lactate Drifts

Since absolute lactate values might be confounded by baseline health status and many other clinical factors, we compared drifts in the lactate values from baseline as 'ratios' to square off effects of any unknown confounding factor both in the numerator and the denominator, thereby giving a more accurate assessment of lactate as a biomarker.

For this purpose, we defined two ratios ie

a) *Lactate drift ratio baseline ie LDRb*

$$LDRb = \frac{\text{Lactate on a particular day or till event (Dv), whichever is later}}{\text{Baseline lacate (Tb)}}$$

b) *Lactate drift ratio intervention ie LDRi*

$$LDRi = \frac{\text{Lactate on a particular day or till event (Dv) whichever is later}}{\text{Lactate immediate post intervention (clipping/coiling) (T0)}}$$

Both the abovesaid ratios were calculated on a daily basis for all patients and serial trends in these drift ratios were noted from baseline and from post intervention day respectively.

4.13 a) LDRb

Table 16: Serial LDRb means for both the groups

Drift	Group A (n=22) Mean ± SD	Group B (n=32) Mean ± SD	p-value
T0/Tb	1.65 ± 0.91	1.80 ± 1.12	0.614
T1/Tb	2.54 ± 0.92	2.63 ± 1.92	0.84
D1/Tb	1.88 ± 0.91	1.84 ± 1.23	0.889
D2/Tb	1.70 ± 0.99	1.64 ± 1.20	0.845
D3/Tb	1.56 ± 0.95	1.64 ± 1.60	0.833
Dv/Tb	2.30 ± 0.74	1.43 ± 1.24	0.005*
Dd/Tb	1.74 ± 0.90	1.14 ± 0.78	0.011*

* p value <0.05, Statistically significant by t-Test for independent sample.

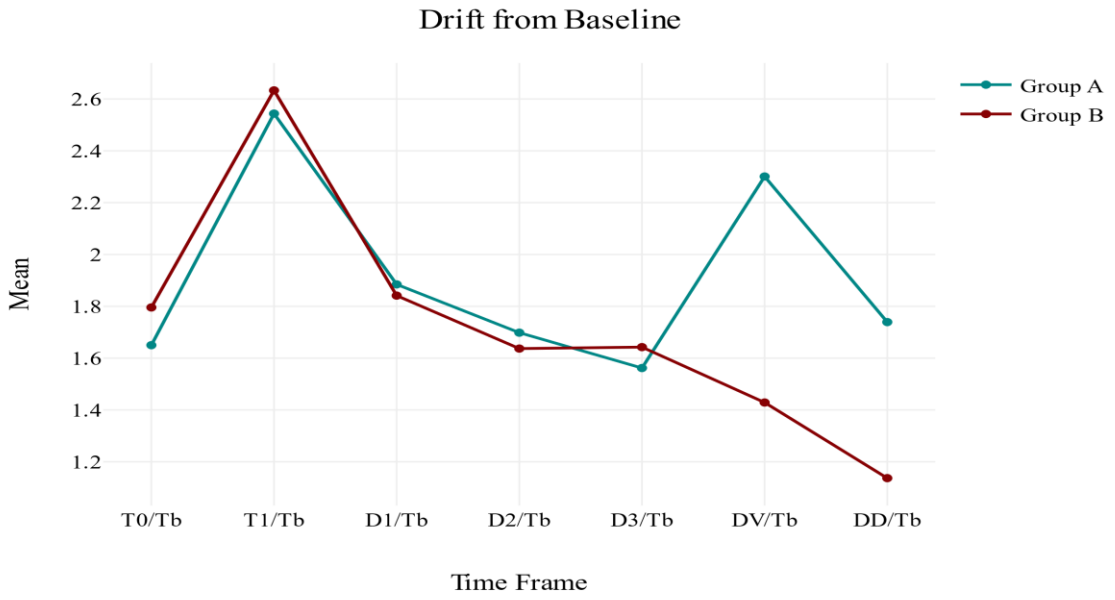


Figure 16: Graphical representation of serial LDRb means.

Table 16 & figure 16 represent the mean of LDRb ratios calculated on daily basis. Line graphs were plotted with the means of serial LDRb values in both groups on y axis & defined time points on x axis. A gradual uptrend with a peaking crest point was observed in both the groups from point T0 to T1.This was

followed by a downtrend and a near plateau phase on subsequent post intervention days. However, a second crest point was noted on day of DCI in Gp A patients whereas the values remained plateaued off in patients who did not develop DCI (ie Gp B patients). Both the curves ran concurrently and almost parallelly except for on the day of DCI in Gp A patients. These means were statistically comparable at all time points except for on the day of DCI when there was a significant difference noted in the mean LDRb values between Gp A & Gp B. The mean LDRb for Gp A on the day of event (Dv) was found to be 2.30$\pm$0.74 whereas the corresponding value for Gp B was 1.43$\pm$1.24. This difference in the mean LDRb values remained statistically significant following the day of event (Dv) till the day of discharge (Dd) with p=0.005 & p=0.011 respectively.

4.13 b) LDRi

Table 17: Serial LDRi means for both the groups

Drift	Group A (n=22) Mean ± SD	Group B (n=32) Mean ± SD	p-value
T1/T0	2.22 ± 1.75	1.49 ± 0.55	0.031*
D1/T0	1.50 ± 1.14	1.06 ± 0.43	0.05*
D2/T0	1.20 ± 0.56	0.92 ± 0.33	0.025*
D3/T0	1.10 ± 0.51	0.87 ± 0.35	0.05*
Dv/T0	1.97 ± 1.54	0.79 ± 0.28	0.0001*
Dd/T0	1.33 ± 0.80	0.66 ± 0.19	< 0.0001*

* p<0.05, statistically significant by t-Test for independent sample.

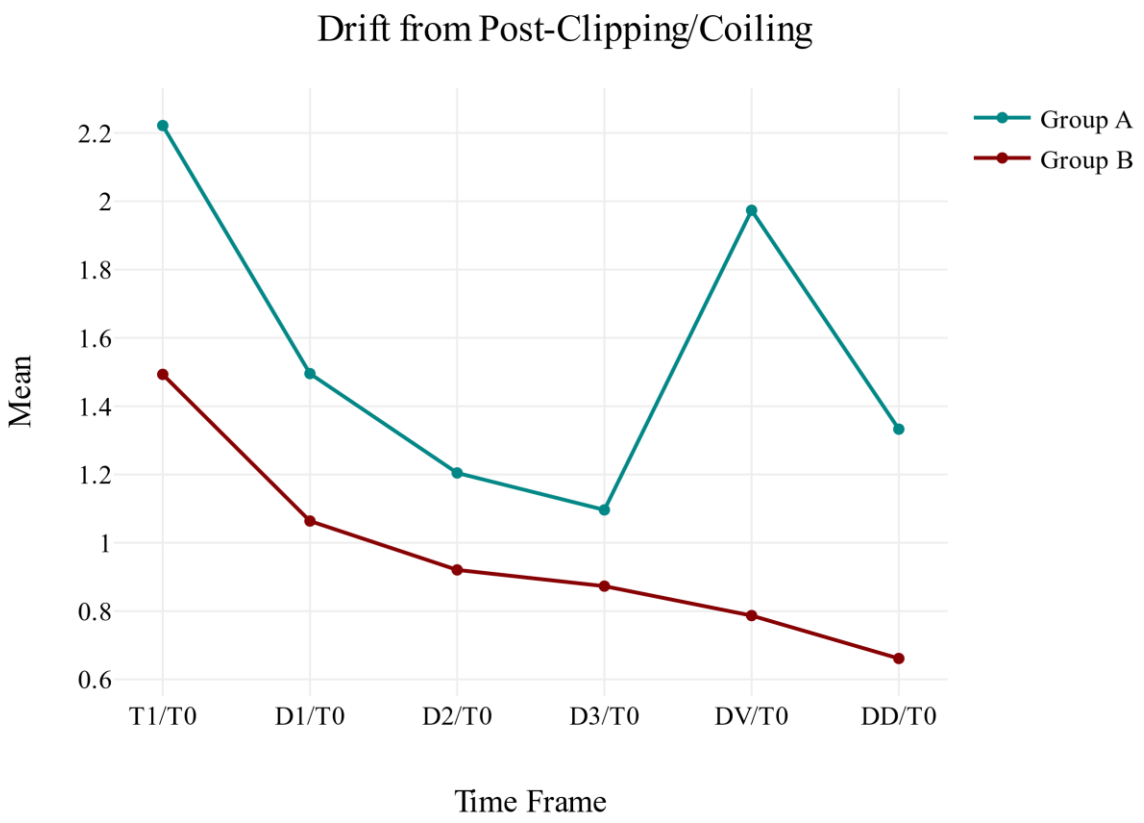


Figure 17: Graphical representation of serial LDRi means.

Table 17 & figure 17 represent the mean of LDRi ratios calculated on daily basis. Line graphs were plotted with the means of serial LDRi values in both groups on y axis & defined time points on x axis. In Gp B patients there was a persistent downtrend and plateauing noted from T1 to Dd. Patients in Gp A also showed similar trends post intervention day, however there was an uptick and the ratio showed a rising trend again on the day of DCI with a distinct peak occurring parallel to DCI. It remained elevated thereafter with marginal decrease noted till Dd (hospital discharge). There was a statistical difference noted in LDRi mean values throughout across all the defined time points with p value <0.05. The mean LDRi for Gp A on the day of event (Dv) was found to be 1.97 ± 1.54 whereas the corresponding value for Gp B was 0.79 ± 0.28.

4.14) Sensitivity, specificity, ROC Curve analysis

To determine the sensitivity, specificity of both the ratios LDRb and LDRi done separately and as combined tests done in parallel, we did the ROC Curve analysis.

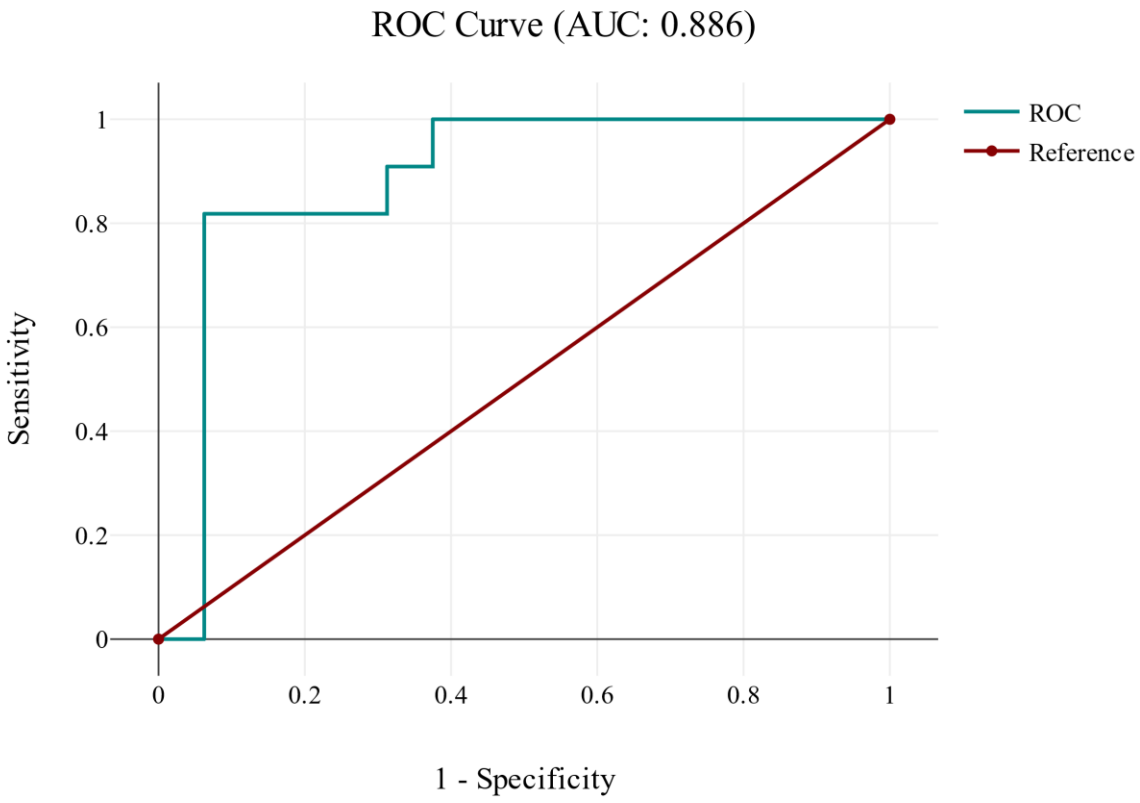


Figure 18: ROC curve analysis for LDRb.

