“PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR DIAGNOSIS OF MINIMAL HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER”

BY

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Dr. MARAGARI MOUNIKA

LIST OF ABBREVIATIONS USED

1. ALT- Alanine Aminotransferase
2. AST- Aspartate Aminotransferase
3. BUN- Blood Urea Nitrogen
4. CTP- Child Turcotte-Pugh score
5. TIMP- Tissue Inhibitors of Metalloproteinases
6. aPTT- Activated partial thromboplastin time
7. NAFLD- Non-Alcoholic Fatty Liver Disease
8. NASH- Non-Alcoholic Steatohepatitis
9. LFT- Liver Function Test
10. INR- International Normalized Ratio
11. GGT- Gamma Glutamyl Transferase
12. ALP- Alkaline Phosphatase
13. MELD- Model for End Stage Liver Disease
14. ALF- Acute Liver Failure
15. ALD- Alcoholic Liver Disease
16. OAA- Oxaloacetic Acid
17. NADH- Nicotinamide adenine Dinucleotide hydrogen
18. SGOT- Serum Glutamine Oxaloacetic Transaminase
19. SGPT- Serum Glutamine Pyruvic Transaminase
20. IgG- Immunoglobulin G
21. HCC- Hepatocellular Carcinoma
22. CT- Computed Tomography
23. MRI- Magnetic Resonance Tomography
24. MRA- Magnetic Resonance Angiography
25. CICP- Critically Ill Cirrhotic Patient

26. HRS- Hepatol Renal Syndrome
27. WHC- West Haven Criteria
28. SONIC- Spectrum of Neurocognitive Impairment in Cirrhosis
29. HE- Hepatic Encephalopathy
30. NCPH- Non-Cirrhotic Portal Hypertension
31. BBB- Blood Brain Barrier
32. NMDA- N Methyl D Aspartate
33. HVPG- Hepatic Vein Pressure Gradient
34. PVT- Portal Vein Thrombosis
35. TGF-B1- Transforming Growth Factor-beta 1
36. HBV/HCV- Hepatitis B/ Hepatitis C
37. AKI- Acute Kidney Injury
38. SBP- Spontaneous bacterial peritonitis
39. OHE- overt hepatic encephalopathy.
39. MHE-minimal hepatic encephalopathy.
40. PHES- psychometric hepatic encephalopathy score
41. NCT-A-number connection test -A
42. NCT-B- number connection test -B
43. SDT-simple dot test
44. LTT- line tracing test
45. DST-digit symbol test
46. LT- liver transplantation

ABSTRACT

BACKGROUND:

- Minimal hepatic encephalopathy (MHE) is a subclinical condition in liver cirrhosis patients, often preceding overt hepatic encephalopathy (OHE).
- MHE impairs driving ability and quality of life but requires specialized neuropsychological tests (e.g., PHES) for diagnosis, as routine exams are insufficient.

Aim

- Establish normative PHES values and assess its diagnostic efficacy for MHE in cirrhosis patients.

Methods

- **Study Design**: Cross-sectional study (May 2023–December 2025) at BLDE(DU) Medical College, Vijayapura.
- **Participants**: 166 cirrhosis patients (cases) and controls. Overt HE patients were excluded.

- **Assessments**:
    - PHES battery (NCT-A, NCT-B, SDT, LTT, DST) administered in a controlled setting.
    - Biochemical tests (ALT, AST, INR, albumin, etc.) and imaging (USG abdomen/pelvis).
    - MHE diagnosis: PHES score <−4 based on healthy nomograms.

Results

- **Demographics**: Cases were older ($p=0.003$) and predominantly male (92.77% vs. 67.47%, $p<0.001$). No educational differences ($p=0.263$).

- **Cognitive Performance**: Cases showed significant impairment in all PHES subtests ($p<0.001$) and lower mean PHES (-4.40 vs. 2.28, $p<0.001$).
- **MHE Prevalence**: 37.35% of cases had MHE; none in controls ($p<0.001$).
- **Biochemical Markers**: No correlation between ammonia levels and MHE status.

Conclusion

PHES is a reliable, non-invasive tool for early MHE detection in cirrhosis, aiding timely intervention. While it should complement clinical evaluation, its cost-effectiveness and accessibility enhance patient management and outcomes.

Key Takeaways

- PHES effectively differentiates MHE from healthy controls.
- MHE was present in over a third of cirrhosis cases.
- Supports PHES as a gold standard for MHE diagnosis per international guidelines.

This study underscores PHES's clinical utility in identifying subtle cognitive deficits in cirrhosis, facilitating better patient care.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

INTRODUCTION:

Introduction to Minimal Hepatic Encephalopathy (MHE) and the Role of PHES

Hepatic encephalopathy (HE) is a neurological complication of advanced liver disease, with minimal hepatic encephalopathy (MHE) representing its mildest form [1]. MHE affects 20–80% of cirrhosis patients, impairing cognitive functions such as memory, attention, and psychomotor skills [1]. Despite its subtle presentation, MHE significantly reduces quality of life (QoL), leading to:

- Sleep disturbances
- Impaired daily functioning
- Increased risk of motor vehicle accidents
- Higher healthcare utilization

MHE and covert HE (CHE), which includes grade I HE, often progress to overt HE (OHE) at a rate of 5–25% within five years, particularly in patients with complications like infections, variceal bleeding, ascites, or metabolic disorders [2].

Diagnostic Challenges and Clinical Impact

- MHE is frequently underdiagnosed due to a lack of routine psychometric screening.
- It negatively impacts QoL domains such as mobility, emotional health, and social interaction, as measured by tools like the *Sickness Impact Profile* [2].
- Early detection is crucial because MHE is reversible with treatments targeting ammonia reduction, including:
    - Lactulose (non-absorbable disaccharide)
    - Rifaximin (antibiotic)
    - Probiotics/prebiotics (shown to be as effective as lactulose in trials)[2].

Evolution of Psychometric Testing for MHE

Psychometric testing has evolved from unstandardized assessments to validated batteries like the Psychometric Hepatic Encephalopathy Score (PHES), introduced in 2001 [3]. PHES originated from the PSE-Syndrome-Test (1980s) and evaluates:

- Attention (Number Connection Tests: NCT-A, NCT-B)
- Visuospatial coordination (Line Tracing Test: LTT)
- Psychomotor speed (Digit Symbol Test: DST, Serial Dotting Test: SDT)

PHES is now considered the gold standard for MHE diagnosis, with normative data from over 400 individuals confirming its reliability [3].

Historical Context and Alternative Diagnostic Tools

- MHE was first recognized in the 1970s when cirrhotic patients with normal neurological exams exhibited abnormal neuropsychological test results.
- Beyond PHES, other diagnostic methods include:
    - Critical flicker frequency test (CFF)
    - Inhibitory control test (ICT)
    - EEG and Scan tests [4].

AIM AND OBJECTIVES

OBJECTIVE OF THE STUDY:

To establish normative values for the Psychometric Hepatic Encephalopathy Score (PHES) in the study population and assess its diagnostic accuracy in identifying minimal hepatic encephalopathy (MHE) among patients with liver cirrhosis.

REVIEW OF LITERATURE

INTRODUCTION

- Cirrhosis is an irreversible liver disease characterized by chronic hepatocyte destruction, fibrosis, and reactive nodule regeneration, disrupting liver architecture.[1] It is anatomically defined as diffuse fibrosis and nodule formation, progressing from micronodular to macronodular cirrhosis in the absence of hepatic inflammation and necrosis.[2]

Pathogenesis:

- Hepatocyte necrosis triggers fibrosis and nodule development.
- Liver injury activates stellate cells, producing cytokines and forming a collagen matrix that resists degradation.
    - Monocytes play a key role, releasing cytokines upon activation by endotoxins, recruiting other immune cells, and contributing to fibrosis.[3]

Cytokines and Factors:

- Platelet-derived growth factor and TGF-beta1 stimulate stellate cells.
- Metalloproteinases (MMPs) 2 and 9 are regulated by TIMP 1 and 2 to limit collagen breakdown.
- Other cytokines like IL-6 and IL-13 further mediate fibrosis.[4]

- Hepatic encephalopathy (HE) is a reversible metabolic disorder that affects central nervous system function in individuals with acute or chronic liver disease. It encompasses a broad spectrum of neurological symptoms and is categorized based on clinical presentation or underlying cause. Minimal hepatic encephalopathy (MHE), the earliest stage of HE, presents no clinical symptoms but is detectable through neuropsychometric testing, showing deficits in attention, visuospatial perception, psychomotor speed, fine motor skills, and short-term memory.[5]

- MHE is common in liver cirrhosis patients (22–74%) and also occurs in non-cirrhotic conditions like portal vein thrombosis or portosystemic shunts. Diagnosis is often missed due to the lack of uniform criteria and overt symptoms. Despite mild neurological impairments, MHE significantly reduces quality of life, work ability, and driving capabilities. Studies have shown higher rates of accidents, falls, and episodic HE in affected patients. It is also an independent predictor of survival in cirrhosis.[6]

- **PATHOPHYSIOLOGY:**

Pathophysiology of Hepatic Encephalopathy (HE)

- Neurological and cognitive impairments in HE arise from systemic factors affecting blood-brain barrier (BBB) integrity. Liver dysfunction allows harmful substances like ammonia and other factors to enter the brain, triggering pathological processes.[7]
- **Ammonia**: Elevated ammonia levels, due to impaired liver function, disrupt inter-organ ammonia metabolism. Ammonia causes cellular swelling, inflammation, oxidative stress, mitochondrial dysfunction, and changes in pH and membrane potential. Its neurotoxic effects vary among individuals, with systemic impacts on the immune system, muscles, and other organs.[8]
- **Inflammation and Oxidative Stress**: Systemic inflammation from liver damage, bacterial translocation, and infections leads to BBB dysfunction and neuroinflammation. Hyperammonaemia induces oxidative stress and neutrophil dysfunction, worsening HE-related brain damage.[9]
- **Bile Acids**: Elevated bile acids, due to disrupted enterohepatic circulation in end-stage liver disease, penetrate the brain, inducing neuroinflammation.

Key Pathophysiological Mechanisms in Hepatic Encephalopathy (HE):

- **Electrolyte Imbalance**: Dilutional hyponatremia, common in cirrhosis, exacerbates HE by interacting with ammonia's osmotic effects. Low sodium levels correlate with higher HE risk, and resolving hyponatremia improves cognitive function.[9]

    - **Neuropathophysiological**: Altered cerebrospinal fluid composition, defective lymphatic clearance, and increased neurosteroids (enhancing GABAergic activity) contribute to cognitive impairment.
    - **Cerebral Energy Metabolism**: Hyperammonaemia induces astrocyte swelling due to glutamine/lactate accumulation, disrupting cell communication and neurotransmission. Elevated brain lactate indicates impaired neuronal energy metabolism.
    - **Neuronal Cell Death**: Chronic HE episodes can lead to neurodegeneration and permanent brain damage. Ammonia toxicity and astrocyte senescence contribute to neuronal death, which persists post-liver transplantation (LT).
    - **Gut-Liver Axis and Microbiome**: The gut microbiome significantly affects HE. Certain bacterial families, like Proteobacteria, produce harmful endotoxins, while microbiome-modulating treatments can improve brain function. Autochthonous bacteria like *Clostridia* may be beneficial by producing short-chain fatty acids and modulating bile acids.
    - Cirrhosis impairs the liver's ability to clear bacterial antigens, increasing pathogenic *Proteobacteria*, endotoxin production, and systemic inflammation, exacerbating HE.
    - Microbial dysbiosis, including bacterial and fungal changes, impacts cirrhosis progression and brain function, influencing therapeutic outcomes.

- **Malnutrition and Sarcopenia**:
- Malnutrition is common in cirrhosis, driven by poor intake, malabsorption, and increased energy expenditure. Muscle protein catabolism worsens hyperammonaemia.
- Sarcopenia (muscle mass depletion) is a major complication, reducing survival and increasing HE risk due to impaired ammonia detoxification. Frailty, associated with sarcopenia, predicts poor outcomes.[10]
- **Neurological Impact Post-Liver Transplantation (LT)**:
- HE is presumed to resolve after LT, but up to 47% of recipients face persistent neurological complications, likely due to irreversible brain damage from repeated HE episodes pre-LT.
- Immunosuppressive neurotoxicity, perioperative factors, and comorbidities may contribute to neurological issues. Long-term recovery of brain function has been observed in some cases.

- **Insights from Neuroimaging Studies in CLD and HE**
- Neuroimaging techniques have advanced the understanding of brain dysfunction in chronic liver disease (CLD), although their clinical application remains limited.
- **Magnetic Resonance Imaging (MRI):**
- Techniques like volumetric MRI, magnetization transfer MRI, diffusion-weighted MRI, functional MRI, and multinuclear MR spectroscopy (1H and 31P) reveal structural and functional brain changes in HE, such as brain volume loss, astrocyte swelling, and disturbances in osmolytes and lipid metabolism.[11]
- Hyperintensity in the basal ganglia (linked to manganese deposition) correlates with extrapyramidal symptoms, while brain edema is evident in acute-on-chronic liver failure (ACLF).[12]
- Proton MR spectroscopy highlights shifts in osmolytes (e.g., increased glutamine, reduced myoinositol) associated with HE severity.

- **Positron Emission Tomography (PET):**
- PET imaging has demonstrated increased ammonia uptake, altered cerebral blood flow, neuroinflammation, and microglial activation, supporting their roles in HE pathogenesis.

Quantitative CT Scanning:

- Altered blood-cerebrospinal fluid barrier permeability in cirrhosis patients (even without overt HE) suggests generalized brain homeostasis defects.

Diagnostic and Predictive Utility:

- Imaging abnormalities, such as changes in glutamine/myoinositol ratios, may help identify patients at risk of HE, enabling preventive measures.
- Despite promising findings, current imaging techniques are more suited for research or trial monitoring, as they lack reliability in clinical diagnosis and primarily exclude other brain dysfunction causes.[12]

Disease-Related Mental Dysfunction and Role of Comorbidities in HE

- The development of hepatic encephalopathy (HE) is influenced not only by liver failure but also by underlying causes of liver disease and comorbid conditions. These factors contribute to variations in neurological dysfunction.

Type C Overt Hepatic Encephalopathy (OHE)

- **Clinical Features:**
- Type C OHE presents as a spectrum of neuropsychiatric symptoms in cirrhotic patients, including:
- **Personality changes**: Apathy, irritability, disinhibition.
- **Consciousness and motor function alterations**: From mild confusion to stupor or coma.
- **Sleep disturbances**: Altered sleep-wake cycles, excessive daytime sleepiness.
- **Motor signs**: Asterixis (flapping tremor).
- **Progressive cognitive decline**: Disorientation in time/space, inappropriate behavior, acute confusional states, agitation, or somnolence.
- The condition can progress gradually through increasingly severe stages or suddenly manifest as advanced HE.
- **Precipitating Factors:**
- Identifying and addressing precipitating factors is essential for effective OHE management. Common triggers include:
- **Infections**[13]
- **Constipation**[14]
- **Dehydration**
- **Electrolyte imbalances**: Hypokalemia, hyponatremia.
- **Gastrointestinal bleeding**
- **Psychoactive drug use**: Opioids, benzodiazepines.
- Failure to manage all coexisting precipitating factors can complicate treatment and worsen outcomes.
- **Role of Serum Albumin:**
- Recent evidence highlights:
- **Low serum albumin levels**: Associated with increased OHE risk in cirrhosis[15].

- **Long-term albumin administration**:
- Reduces incidence and severity of grade 3–4 OHE in decompensated cirrhosis.
- Improves 18-month survival.

Refractory HE and Diagnosis

- **Differential Diagnosis**: Exclude alcohol withdrawal, meningitis, and encephalitis in HE unresponsive to standard therapy.
- **Chronic/Refractory HE**: Often lacks clear precipitating factors. SPSS(spontaneous portosystemic shunts), present in 46–70% of such cases, should be identified via imaging.
- **TIPS and HE**: While TIPS alleviates portal hypertension, PTFE(polytetrafluoroethylene) -covered stents lower shunt insufficiency but increase OHE risk.
- **Diagnostic Tools**:
    - Clinical examination is key.
    - West haven criteria and simpler scales assess severity.
    - A combination of tests is needed for HE's full spectrum.
- **Exclusion Diagnosis**: HE is diagnosed by ruling out other causes of altered mental status through labs and imaging.

Hepatic encephalopathy (HE) is defined as a brain dysfunction resulting from liver failure or portosystemic hypertension, based on the 2014 AASLD/EASL guidelines. In 1998, the World Congress of Gastroenterology in Vienna sought to standardize the description of HE-related symptoms. During the conference, it was decided to discontinue the use of the term "portosystemic encephalopathy" since not all HE cases require the presence of portosystemic shunts. Another key change was the classification of HE into four major components or axes.[15]

Axis One

- Hepatic encephalopathy is classified into three types based on its cause: type A, type B, and type C.
- **Type A** is associated with acute liver failure.
- **Type B** occurs due to portosystemic shunts or bypasses, without the presence of underlying liver disease.
- **Type C** is linked to chronic liver disease or cirrhosis.

Axis two

HE is classed as either covert or overt, depending on its severity. The modified West Haven Criteria (WHC) is used to classify hepatic encephalopathy. The subjective scale, which includes early stages of higher education, is not preferred. However, it is the most widely used scale due to its lack of equipment or training requirements.

The **Spectrum of Neurocognitive Impairment in Cirrhosis (SONIC)** encompasses hepatic encephalopathy, which can range from an alert mental state to a comatose condition. Covert HE, which includes minimal and grade 1 HE, is diagnosed based on modest cognitive changes detected by particular tests rather than symptoms. Overt HE (grades 2–4) is easily detected clinically.

Axis three

Based on the course, Overt HE has been divided into three categories:
Episodic HE occurs every six months with varying intensity and duration.
Recurrent HE is defined as HE occurring at least twice per year.
Persistent HE is characterized by cognitive changes lasting beyond two months. Each episode represents a fresh baseline.

Axis Four

Overt HE episodes can be caused by a variety of reasons and an etiologies, categorized as episodic or recurring. Overt HE can occur spontaneously or persistently.

Grades of hepatic encephalopathy (west haven criteria)		
covert	Grade 1	Inattention, euphoria/anxiety, altered sleep pattern, decreased attention span
overt	Grade 2	Lethargy, behavior changes, time disorientation,asterixis,personality changes, hypoactive deep tendon reflexes.
	Grade 3	Somnolence to semi stupor, responsive to stimulus, time and place disorientation, asterixis, hyperactive Deep tendon reflexes
	Grade 4	Coma

ETIOPATHOGENESIS:

The exact cause of hepatic encephalopathy is not fully understood. However, researchers suggest that intestinal toxins produced by the gut microbiome may contribute to its development. Early investigations suggested that ammonia was the primary toxin causing hepatic encephalopathy in cirrhosis patients.

However, there is no obvious correlation between ammonia levels and clinical characteristics, therefore other toxins or processes should also be addressed. Few researchers have explored the potential causes of hepatic encephalopathy, including inflammatory cytokines, manganese, and mercaptans.[16]

Although ammonia plays a function in cirrhosis-related OHE, its involvement in non-cirrhotic portal hypertension (NCPH) remains unclear. In cases of NCPH or portal shunting without severe disease, the existence of pre-existing liver disease is required, even if the patient has Covert HE. Hepatic encephalopathy can be caused by toxins that are not properly metabolized by the liver, leading to a rise in their concentration.[17]

Multiple brain imaging investigations show that the outcomes include cerebral cytotoxic edema and neurological changes. The specific process of cerebral edema leading to hepatic encephalopathy is unclear, but it is believed to be linked to osmolar alterations in neurons.

AMMONIA:

Several investigations have suggested ammonia as the causal cause of HE. Elevated levels have no accurate diagnostic or prognostic value for HE. However, it must be high in Overt HE. If normal, another diagnosis should be investigated. Ammonia can compromise the integrity of the blood-brain barrier (BBB) by inducing mitochondrial dysfunction and generating free radicals.
Ammonia combines with glutamate to generate glutamine (via Glutamine synthase), leading to cytotoxic edema of astrocytes within the brain.[18]

Astrocytes have been extensively researched, while neurons are thought to be similarly damaged and malfunctioning. While chronic HE may cause cerebral edema, but there is no evidence of elevated intracranial pressure. However, ALF can cause cerebral hyperaemia and elevated intracranial pressure, resulting in seizures.

Liver transplantation eliminates all signs of pre-transplant cerebral edema. Ammonia-related neurotoxicity can occur through NMDA receptors and free radicals, in addition to cerebral edema.

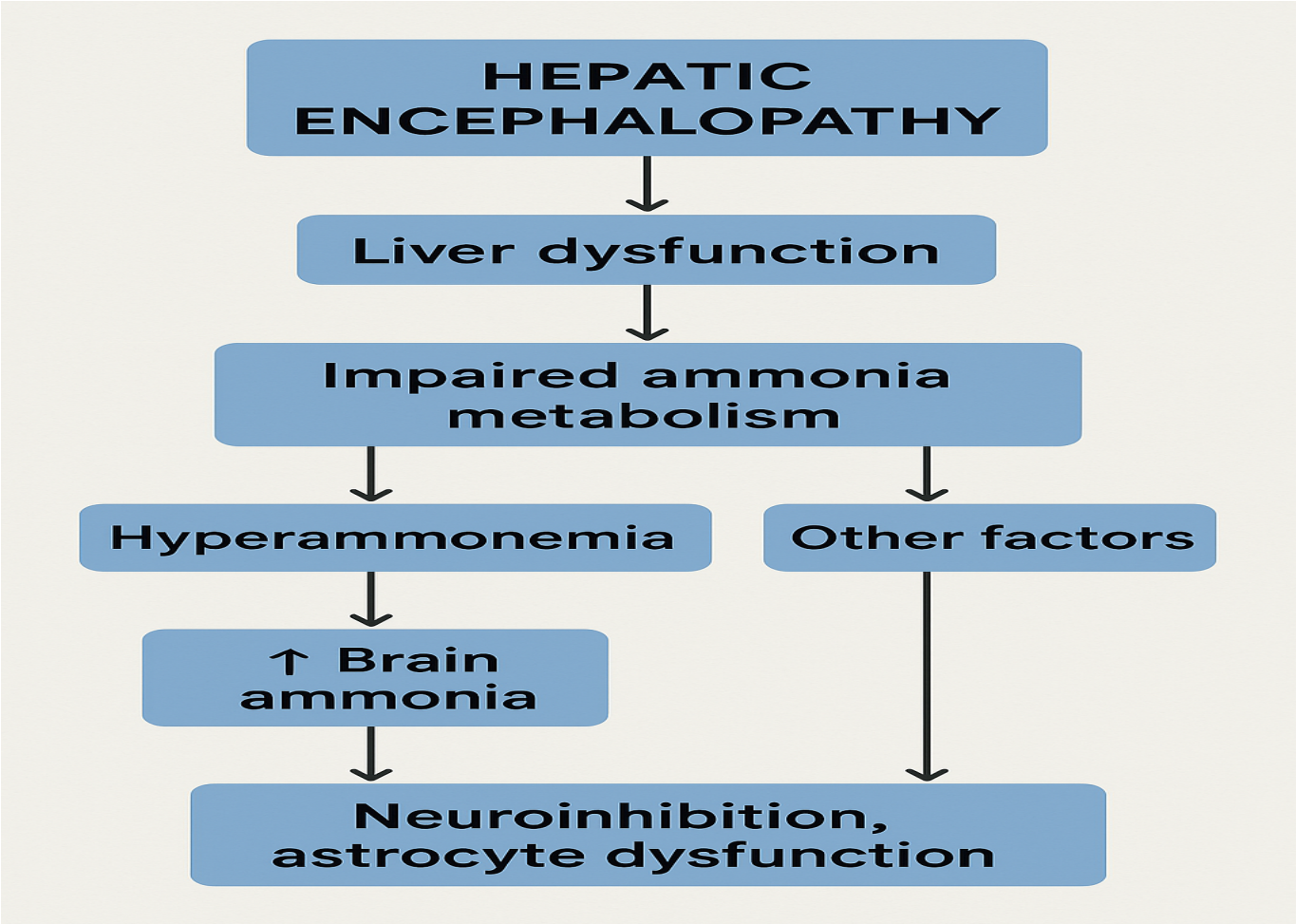

FIGURE 1 : showing pathophysiology of hepatic encephalopathy

- Hepatic encephalopathy can produce altered sensorium, including sleep problems, disorientation, and coma. Women may also experience menstrual irregularities due to anovulation. Men may develop hypogonadism, which can manifest as impotence, reduced libido, testicular atrophy, and infertility. Additionally, portal hypertension may cause ascites and bleeding from esophagogastric varices, leading to decompensated cirrhosis.[19]

- Cirrhosis can cause a reduction in mean arterial pressure over time.
- Patients with hypertension may become normotensive.
- Patients reported mild fever (37.5-38*C).
- "This is most likely due to gram negative bacteria. Hepatocyte necrosis and hepatocellular carcinoma may also contribute to this."
- Jaundice occurs when hepatocyte death causes more functional damage than regeneration. Deeper jaundice indicates significant hepatic decompensation.[20]

  - **Methods for Assessing Neurological Function in MHE Diagnosis**

- Numerous methods have been developed to evaluate neurological function in patients with Minimal Hepatic Encephalopathy (MHE). These techniques focus on identifying abnormalities in the central nervous system (CNS) caused by liver failure.[21] While any method demonstrating CNS impairment linked to liver dysfunction is valid, the diagnosis of MHE traditionally relies on neuropsychological and neurophysiological testing. Imaging techniques like PET scans, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy can detect structural and functional changes in the brain. However, these techniques are not considered definitive diagnostic tools for minimal hepatic encephalopathy (MHE).[22]

- **Neuropsychological Assessment**
- Neuropsychological assessment is a fundamental method for diagnosing MHE. This involves applying various tests that measure brain dysfunction, interpreting the results, and observing behaviour to identify functional abnormalities in cognition and behavior.[23]
- MHE affects multiple brain functions, including:
- **Feelings**
- **Motivation**
- **Circadian rhythms**
- The most extensively studied effects of MHE are on cognition, covering:
- **Perception**
- **Memory**
- **Learning**
- **Executive functions**
- **Expression** (e.g., language, motor control, constructive abilities)
- **Mental activity** (e.g., attention, mental speed)
- A hallmark feature of overt hepatic encephalopathy is a **reduced level of consciousness**, which can range from mild inattentiveness to a significantly impaired awareness. In MHE, this spectrum often manifests as:
- **Abnormalities in attention tests[24]**
- **Slower information processing speeds**
- **Fine motor dysfunction**
- Minimal hepatic encephalopathy (MHE) can also affect memory, perception, and constructive abilities, with the severity of impairment differing among patients. Even if cognitive test results appear normal, MHE can reduce overall productivity due to **inattentiveness** and **fatigue** stemming from attention deficits.