At a cut-off point of 1.78 for the LDRb, the AUC was 0.878 (95% CI: 0.778-0.978); sensitivity was 81.8% and specificity was 85.5% ($p < 0.000$)

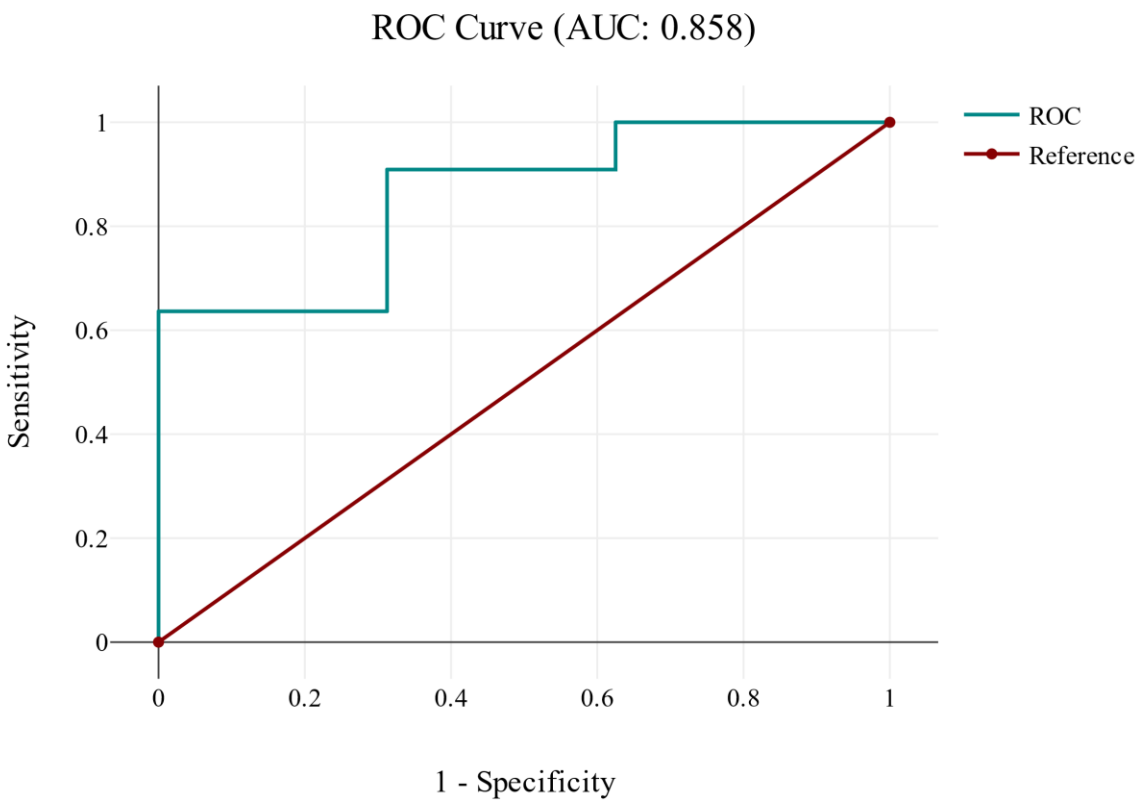


Figure 19: ROC curve analysis for LDRi

At a cut-off point of 1.01 for the LDRi, the AUC was 0.858 (95% CI: 0.756-0.960); sensitivity was 72.7% and specificity was 68.7% ($p < 0.000$)

For both the tests LDRb and LDRi, the combined sensitivity and specificity calculated (in Parallel) was as follows

Combined sensitivity = 1 – (1 – sensitivity of test 1) × (1 – sensitivity of test 2)

Combined Sensitivity = 0.950

Combined Specificity = Specificity of test 1 × Specificity of test 2

Combined Specificity = 0.587

4.15) Kaplan-Meier and Log-Rank Test for LDRb

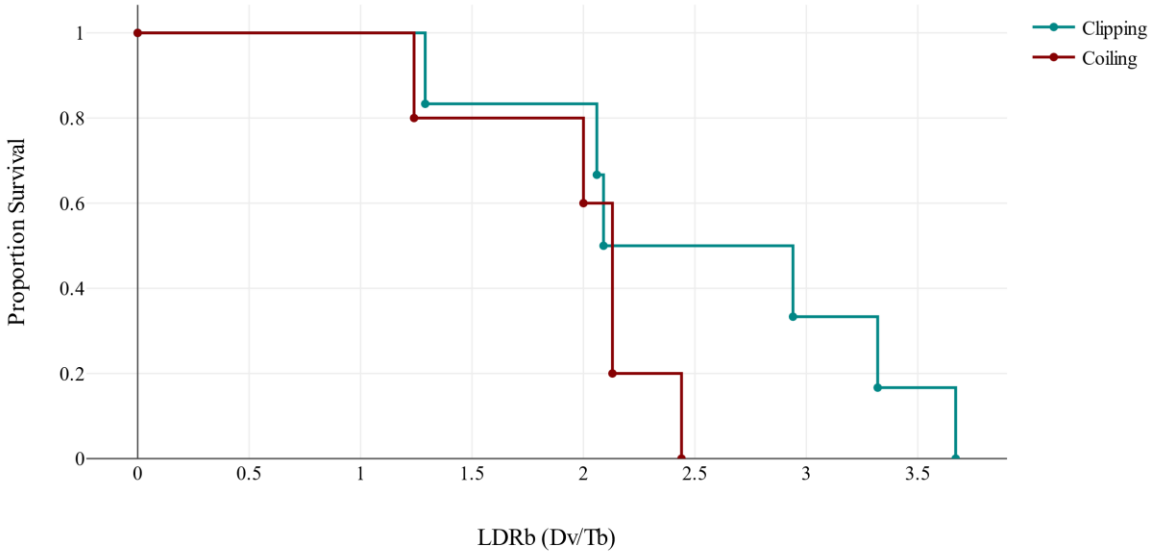


Figure 20: Kaplan-Meir analysis- LDRb

Log rank Test

	Chi-Square	df	p
Log Rank	3.26	1	.071

A log-rank test was calculated to see if there was a difference between groups Clipping and Coiling in terms of the distribution of LDRb to event occurrence.

For the present data, the log-rank test showed that there is no difference between the groups in terms of the distribution of time until the event occurs, p=.071.

4.16) Kaplan-Meier and Log-Rank Test for LDRi

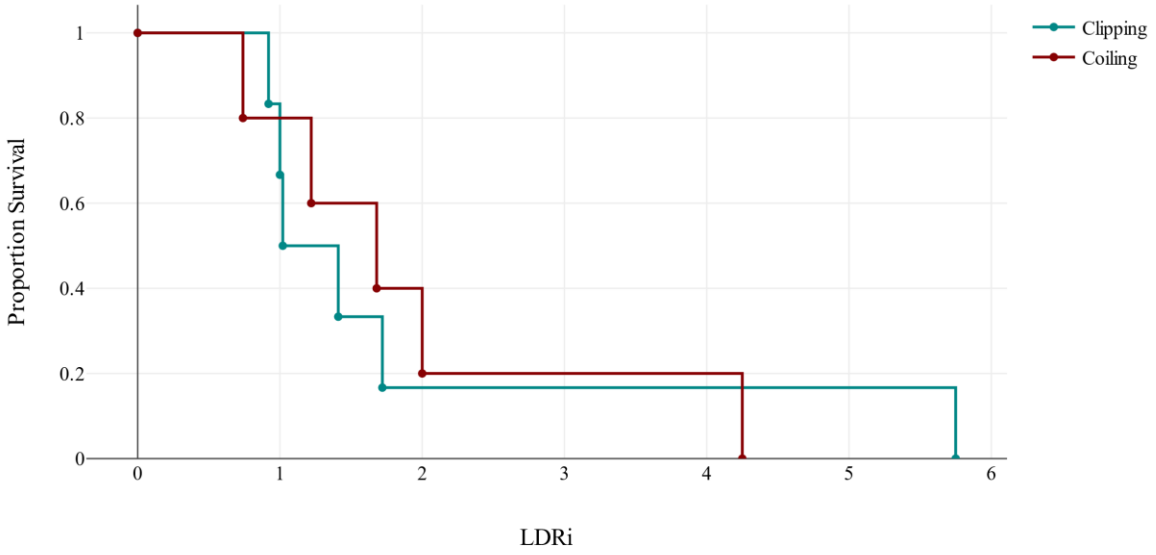


Figure 21: Kaplan- Meir analysis- LDRi

Log rank Test

	Chi-Square	df	p
Log Rank	0.02	1	.895

A log-rank test was calculated to see if there was a difference between groups Clipping and Coiling in terms of the distribution of LDRi to event occurrence.

For the present data, the log-rank test showed that there is no difference between the groups in terms of the distribution of time until the event occurs, p=0.895.

5. Discussion

5. DISCUSSION

DCI is a complex pathophysiological phenomenon which occurs following aSAH with an uncertain predictability but can exponentially worsens the outcomes of a patient. This secondary injury can be limited if diagnosed and treated early. Biomarkers can aid in this process of early diagnosis and be a part of an effective bedside screening tool. Towards this purpose, the utility of lactate as a biomarker has been evaluated in single/ paired samples by many authors exploring it in various bodily fluids like cisternal or EVD CSF samples, cerebral microdialysis aspirates and in venous blood samples etc.

Values in venous samples may be confounded by site of sampling ie capillary vs peripheral venous v/s mixed venous v/s jugular bulb. Cisternal or EVD samples and cerebral microdialysis aspirate are all highly invasive techniques fraught with procedure related complications along with the risk of meningitis on repeated sampling.

Arterial samples on the other hand are minimally invasive, serially doable and whose values are not affected by the site of sampling. Hence this study explored the potential of arterial lactate as a biomarker in DCI.

5.1 ***DCI Burden***- In our study out of total enrolled patients n=54, 22 patients (40.74%) developed DCI and 32 patients (59.26%) did not develop DCI. We had a slightly higher incidence of DCI as compared with the data from past studies. Dorsch, et al (72) reported an incidence of 33% in over 30,000 cases of SAH reported before 1994, and in 29% of 23,806 cases reported between 1994 and 2009. Further in their study DCI was diagnosed in 22% of 10,739 patients who received calcium channel antagonists compared with 32% of 13,267 who did not receive such drugs.

5.2 Demographics: In our study there was a female preponderance with n=34 patients (62.96%) being female and n= 20 patients (37.03%) being male. Female is to male ratio was 1.7:1. This almost concurs with finding of various other authors like Linn et al (73) , who in their study reported women to have 1.6 times (95% CI 1.5–2.3) higher risk than men. The mean age of patients in our study was 51.85 $\pm$ 10.15 years. This finding also corroborates with the finding of previous studies. Suarez et al (74) reported 75% of their aSAH patients to be in the age bracket of 41-65 years.

5.3 Lactate Kinetics

To the best of our knowledge, this is the first study exploring arterial lactate kinetics through the entire temporal course of disease evolution across different phases in patients with aSAH surviving the initial bleed (EBI Period). We evaluated baseline lactate and daily lactate drift ratios. Drift ratios were noted from baseline (LDRb) and from the day of intervention (LDRi). Ratios were analysed to negate the effect of any unknown confounders in absolute values both in the numerator and the denominator.

In post -hoc analysis, we explored a) if there was any relation between baseline elevated lactate levels and occurrence of DCI and b) further how the kinetics of these drift ratios varied in patients who developed DCI (Group A) v/s in patients who did not (Group B).

With the help of ROC curve analysis, we derived a cutoff range value for these drift ratios (assessed both individually and as tests done in parallel) which can be predictive of an impending DCI and be used as an effective bedside screening tool to forewarn the treating intensivist before the actual insult sets in.

We present our findings followed by comparisons with those of other authors who have investigated the role of lactate as a biomarker for EBI &/or DCI

in various other bodily fluids (eg CSF via EVD/ Cisternal samples, CMD dialysate, and venous blood). Authors in past have mostly relied on comparing the absolute values in their data analysis.

5.3.1 ***Baseline Lactate***- We noted baseline lactate (Tb) to be elevated in n=14 patients, 25.92%. Of these 14 patients, 12 patients (85.71%) went on to develop DCI as their disease evolved and hence became a part of Gp A. Elevated baseline lactate on presentation is hence a good prognostic marker in our study for predicting the occurrence of DCI.

5.3.2 ***Drift Ratios***-

a) *LDRb*- The mean LDRb for Gp A on the day of event (Dv) was found to be 2.30±0.74 whereas the corresponding value for Gp B was 1.43±1.24. This difference in the mean LDRb values remained statistically significant following the day of event (Dv) till the day of discharge (Dd). In the ROC analysis, at a cut-off point of 1.78 , the AUC was 0.878 (95% CI: 0.778-0.978); with a sensitivity of 81.8% and a specificity of 85.5%.

b) *LDRi*- The mean LDRi for Gp A on the day of event (Dv) was found to be 1.97±1.54 whereas the corresponding value for Gp B was 0.79±0.28. There was a statistical difference noted in LDRi mean values throughout across all the defined time points. In the ROC analysis, at a cut-off point of 1.01, the AUC was 0.858 (95% CI: 0.756-0.960); with a sensitivity of 72.7% and a specificity of 68.7%

We hence concluded that for both the tests ie LDRb and LDRi done in parallel with a cutoff values 1.78 and 1.01 respectively, the combined sensitivity predictive of DCI was 95% and the combined specificity was 58.7%.

5.3.3 Studies investigating Lactate in CSF -

Anan et al (75) in their study analysed the concentrations of lactate and LDH in carotid cisternal CSF in patients with aSAH and found these levels to be significantly higher in the DCI group than in the non-DCI group on post bleeding day (PBD) 1-2, 3-4, and 5-6. However, in their results neither lactate nor LDH levels in venous blood differed significantly between DCI and non-DCI groups on PBD 1-2. Authors hence concluded that lactate and LDH concentrations in carotid cisternal CSF may vividly reflect the EBI and may thus represent predictive biomarkers of DCI following aSAH.

Their graphic representation of temporal course of lactate levels almost mirrors our findings with traces showing two peaking crests on PBD 1-2 and at the time of DCI along-with no significant peaks in the non-DCI group.

In another study by ***Messina et al*** (76) authors investigated the role of cerebrospinal fluid lactate and glucose levels as predictors of symptomatic DCI. They enrolled n=133 aSAH patients, of which 48 patients had an EVD insitu. Authors found that independent predictors of symptomatic DCI were a) elevated CSF lactate b) WFNS grade IV-V and c) elevated CSF glucose. They concluded that elevated CSF lactate and glucose levels in the first 3 days following aSAH were independent predictors of subsequent DCI-related neurological impairment and advocated the use of CSF lactate and glucose monitoring as a point-of-care test for the prediction of DCI.

Renfrow et al (77) in their study evaluated the role of CSF lactate with outcomes in aSAH. In multivariate regression analysis, they found that a) unfavourable outcomes at discharge, b) elevated CSF protein and c) admission Hunt and Hess score 3–5 were significantly associated with higher CSF lactate values. In their analysis, the risk of symptomatic vasospasm increased with lactate

in univariate analysis, but did not reach a statistical significance. Authors hence concluded that elevated CSF lactate correlates well with patient outcomes.

5.3.4 Studies investigating Lactate in CMD dialysate

Ette K. Schulz et al (78) investigated CNS parenchymal ECF concentrations of glucose, pyruvate, lactate, glutamate & glycerol by using low-flow CMD in 46 patients with poor grade SAH. The results were analysed as two subgroup ie a) patients who had no clinical or radiological signs of cerebral ischemia and b) patients who succumbed to brain death. Significantly lower levels of energy substrates (glucose, pyruvate) and significantly higher levels of lactate and neuronal injury markers were observed in patients with severe and complete ischemia when compared with patients without symptoms of ischemia. Immediately after catheter placement, glutamate concentrations declined over the first 4 to 6 hours to reach stable values. The remaining parameters exhibited stable values after 1 to 2 hours. Authors concluded that cerebral biochemistry by CMD can hence help in detection of cerebral ischemia.

Rostami et al (79) in their study explored if low CBF and deranged CMD parameters can be observed early in patients with aSAH who later develop DCI. Authors included 30 patients with severe aSAH. The CBF measurements were performed at Day 0–3 after disease onset, using bedside xenon-CT. Interstitial glucose, lactate, pyruvate, glycerol, and glutamate were measured using CMD. They observed that 09 patients who later developed DCI had a significantly early lower global and regional CBF, with a significantly increased lactate on CMD. A high early lactate/pyruvate ratio was also detected in patients with DCI. Authors opined that low CBF measurements, a high lactate and lactate/pyruvate ratios on CMD may be early warning signs of the risk of developing DCI .

Patet et al (80) studied 20 comatose aSAH patients with CMD monitoring for hourly sampling of cerebral extracellular lactate/pyruvate ratio (LPR), glucose and CT perfusion brain. Patients were categorised as DCI when CT perfusion (8±3 days after aSAH) showed cerebral hypoperfusion, defined as cerebral blood flow <32.5ml/100gm/min with a mean transit time >5.7 sec. Only patients who developed cerebral hypoperfusion in ACA &/or MCA were analysed. Authors reported that DCI was associated with higher CMD LPR and lower CMD glucose. In patients with DCI, CMD changes over the 18 hours preceding CT perfusion diagnosis revealed a pattern of CMD LPR increase with simultaneous CMD glucose decrease. No significant CMD changes were noted in patients without DCI. Authors concluded that in comatose patients with aSAH, delayed cerebral hypoperfusion correlates well with a CMD pattern of lactate increase and simultaneous glucose decrease and that these CMD abnormalities became apparent in the hours preceding CT Perfusion findings, thereby suggesting that CMD monitoring may anticipate targeted therapeutic interventions.

5.3.5 Studies investigating Venous Lactate

Poblete et al (81) in their retrospective observational study investigated 105 patients for their admission serum lactate values. They studied only absolute single admission lactate value with the primary objective to determine the incidence of admission lactic acidemia, and factors which are positively and negatively associated with it. They found that admission serum lactic acid was elevated in n=56 patients (53%) and these levels were positively associated with a) Hunt & Hess and modified Fisher grade b) glucose, c) troponin I and d) white blood cell counts, and negatively associated with a) GCS and ventilator-free days. They reported that admission lactate was not associated with the development of vasospasm/DCI because patients with elevated lactic acid more often died during

hospitalization, and less often were discharged home. After adjusting for other predictors of poor outcome, the adjusted odds of inpatient mortality and discharge to home was not associated with admission lactic acid. Authors studied only the admission lactate values and did not follow up for the trends as the disease evolved in patients who did develop DCI .

In another study by ***Zheng et al*** (82) , authors investigated whether preoperative serum LDH levels were associated with Hunt–Hess grade, Fisher grade, and functional neurological outcome in patients with aSAH. In total, 2,054 patients with aSAH were enrolled, 874 of whom were treated using microsurgical clipping. The average serum LDH level (U/L) was significantly lower in the good outcome group than in the poor outcome group. After propensity score matching, the average serum LDH level (U/L) was still lower in the good outcome group than in the poor outcome group. The area under the ROC curve was 0.702. Based on the ROC curve, authors found that the optimal cutoff value for serum LDH levels as a predictor of poor 3-month outcome (mRS > 2) was 201.5 U/L. Their results revealed that Hunt–Hess grade, Fisher grade, DCI, pneumonia, and serum LDH (>201.5 U/L) were significantly associated with poor outcome. After propensity score matching, serum LDH levels > 201.5 U/L was still considered an independent risk factor for poor outcome.

Van Donkelaar et al (83) in their study explored the association between early circulating lactate and glucose with DCI and poor outcomes. In their cohort DCI occurred in 84 patients (29%), and 106 patients (39%) had poor outcomes. They found that lactate and glucose were both independently associated with DCI and poor outcome in multivariate analysis with either lactate or glucose as covariates. When both lactate and glucose were included, only glucose showed an independent association with DCI and only lactate showed an independent association with poor outcome .

Aisiku, et al (84) in their study correlated the admission serum lactate for predicting mortality in aSAH, and found that with multivariate analysis after controlling for Hunt and Hess grades, lactic acid level was an independent predictor of mortality. The authors advocated the use of Lactic acid as a biomarker of mortality (and not DCI) in patients with aSAH .

5.4 Associated Comorbidities and addictions : The most common comorbidity in our study cohort was essential hypertension. Other common comorbidities noted were diabetes mellitus, hypothyroidism, CAD, COPD, asthma, hepatitis B infection, congenital heart disease and thrombocytosis. Tobacco abuse was noted in n=13 patients and alcohol abuse in n=10 patients.

Malinova et al (85) in their retrospective study evaluating the value of comorbidities and illness severity scores as prognostic tools for early outcome estimation in 315 patients with aSAH noted hypertension (34%) to be the most common associated comorbidity followed by nicotine abuse (11.9%), cardiac disease (11.4%), and thyroid gland dysfunction (10.5%). They found that at least one comorbidity was present in 73.3% (231/315) of all their enrolled patients.

Etminan et al (7) in their meta-analysis of 8176 patients, compared the worldwide incidence of aSAH to the altering prevalence of BP & Smoking & concluded that the global incidence of SAH had decreased by 7.1% with every mmHg decrease in systolic blood pressure, 11.5% for every mmHg decrease in diastolic blood pressure, and 2.4% for every percentage decrease in smoking prevalence with the potential that further reducing blood pressure and smoking prevalence may yield a diminished SAH burden overall.

The American Heart Association (AHA)/American Stroke Association (ASA) also identifies Hypertension and tobacco as important modifiable risk factors for aSAH. (Class I; Level of Evidence B) (86) .

5.5 Location of the aneurysm: ICA (all segments included) was the most common vessel involvement noted in our study. The next most common vessel involved was ACOM. Other vessels involved were ACA and MCA.

Various authors have reported varying frequencies of involvement of different blood vessels in aSAH. Kassell et al (49) in their seminal paper titled 'The international cooperative study on the timing of aneurysm surgery' reported most aneurysms to be located in the anterior circulation, with the junction of the ACOM and ACA being the most common (39%) followed by ICA (30%), middle cerebral artery (22%) and posterior circulation (08% posterior cerebral, basilar, and vertebral arteries combined).

5.6 Baseline health status: In our study, at presentation (Tb) depending on their clinical status (WFNS Grades) and by the severity on CT imaging (MFG Score) patients were grouped into either good grade aSAH (WFNS I-II, MFG I-II) or a poor grade aSAH (WFNS III-V, MFG III-IV).

By clinical status (WFNS Grade), a total of n=24 patients (44.44%) had a good grade aSAH and n=30 patients (55.55%) had a poor grade aSAH.

Similarly, as per the CT findings (MFG Scores)- a total of n= 28 patients (51.85%) had a good grade aSAH whereas n=26 patients (48.14%) had a poor grade aSAH.

Investigators in past have reported varying proportions of good grade v/s poor grade aSAH in their study cohorts with no trends or patterns of the disease noted. Different authors have reported a varied case mix of the enrolled study populations (eg clinical grade, CT grade, location of the aneurysm, timing of presentation etc). For eg in the ISAT study ie International subarachnoid aneurysm trial (ISAT) authors had 88% of patients belonging to good grade aSAH (ie WFNS I & II) (87). The anterior circulation coil-to-coil subcohort in BRAT study had 60% good grade aSAH and 16% poor grade aSAH. (88)

5.7 Mode of treatment and interval to definitive management: In our study a total of n=25 patients (46.29%) underwent clipping and n=29 patients (53.70%) underwent coiling of the ruptured aneurysm. The average mean interval (in days) from ictus onset to definitive treatment for all patients combined was 5.02±2.05 days. Hence most patients in our study group presented in the intermediate time frame (ie from day 4 to day 7 of ictus).

The age-old debate of clipping v/s coiling is a complex research question which has intrigued many investigators. Some noteworthy studies are the study by Li et al (89), the Finnish study (90), the ISAT study (87) , the BRAT study (88) , and a Cochrane review by Lindgren et al (91).

AHA in its recent 2023 guidelines stated that 'the quality of the evidence supporting recommendations for treatment modality is relatively limited, with a particular paucity of data on comparison of different endovascular techniques with surgical techniques or with each other and that further studies are warranted for this knowledge gap (92).

Factors favouring surgical clipping include age less than 40 years, presence of an intraparenchymal hematoma, very wide-neck with dome-to-neck <1.2, aspect ratio <1.2, DACA aneurysms, fusiform or giant aneurysms, aneurysms at arterial bifurcations, etc. Factors favouring endovascular coiling include elderly frail patients with high surgical risk, posterior circulation aneurysms (eg Basilar tip aneurysms), clinical equipoise etc.