- **Expert Neuropsychological Assessment**[25]
- This is considered the gold standard for diagnosing MHE. A neuropsychologist administers a battery of psychometric tests, comparing the results to normative data adjusted for age, gender, and education.
- These tests typically evaluate domains expected to show abnormalities, such as:
- **Attention**
- **Executive function**
- **Psychomotor skills**
- **Speed of information processing**[26]
- Results are interpreted based on established thresholds, such as scores that fall **2 standard deviations (SD)** below the mean being deemed abnormal. Some experts argue that scores between **1 and 2 SD** indicate mild deficits.
- Neuropsychological impairments in MHE are often consistent with dysfunction in the **frontal-subcortical circuits**. Although this pattern supports an MHE diagnosis, it is neither exclusive nor specific and can occur in other diseases.

- **Short Neuropsychological Batteries**
- Comprehensive neuropsychological assessment can be time-consuming and require expertise. To address this limitation, researchers have developed **short neuropsychological batteries**, which simplify evaluation by using a smaller set of tests.
- **Advantages and Limitations**
- These tests are easier and faster to administer but may sacrifice sensitivity due to the reduced number of components.[27]
- There is no agreed-upon standard regarding the number of tests to be included or the criteria for determining abnormal results.
- Short batteries can serve two main purposes:[28]

- **Research tools**: Measure cognitive function for studies.
- **Diagnostic tests**: Quickly screen for MHE in clinical practice.
- A frequently utilized brief assessment tool is the Psychometric Hepatic Encephalopathy Score (PHES), which consists of five paper-and-pencil tests.
- PHES has been validated in German, Italian, and Spanish populations, but cross-cultural differences in results complicate its application.

Computerized Tests

- Computerized tests are gaining popularity due to their simplicity and reliability, especially for repeated assessments. These tests primarily measure:
- **Speed of mental processing**
- **Reaction time**
- **Accuracy**
- One specific test, the **Critical Flicker Frequency (CFF)**, measures vigilance and has shown promise in assessing low-grade encephalopathy. Early findings suggest a correlation between CFF scores and encephalopathy severity, but more studies are needed to confirm its clinical relevance.[29]

Neurophysiological Tests

- Neurophysiological tests analyse the brain's electrical activity, including:
- **Electroencephalography (EEG)**: Examines brain waves.
- **Evoked potentials**: Records electrical responses to stimuli.
- **Transcranial magnetic stimulation**: Measures cortical excitability.[30]
- These tests often detect abnormalities in cirrhotic patients and are considered more sensitive than neuropsychological tests.

Advantages

- **Objectivity**: Results are less influenced by factors like age or education.
- **No learning effects**: Unlike cognitive tests, repeated use does not produce practice effects.

- **Limitations**
- Lack of behavioural context: Neurophysiological results do not directly indicate how a patient's daily life is affected.
- Questionable clinical relevance: Patients with significant abnormalities may function normally in daily life.
- Despite these limitations, neurophysiological tests are valuable in complex cases, such as patients with multiple comorbidities or low educational backgrounds.[31]

- **Diagnosis of MHE**
- Diagnosing MHE lacks a universal standard, but certain requirements are generally agreed upon:
- **Disease That Can Cause MHE**
- Patients must have a condition like **cirrhosis** or **portosystemic shunting**. The diagnosis of cirrhosis may be straightforward in patients with clinical signs, such as ascites or variceal bleeding. In less obvious cases, imaging (e.g., CT scans) and endoscopy can help identify complications like varices or shunts.[32]

Normal Mental Status on Clinical Exam

- Mental status must be deemed normal by the physician, based on the absence of overt encephalopathy symptoms, such as:
- Dysarthria
- Ataxia
- Flapping tremor

- Disorientation
- Slowed mental processing.[33]
- Some studies use specific criteria to define normal mental status, such as orientation in time/place/person or the ability to subtract serial sevens from 100.

- **Evidence of Neurological Impairment**
- Neurological impairment must be documented using methods like:
- Comprehensive neuropsychological evaluation
- Brief neuropsychological assessments
- Digital/computer-based testing
- Neurophysiological examinations
- Ruling out alternative causes
- Other conditions that might explain the neurological impairment, such as alcohol use, visual impairment, or other comorbidities, must be ruled out. In clinical practice, this often requires careful judgment.[34]

Alcohol Abuse

- Alcohol, a direct neurotoxin, complicates the differentiation between alcohol-induced brain injury and HE.
- Patients with alcohol-related cirrhosis show incomplete recovery of neuropsychometric function, MRI abnormalities, and structural brain injury.
- Wernicke-Korsakoff syndrome and alcohol withdrawal can mimic HE but are distinguishable by features like loss of spatial and temporal orientation unique to HE.

Non-Alcoholic Fatty Liver Disease (NAFLD)

- NAFLD is now a leading cause of cirrhosis and is associated with impaired psychometric function, reduced brain volume, and neuroinflammation, even in non-cirrhotic stages.
- Urea cycle dysfunction in NAFLD leads to hyperammonemia, contributing to astrocytic and microglial activation.
- Further studies are needed to delineate specific mechanisms and their role in early HE diagnosis in NAFLD patients.[35]

Hepatitis C Virus (HCV)

- HCV is linked to neuropsychiatric symptoms like fatigue, depression, and cognitive impairment, independent of liver disease severity.
- Brain imaging shows distinct neuroinflammation, resembling patterns seen in HIV.
- HCV directly infects brain cells, causing neuroinflammation, but eradication of the virus improves neuropsychiatric function.
- Obesity, diabetes, and ageing are associated with increased risk of HE due to factors like cerebrovascular disease, systemic inflammation, oxidative stress, and cellular senescence.[36]
- Diabetes significantly elevates HE risk, while ageing poses challenges such as higher HE susceptibility after TIPS procedures.

STEATOSIS:

- Alcohol use can lead to the formation of triacylglycerol in the liver, visible as fat droplets under a microscope. Special stains, such as Sudan black, are used to detect this impact.
- Alcohol inhibits the enzyme microsomal triglyceride transfer protein, which transfers cholesterol from the liver to the periphery, resulting in the buildup of triacylglycerol. Increased damage to cell organelles, particularly mitochondria, can cause antioxidants to lose their protective action, resulting in oxidative stress and membrane damage.

CYTOKINES:

- Alcohol-induced liver impairment is mostly caused by cytokines, which appear clinically and histologically.
- Tumor necrosis factor alpha causes steatosis, reactive oxygen species, free radicals, and hepatocyte death.
- Interleukin 8 is responsible for neutrophil activation and recruitment.[37]

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HISTOLOGY:

FATTY LIVER:

- mostly occurs in zones 2 and 3 and initially appears in microvesicles before moving on to macrovesicles.
  Fatty acid oxidation inhibition brought on by mitochondrial failure results in microvesicular fat.[38]

ALCOHOLIC HEPATITIS:

- When hepatocytes fail to excrete microtubular proteins and hold water, ballooning degeneration takes place. Apoptosis results in the formation of acidophilic entities.
  "A satellite of polymorphs that resemble intracytoplasmic inclusions made of purple intermediate filaments envelop Mallory Denk bodies."
- Giant mitochondria can be seen using Masson's trichrome dye.Near the sinusoids, pericellular fibrosis, also referred to as "creeping collagenosis," is most prevalent.
  Drug delivery is hampered by collagen deposition, which is mostly localized in the space of Disse. Lower survival is associated with cholestasis in the bile canaliculi.

Clinically, there are two types of cirrhosis: compensated and decompensated.

COMPENSATED

“The cirrhosis is not severe enough to impair function at this point. Fatigue, appetite loss, weight loss, flatulence, dyspepsia, and abdominal pain are all possible side effects for patients. Spider nevi, pedal edema, and palmar erythema may be signs of liver cirrhosis upon examination.

DECOMPENSATED:

- These individuals have bleeding symptoms, jaundice, altered sensorium, and ascites when they first arrive.[38]

“NAFLD is distinguished by the buildup of lipids in the liver of individuals who do not have a notable history of alcohol intake. It encompasses a range of diseases, spanning from basic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. The increase in NAFLD is closely connected to contemporary lifestyle issues, such as lack of physical activity, bad eating habits, and the growing occurrence of metabolic syndrome.”

- The gold standard for diagnosing liver cirrhosis and fibrosis at the moment is liver biopsy .If a comprehensive serologic and radiographic assessment is unable to confirm a diagnos is of cirrhosis or fibrosis, a referral for a liver biopsy should be taken into consideration.

CLINICAL FEATURES:

- Individuals may present with cirrhosis for the first time or may be asymptomatic and only be diagnosed after a routine examination due to abnormal liver tests or unrelated reasons.

  Cirrhosis with extra symptoms including jaundice, ascites, hepatic encephalopathy, or bleeding varices is referred to as decompensation.

  Ascites is not a sign of decompensation or portal hypertension problems in compensated cirrhosis.

  A decompensated patient's prognosis can be improved by eliminating the underlying cause. A liver transplant should be considered for patients with decompensated liver disease.

SKIN FINDINGS:

Hemochromatosis causes bronze-colored skin pigmentation.

“The presence of spider angioma are found in the venous drainage zones of the superior vena cava. As liver function deteriorates**,** new veins may appear. They are usually associated with alcoholic cirrhosis.”

“These conditions are common during pregnancy and in some healthy persons.

Hepatopulmonary syndrome is defined by several spider naevi and clubbing.

Palmar erythema is characterized by warm, red palms, especially over the thenar and hypothenar eminences and finger pulps**.**”

Excessive estrogen may cause arterial spidering and palmar erythema. The estrogens are deactivated in the liver.

Serum estradiol levels are normal, whereas free testosterone levels are low.

- The high estradiol/free testosterone ratio could explain these findings.

- “Leukonychia may be associated with hypoalbuminemia. Clubbing can occur digitally**,** especially if you have liver-lung disease or cystic fibrosis. Hypertrophic osteoarthropathy has also been reported. Dupuytren's contracture may occur.” Unorganized fibroblast proliferation causes thicker palmar fascia.

HEAD AND NECK FINDINGS:

- Wilson's disease can cause parotid enlargement, baldness, fetor hepatitis, and KF rings in the eyes.
- The term "fetor hepaticus" refers to fragrant, pungent breath. This is due to the existence of mercaptans.

CHEST FINDINGS:

- Males with gynecomastia may exhibit other signs of feminization, such as changes in pubic hair pattern, axillary hair loss, and chest hair.
- Gynecomastia occurs when the adrenals synthesize androstenedione, which is then aromatized into estrone and finally estradiol in adipose tissue.