Within the cohort of patients >65 years of age in ISAT study, outcome was dependent on aneurysm location, with coiling superior in those with ICA and PCOM aneurysms but clipping superior for those with ruptured MCA aneurysms (87). However, non-randomized trials and observational studies have so far failed to demonstrate conclusively an effect of treatment modality on outcomes in the elderly (>75 years of age).

The present literature supports early and complete obliteration for ruptured aneurysms within 24 hours of aSAH. Studies also support the benefit of treatment in the intermediate time frame (from day 04 to day 07) in patients presenting beyond Day 03. Treatment should not be delayed to after 7-10 days (DCI period) in patients presenting during the intermediate time frame.

IHAST Study reported a mean of 3±3 days and a median of 2 days for interval from ictus onset to day of definitive treatment for both the normothermic and hypothermic groups (93).

5.8 Medical & Surgical Complications, ICU days & Ventilator days

The most common medical complication in our study population for both the groups combined was seizures. Other common medical complication noted were anaemia, UTI, VAP/ARDS, SCM/ HSA, DVT & AKI. The frequency of occurrence of VAP/ ARDS, UTI, & AKI was statistically significant with more patients in Gp A developing these complications vis a vis Gp B. The frequency of occurrence of other medical complications was statistically comparable across both the groups.

The most common combined surgical complication noted in our study was meningitis seen in n=14 patients. Of these 14 patients, n=06 patients had an indwelling EVD or a VP Shunt done, whereas rest patients developed meningitis spontaneously without any invasive ventriculostomy. The next most common surgical complication seen was hydrocephalus noted in n=12 patients

Patients in Gp A had a significantly higher average mean of ICU and ventilator days (expressed as a % of total hospitalisation days) as compared to average means of Gp B

Hence in our study, the overall incidence of medical complications, ICU days and Ventilator days and surgical complications were significantly higher in Gp A (DCI group) as compared to Gp B (Non DCI group)

In our study, n=22 patients, 40.74% had seizures as a medical complication. Rhoney et al (94) and Bnr et al (95) in their studies found that approximately 20% of aSAH patients have seizures prior to hospital arrival, and another 5–10% experience seizures after admission.

Anaemia (Hb<10g/dl) was noted in n=18 patients, 33.33% in our study. Ayling et al (96) in their secondary analysis of CONSCIOUS-I data (413 patients with aSAH) found that anaemia (Hb<10g/dl) was present in 5% of patients at presentation, in 29% of patients after aneurysm securing (days 1–3), and in 32% of patients during the peak DCI risk period (days 5–9). They concluded that anaemia after aneurysm securing and during the delayed cerebral ischemia window was independently associated with poor neurological outcome.

Pulmonary complications in our study were noted in n= 08 patients, 14.81%. Pulmonary complications including NPE, pulmonary embolism, aspiration pneumonia, ALI, ARDS can occur from 3.6% to 27% of patients in aSAH and is associated with higher treatment intensity, longer ICU stay, and unfavourable overall outcomes (97).

Severe cardiac complications in our study were noted in n=07 patients, 12.96%. aSAH can have varied cardiac complications including benign/ malignant arrhythmias, ST-T changes, elevated troponins, regional/global ventricular wall motion abnormalities, myocardial stunning etc. Cardiac dysfunction, with reduction in EF or RWMA, can occur in 20 to 30% of patients with aSAH and is mainly driven by the brain heart interactions causing central sympathetic overdrive when certain specific areas of brain get injured (eg insular cortex, hypothalamus, brainstem) (98,99).

Hydrocephalus was noted in n=12 patients, 22.22% in our study. Lu J et al (100) , and Hasan D et al (101) in their studies found hydrocephalus to complicate 20%-30% patients in their study groups. It occurs both as communicating (impaired absorption of CSF at arachnoid granulations) and noncommunicating (mechanical obstruction from clot or compression) types.

Meningitis was noted in n=14 patients, 25.92% in our study population. This included both patients who had undergone EVD placement and others who developed it spontaneously (without ventriculostomy). One of the major risks associated with EVD insertion is infection. The EVD infection rates have a variable prevalence (and variable isolates) depending on local centre to centre antibiograms and hospital antibiotic policies. A meta-analysis from 2015 found the mean EVD infection prevalence to be 7.9% (98).

5.9 Limitations of our study-

- Ours was a single site study, the findings of which are not externally validated. It needs to be replicated in a similar study model with a multicentric trial protocol.

- We had a small sample size and hence our findings cannot be generalized to the entire patient population at large. Further studies with a larger cohort sample are needed to explore if our findings can be universally applied to all subsets of patient population with aSAH.

- The average mean time interval from bleed onset to presentation in our study was beyond the EBI period (72 hours) and hence our results generally only apply to patients who survived the first 72 hours of bleed.

- Since posterior circulation aSAH was excluded in this study, our results cannot be extrapolated to this subset of patients.

- DCI severity/ reversibility/ trends after treatment v/s no treatment were not analysed.

5.10 Strengths of our study-

- It's the first study evaluating arterial lactate through entire temporal course of aSAH.

- It's the first study to postulate and give cutoff values for arterial lactate drift ratios as a biomarker for DCI.

- It's a prospective study model which can be easily replicated

- Arterial Lactate drift ratios can be easily computed by nursing staff bedside and doesn't require any skilled expertise for serial evaluation. It's a minimally invasive test which is economical, readily available and has no lag phase with results being instantly available for interpretation. When analysed in parallel these drift ratios had a high sensitivity of 95% (and hence can be used as a part of an effective bedside screening protocol)

6. Summary & Conclusion

6. SUMMARY AND CONCLUSIONS

We hypothesised that arterial blood lactate levels have a positive correlation with onset and occurrence of DCI in patients presenting with aSAH and that it can be used as a predictive biomarker for bedside screening of this secondary complication. To test this, we formulated a prospective observational study model wherein the temporal course of serial lactate values and also the trends of serially derived lactate drift ratios (LDRb and LDRi) were investigated on a daily basis. In post-hoc analysis of our study cohort we divided the enrolled participants into two groups, Group A (ie patients who developed DCI as their disease evolved) and Group B (ie patients who did not develop DCI). In the results presented here, we compare and contrast these temporal trends in both the groups and propose upper maximum cutoff values for the lactate drift ratios (LDRb and LDRi, when used in parallel) which can be predictive of DCI.

Our defined time points were as follows-

- Tb- Baseline on admission, T0- Immediate post intervention (clipping/coiling) , T1- Postop Day0
- D1/2/3…till DV- Postop Day 1/2/3 till Day of Event ie Dv
- Day of Event (Dv) for Group A was the day of DCI,
- Day of Event (Dv) for Group B was the day of ICU Discharge
- Dd- Day of Hospital discharge.

Main findings of our study are summarized as below-

1) Absolute Lactate Values- We noted baseline lactate (Tb) to be elevated in n=14 patients, 25.92%. Of these 14 patients, 12 patients (85.71%) went on to develop DCI as their disease evolved and hence became a part of Gp A. Elevated

baseline lactate on presentation is hence a good prognostic marker in our study for predicting the occurrence of DCI.

On the line graph analysis an uptrend followed by a crest point was observed in both the groups from point Tb to T1. This was followed by a downtrend and a near plateau phase on subsequent post intervention days. However, a second crest point was noted on day of DCI in Gp A patients whereas the values plateaued off in patients who did not develop DCI (ie Gp B patients). Hence a significant rise in lactate resulting in a second crest point was noted on the day of DCI in Group A.

2) Drift ratios LDRb and LDRi-

2a) *LDRb-* The mean LDRb for Gp A on the day of event (Dv) was found to be 2.30±0.74 whereas the corresponding value for Gp B was 1.43±1.24. The difference in the mean LDRb values was statistically significant and remained significant throughout ie following the day of event (Dv) till the day of discharge (Dd). In the ROC analysis, at a cut-off point of 1.78, the AUC was 0.878 (95% CI: 0.778-0.978); with a sensitivity of 81.8% and a specificity of 85.5%.

2b) *LDRi*- The mean LDRi for Gp A on the day of event (Dv) was found to be 1.97±1.54 whereas the corresponding value for Gp B was 0.79±0.28. There was a statistical difference noted in LDRi mean values throughout across all the defined time points. In the ROC analysis, at a cut-off point of 1.01, the AUC was 0.858 (95% CI: 0.756-0.960); with a sensitivity of 72.7% and a specificity of 68.7% .

2c) Combined tests done in parallel (LDRb and LDRi)- for both the tests ie LDRb and LDRi done in parallel with a cutoff values 1.78 and 1.01 respectively, the combined sensitivity predictive of DCI was 95% and the combined specificity was 58.7%.

Other findings:

a) DCI Burden- In our study out of total enrolled patients n=54, 22 patients (40.74%) developed DCI and 32 patients (59.26%) did not develop DCI. We had a slightly higher incidence of DCI as compared with the data from past studies.

b) *Demographics*: In our study there was a female preponderance with n=34 patients (62.96%) being female and n= 20 patients (37.03%) being male. Female is to male ratio was 1.7:1.

c) *Associated Comorbidities and addictions*: The most common comorbidity in our study cohort was essential hypertension (n=32, 59.25%). Other common comorbidities noted were diabetes mellitus, hypothyroidism, CAD, COPD, asthma, hepatitis B infection, congenital heart disease and thrombocytosis. Tobacco abuse was noted in n=13 patients (24.07%) and alcohol abuse in n=10 patients (18.51%)

d) *Location of the aneurysm*: ICA (all segments included) was the most common vessel involvement noted in our study (n=20, 37.03%). The next most common vessel involved was ACOM. Other vessels involved were ACA and MCA.

e) *Mode of treatment and interval to definitive management*: In our study a total of n=25 patients (46.29%) underwent clipping and n=29 patients (53.70%) underwent coiling of the ruptured aneurysm. The average mean interval (in days) from ictus onset to definitive treatment for all patients combined was 5.02$\pm$2.05 days. Hence most patients in our study group presented in the intermediate time frame (ie from day 4 to day 7 of ictus).

f) *Medical & Surgical Complications, ICU days & Ventilator days*- The mean day of occurrence of DCI in Group A was 10$\pm$1.93. The most common medical complication for both the groups combined was seizures (n=22, 40.74%). Other common medical complication noted were anaemia, UTI, VAP/ARDS, SCM/ HSA, DVT & AKI. Patients in Gp A had a significantly higher average mean of

ICU and ventilator days (expressed as a % of total hospitalisation days) as compared to average means of Gp B. The most common combined surgical complication noted in our study was meningitis seen in n=14 patients (25.92%). Other surgical complications noted were HCP, Periop rupture, EDH.

Hence in our study, the overall incidence of medical complications, ICU days and Ventilator days and surgical complications were significantly higher in Gp A (DCI group) as compared to Gp B (Non DCI group)

g) Outcomes at discharge- A total of 28 patients (51.85%) had a favourable outcome at discharge (mRS Score 0-3) and 26 patients (48.15%) had an unfavourable outcome at discharge (mRS Score 4-6).

Conclusions

- Arterial lactate drift ratios measured as drifts from baseline (LDRb) and as drifts from post intervention values (LDRi) can be used together as an effective bedside screening tool for DCI in patients with anterior circulation aSAH who survive the initial bleed.

- Elevated baseline lactate on presentation is a good prognostic marker for predicting the occurrence of DCI.

- The mean LDRb for Gp A on the day of event (Dv) was found to be 2.30 ± 0.74.

- The mean LDRi for Gp A on the day of event (Dv) was found to be 1.97 ± 1.54.

- The tests when done in parallel have a combined sensitivity of 95% and a combined specificity of 58.7% at an upper cutoff value of LDRb= 1.78 and LDRi= 1.01

- Further studies are required for external validation of our findings by replicating a similar study model with a multicentric trial protocol.

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Annexures

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY,

THIRUVANANTHAPURAM, KERALA – 695011

Division of Neuroanaesthesia and Neurocritical Care, Department of Anaesthesiology

Title - 'Arterial Lactate Drift Ratio In patients with aneurysmal subarachnoid haemorrhage- a predictive biomarker of Delayed cerebral ischemia (ALDRID Study): a prospective observational study'.