ABDOMINAL FINDINGS:

- “Abdominal examination reveals ascites, hepatomegaly, splenomegaly, and dilated veins. Ascites is the excessive collection of peritoneal fluid.”
- Hepatomegaly refers to the enlarged, shrunken, or normal size of the cirrhotic liver. On palpation, the consistency is firm and nodular.
- Palpation is more effective in assessing liver shape and composition, while imaging methods do not reliably assess liver size. “A palpable liver may

indicate liver cirrhosis, including alcoholic liver disease, primary biliary cirrhosis, hemochromatosis, hepatocellular carcinoma and Budd Chiari syndrome.”

- Splenomegaly in cirrhosis is caused by congestion from portal hypertension.
- The low association between splenic size and portal pressure suggests that other factors may also play a role.

“In cirrhosis, portal hypertension causes blood to flow through the periumbilical veins into the umbilical vein, which becomes patent. The blood then drains into the upper and lower abdominal veins before entering the systemic circulation (Caput medusae).
These veins become enlarged. “As a result, portal blood is directed into systemic circulation. The appearance recalls the head (Caput) of the mythical Gorgon Medusa, hence the name caput medusae.

To differentiate between dilated abdominal veins due to superior or inferior vena cava (SVC/IVC) obstruction and those caused by cirrhosis, observe blood flow direction. In IVC obstruction, blood flows upward, whereas in cirrhosis, it moves away from the site of obstruction.

The flow is below upwards due to an IVC obstruction. However, without valves, the flow in these veins may be bidirectional, making the test potentially inaccurate. Obstruction often results in dilated veins in the back and loin.

Peptic ulcers develop in 11% of cirrhosis patients. “Duodenal ulcer is more predominant than gastric ulcer**.** Helicobacter pylori colonization is more common in cirrhosis than in the general population. People with ascites are more likely to have an abdominal hernia. Corrections should only be made if they are severe enough to cause death. Chronic pancreatitis, which may recur**,** should be considered as a differential diagnosis in patients with alcoholic cirrhosis who present with abdominal pain.”

Asterixis or a liver flap can suggest hepatic encephalopathy.
Male genitourinary findings include testicular atrophy.

HAEMATOLOGICAL FINDINGS**:**

Hematologic disorders like thrombocytopenia, anemia, and leucopenia may develop[39]. Thrombocytopenia is the first anomaly to appear and can indicate the onset of portal hypertension.
Pancytopenia can be a presenting characteristic in asymptomatic compensated cirrhosis. This is caused by cells being sequestered in the larger spleen.
Platelet counts typically do not go below 50,000. Although this does not cause bleeding, it can worsen if there is coagulopathy present.

Anemia in cirrhosis is primarily caused by upper G1 bleed.
Anemia can develop from alcohol-induced bone marrow suppression, splenic sequestration and hemolysis, or folate insufficiency.

OTHERS:

"In cirrhosis, globulin levels are elevated. Bacterial antigens in portal venous blood, which are ordinarily filtered by the liver, are shunted into systemic circulation, causing immunoglobulin synthesis.
Elevated IgG levels may indicate autoimmune hepatitis."

LIVER PARAMETERS:

Liver function tests (LFTs) and biochemical testing can detect liver disease, guide diagnostics, and evaluate treatment outcomes. The term "LFT" is incorrect as it only provides indirect evidence of hepatobiliary illness, despite its widespread use in medical literature. Serum albumin, bilirubin, and prothrombin time are more accurate indicators of liver function and are standardized to the international normalized ratio (INR). Given the low prevalence of liver illness in the general population (2-4%), more examinations are necessary to detect biochemical abnormalities. To test established values, conduct a few easy tests and repeat any abnormalities to prove their validity.

- “Symptoms can be hepatocellular **(**increased AST and ALT), cholestatic **(**ALP**, γ-**GT and bilirubin**)** and infiltrative **(**ALP, γ-GT and sometimes increased bilirubin **).** ALP, aminotransferase, and bilirubin tests are most effective in diagnosing jaundice. Elevated serum unconjugated bilirubin may indicate Gilbert's syndrome, hemolysis, ineffective erythropoiesis.
- Serial assessments of total bilirubin, albumin, and prothrombin time after vitamin K administration help determine the extent of liver cell damage. The Child-Pugh (CP) score evaluates disease severity and prognosis, while the Model for End-Stage Liver Disease (MELD) score is utilized to assess transplant eligibility.[39]
- “Elevated arterial ammonia levels indicate significant liver dysfunction in patients with acute liver failure (ALF). However, hyperammonemia in decompensated cirrhosis does not usually indicate hepatic encephalopathy or progression of liver disease.
- Low levels of aminotransferases and serum bilirubin may indicate mild liver damage**.**
- Heavy drinkers, with or without liver disease (ALD), may have elevated γ-GT levels without biochemical evidence of liver damage. However, biochemical abnormalities can also be present in well-compensated cirrhosis, heart failure and fever, **s**uggesting difficulty in assessing the severity of liver disease.”

BILIRUBIN:

- Bilirubin levels are often higher in cholestatic and hepatocellular liver diseases than in infiltrative diseases. It is often associated with elevated liver enzyme levels.[39] Bilirubin is primarily conjugated and water-soluble. Patients with significant hyperbilirubinemia (bilirubin > 425 μmol/L) may suffer from severe liver disease, renal failure, or other conditions leading to unconjugated hyperbilirubinemia, such as hemolysis. To identify if a spike in bilirubin without enzyme elevation is caused by hemolysis or a family history, it should be fractionated.
- The van den Bergh diazo reaction is used to measure serum bilirubin by detecting azo derivatives formed when plasma reacts with sulfanilic acid's diazonium ions.[40]

- "The process converts bilirubin into two forms: conjugated bilirubin (water soluble**)** and unconjugated bilirubin (lipid soluble). Low serum bilirubin can cause errors in diazo reactions. More reliable evaluation methods include alkaline methanolysis with chloroform extraction, high pressure liquid chromatography (HPGLC), thin layer
- chromatography (TLC) and spectrophotometric measurement." However, these procedures are not therapeutically relevant because to their complexity[40].

"Examination of stools is an integral part of the examination of jaundice**.** Clay-colored stools usually indicate cholestatic jaundice, but can also occur in hepatocellular jaundice. The hue is normal in hemolytic jaundice. Pale stools may occur in severe bilirubin glucuronyl transferase deficiency."

Normal urine does not contain bilirubin due to its unconjugated, insoluble, and albumin-bound nature. Bilirubin conjugation produces water-soluble bilirubin glucuronides. Conjugated bilirubin can be seen in urine even with normal serum total bilirubin levels due to a low threshold for glomerular filtration[40].

Prolonged and severe jaundice causes conjugated bilirubin to bind covalently to albumin, forming the δ bilirubin (or bilioprotein) complex. Beta bilirubin has a long half-life and cannot be eliminated by the kidneys. This is why patients recovering from severe hepatobiliary illness may not have bilirubinuria and experience slow recovery of jaundice.

UROBILINOGEN:

In the colon, bacterial β-glucuronidases convert bilirubin into urobilinogen, a group of colorless tetrapyrroles found in stool. Around 80-90% of urobilinogen is excreted unchanged or as oxidized orange pigments known as urobilin's. The remaining 10-20% is reabsorbed and recirculated into bile by the liver, with a tiny amount excreted in urine. Urine flow rate and pH are key components in this process. Urinary urobilinogen is not a reliable indicator of liver illness and often yields false negative results.

AMINOTRANSFERASES:

"Aminotransferases (formerly called aminotransaminases) transfer amino groups from aspartate or alanine to the keto group of α-ketoglutarate, resulting in oxaloacetic acid (OAA) and pyruvic acid, respectively." Enzymes play a crucial role in gluconeogenesis, converting non-carbohydrate substrates into glucose through catalysis. Oxaloacetic acid and pyruvic acid are reduced enzymatically to malate and lactate, respectively.

Nicotinamide adenine dinucleotide (NADH) is oxidized to its NAD form. Since NADH absorbs light at 340 nm, it enables accurate spectrophotometric analysis of enzymatic activity.

Aspartate aminotransferase (AST), also known as serum glutamic-oxaloacetic transaminase (SGOT), is an enzyme present in both the cytoplasm and mitochondria of various tissues. While normal serum AST activity primarily comes from the cytosol, approximately 80% of hepatic AST activity is mitochondrial, predominantly located in periportal hepatocytes. "AST is abundant in the liver, heart, skeletal muscle, kidney, brain, pancreas, lung, leukocytes and erythrocytes, in decreasing concentration. Macro-AST is a rare condition that causes elevated AST levels due to the binding of immunoglobulins that cannot be removed by the blood or kidneys. This is a harmless condition and does not indicate liver disease. Low AST has been observed in chronic hemodialysis patients, presumably due to pyridoxine deficiency."

"Alanine aminotransferase (ALT), commonly known as serum glutamine-pyruvine transaminase (SGPT), is a cytosolic enzyme present in the liver. Although the amount is less than AST, the liver has a higher proportion than the kidney, heart and skeletal muscle. Serum elevations are more selective for liver damage than AST levels."

Measuring transferase levels alongside viral serologies can help in the early diagnosis of viral hepatitis. However, there is no direct correlation between transferase levels and the extent of hepatocyte necrosis or disease prognosis. These enzymes have short half-lives, with AST lasting approximately 12–22 hours and ALT persisting for 37–47 hours, necessitating prompt testing. Even if transaminase levels decrease, patients may still suffer deadly acute liver

necrosis.

“A routine screening test may reveal an unexpectedly high aminotransferase level. They are usually caused by non-alcoholic fatty liver disease (NAFLD), alcoholism, viral hepatitis and hemochromatosis. Some fewer common causes include autoimmune hepatitis, α1-antitrypsin deficiency, Wilson's disease, drug-induced liver disease, and non-hepatic diseases such as Addison's disease, anorexia nervosa, celiac disease, and hyperthyroidism.”

Viral hepatitis (including herpes simplex), drug-induced hepatotoxicity from paracetamol (acetaminophen), ischemic hepatitis, and severe autoimmune hepatitis can all cause increased transaminases. Calculous biliary obstruction with cholangitis is a common cause of AST elevation above 10 times the upper limit of normal. Antibiotics can relieve symptoms over 48-72 hours, even if the obstruction remains unresolved.

“High levels are rare in ALD and may indicate an underlying disease such as paracetamol toxicity or severe viral hepatitis. A higher AST to ALT ratio can help diagnose ALD. Due to mitochondrial damage, more AST is released into the system. In addition, ALT synthesis is more sensitive to pyridoxal-5-phosphate deficiency, as a result of which the level of ALT in the blood decreases.”

ALKALINE PHOSPHATASE:

“Alkaline phosphatases (ALP) hydrolyze phosphate esters at neutral pH. Magnesium and zinc are important common factors. Hepatic ALP levels are cytosolic and associated with sinusoidal and ductal membranes. They increase during cholestasis and to a lesser extent when liver cells are damaged. ALP is found in varying amounts in the placenta, ileal mucosa, kidney, bone and liver, with liver and bone accounting for more than 80% of serum levels. The half-life of ALP is three days. Bone, liver and kidney ALP genes share the same protein structure but differ in carbohydrate content.[40]”

Elevated ALP levels result from increased hepatobiliary synthesis, driven by the accelerated translation of ALP messenger RNA, as well as its secretion into the bloodstream through canalicular leakage into the sinusoid. This rise is due to enhanced production rather than an impaired ability to eliminate ALP.

Acute biliary obstruction causes de novo ALP synthesis, resulting in normal serum levels despite significant transferase increases. Isoenzyme fractionation can separate serum hepatic ALP from bone ALP, although it is not commonly used as a rise in γ-GT confirms hepatobiliary origin. Patients with blood group O and B who release intestinal ALP postprandially may experience an isolated elevation in ALP. Enzyme levels must be measured under fasting conditions, as they can remain elevated for up to 12 hours.

In cases of mild isolated ALP elevation (less than twice the normal level), up to 52% of individuals will see normalization within 1–3 months. However, among hospitalized patients, sepsis without jaundice may contribute to approximately 32% of cases. Elevated ALP levels can also suggest the presence of primary or secondary hepatic tumors, even in the absence of jaundice or bone disease.

Elevated ALP levels without jaundice may suggest infiltrative diseases or space-occupying lesions, including amyloidosis, abscesses, lymphoma, or granulomas. Mild elevations can also be associated with conditions such as Hodgkin's disease, heart failure, and hyperthyroidism. Stauffer's syndrome, occurring in up to 15% of renal cell carcinoma cases, presents without hepatobiliary or bone involvement. Conversely, low ALP levels may indicate hypothyroidism, Wilson's disease with hemolysis, congenital hypophosphatasia, pernicious anemia, zinc deficiency, acute liver failure, or recovery from severe enteritis in children.

GAMMA-GLUTAMYL TRANSFERASE:

Gamma-glutamyl transferase (γ-GT) is a membrane-associated enzyme responsible for transferring γ-glutamyl groups from peptides like glutathione to amino acids. Increased levels are commonly observed in cholestasis, liver disease, and various hepatobiliary conditions, often alongside elevated ALP. γ-GT is present in multiple tissues, including the proximal renal

tubules, liver, pancreas (both acinar cells and ductules), and intestines.

The liver is the primary source of serum γ-GT activity, with the maximum concentration seen in the epithelial lining of tiny bile channels. This test confirms that a high ALP is hepatobiliary in origin.

"Alcohol abuse can increase γ-GT levels even in the absence of liver disease due to stimulation of microsomal enzymes and poor elimination, resulting in a half-life of 28 days instead of 7-10 days. γ-GT screening may have detected more alcohol abusers, although a third of people did not have high levels. In patients with biopsy-proven alcoholic liver disease, there is no association between alcohol consumption and higher serum γ GT levels or hepatic γ-GT." Increased levels may result in over-investigation of individuals who have never consumed alcohol or social drinkers who have never abused it.

IMAGING STUDIES:

Ultrasonography is a non-invasive imaging technique commonly used to assess cirrhosis. It evaluates liver size, surface texture, portal vein diameter, the presence of ascites, and spleen enlargement.

- Doppler studies are useful for diagnosing portal hypertension by analysing blood flow direction in the portal vein. Additionally, they can help detect hepatocellular carcinoma (HCC) and portal vein thrombosis.
- CT scans are not the primary diagnostic tool for cirrhosis but can be valuable in identifying liver cancer, metastatic diseases, and pancreatic abnormalities.
- MRI plays a crucial role in detecting iron overload in conditions such as hemochromatosis.
- MRA is beneficial for assessing portal vein blood flow and hemodynamics.
- Elastography is an effective method for measuring liver tissue stiffness.

“A liver biopsy is the most reliable way to diagnose cirrhosis. Liver biopsy rarely diagnoses cirrhosis today**.** A liver biopsy may be necessary to diagnose underlying metabolic causes of cirrhosis, such as NASH, Wilson's disease, hemochromatosis, or alpha-1 antitrypsin deficiency.”

GASTRIC VARICES AND PORTAL HYPERTENSON:

- One of the main causes of upper gastrointestinal hemorrhage is Varices.

- **Portal Hypertension (PH):**
- Variables suggest the presence of portal hypertension, which is defined as a greater than 5 mmHg hepatic venous portal gradient[41].
    - PH is defined as the formation of portosystemic collaterals, with or without cirrhosis.
    - A hallmark of PH is the formation of varices, most commonly in the esophageal and gastric regions, which increase the risk of gastrointestinal bleeding

Anatomy and Physiology of the Portal Venous System:

- The portal vein is formed by the union of the superior mesenteric vein and splenic veins. The splenic vein is responsible for draining blood from the pancreas, stomach, and spleen. Blood from the large intestine, comprising the rectum, descending colon, and transverse colon, will be drained by the inferior mesenteric vein. Blood from the stomach, pancreas, appendix, and small and large intestines is transported by the superior mesenteric veins. Variceal hemorrhage and ascites are the two main consequences of portal hypertension.

PATHOPHYSIOLOGY OF VARICES:

- Anatomical collaterals that link the portal and systemic venous systems at certain locations cause varices. The portal system receives blood from the systemic circulation. Extrahepatic obstruction or intrahepatic resistance from cirrhosis and regenerative

nodules can both result in portal hypertension. The two primary causes are as follows. Vasodilation increases splanchnic blood flow; cirrhosis causes intrahepatic resistance or extrahepatic blockage, which increases portal vein flow resistance.[41]

- The presence of red color signs (RCS) marks, higher HVPG, higher grade of the CTP class, larger varices (>5 mm), active alcohol intake, and sepsis are some of the risk factors for VH. A pressure gradient observed within 24 hours is one of the high-risk variables for rebleeding.

- When the portal veins resistance is higher than the systemic, flow reversal results in portal hypertension. At portosystemic junctions, this results in dilated and distended collaterals.
  The goal of angiogenesis and the formation of new blood vessels is to reduce portal hypertension and expand the collateral bed. Vessels dilate, though, if the collateral is unable to withstand the pressure. Additional compromise may result in problems including bleeding and rupture.

  It is crucial to take varices into account while treating patients who have liver cell failure. After receiving a cirrhosis diagnosis, patients should have an endoscopy to rule out varices and start the right treatment. In the event of absence, yearly endoscopies and periodic checkups are advised. [41]

CAUSES OF PORTAL HYPERTENSION:

1. Prehepatic causes

-“Possible causes of portal vein obstruction include idiopathic conditions, cirrhosis, infections, pancreatitis, abdominal trauma, and coagulation abnormalities.

- Polycythemia Vera
- Essential thrombocytosis
- Protein C and S deficiency
- Antithrombin 3 deficiency
- Factor V Leiden.”

Symptoms may include splenic vein thrombosis, massive splenomegaly.

2. Hepatic Causes

a) “Presinusoidal Causes:

- Schistosomiasis
- Congenital hepatic fibrosis
- Sinusoidal cirrhosis (which can result from various underlying conditions)
- Alcoholic hepatitis”

b) “Postsinusoidal and Hepatic Sinusoidal Blockage”.

3. “Post-hepatic causes

- Budd-Chiari syndrome
- Webs in the inferior vena cava” - Caused by the heart
- Possible diagnoses include restrictive cardiomyopathy, constrictive pericarditis, and severe congestive heart failure.

"Increased levels of factor VIII (procoagulant driver) and decreased levels of protein C (anticoagulant driver), combined with reduced portal vein flow velocity and endothelial injury, increase the risk of portal vein thrombosis (PVT)." [41]

- The gastric collateral bed frequently experiences variceal development and hemorrhage. When HVPG levels rise above 10 mmHg, esophageal varices develop. The bottom 2 to 3 cm submucosa, which has a thin, fragile wall and is prone to bleeding, is usually where oesophageal varices are found. These arteries are challenging to decompress because they are unable to communicate with the periesophageal veins.
  Esophageal varices can range in size from little (less than 5 mm) to large (greater than 5 mm). Over time, tiny varices develop into enormous ones.

First bleeding in cirrhotic patients with varices can be predicted using several key risk factors:

- **Number of Varices** – More varices increase the risk.
- **Degree of Cirrhosis** – Higher Child-Pugh scores (especially **Child B or C**) indicate a greater risk.
- **Variceal Pressure** – A **hepatic venous pressure gradient (HVPG) >12 mmHg** is a strong predictor of bleeding.
- **Endoscopic Findings** – The presence of **red wale marks** (longitudinal red streaks on varices) suggests an increased likelihood of rupture

- **Epidemiology of Varices:**
  - The likelihood of developing varices rises as cirrhosis worsens. Approximately **40% of individuals with Child-Pugh class A** cirrhosis have varices, whereas the prevalence increases to **85% in those classified as Child-Pugh class C**.
  - Gastric varices (GVs) occur in 2–20% of cases, approximately one in five cirrhotic patients, and are less common but more severe than esophageal varices.
- **Types and Risks of Gastric Varices:**
  - GVs are commonly classified using the Sarin system:
    - Type 1 gastroesophageal varices (GOV1) represent 70% of GVs.
    - Type 2 gastroesophageal varices (GOV2) represent 21% of GVs.
  - IGV1(isolated gastric varices) has the highest risk of bleeding among GVs.
  - Cumulative bleeding risk from GVs: 16% at one year, 36% at three years, and 44% at five years.[42]
- **Clinical Impact of Variceal Bleeding:**
  - Acute variceal bleeding has a high mortality rate, with one-third of patients succumbing within six weeks.
  - Though less frequent than esophageal varices, GVs bleed more severely, with higher transfusion needs, rebleeding, and mortality rates.
- **Determinants of Bleeding Risk:**
  - For esophageal varices, hepatic venous pressure gradient (HVPG) predicts bleeding risk.
  - In GVs, bleeding risk depends on varix size, wall tension, and red colour signs rather than solely on PH severity.[43]

Management Considerations:

- Understanding the anatomy and pathophysiology of collateral pathways is essential for selecting optimal treatment options for bleeding from GVs.

ECTOPIC VARICES:

- Ectopic varices can occur in any part of the digestive system. Ectopic varices are ones that are not located in the stomach or esophagus but rather in another part of the gastrointestinal tract.[43]
- They are hard to spot and continue to be a covert bleeding source. For recognized cases, there aren't many known treatment choices. Upper gastrointestinal hemorrhage is now mostly diagnosed and treated using endoscopy[44.]

HEPATITIS B:

Definition:

- Hepatitis B virus is the most prevalent liver infection worldwide, caused by a DNA virus transmitted through percutaneous and per mucosal routes, as well as through sexual contact.
- **Transmission**: HBV is transmitted via blood, bodily fluids, sexual contact and from mother to child (perinatal transmission).[45]

- **Clinical Presentation**:
    - **Self-Limiting Infection**: In most adult-acquired cases, the infection resolves without treatment.
    - **Chronic Infection**: Infections acquired perinatally or during early childhood are more likely to progress to chronic HBV, which can lead to cirrhosis, hepatocellular carcinoma, or liver failure over time.

The **immune response** progresses through three distinct stages:

1. **Immune tolerance phase** – The immune system initially coexists with the pathogen without a strong response.
2. **Immune clearance phase** – Active immune mechanisms work to eliminate the pathogen.
3. **Quiescence phase** – The immune system stabilizes, with reduced activity and potential long-term viral persistence or resolution.

- Neonates are thought to be immunologically resistant since they have little immune reactivity, liver damage and a slight increase in transaminase levels. Nonetheless, the viral load is significant and the patient is HBeAg positive.

  A highly reactive immune system causes viral clearance and liver damage during the immune clearance phase, which lasts from the ages of 10 to 20. Enzyme levels are markedly increased during this period, although the HBV load is low.

  A weak immune response in older adults, typified by low levels of HBV DNA and enzymes, is referred to as the quiescent stage.

  Infrequently, they progress to chronic hepatitis. When HbsAg is detected for longer than six months, then it is diagnosed as chronic hepatitis B infection.

The estimated 5-year survival rate for individuals with chronic hepatitis B infection varies depending on disease progression. Approximately 10-20% of cases advance to cirrhosis over time.

"Compensated cirrhosis to Decompensated Cirrhosis" : 20-30%

Approximately 5-15% of compensated cirrhosis cases progress to HCC.

"Survival rates for compensated cirrhosis are 85 percent at 5 years and for decompensated cirrhosis, the rates range from 55 to 70 percent in the first year and 15 to 35 percent at 5 years."

"Factors modifying the course of Hepatitis B Infection":

1. **DURATION AND AMOUNT OF REPLICATION-**

Markers like HBeAg positivity and HBV DNA levels can provide insights into the duration and extent of viral replication. The severity and persistence of viral replication play a crucial role in the progression to Cirrhosis and Hepatocellular carcinoma (HCC)**.** Currently, Hepatitis B DNA levels are a key indicator for chronic hepatitis B (CHB) management and are incorporated into treatment guidelines. Effective treatment of CHB can significantly reduce the risk of liver disease progression.[46]

2. **ALCOHOL :**

Heavy alcohol intake with HBV can accelerate liver disease progression, increase the risk of HCC, and cause cirrhosis.

Indications for anti-viral therapy in CHB patients include the recently published German Guidelines.

- HBV DNA level exceeds 2000 IU/ml or 10,000 copies/ml.
- Any rise in ALT, as well as histological grading and staging.
- Patient with cirrhosis or advanced cirrhosis with detectable viremia.
- Immunosuppression can reactivate HBV replication and therefore preventative treatment is recommended.
- Alcohol and drug use are not contraindications for treatment.
- Antiviral in pregnancy: Lamivudine and tenofovir."

The primary goal of hepatitis B virus (HBV) treatment is to prevent the progression of liver disease, reducing the risk of cirrhosis and hepatocellular carcinoma (HCC)**.**

The clinical parameters used in assessing chronic hepatitis B include:

1. HBeAg seroconversion – The disappearance of HBeAg in an HBeAg-positive patient, leading to the development of anti-HBe antibodies.
2. HBsAg clearance – The disappearance of HBsAg and the subsequent formation of anti-HBs antibodies.
3. Liver enzyme normalization – The return of serum transaminase levels to a normal range, indicating reduced liver inflammation.
4. Suppression of viral replication – Extremely low or undetectable HBV DNA levels, signifying effective viral control.

Medications for Chronic Hepatitis B Treatment:

- Lamivudine
- Adefovir
- Telbivudine
- Tenofovir
- Pegylated Interferon-alpha 2a

HEPATITIS C:

"Co-infection with HCV and HBV leads to HCV symptoms, with low replication but rapid progression to cirrhosis and malignancy. CHB patients with HBV and HCV infection are more likely to progress to "Hepatorenal syndrome"(HRS).