Patient Demographic details

a) Age b) Sex c) Occupation d) Residence e) DOA f) Date of Ictus g) Handedness h) Site of Aneurysm

Comorbidities and Addictions DM ( ) HTN ( ) IHD ( ) CAD ( ) Dyslipidemia ( ) COPD ( ) Others ( ) Addictions ( )

Baseline Neurological Deficits

GCS Score- WFNS Score- Modified Hunt & Hess Grade

Modified Fischer Scale-

Observation S.No	Time from Ictus	Vital Parameters						Arterial Blood Gas							Glasgow Outcome Score	mRS at ICU Discharge	Special Comments/Adverse Event
		BP Systolic	BP Diastolic	BP Mean	HR	SPO2	Temperature	pH	Lactate	pO2	pCO2	Bicarbonate	Base Excess	Blood Sugar			

Time of Acute Event (in hours from ictus)

Neuroimaging Confirmation Findings

Acute Neurological Deficits

Adverse Outcomes

mRS at ICU Discharge

Total Ventilator Days

Total ICU Days

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, THIRUVANANTHAPURAM, KERALA – 695011

Department of Neuroanaesthesia and Neurocritical Care

INFORMED CONSENT FORM

Title of the Study: "A Prospective observational study to evaluate serial Arterial lactate as a marker and predictor of delayed cerebral ischemia and poor outcome in patients with aneurysmal SAH"

Name of Investigators: Dr Arvin Ahuja (PI), Dr Ajay Prasad Hrishi P. (Guide and CO-PI), Dr Unnikrishnan P (Co-guide and CO-PI), Dr Manikandan S (Co-guide and CO-PI)

Please tick the following points:

(i) I agree to participate as a participant in the study described in the Patient Information Sheet attached to this form.	[ ]
(ii) I acknowledge that I have read the Patient Information Sheet , which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the information sheet has been explained to me to my satisfaction.	[ ]
(iii) Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation, and I have received satisfactory answers.	[ ]
(iv) I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
(v) I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.	[ ]
(vi) I understand that if I have any questions relating to my participation in this research, I may contact my doctor, who will be happy to answer them.	[ ]
(vii) I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet attached to this form	[ ]

Name of Participant

Signature of Participant Date Time

Name of Caretaker or Next of Kin
(If patient not directly consented)

Relationship with the patient

Signature of Caretaker or Next of Kin Date Time

Name of Witness

Signature of Witness Date Time

Name of Person conducting Informed Consent discussion

Signature of Person conducting Informed Consent discussion Date Time

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി, തിരുവനന്തപുരം

ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോ അനസ്തീഷ്യ ആന്റ് ന്യൂറോക്രിട്ടിക്കൽ കെയർ

കാര്യബോധത്തോടെയുള്ള സമ്മതപത്രം

പഠനശീർഷകം: "തലച്ചോറിലെ അന്യൂറിസവുമായി ബന്ധപ്പെട്ടുണ്ടാകുന്ന സബ്അരക്നോയിഡ് ഹെമറേജ് ഉള്ള രോഗികളിൽ, രക്തത്തിലെ ലാക്റ്റേറ്റിന്റെ തുടർ നിരീക്ഷണം, മോശം രോഗാവസ്ഥയിലേക്കോ ഡിലെയ്ഡ് സെറിബ്രൽ ഇസ്ക്കീമിയ എന്ന പ്രത്യാഘാതത്തിലേയ്ക്കോ ഉള്ള രോഗപരിണാമത്തിന്റെ സൂചികയായി ഉപയോഗിക്കാമോ എന്ന് വിലയിരുത്തുന്ന നിരീക്ഷണാത്മകമായ പഠനം"

ഗവേഷകരുടെ പേര്: ഡോ. അർവിൻ അഹൂജ (പ്രധാന ഗവേഷകൻ),
ഡോ. അജയ് പ്രസാദ് ഉഷ്കി.പി (ഗൈഡും സഹഗവേഷകനും),
ഡോ. ഉണ്ണികൃഷ്ണൻ പി (സഹഗൈഡും സഹ ഗവേഷകനും),
ഡോ. മണികണ്ഠൻ എസ് (സഹ ഗൈഡും സഹ ഗവേഷകനും)

(കോളങ്ങൾ അടയാളപ്പെടുത്തുക).

ഈ പത്രികയോടൊപ്പമുള്ള, പങ്കെടുക്കുന്നവർക്കുള്ള കാര്യവിവരണപത്രത്തിൽ വിശദീകരിക്കുന്ന പഠനത്തിൽ പങ്കെടുക്കാൻ ഞാൻ സമ്മതിക്കുന്നു.	[ ]
എന്നെ എന്തുകൊണ്ട് തിരഞ്ഞെടുത്തു, പഠനത്തിന്റെ ഉദ്ദേശം, സ്വഭാവം, പരിശോധനയിൽ ഉണ്ടാവാനിടയുള്ള അപായങ്ങൾ എന്നിവ വിവരിക്കുന്ന പങ്കെടുക്കുന്നവർക്കുള്ള കാര്യവിവരണപത്രം വായിച്ചതായും എന്റെ തൃപ്തിയ്ക്കനുസരിച്ച് വിശദീകരിച്ചുതന്നതായും ഞാൻ സമ്മതിക്കുന്നു.	[ ]
സമ്മതപത്രത്തിൽ ഒപ്പു വയ്ക്കുന്നതിനുമുമ്പ്, ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് ശാരീരികവും മാനസികവുമായ എന്തെങ്കിലും ഹാനി എനിക്ക് ഉണ്ടാകാൻ സാദ്ധ്യതയുണ്ടോ എന്നതുമായി ബന്ധപ്പെട്ട ചോദ്യങ്ങൾ ചോദിക്കാൻ എനിക്ക് അവസരം ഉണ്ടാവുകയും തൃപ്തികരമായ മറുപടി ലഭിക്കുകയും ചെയ്തു	[ ]
എന്റെ പങ്കാളിത്തം സ്വമേധയായാണെന്നും, കാരണമൊന്നും നൽകാതെയും എന്റെ വൈദ്യപരിചരണത്തെ ബാധിക്കാതെയും ഏതു സമയത്തും എനിക്ക് പിൻമാറാൻ സ്വാതന്ത്ര്യമുണ്ടെന്നും മനസ്സിലാക്കുന്നു.	[ ]
പഠനഫലമായി ശേഖരിച്ച വിവരങ്ങൾ പ്രസിദ്ധീകരിക്കുമ്പോൾ എന്നെ തിരിച്ചറിയാനിടയാകുന്നതൊന്നും വെളിപ്പെടുത്തുകയില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു.	[ ]
ഗവേഷണത്തിൽ പങ്കെടുക്കുന്നതുമായി ബന്ധപ്പെട്ട് എനിക്ക് ചോദ്യങ്ങളുണ്ടെങ്കിൽ എനിക്ക് ഡോക്ടറെ ബന്ധപ്പെടാമെന്നും ഉത്തരം തരുന്നതിൽ അദ്ദേഹത്തിന് സന്തോഷമേയുള്ളൂവെന്നും ഞാൻ മനസ്സിലാക്കുന്നു.	[ ]
ഈ പത്രികയോടൊപ്പം നൽകിയിട്ടുള്ള പങ്കാളികൾക്കുള്ള വിവരണപത്രവും സമ്മതപത്രവും കിട്ടിയതായി ഞാൻ അറിയിക്കുന്നു.	[ ]

പങ്കെടുക്കുന്നയാളുടെ പേര്

പങ്കെടുക്കുന്നയാളുടെ ഒപ്പ് തീയതി സമയം

പരിചയപ്പെടുത്തുന്നയാളുടെ അല്ലെങ്കിൽ അടുത്തബന്ധുവിന്റെ പേര്

(ബാധകമെങ്കിൽ മാത്രം പൂരിപ്പിക്കുക)

ഗവേഷണവുമായുള്ള ബന്ധം

പരിചയപ്പെടുത്തുന്നയാളുടെ അല്ലെങ്കിൽ അടുത്തബന്ധുവിന്റെ ഒപ്പ് തീയതി സമയം

സാക്ഷിയുടെ പേര്

സാക്ഷിയുടെ ഒപ്പ് തീയതി സമയം

സമ്മതപത്രത്തെപ്പറ്റി ചർച്ച ചെയ്തയാളുടെ പേര്

സമ്മതപത്രത്തെപ്പറ്റി ചർച്ച ചെയ്തയാളുടെ ഒപ്പ് തീയതി സമയം

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY,

THIRUVANANTHAPURAM, KERALA – 695011

Division of Neuroanaesthesia and Neurocritical Care, Department of Anaesthesiology

PATIENT INFORMATION SHEET

Title of the Study: 'Arterial Lactate Drift Ratio In patients with aneurysmal subarachnoid haemorrhage- a predictive biomarker of Delayed cerebral ischemia (ALDRID Study): a prospective observational study'.

Name of Investigators: Dr Arvin Ahuja (PI), Dr Ajay Prasad Hrishi P. (Guide and CO-PI), Dr Unnikrishnan P (Co-guide and CO-PI)

Ma'am/Sir,

We invite you to take part in our research study titled 'Arterial Lactate Drift Ratio In patients with aneurysmal subarachnoid haemorrhage- a predictive biomarker of Delayed cerebral ischemia (ALDRID Study): a prospective observational study'. Before you agree to participate in this study, it is important that you read and understand this information sheet which will provide you all the requisite information to clear your doubts and make a well-informed decision about your participation in this study. In addition, should you have any further questions, please feel free to ask us the same. Investigator and his team members will be happy to answer them and explain to you in more detail.

- **What is the Purpose of conducting this study and what are investigators studying?**

Towards partial fulfilment of criterion for the award of degree of DM Neuroanaesthesia, I Dr Arvin Ahuja have to carry out a research study. The research study is concerned with the evaluation of arterial lactate levels (a blood test) as a marker and predictor of DCI (DCI is a neurological complication of your disease state i.e., aSAH)

- **If you take part, what will you have to do?**

In this research study we will first record your demographic information and do a baseline neurological examination. Subsequently through an arterial blood collection your serial blood lactate levels and their trends will be analysed till the time of your discharge from the hospital. Analysis of arterial blood is a part of the routine management of patients with blood clots in the subarachnoid space around the brain due to the rupture of aneurysms (a bleb in the vessel wall). Insertion of an arterial cannula is an invasive test but it will be done, under local anaesthesia and subsequent arterial blood collections will happen through the same cannula thus avoiding repeated punctures. At every blood draw, your vital parameters (B.P., MAP, HR, SPO2, RR, Temperature) and blood sugar values will be recorded along with your neurological assessment score i.e., WFNS score. Any acute event, DCI / vasospasm as determined by clinical exam/imaging modalities will be noted for the time of occurrence with simultaneous blood lactate sample draw and vitals recording. Your physical functionality as measured on a modified Rankin scale also will be noted at the time of discharge. IEC/Ver3/09 23

- **What about confidentiality?**

All your relevant medical complaints, signs and symptoms and past medical history will be analysed, and relevant data will be collected. I will ensure that no clues to your identity appear in study at any point of time. Any extracts from what

you say that are quoted in the study will be entirely anonymous. Confidentiality of your participation and your records will be strictly adhered to. Records will be maintained anonymously under a subject identification number and data will be kept confidential for the entire duration of study.

- **Why is your participation solicited?**

Your participation is requested because you are suitable to provide data for this research study. The results of this study may benefit medical fraternity in evolving a better understanding of the concerned research topic and will supplement the current evidence based medical practices. The results will be presented in the thesis. They will be seen by my supervisor, a second marker and the external examiner. The thesis may be read by future students on the course. The study may be published in a research journal.

- **Can you withdraw from the study after it starts?**

I don't envisage any negative consequences for you in taking part in this study. Your participation is entirely voluntary and you have the freedom to withdraw your participation from study at any time. You won't be subjected to any additional tests and further you won't be bearing any additional costs due to your participation (as blood lactate levels are already reported in the Arterial Blood Gas analysis, a test routinely carried out for your disease state

- **What about the necessary regulatory approvals?**

Approval to conduct this research study has been sought by the Department of Neuro-Anesthesiology, SCTIMST, and Institutional Ethics Committee and Technical Advisory Committee. The study will commence only after the same has been obtained.

- **Whom to contact incase of further queries?**

If you need any further information, you can contact me.

My name is Dr. Arvin Ahuja, Mob no.7020693549,

E-mail:drarvinahuja@sctimst.ac.in.

In-case of any grievances/suggestions, you can contact Institutional Ethics Committee as below: Dr. Srinivas G Member Secretary, Institutional Ethics Committee, Sree Chitra Tirunal Institute for Medical Sciences and Technology Tel: 0471- 2524689, Email: iec.mem.sec@sctimst.ac.in Kindly sign the consent form overleaf, if you agree to take part in the study.