Hepatorenal syndrome is a serious form of renal dysfunction in patients with cirrhosis and ascites.

Renal dysfunction is the most common complication in patients with liver cirrhosis and ascites, occurring in 20–49% of patients[47.]

For a long time, renal dysfunction in cirrhosis was synonymous with type 1 hepatorenal syndrome (HRS1), a condition associated with a fatal outcome in days to weeks if left untreated."

Treatment option for hepatorenal syndrome include Terlipressin which shown significant improvement in many patients.[48]

"Spontaneous bacterial peritonitis is diagnosed after paracentesis with ascites concentrations of neutrophil count greater than 250/μL. Up to one-third of patients with spontaneous bacterial peritonitis do not have fever or pain. Therefore, diagnostic paracentesis is recommended for all hospitalized patients with cirrhosis and ascites."

CHILD PUGH SCORE:

The Child-Pugh scoring system is a valuable tool for predicting survival outcomes in various liver diseases. It helps assess the likelihood of complications such as cirrhosis, esophageal varices, and spontaneous bacterial peritonitis**.**

Cirrhosis can be classified into different stages based on clinical assessment**.** The modified Child-Pugh score**,** ranging from **5 to 15**, is a widely used and reliable method for staging cirrhosis.

- "Child Pugh CLASS A: Scores of 5-6 indicate compensated cirrhosis.
- Child Pugh CLASS B: Scores of 7 to 9 indicate decompensated cirrhosis.
- Child Pugh CLASS C: Scores >10 indicate decompensated cirrhosis."

The Child-Pugh scoring system evaluates liver function based on five key factors:

1. Serum bilirubin levels
2. Serum albumin levels
3. Presence of ascites
4. Severity of hepatic encephalopathy
5. Prothrombin time (or INR)

These parameters help determine the severity of liver disease and guide prognosis and treatment decisions.

"It accurately predicts survival and major complications such as variceal bleeding and SBP. It has been used to assess the prognosis of liver cirrhosis and to establish uniform criteria for listing liver transplant patients."

MATERIAL AND METHODS

METHODOLOGY

Source of Data

- **Study Setting**:
  Conducted at BLDE (Deemed-to-be University) Shri B.M. Patil Medical College, Hospital & Research Centre, Vijayapura, Karnataka, India**.**

- **Study Period**:
  Data collected from May 2023 to December 2025**.**

- **Study Population**:
  Patients diagnosed with chronic liver disease (cirrhosis) from Medicine wards (IPD/OPD)**.**

2. Data Collection Method

- **Structured Proforma**:
  - Demographic, clinical, and laboratory data recorded.
  - Face-to-face interviews for sociodemographic details.
  - Informed consent obtained with confidentiality assurance.

- **Laboratory & Radiological Investigations**:
  - **Blood tests**: Albumin, ALT, AST, serum ammonia, aPTT, BUN, creatinine, glucose, Hb, Hct, INR, platelet count, PT.
  - **Imaging**: USG abdomen and pelvis.

3. Inclusion Criteria

- **Confirmed cirrhosis** (clinical, lab, radiological evidence).

4. Exclusion Criteria

- Recent OHE, GI bleed, or infections (past 2 weeks).
- **Medications**: Lactulose/antibiotics/psychoactive drugs (past 2 weeks).
- **Comorbidities**:
    - Neurological/psychiatric disorders (MMSE < 25).
    - Heart/respiratory/renal failure, HCC, malignancies, TIPS/shunt surgery.
- **Illiteracy** affecting consent/PHES administration.

5. Study Design

- Type**:** Prospective cross-sectional study**.**

6. Sample Size Calculation

- **Justification**:
    - Detecting ammonia level differences between MHE vs. non-MHE groups.
    - **Parameters**:
        - MHE group (Mean NH_3 = 15.91 μmol/L, SD = 3.01).
        - Non-MHE group (Mean NH_3 = 19.41 μmol/L, SD = 4.83).
    - **Power**: 80%, $\alpha = 0.05$ (two-tailed).
    - **Tool**: G*Power 3.1.9.4 → Total sample = 166 (83 per group).

7. Statistical Analysis

- **Software**: SPSS v20.

- **Descriptive Statistics**:
    - Mean ± SD (continuous variables).
    - Counts/percentages (categorical variables).

- **Comparative Tests**:
    - Independent t-test: Normally distributed variables.
    - Mann-Whitney U test: Non-normal distributions.
    - Chi-square/Fisher's exact test: Categorical variables.
- Significance Threshold**:** $p < 0.05$.

RESULTS

Results

Comparison of Age Categories Between the Groups

Age Category	Controls n (%)	Cases n (%)	
<=29	14 (16.87%)	4 (4.82%)	
30-39	23 (27.71%)	16 (19.28%)	
40-49	17 (20.48%)	36 (43.37%)	
>=50	29 (34.94%)	27 (32.53%)	

Table 2 : It represents the distribution of age categories among the control and case groups. The age distribution significantly differed between the groups , with a higher proportion of individuals aged 40-49 years in the case group (43.37%) compared to the control group (20.48%).

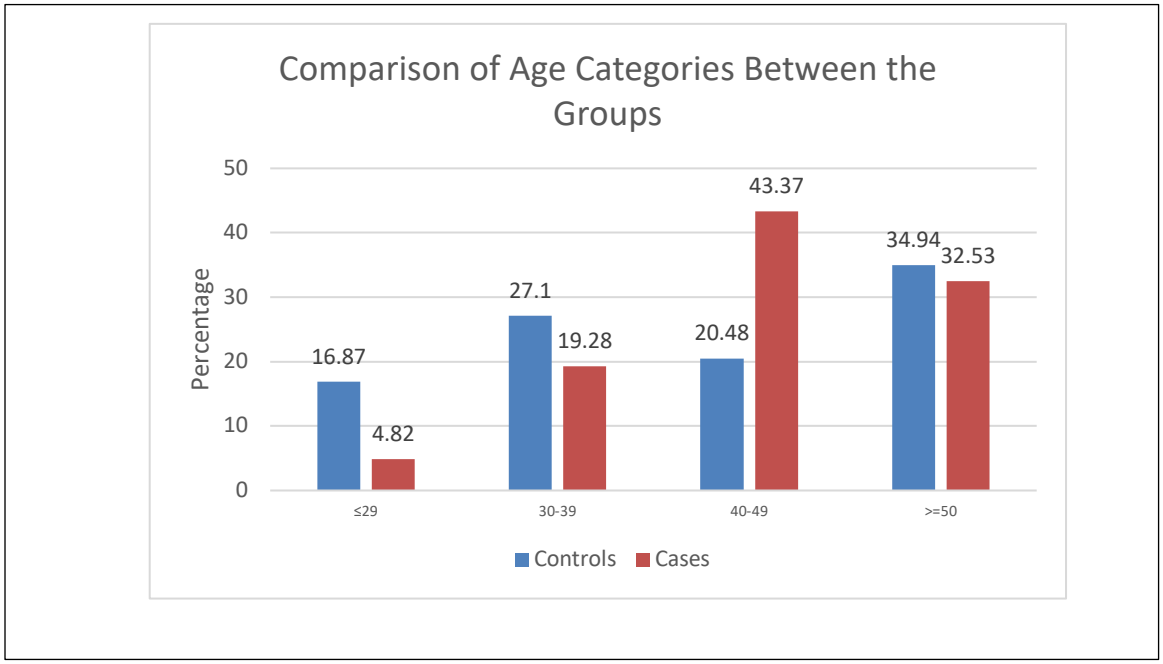


FIGURE 4 :AGE GRAPH

Comparison of Gender Between the Groups

Gender	Controls n (%)	Cases n (%)	
Female	27 (32.53%)	6 (7.23%)	
Male	56 (67.47%)	77 (92.77%)	

Table 3:The gender distribution between cases and controls is shown. A significantly higher proportion of males were in the case group (92.77%) compared to the control group (67.47%) .

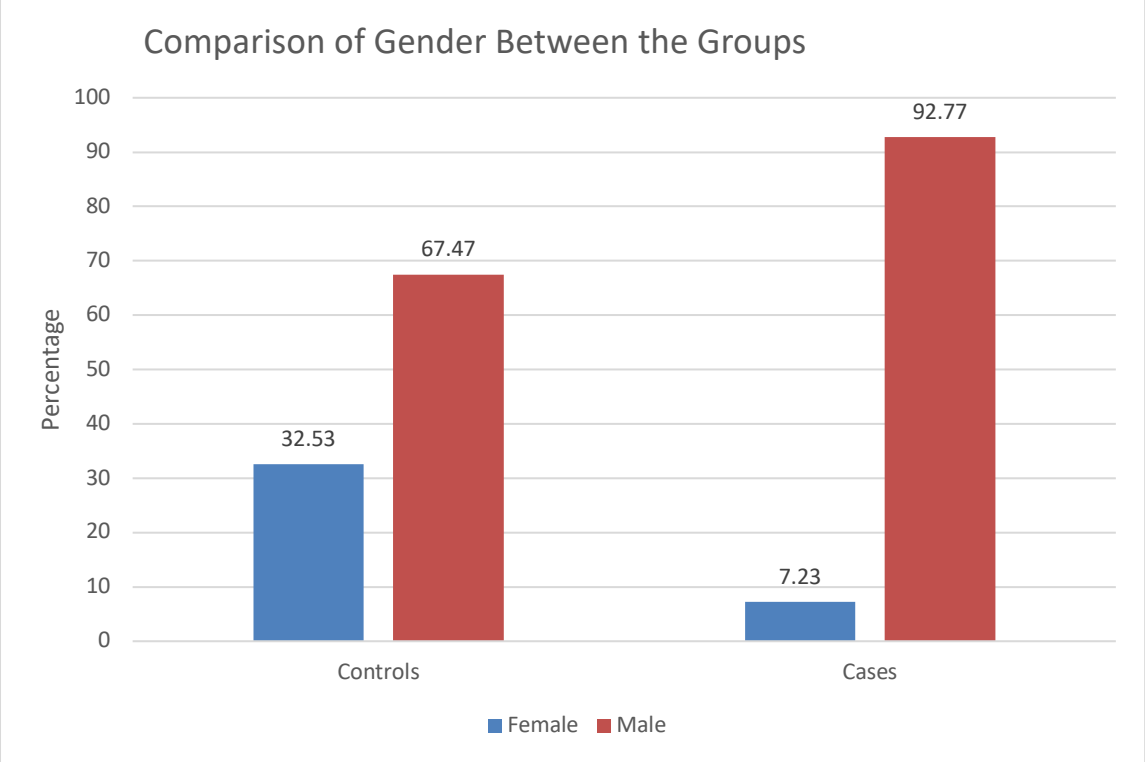


FIGURE :5 GENDER GRAPH

Correlations between psychometric tests and age and education years

Variable	NCTA	NCTB	SDT	LTT	DST
Age	0.0424	-0.0038	-0.0645	-0.0683	0.0167
Education	-0.0360	-0.0117	-0.0690	-0.0795	-0.1570

Table 4: This table shows the correlation coefficients between age, education, and different psychometric tests. Age demonstrated weak correlations with all tests, while education showed weak negative correlations across all cognitive test scores.