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ്

ആന്റ് ടെക്നോളജി, തിരുവനന്തപുരം

ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോഅനസ്തീഷ്യ, ആന്റ് ന്യൂറോക്രിട്ടിക്കൽ കെയർ

ഗവേഷണത്തിൽ പങ്കെടുക്കുന്ന രോഗികൾക്കുള്ള കാര്യവിവരണപത്രവും
കാര്യബോധത്തോടെയുള്ള സമ്മതപത്രവും

പഠനശീർഷകം: "തലച്ചോറിലെ അന്യൂറിസവുമായി ബന്ധപ്പെട്ടുണ്ടാകുന്ന സബ്അരാക്നോയിഡ് ഹെമറേജ് ഉള്ള രോഗികളിൽ, രക്തത്തിലെ ലാക്റ്റേറ്റിന്റെ തുടർ നിരീക്ഷണം, മോശം രോഗാവസ്ഥയിലേക്കോ ഡിലേയ്ഡ് സെറിബ്രൽ ഇസ്ക്കീമിയ എന്ന പ്രത്യാഘാതത്തിലേയ്ക്കോ ഉള്ള രോഗപരിണാമത്തിന്റെ സൂചികയായി ഉപയോഗിക്കാമോ എന്ന് വിലയിരുത്തുന്ന നിരീക്ഷണാത്മകമായ പഠനം"

ഗവേഷകരുടെ പേര്:

ഡോ. അർവിൻ അഹൂജ (പ്രധാന ഗവേഷകൻ), ഡോ. അജയ് പ്രസാദ് ഋഷി. പി (ഗൈഡും സഹഗവേഷകനും), ഡോ. ഉണ്ണികൃഷ്ണൻ പി (സഹഗൈഡും സഹഗവേഷകനും), ഡോ. മണികണ്ഠൻ എസ് (സഹഗൈഡും സഹഗവേഷകനും)

ശ്രീ/ശ്രീമതി,

"തലച്ചോറിലെ അന്യൂറിസവുമായി ബന്ധപ്പെട്ടുണ്ടാകുന്ന സബ്അരാക്നോയിഡ് ഹെമറേജ് ഉള്ള രോഗികളിൽ, രക്തത്തിലെ ലാക്റ്റേറ്റിന്റെ തുടർ നിരീക്ഷണം, മോശം രോഗാവസ്ഥയിലേക്കോ ഡിലേയ്ഡ് സെറിബ്രൽ ഇസ്ക്കീമിയ എന്ന പ്രത്യാഘാതത്തിലേയ്ക്കോ ഉള്ള രോഗപരിണാമത്തിന്റെ സൂചികയായി ഉപയോഗിക്കാമോ എന്ന് വിലയിരുത്തുന്ന നിരീക്ഷണാത്മകമായ പഠനം" എന്ന ഗവേഷണപഠനത്തിൽ പങ്കെടുക്കുവാൻ താങ്കളെ ഞങ്ങൾ ക്ഷണിക്കുന്നു.

ഈ പഠനത്തിൽ പങ്കെടുക്കുവാൻ താങ്കൾ സമ്മതിക്കുന്നതിനു മുമ്പ് ഈ പഠന സംബന്ധമായി അറിയേണ്ടുന്ന പ്രസക്തമായ എല്ലാ വിവരങ്ങളും നൽകുന്ന ഈ കാര്യവിവരണപത്രം വായിക്കുകയും മനസ്സിലാക്കുകയും ചെയ്യേണ്ടത് കാര്യബോധത്തോടെ സമ്മതം നൽകാൻ
തീരുമാനമെടുക്കുന്നതിൽ പ്രധാനമാണ്.

അതിനൊപ്പം താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ അവ വിശദീകരിച്ചു തരുവാൻ ഗവേഷകനും സംഘാംഗങ്ങളും സന്തോഷത്തോടെ തയാറാകുകയും, ഗവേഷണ പഠനം, ഉൾപ്പെട്ട നടപടികൾ ബന്ധപ്പെട്ട വിഷയങ്ങൾ എന്നിവയെപ്പറ്റി കൂടുതൽ വിശദീകരണം നൽകുകയുംചെയ്യും.

ഈ പഠനത്തിന്റെ ഉദ്ദേശമെന്ത്, ഗവേഷകർ എന്തിനെപ്പറ്റിയാണ് പഠനം നടത്തുന്നത്?

ഡിഎം ന്യൂറോഅനസ്തീഷ്യ ഡിഗ്രി പൂർത്തികരിക്കുന്നതിന് അവശ്യമായ പഠനത്തിന്റെ ഭാഗമായി ഞാൻ, ഡോ. അർവിൻ അഹൂജ ഒരു ഗവേഷണപഠനം നടത്തണ്ടതുണ്ട്. തലച്ചോറിലെ രക്തക്കുഴലുകളുടെ ഭിത്തിയുടെ ഏതെങ്കിലും ഒരു ഭാഗം നേർത്ത് ബലഹീനമാകുന്ന അവസ്ഥയാണ് അന്യൂറിസം. ഇവ പൊട്ടുമ്പോൾ തലച്ചോറിൽ ഉണ്ടാകുന്ന ഒരു തരം രക്തപ്രവാഹത്തെയാണ് സബ് അരാക്നോയിഡ് ഹെമറേജ് (എസ്.എ.എച്ച്) എന്നു പറയുന്നത്. ഇതെ തുടർന്ന് ഉണ്ടാകുന്ന പ്രധാനപ്പെട്ട ഒരു പ്രത്യാഘാതമാണ് ഡിലേയ്ഡ് സെറിബ്രൽ

ഇസ്കീമിയ അഥവാ ഡിസിഐ. ഈ കാലഘട്ടത്തിൽ തലച്ചോറിലെ കോശങ്ങൾ രക്തചംക്രമണം അല്ലെങ്കിൽ ഓക്സിജൻ ഇല്ലാതെ മൃതമാകുന്നു. ഇതടക്കമുള്ള നിരവധി കാര്യങ്ങൾ ഇത്തരം രോഗികളിൽ ഒരു നിശ്ചിത ശതമാനത്തെ ഒരു മോശം രോഗപരിണിത അവസ്ഥയിലേക്ക് നയിച്ചേക്കാം. രക്തത്തിലെ ലാക്റ്റേറ്റിന്റെ അളവ് കണക്കാക്കുക എന്നത്, ഇത്തരം രോഗികളിൽ സാധാരണ ചെയ്യാറുള്ള 'ആർട്ടീരിയൽ ബ്ലഡ്ഗ്യാസ് അനാലിസിസ്' എന്ന പരിശോധനയ്ക്കൊപ്പം ലഭ്യമാകുന്ന വിവരമാണ്. കൈയിലെയോ കാലിലെയോ ഏതെങ്കിലും രക്തധമനിയിൽ ചെറിയ ഒരു പ്ലാസ്റ്റിക് ക്യാനുല (സൂചി) കടത്തി രക്തം എടുത്താണ് ഇത് സാധ്യമാക്കുന്നത്. തുടർച്ചയായി ഈ പരിശോധന നടത്തിയാൽ ലാക്റ്റേറ്റിന്റെ അളവിലുണ്ടാകുന്ന വ്യതിയാനം, മേൽപറഞ്ഞ ഡിസിഐ എന്ന് പ്രത്യാഘാതത്തിലേക്കോ ഒരു മോശം രോഗപരിണിത അവസ്ഥയിലേക്കോ ഉള്ള രോഗപരിണാമത്തിന്റെ സൂചികയായി ഉപയോഗിക്കാൻ കഴിയുമോ എന്നറിയാനാണ് ഈ പഠനം നടത്തുന്നത്.

പങ്കെടുക്കുകയാണെങ്കിൽ താങ്കൾ എന്തു ചെയ്യണം?

ഈ പഠനത്തിൽ പങ്കെടുക്കുകയാണെങ്കിൽ, ആദ്യം താങ്കളുടെ വ്യക്തിവിവരങ്ങളും നാഡീവ്യൂഹവുമായി ബന്ധപ്പെട്ട ഒരു പ്രഥമിക പരിശോധന നടത്തി അതിൽനിന്നും ലഭ്യമായ വിവരങ്ങളും രേഖപ്പെടുത്തും. മേൽപ്പറഞ്ഞതുപോലെ, ഈ അസുഖമുള്ള രോഗികളിൽ ഓപ്പറേഷൻ തീയേറ്ററിലും ഐസിയുവിലും തുടർ നിരീക്ഷണത്തിനുപയോഗിക്കുന്ന ഒരു രക്തപരിശോധനയാണ് 'ആർട്ടീരിയൽ ബ്ലഡ്ഗ്യാസ് അനാലിസിസ്' അഥവാ (എബിജി). കൈയിലെയോ കാലിലെയോ അതാതു ഭാഗത്തെ രക്തധമനിയിലേക്ക് മുകളിലുള്ള തൊലി വേദന നിവാരണത്തിനുവേണ്ടി മരവിപ്പിച്ചശേഷം, ധമനിയിൽ നിന്നും രക്തം ശേഖരിക്കുകയും ഇത് പരിശോധനക്ക് വിധേയമാക്കുകയും ചെയ്യും. ഇതിനുപയോഗിക്കുന്ന ക്യാനുല അതാതു ശരീരഭാഗത്തു തന്നെ (കൈയിലോ കാലിലോ) പ്ലാസ്റ്റർ ഉപയോഗിച്ച് ഘടിപ്പിക്കുന്നതിനാൽ തുടർന്നുള്ള രക്തശേഖരണം ഇതിലൂടെ നടത്താനാവും. എ.ബിജി പരിശോധനയിൽ ലഭ്യമാകുന്ന ലാക്റ്റേറ്റിന്റെ അളവ് ഉൾപ്പെടെയുള്ള വിവരങ്ങളിൽ ഈ പഠനത്തിന് ആവശ്യമായവ രേഖപ്പെടുത്തും. നിശ്ചിത ഇടവേളകളിൽ ഇതേ ക്യാനുലയിൽക്കൂടി ഈ പരിശോധന നടത്തുന്നതിനൊപ്പം രോഗാവസ്ഥയിൽ വന്നിട്ടുള്ള മാറ്റം നിരീക്ഷിക്കുന്ന സൂചികകളുമായി ബന്ധപ്പെട്ട വിവരങ്ങളും പരിശോധനകൾക്കുശേഷം രേഖപ്പെടുത്തുന്നതായിരിക്കും.

രഹസ്യ സ്വഭാവം ഉണ്ടാകുമോ?

താങ്കളുടെ രോഗസംബന്ധമായ പ്രസക്തമായ പ്രശ്നങ്ങൾ, സൂചകങ്ങളും രോഗലക്ഷണങ്ങളും കഴിഞ്ഞ കാലത്തെ രോഗ ചരിത്രവും വിശകലനം ചെയ്യുകയും പ്രസക്തമായ വിവരങ്ങൾ ശേഖരിക്കുകയും ചെയ്യും. പഠനത്തിന്റെ ഒരു ഘട്ടത്തിലും താങ്കളെ തിരിച്ചറിയാനുതകുന്നതൊന്നും പ്രകടമാവില്ലെന്ന് ഞാൻ ഉറപ്പുവരുത്തും. താങ്കൾ പറയുന്നവയിൽ നിന്നും ഉദ്ധരിക്കുന്നവയെല്ലാം അജ്ഞാതനാമാവായിരിക്കും. താങ്കളുടെ പങ്കാളിത്തത്തവും രേഖകളും തികച്ചും രഹസ്യമായിരിക്കും. രേഖകൾ പങ്കെടുക്കുന്നയാളുടെ ഒരു തിരിച്ചറിയൽ നമ്പറിലുടെയായിരിക്കും ശേഖരിക്കുക, വിവരങ്ങൾ പഠനകാലം മുഴുവൻ രഹസ്യമായി സൂക്ഷിക്കും.

താങ്കളോട് പങ്കെടുക്കാൻ എന്തുകൊണ്ട് അഭ്യർത്ഥിക്കുന്നു?

ഈ ഗവേഷണപഠനത്തിന് വിവരങ്ങൾ നൽകാൻ താങ്കൾ യോഗ്യമാണെന്നതിനാലാണ് താങ്കളോട് പങ്കെടുക്കാനഭ്യർത്ഥിക്കുന്നത്. ഗവേഷണ വിഷയത്തിൽ മെച്ചപ്പെട്ട ധാരണകളുണ്ടാകാനും സമകാലീന തെളിവുകളുടെ അടിസ്ഥാനത്തിലുള്ള വൈദ്യചികിത്സയ്ക്ക് അനുപൂരകമാകാനും പഠനഫലങ്ങൾ വൈദ്യശാസ്ത്ര സമൂഹത്തന് സഹായകമായേക്കാം. പഠനഫലങ്ങൾ ഗവേഷണപ്രബന്ധത്തിൽ അവതരിപ്പിക്കും. അവ എന്റെ മേലധികാരിയും മറ്റൊരാളും പുറമേനിന്നുള്ള പരീക്ഷകനും കാണും. ഭാവിയിൽ ഈ വിഷയം പഠിക്കുന്ന വിദ്യാർത്ഥികൾ ഈ ഗവേഷണ പഠനം വായിച്ചേക്കാം. പഠനം ഒരു വൈദ്യശാസ്ത്ര ജേർണലിൽ പ്രസിദ്ധീകരിച്ചേക്കാം.

പഠനമാരംഭിച്ചശേഷം താങ്കൾക്ക് പിൻമാറാനാകുമോ?

ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് താങ്കൾക്ക് ദോഷകരമായി എന്തെങ്കിലുമുണ്ടാകുമെന്ന് ഞാൻ പ്രതീക്ഷിക്കുന്നില്ല. താങ്കളുടെ പഠനത്തിലുള്ള പങ്കാളിത്തം പൂർണമായും സ്വമേധയാ ഉള്ളതും പഠനത്തിൽ നിന്ന് പിൻമാറാൻ സ്വാതന്ത്ര്യം ഉള്ളതും ആണ്. താങ്കൾ പങ്കെടുക്കുന്നതുകൊണ്ട് കൂടുതൽ പരിശോധനകൾക്ക് വിധേയമാകേണ്ടിവരികയോ അധികം ചിലവ് ഉണ്ടാകുകയോ ഇല്ല (താങ്കളുടെ ഗർഭാവസ്ഥയിൽ പതിവായി ചെയ്യുന്ന, രക്തത്തിലെ ലാക്ടേറ്റ് നിലവാരം അളക്കുന്നതിനായി രക്ത വാതകത്തിന്റെ വിലയിരുത്തലായി മാത്രപ്പെടുത്തപ്പെടുന്നവയാണ് എന്നതിനാൽ).

ഗവേഷണത്തിനുള്ള അനുവാദം നിയന്ത്രണ അധികാരികളിൽ നിന്നും ലഭിക്കുന്നത് സംബന്ധിച്ചെന്ത്?
സ്ഥാപനത്തിലെ എത്തിക്സ് കമ്മിറ്റിയുടെയും ടെക്നിക്കൽ അഡ്വൈസറി കമ്മിറ്റിയുടെയും ഗവേഷണ പഠനം നടത്തുന്നതിനായുള്ള അനുവാദത്തിനായി നൂറോജനസ്തീഷ്യോളജി ഡിപ്പാർട്ട്മെന്റ് സമീപിച്ചിട്ടുണ്ട്. അവ ലഭിച്ചശേഷമേ പഠനം ആരംഭിക്കുകയുള്ളൂ.

കൂടുതൽ അന്വേഷണങ്ങൾക്ക് ആരെ സമീപിക്കണം

താങ്കൾക്ക് കൂടുതൽ വിവരങ്ങൾ ആവശ്യമെങ്കിൽ എന്നെ ബന്ധപ്പെടാം. എന്റെ പേര് ഡോ. അർവിൻ അഹൂജ, മൊബൈൽ നമ്പർ: 7020693549, ഇമെയിൽ: drarvinahuja@sctimst.ac.in

എന്തെങ്കിലും പരാതികളോ നിർദ്ദേശങ്ങളോ ഉണ്ടെങ്കിൽ താങ്കൾക്ക് സ്ഥാപന ത്തിലെ എത്തിക്സ് കമ്മിറ്റിയെ താഴെപ്പറയുന്നപ്രകാരം ബന്ധപ്പെടാം.

ഡോ. ശ്രീനിവാസ് ജി, മെമ്പർ സെക്രട്ടറി, സ്ഥാപനത്തിലെ എത്തിക്സ് കമ്മിറ്റി,

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി,
തിരുവനന്തപുരം,

ഫോൺ: 04712524669, ഇമെയിൽ:iec.mem.sec.@sctimst.ac.in

ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ താങ്കൾക്ക് സമ്മതമെങ്കിൽ ഇതിനോടൊപ്പമുള്ള സമ്മതപത്രം ഒപ്പിടുക.

Institutional Ethics Committee (IEC) approval letter

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1801/JANUARY/2022 22.04.2022

Dr. Arvin Ahuja
Senior Resident
Department of Anaesthesiology
SCTIMST, Thiruvananthapuram

Dear Dr. Arvin Ahuja,

The Institutional Ethics Committee held on 29th January, 2022, reviewed and discussed your application to conduct the study titled "**A PROSPECTIVE OBSERVATIONAL STUDY TO EVALUATE SERIAL ARTERIAL LACTATE AS A MARKER AND PREDICTOR OF DELAYED CEREBRAL ISCHEMIA AND POOR OUTCOME IN PATIENTS WITH ANEURYSMAL SAH**" (IEC/1801)

The following members of the Ethics Sub-committee were present at the meeting held on 29th January, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Adv. N Anand	BAL, L LB	Male	Legal Expert	No
3.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
4.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
5.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
6.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 18.11.2021*
2. *IEC Application Form*
3. *Study Proposal*
4. *Declaration form*
5. *Patient Information Sheet in English and Malayalam*
6. *Informed Consent Form in English and Malayalam*
7. *CV of PI and Co-PIs*
8. *Proforma*
9. *Checklist Form*
10. *SRC Recommendation*

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 22.04.2022*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 18.11.2021*
3.
4. *IEC Application Form*
5. *Study Proposal*
6. *Declaration form*
7. *Patient Information Sheet in English and Malayalam*
8. *Informed Consent Form in English and Malayalam*
9. *CV of PI and Co-PIs*
10. *Proforma*
11. *Checklist Form*
12. *SRC Recommendation*

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC) SCTIMST THIRUVANANTHAPURAM

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

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Group	Age	Sex	Location	Comorb	Addiction
A	54	1	1	0	1,2
A	59	2	4	1,3	0
A	56	2	2	1,3	0
A	53	2	4	1,2,3	0
A	45	2	3	0	0
A	36	2	2	6,7	0
A	58	2	4	1	0
A	38	2	1	1	0
A	29	1	3	0	1,2
A	69	2	1	1,2	0
A	55	1	1	1	1
A	54	1	1	0	1,2
A	59	2	4	1,3	0
A	56	2	2	1,3	0
A	53	2	4	1,2,3	0
A	45	2	3	0	0
A	36	2	2	6,7	0
A	58	2	4	1	0
A	38	2	1	1	0
A	29	1	3	0	1,2
A	69	2	1	1,2	0
A	55	1	1	1	1
B	62	2	2	1	0
B	41	1	1	0	0
B	49	1	2	0	0
B	52	1	3	0	1
B	60	2	4	1	0
B	43	1	4	1,2	2
B	53	2	1	1,9	0
B	42	1	4	5	2
B	65	2	1	1,3	0
B	42	1	3	8	1
B	49	1	2	0	1,2
B	72	2	1	1,2,4	0
B	52	2	4	1	0
B	75	2	1	1	0
B	51	2	1	1	0
B	40	2	3	0	0
B	62	2	2	1	0
B	41	1	1	0	1
B	49	1	2	0	0
B	52	1	3	0	1
B	60	2	4	1	0
B	43	1	4	1,2	2
B	53	2	1	1,9	0
B	42	1	4	5	2
B	65	2	1	1,3	0
B	42	1	3	8	1
B	49	1	2	0	1,2
B	72	2	1	1,2,4	0
B	52	2	4	1	0
B	75	2	1	1	0
B	51	2	1	1	0
B	40	2	3	0	0

GCS	WFNS	MHH	MFG	Treatment	Interval days
13	4	4	3	1	4
12	4	4	3	2	2
12	4	4	2	1	3
12	3	4	4	2	4
14	3	2	2	2	6
3	5	5	4	1	3
12	5	5	4	1	3
9	4	4	4	2	2
14	2	3	2	1	6
11	4	4	3	2	4
8	4	4	3	1	2
13	4	4	3	1	4
12	4	4	3	2	2
12	4	4	2	1	3
12	3	4	4	2	4
14	3	2	2	2	6
3	5	5	4	1	3
12	5	5	4	1	3
9	4	4	4	2	2
14	2	3	2	1	6
11	4	4	3	2	4
8	4	4	3	1	2
15	1	2	1	2	6
15	3	3	2	1	5
15	3	4	3	2	8
13	3	4	4	1	4
15	2	2	3	2	7
15	2	3	2	1	8
15	2	2	2	2	9
14	2	2	2	2	6
14	2	2	2	1	7
15	2	2	2	2	9
15	3	4	3	1	6
9	4	4	3	2	2
15	1	2	1	2	8
13	2	2	2	1	6
15	1	2	1	2	3
14	2	2	2	2	7
15	1	2	1	2	6
15	3	3	2	1	5
15	3	4	3	2	8
13	3	4	4	1	4
15	2	2	3	2	7
15	2	3	2	1	8
15	2	2	2	2	9
14	2	2	2	2	6
14	2	2	2	1	7
15	2	2	2	2	9
15	3	4	3	1	6
9	4	4	3	2	2
15	1	2	1	2	8
13	2	2	2	1	6
15	1	2	1	1	3
14	2	2	2	2	7

Day of Occur	Seizure	SCM/HAS	VAP/ARDS	Anemia	UTI	AKI
10	0	0	0	0	1	0
8	0	0	1	0	0	0
9	0	0	0	0	0	0
12	1	0	0	1	0	0
14	0	0	1	1	0	0
9	1	0	1	0	0	0
8	1	0	0	1	1	0
8	1	1	0	1	0	0
13	0	0	0	0	0	0
12	0	0	0	0	1	1
9	1	1	0	1	0	1
12	0	0	0	0	1	0
8	0	0	1	0	0	0
9	0	0	0	0	0	0
9	1	0	0	1	0	0
11	0	0	1	1	0	0
8	1	1	1	0	0	0
10	1	0	0	1	1	0
9	1	1	0	1	0	0
13	0	0	0	0	0	0
11	0	0	0	0	1	0
8	1	1	0	1	0	1
	0	0	0	0	0	0
	0	1	0	0	0	0
	1	0	0	0	0	0
	1	0	0	1	0	0
	0	0	0	0	1	0
	0	0	0	0	0	0
	1	0	0	0	0	0
	0	0	0	1	0	0
	1	0	0	1	0	0
	0	0	0	0	0	0
	0	0	0	0	0	0
	1	0	1	1	0	0
	0	0	0	0	0	0
	0	0	0	0	0	0
	0	0	0	0	0	0
	1	0	0	0	0	0
	0	0	0	0	0	0
	0	1	0	0	0	0
	1	0	0	0	0	0
	1	0	0	1	0	0
	0	0	0	0	1	0
	0	0	0	0	0	0
	1	0	0	0	0	0
	0	0	0	1	0	0
	1	0	0	1	0	0
	0	0	0	0	0	0
	0	0	0	0	0	0
	1	0	1	1	0	0
	0	0	0	0	0	0
	0	0	0	0	0	0
	0	0	0	0	0	0
	1	0	0	0	0	0