Regression Results for Cognitive Tests

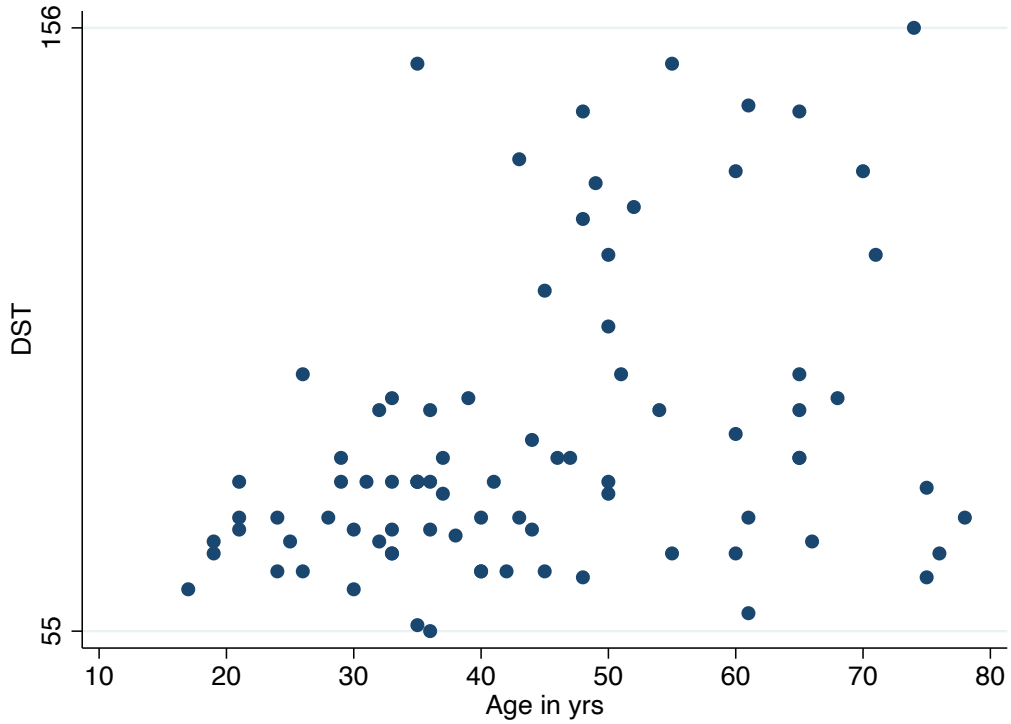
Test	Equation	SD
NCTA	36.153 + 0.749 × Age + 2.892 × Education	53.667
NCTB	77.946 + 0.749 × Age + 2.334 × Education	51.510
SDT	21.837 + 0.443 × Age + 1.644 × Education	40.089
LTT	52.123 + 0.751 × Age + 3.465 × Education	90.903
DST	72.089 + 1.193 × Age + 3.883 × Education	86.587

Table 5: The regression equations indicate that both age and education significantly influence cognitive test performance. For NCT-A, the equation suggests that for every additional year of age, the score increases by 0.749, and for each additional year of education, the score increases by 2.892. Similarly, NCT-B scores follow a comparable trend, with an increase of 0.749 per year of age and 2.334 per year of education.

The SDT equation indicates a comparatively smaller effect of both predictors, with coefficients of 0.443 for age and 1.644 for education. The LTT and DST models show larger coefficients for education, suggesting that individuals with higher education levels tend to perform better on these tests. The standard deviations for each test indicate variability in the cognitive test scores, with the highest variability observed in LTT (SD = 90.903) and DST (SD = 86.587).

These findings suggest that age has a positive association with cognitive test scores, implying that older individuals may take longer to complete the tests, indicating cognitive slowing.

On the other hand, education appears to have a beneficial effect, improving test performance and reducing response time. These results highlight the significant influence of demographic factors on cognitive function, which is crucial when assessing cognitive impairments such as minimal hepatic encephalopathy (MHE) using psychometric tests.



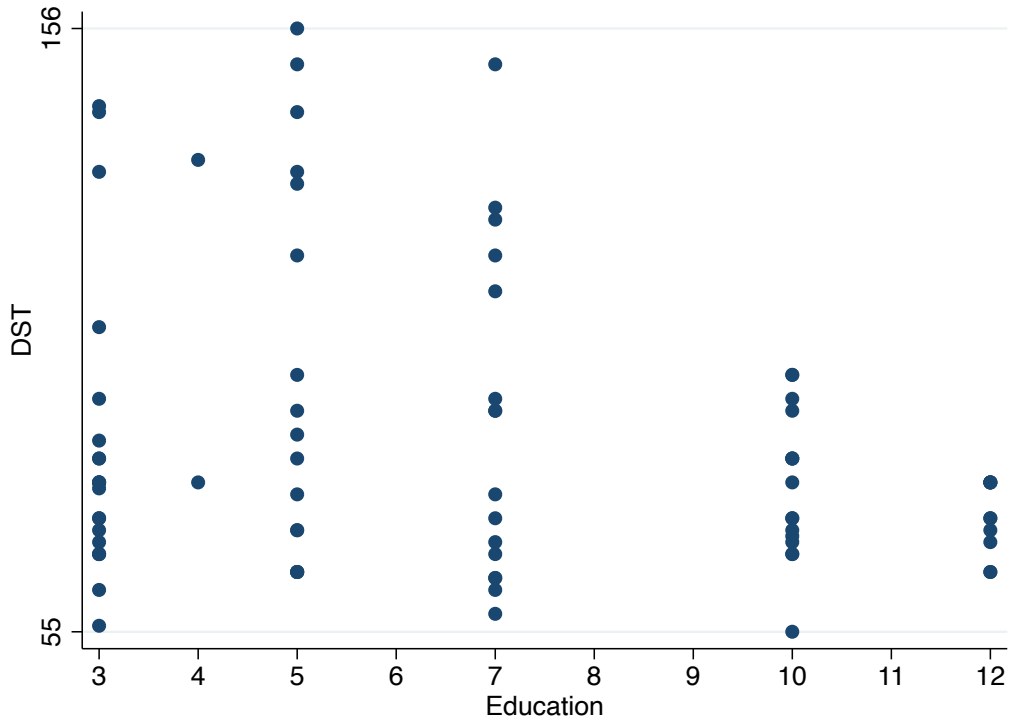


Figure 4 & 5: Distribution of the results from the digit symbol test in healthy individuals to age and education years

Clinical characteristics of patients with liver cirrhosis

Variable	No MHE Mean (SD)	MHE Mean (SD)	t-value/U/χ^2	P-value
Age	46.90 (9.89)	42.39 (10.64)	1.93	0.057
Education	7.59 (3.63)	8.48 (3.13)	-1.13	0.263
Sex				
Female	3 (6.12%)	0 (0%)	χ^2=1.97	0.160
Male	46 (93.88%)	31 (100%)		
SAMMONIA	40.00 (11.22)	33.52 (11.08)	2.53	0.013
CTP SCORE	8.47 (1.42)	9.52 (1.53)	-3.13	0.002
NCTA	95.37 (36.53)	173.35 (42.67)	-8.71	<0.001
NCTB	135.85 (29.12)	204.58 (50.49)	-7.67	<0.001
SDT	55.80 (22.34)	116.52 (36.60)	-9.23	<0.001
DST	177.52 (51.46)	286.42 (48.34)	-9.40	<0.001

Table 6: This table compares clinical characteristics between patients with and without minimal hepatic encephalopathy (MHE). Patients with MHE had significantly higher CTP scores, NCTA, NCTB, SDT, and DST scores ($p < 0.001$ for all), indicating cognitive impairment associated with MHE. Additionally, AMMONIA levels were significantly lower in the MHE group ($p = 0.013$), while age and education did not differ significantly.

Comparisons between psychometric hepatic encephalopathy score (MHE status) and number connection test-A, number connection test-B, and digit symbol test

Diagnostic Test	Sensitivity	Specificity	PPV	NPV	AUC	Kappa
NCT-A + NCT-B abnormal	93.55%	78.03%	50.00%	98.10%	0.858	0.537
NCT-A + DST abnormal	77.42%	90.15%	64.86%	94.44%	0.838	0.560
NCT-B + DST abnormal	77.42%	88.64%	61.54%	94.35%	0.830	0.545
All of the three tests were abnormal	77.42%	90.15%	64.86%	94.44%	0.838	0.560
At least One of NCT-A/NCT-B abnormal	100.00%	54.55%	34.07%	100.00%	0.773	0.401
At least One of NCT-A/DST abnormal	100.00%	62.12%	38.27%	100.00%	0.811	0.449
At least One of NCT-B/DST abnormal	93.55%	68.94%	41.43%	97.85%	0.812	0.471
At least one of NCT-A/NCT-B/DST abnormal	100.00%	54.55%	34.07%	100.00%	0.773	0.401
At least two of NCT-A/NCT-B/DST abnormal	16.13%	86.36%	21.74%	81.43%	0.512	0.220

- Table 7: The combination of NCT-A and NCT-B abnormalities had high sensitivity (93.55%) and moderate specificity (78.03%), with an AUC of 0.858 and a kappa value of 0.537, indicating a moderate agreement.
- Similarly, the combination of NCT-A and DST showed slightly lower sensitivity (77.42%) but higher specificity (90.15%), with an AUC of 0.838 and a kappa value of 0.560, suggesting good diagnostic accuracy. The combination of NCT-B and DST had a similar sensitivity (77.42%) and slightly lower specificity (88.64%), with an AUC of 0.830 and a kappa of 0.545.

- The use of all three tests resulted in an AUC of 0.838, indicating strong diagnostic value, while at least one of NCT-A/NCT-B

abnormalities had 100% sensitivity but lower specificity (54.55%), leading to an AUC of 0.773 and a kappa value of 0.401, which suggests limited agreement. The use of at least two tests abnormal had significantly lower sensitivity (16.13%) but higher specificity (86.36%), indicating its potential role in ruling out MHE rather than diagnosing it.

- Overall, these findings demonstrate that while combining multiple psychometric tests increases sensitivity, it can reduce specificity, and tests that balance both sensitivity and specificity (such as NCT-A + DST or NCT-B + DST) may be more useful for accurate detection of MHE. The AUC values and kappa statistics further support these observations, highlighting the importance of selecting appropriate diagnostic tools for evaluating cognitive impairment in liver disease patients.

Comparison of Education Categories Between the Groups

Education Category	Controls n (%)	Cases n (%)	P-value
Primary	57 (68.67%)	48 (57.83%)	0.330
Secondary	16 (19.28%)	20 (24.10%)	
Higher Secondary and Above	10 (12.05%)	15 (18.07%)	

Table 8: The comparison of education categories between the groups shows that a higher proportion of controls had primary education (68.67%) compared to cases (57.83%), while secondary and higher secondary education levels were slightly more prevalent among cases. However, the difference was not statistically significant (p=0.330).

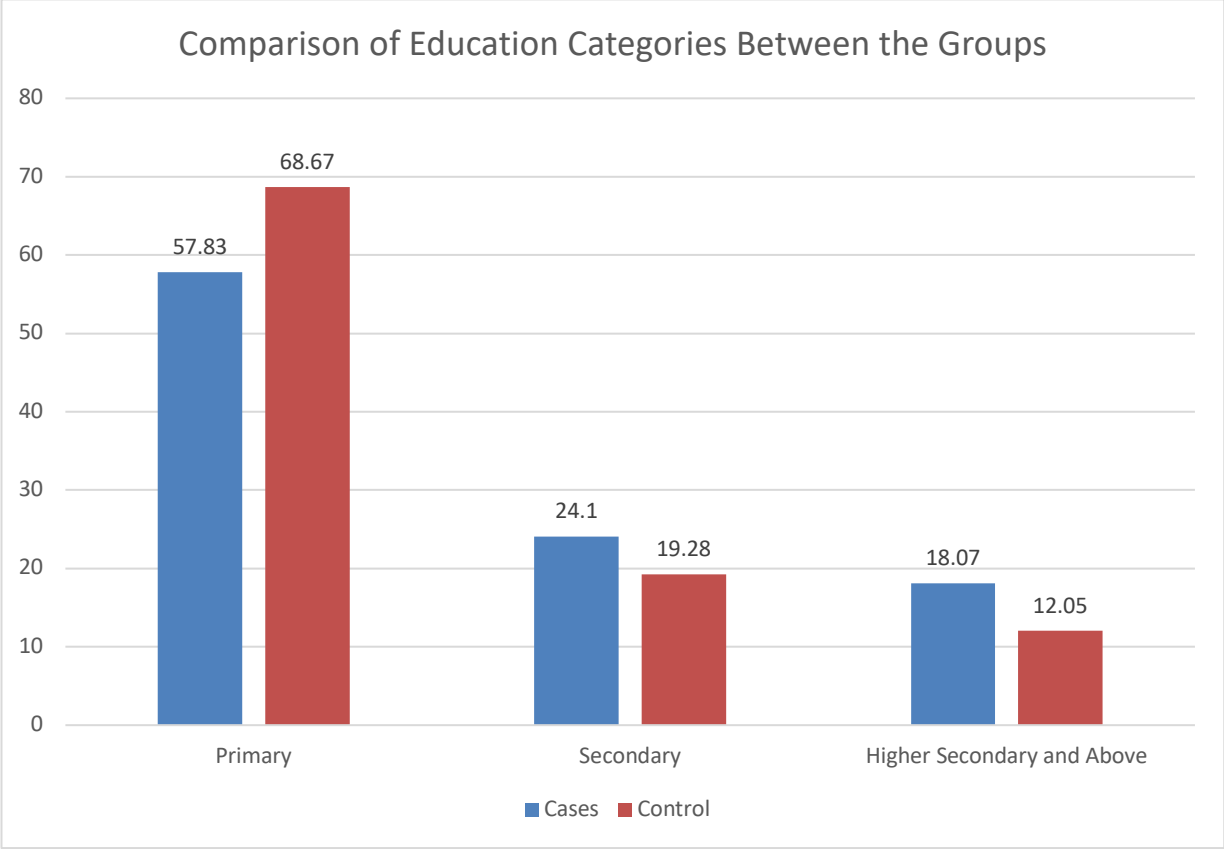


FIGURE : 6 EDUCATION GRAPH

Comparison of MHE Status Between the Groups

MHE Status	Controls n (%)	Cases n (%)	P-value
MHE	0 (0.00%)	31 (37.35%)	<0.001
No MHE	83 (100.00%)	49 (59.04%)	
Not Completed	0 (0.00%)	3 (3.61%)	

Table 9: The comparison of MHE status between the groups indicates that MHE was present in 37.35% of cases, whereas no controls had MHE. Additionally, 3.61% of cases had incomplete MHE assessments. This difference was highly significant (p<0.001).