DVT	ICU days %	Vent days %	POR/MT	HCP	Meningitis	EDH	mRS
0	71	40	0	0	1	0	4
0	40	20	0	1	0	0	3
0	28	14	0	0	0	1	2
0	70	50	1	0	1	0	4
1	67	53	1	0	0	0	3
0	100	100	1	0	0	0	6
0	77	53	0	0	1	1	4
0	100	66	0	1	0	0	5
0	50	16	0	0	1	0	2
0	75	16	0	0	0	0	4
0	100	100	0	1	1	0	6
0	71	40	0	0	1	0	4
0	40	20	0	1	0	0	3
0	28	14	0	0	0	1	2
0	70	50	1	0	1	0	4
1	67	53	1	0	0	0	3
0	100	100	1	0	0	0	6
0	77	53	0	0	1	1	4
0	100	66	0	1	0	0	5
1	50	16	0	0	1	1	2
0	75	16	0	0	0	0	4
0	100	100	0	1	1	0	6
0	30	10	0	0	0	0	2
0	50	28	0	0	0	0	4
0	70	38	0	0	1	0	4
0	62	35	1	0	1	0	4
0	44	22	0	0	0	0	3
0	54	27	0	1	0	0	2
0	44	22	0	0	0	0	2
0	33	11	1	0	0	0	2
0	37	12	0	0	0	0	2
0	40	20	0	0	0	0	2
0	68	23	0	1	0	0	4
1	55	37	0	0	0	0	4
0	42	14	0	0	0	0	2
0	80	47	0	1	0	0	4
0	40	20	0	0	0	0	2
0	42	28	0	0	0	0	2
0	30	10	0	0	0	0	2
0	50	28	0	0	0	0	4
0	70	38	0	0	1	0	4
0	62	35	1	0	1	0	4
0	44	22	0	0	0	0	3
0	54	27	0	1	0	0	2
0	44	22	0	0	0	0	2
0	33	11	1	0	0	0	2
0	37	12	0	0	0	0	2
0	40	20	0	0	0	0	2
0	68	23	0	1	0	0	4
0	55	37	0	0	0	0	4
0	42	14	0	0	0	0	2
0	80	47	0	1	0	0	4
0	40	20	0	0	0	0	2
0	42	28	0	0	0	0	2

Tb	T0	T1	D1	D2	D3	DV	DD
1.7	3.8	2.8	1.9	1.8	2	3.5	2.2
1.1	1.8	1.7	2.3	2.1	2.3	2.2	1.3
2.2	0.8	4.6	2.3	1.7	1.5	4.6	2.5
2.4	1.2	6.7	5.3	2.2	1.9	5.1	2.9
0.9	1.1	2.7	1.2	1.7	1.5	2.2	1.4
1.5	3.2	6.7	5.4	6.2	5.8	5.5	5.2
1.6	4.7	5.5	4.3	2.8	2.2	4.7	3.2
2.1	3.5	5.2	3.1	2.5	1.9	2.6	2.2
2.4	2.2	2.7	1.4	1.8	1.7	3.1	3.3
1.5	1.9	4.2	2.3	2.2	2	3.2	1.9
1.9	6.2	4.9	5.8	5.4	4.9	6.3	6.8
1.7	3.8	2.8	1.9	1.8	2	3.5	2.2
1.1	1.8	1.7	2.3	2.1	2.3	2.2	1.3
2.2	0.8	4.6	2.3	1.7	1.5	4.6	2.5
2.4	1.2	6.7	5.3	2.2	1.9	5.1	2.9
0.9	1.1	2.7	1.2	1.7	1.5	2.2	1.4
1.5	3.2	6.7	5.4	6.2	5.8	5.5	5.2
1.6	4.7	5.5	4.3	2.8	2.2	4.7	3.2
2.1	3.5	5.2	3.1	2.5	1.9	2.6	2.2
2.4	2.2	2.7	1.4	1.8	1.7	3.1	3.3
1.5	1.9	4.2	2.3	2.2	2	3.2	1.9
1.9	6.2	4.9	5.8	5.4	4.9	6.3	6.8
0.7	0.8	1.5	1.5	1.2	1.3	0.6	0.8
1.8	2.1	5.6	1.8	1.4	1.6	2.2	1.9
2.1	3.4	4.2	1.5	1.4	1.5	1.7	1.6
2.7	3.1	6.8	3.3	2	1.7	3.2	2.5
0.5	0.8	1.8	1.7	1.2	1.2	0.9	0.6
0.8	1.8	1.5	1.6	1.8	1.9	1.4	1.1
1.6	2.1	3.8	1.7	1.9	2.1	1.7	1.5
1.3	1.6	1.9	1.7	1.8	1.6	1.2	0.9
0.6	1.3	1.9	2.1	1.3	1.1	0.8	0.7
0.8	1.8	1.5	1.6	1.4	1.2	1.1	0.6
2.1	2.8	4.2	2.9	3.2	1.9	2.1	1.8
1.1	2.4	3.5	1.8	1.7	0.9	1.4	1.2
1.2	0.8	0.9	1.1	1	0.7	0.9	0.8
1.7	2.3	1.7	1.9	1.6	1.4	1.5	1.4
1.1	1.8	1.9	0.8	0.7	1.2	0.7	0.8
0.3	1.7	2.8	1.6	1.7	2.2	1.8	1.2
0.7	0.8	1.5	1.5	1.2	1.3	0.6	0.8
1.8	2.1	5.6	1.8	1.4	1.6	2.2	1.9
2.1	3.4	4.2	1.5	1.4	1.5	1.7	1.6
2.7	3.1	6.8	3.3	2	1.7	3.2	2.5
0.5	0.8	1.8	1.7	1.2	1.2	0.9	0.6
0.8	1.8	1.5	1.6	1.8	1.9	1.4	1.1
1.6	2.1	3.8	1.7	1.9	2.1	1.7	1.5
1.3	1.6	1.9	1.7	1.8	1.6	1.2	0.9
0.6	1.3	1.9	2.1	1.3	1.1	0.8	0.7
0.8	1.8	1.5	1.6	1.4	1.2	1.1	0.6
2.1	2.8	4.2	2.9	3.2	1.9	2.1	1.8
1.1	2.4	3.5	1.8	1.7	0.9	1.4	1.2
1.2	0.8	0.9	1.1	1	0.7	0.9	0.8
1.7	2.3	1.7	1.9	1.6	1.4	1.5	1.4
1.1	1.8	1.9	0.8	0.7	1.2	0.7	0.8
0.3	1.7	2.8	1.6	1.7	2.2	1.8	1.2

T0/Tb	T1/Tb	D1/Tb	D2/Tb	D3/Tb	DV/Tb	DD/Tb
2.24	1.65	1.12	1.06	1.18	2.06	1.29
1.64	1.55	2.09	1.91	2.09	2	1.18
0.36	2.09	1.05	0.77	0.68	2.09	1.14
0.5	2.79	2.21	0.92	0.79	2.13	1.21
1.22	3	1.33	1.89	1.67	2.44	1.56
2.13	4.47	3.6	4.13	3.87	3.67	3.47
2.94	3.44	2.69	1.75	1.38	2.94	2
1.67	2.48	1.48	1.19	0.9	1.24	1.05
0.92	1.13	0.58	0.75	0.71	1.29	1.38
1.27	2.8	1.53	1.47	1.33	2.13	1.27
3.26	2.58	3.05	2.84	2.58	3.32	3.58
2.24	1.65	1.12	1.06	1.18	2.06	1.29
1.64	1.55	2.09	1.91	2.09	2	1.18
0.36	2.09	1.05	0.77	0.68	2.09	1.14
0.5	2.79	2.21	0.92	0.79	2.13	1.21
1.22	3	1.33	1.89	1.67	2.44	1.56
2.13	4.47	3.6	4.13	3.87	3.67	3.47
2.94	3.44	2.69	1.75	1.38	2.94	2
1.67	2.48	1.48	1.19	0.9	1.24	1.05
0.92	1.13	0.58	0.75	0.71	1.29	1.38
1.27	2.8	1.53	1.47	1.33	2.13	1.27
3.26	2.58	3.05	2.84	2.58	3.32	3.58
1.14	2.14	2.14	1.71	1.86	0.86	1.14
1.17	3.11	1	0.78	0.89	1.22	1.06
1.62	2	0.71	0.67	0.71	0.81	0.76
1.15	2.52	1.22	0.74	0.63	1.19	0.93
1.6	3.6	3.4	2.4	2.4	1.8	1.2
2.25	1.88	2	2.25	2.38	1.75	1.38
1.31	2.38	1.06	1.19	1.31	1.06	0.94
1.23	1.46	1.31	1.38	1.23	0.92	0.69
2.17	3.17	3.5	2.17	1.83	1.33	1.17
2.25	1.88	2	1.75	1.5	1.38	0.75
1.33	2	1.38	1.52	0.9	1	0.86
2.18	3.18	1.64	1.55	0.82	1.27	1.09
0.67	0.75	0.92	0.83	0.58	0.75	0.67
1.35	1	1.12	0.94	0.82	0.88	0.82
1.64	1.73	0.73	0.64	1.09	0.64	0.73
5.67	9.33	5.33	5.67	7.33	6	4
1.14	2.14	2.14	1.71	1.86	0.86	1.14
1.17	3.11	1	0.78	0.89	1.22	1.06
1.62	2	0.71	0.67	0.71	0.81	0.76
1.15	2.52	1.22	0.74	0.63	1.19	0.93
1.6	3.6	3.4	2.4	2.4	1.8	1.2
2.25	1.88	2	2.25	2.38	1.75	1.38
1.31	2.38	1.06	1.19	1.31	1.06	0.94
1.23	1.46	1.31	1.38	1.23	0.92	0.69
2.17	3.17	3.5	2.17	1.83	1.33	1.17
2.25	1.88	2	1.75	1.5	1.38	0.75
1.33	2	1.38	1.52	0.9	1	0.86
2.18	3.18	1.64	1.55	0.82	1.27	1.09
0.67	0.75	0.92	0.83	0.58	0.75	0.67
1.35	1	1.12	0.94	0.82	0.88	0.82
1.64	1.73	0.73	0.64	1.09	0.64	0.73
5.67	9.33	5.33	5.67	7.33	6	4

T1/T0	D1/T0	D2/T0	D3/T0	DV/T0	DD/T0
0.74	0.5	0.47	0.53	0.92	0.58
0.94	1.28	1.17	1.28	1.22	0.72
5.75	2.88	2.13	1.88	5.75	3.13
5.58	4.42	1.83	1.58	4.25	2.42
2.45	1.09	1.55	1.36	2	1.27
2.09	1.69	1.94	1.81	1.72	1.63
1.17	0.91	0.6	0.47	1	0.68
1.49	0.89	0.71	0.54	0.74	0.63
1.23	0.64	0.82	0.77	1.41	1.5
2.21	1.21	1.16	1.05	1.68	1
0.79	0.94	0.87	0.79	1.02	1.1
0.74	0.5	0.47	0.53	0.92	0.58
0.94	1.28	1.17	1.28	1.22	0.72
5.75	2.88	2.13	1.88	5.75	3.13
5.58	4.42	1.83	1.58	4.25	2.42
2.45	1.09	1.55	1.36	2	1.27
2.09	1.69	1.94	1.81	1.72	1.63
1.17	0.91	0.6	0.47	1	0.68
1.49	0.89	0.71	0.54	0.74	0.63
1.23	0.64	0.82	0.77	1.41	1.5
2.21	1.21	1.16	1.05	1.68	1
0.79	0.94	0.87	0.79	1.02	1.1
1.88	1.88	1.5	1.63	0.75	1
2.67	0.86	0.67	0.76	1.05	0.9
1.24	0.44	0.41	0.44	0.5	0.47
2.19	1.06	0.65	0.55	1.03	0.81
2.25	2.13	1.5	1.5	1.13	0.75
0.83	0.89	1	1.06	0.78	0.61
1.81	0.81	0.9	1	0.81	0.71
1.19	1.06	1.13	1	0.75	0.56
1.46	1.62	1	0.85	0.62	0.54
0.83	0.89	0.78	0.67	0.61	0.33
1.5	1.04	1.14	0.68	0.75	0.64
1.46	0.75	0.71	0.38	0.58	0.5
1.13	1.38	1.25	0.88	1.13	1
0.74	0.83	0.7	0.61	0.65	0.61
1.06	0.44	0.39	0.67	0.39	0.44
1.65	0.94	1	1.29	1.06	0.71
1.88	1.88	1.5	1.63	0.75	1
2.67	0.86	0.67	0.76	1.05	0.9
1.24	0.44	0.41	0.44	0.5	0.47
2.19	1.06	0.65	0.55	1.03	0.81
2.25	2.13	1.5	1.5	1.13	0.75
0.83	0.89	1	1.06	0.78	0.61
1.81	0.81	0.9	1	0.81	0.71
1.19	1.06	1.13	1	0.75	0.56
1.46	1.62	1	0.85	0.62	0.54
0.83	0.89	0.78	0.67	0.61	0.33
1.5	1.04	1.14	0.68	0.75	0.64
1.46	0.75	0.71	0.38	0.58	0.5
1.13	1.38	1.25	0.88	1.13	1
0.74	0.83	0.7	0.61	0.65	0.61
1.06	0.44	0.39	0.67	0.39	0.44
1.65	0.94	1	1.29	1.06	0.71

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