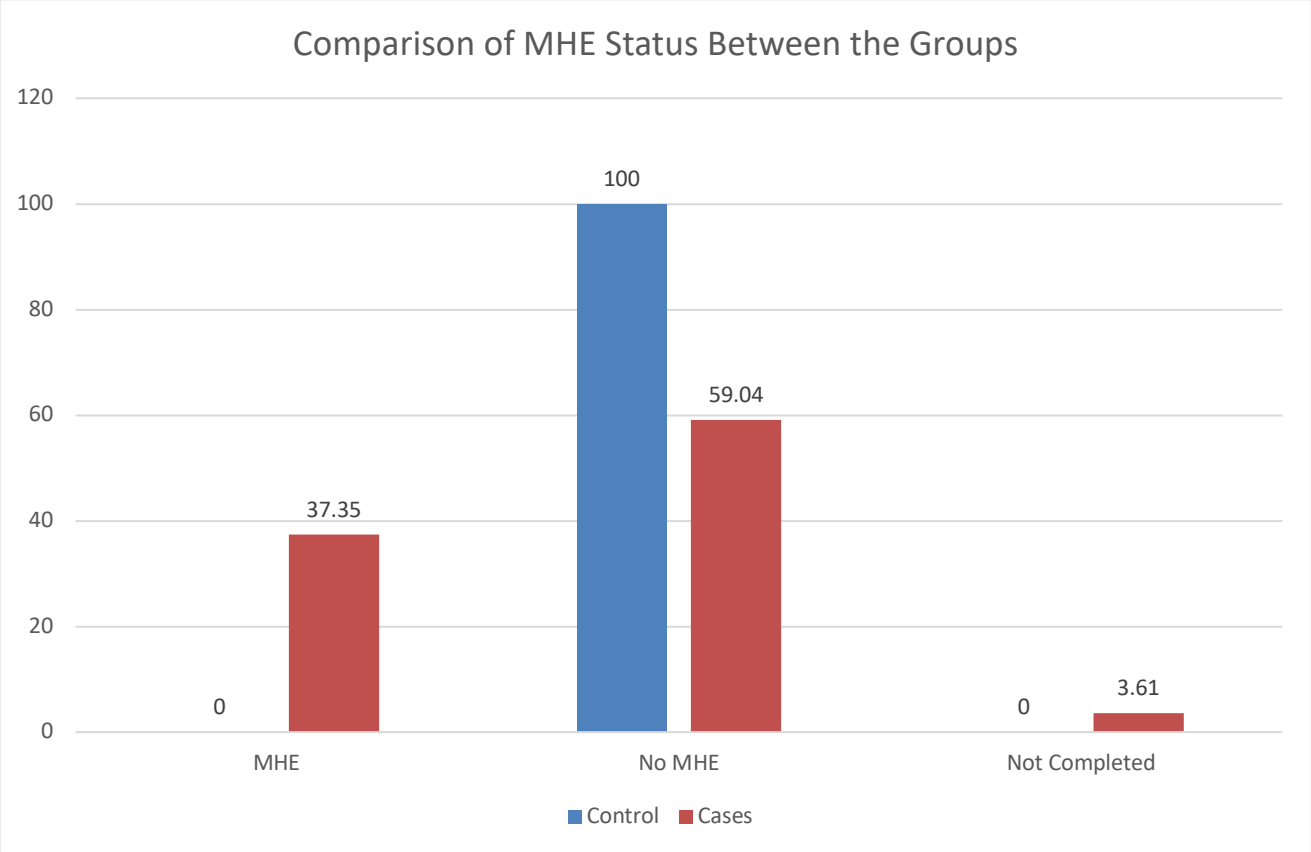


FIGURE : 7 MHE GRAPH

Comparison of NCTA Between the Groups

Groups	Mean	SD	t	P-value
Cases	127.31	54.33	-11.69	<0.001
Controls	54.48	16.48		

Table 10:The comparison of NCTA scores between the groups shows that cases had a significantly higher mean score (127.31 ± 54.33) compared to controls (54.48 ± 16.48). The large difference in means resulted in a highly significant t-value of -11.69 ($p<0.001$), indicating that cases had significantly poorer performance in this test, which is indicative of cognitive impairment.

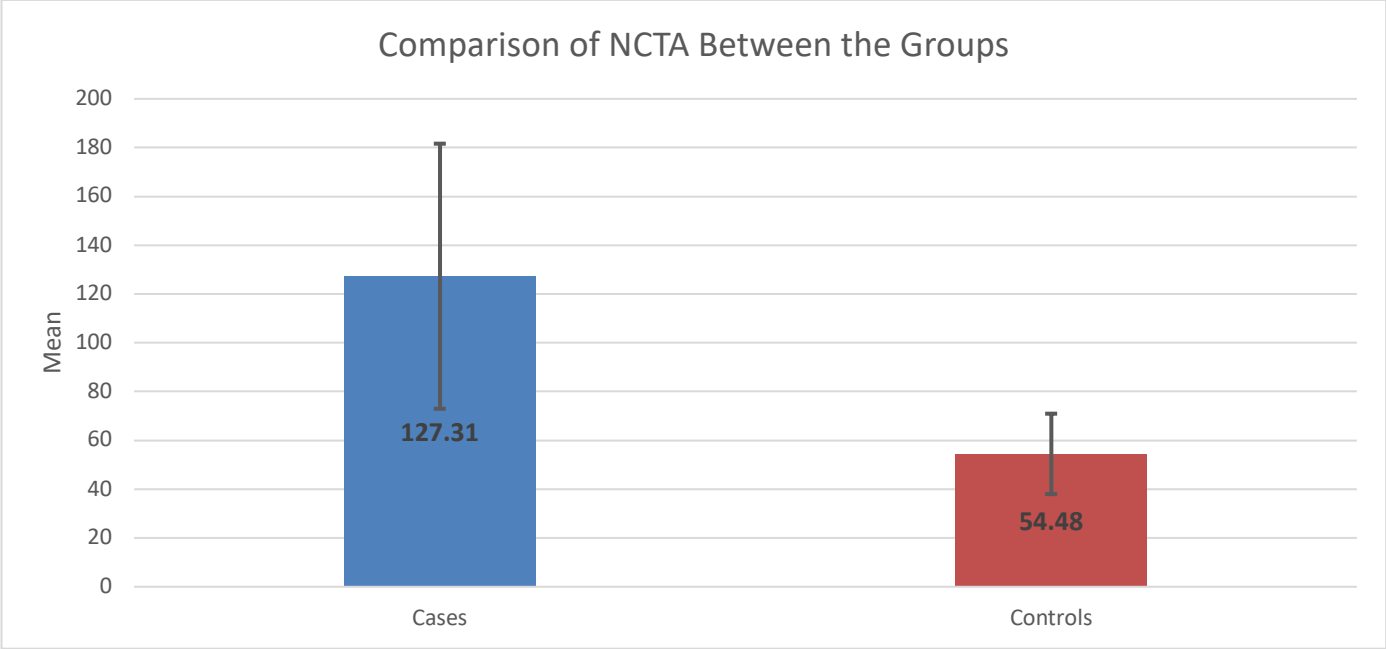


FIGURE:10 NCT-A GRAPH

Comparison of NCTB Between the Groups

Groups	Mean	SD	t	P-value
Cases	162.82	51.30	-10.76	<0.001
Controls	95.70	23.86		

Table 11:The comparison of NCTB scores revealed a similar trend, with cases having a substantially higher mean score (162.82 ± 51.30) compared to controls (95.70 ± 23.86). The statistical analysis yielded a t-value of -10.76 ($p<0.001$), further supporting the presence of significant cognitive dysfunction in cases as assessed by this test.

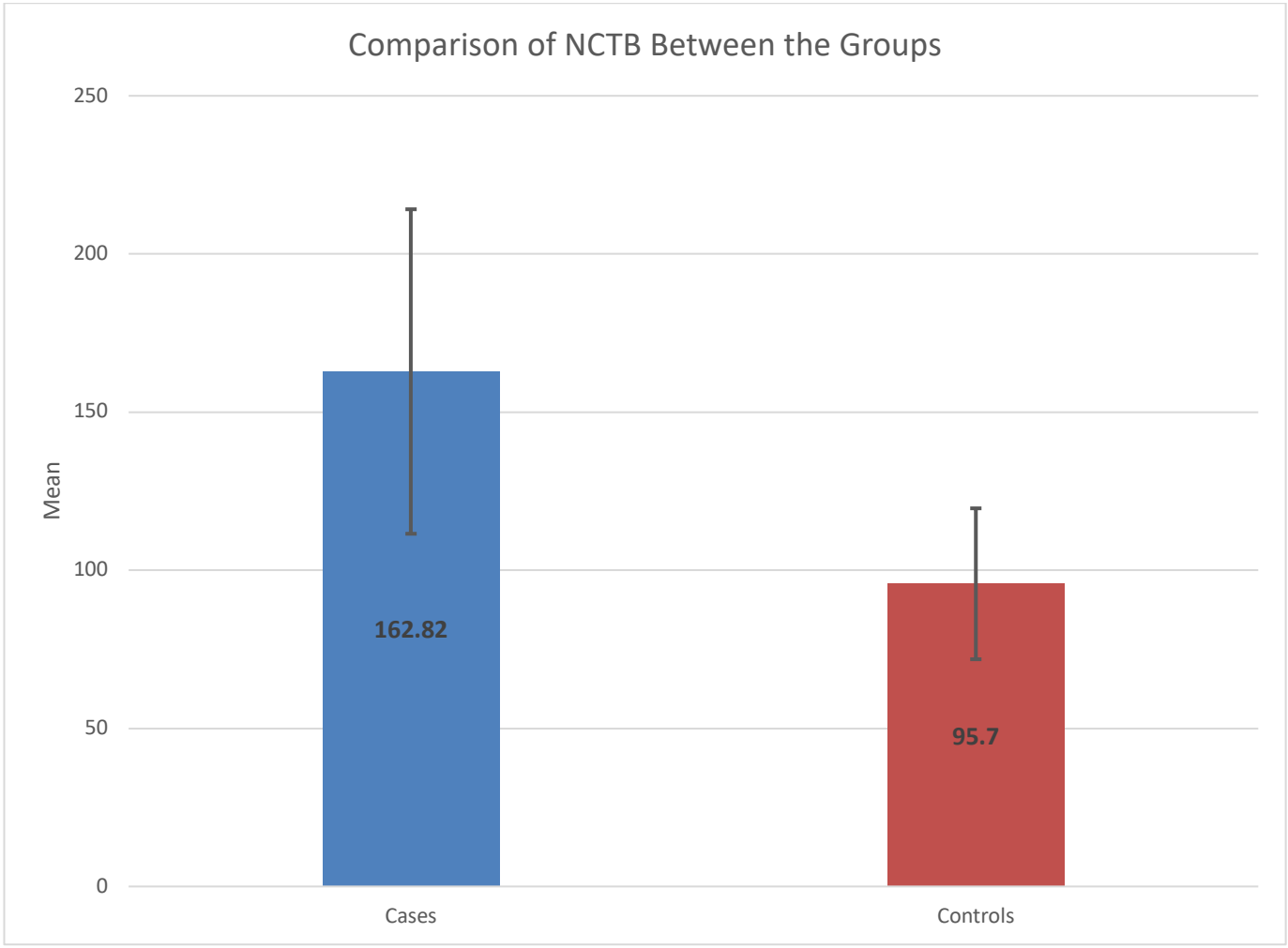


FIGURE :9 NCT-B GRAPH

Comparison of SDT Between the Groups

Groups	Mean	SD	t	P-value
Cases	80.23	41.75	-11.25	<0.001
Controls	27.29	9.76		

Table 12: For SDT, cases had a much higher mean score (80.23 ± 41.75) than controls (27.29 ± 9.76), indicating a significant difference in performance. The t-value of -11.25 and a p-value <0.001 highlight the substantial disparity between the two groups, reinforcing the association between cognitive decline and the condition under study.

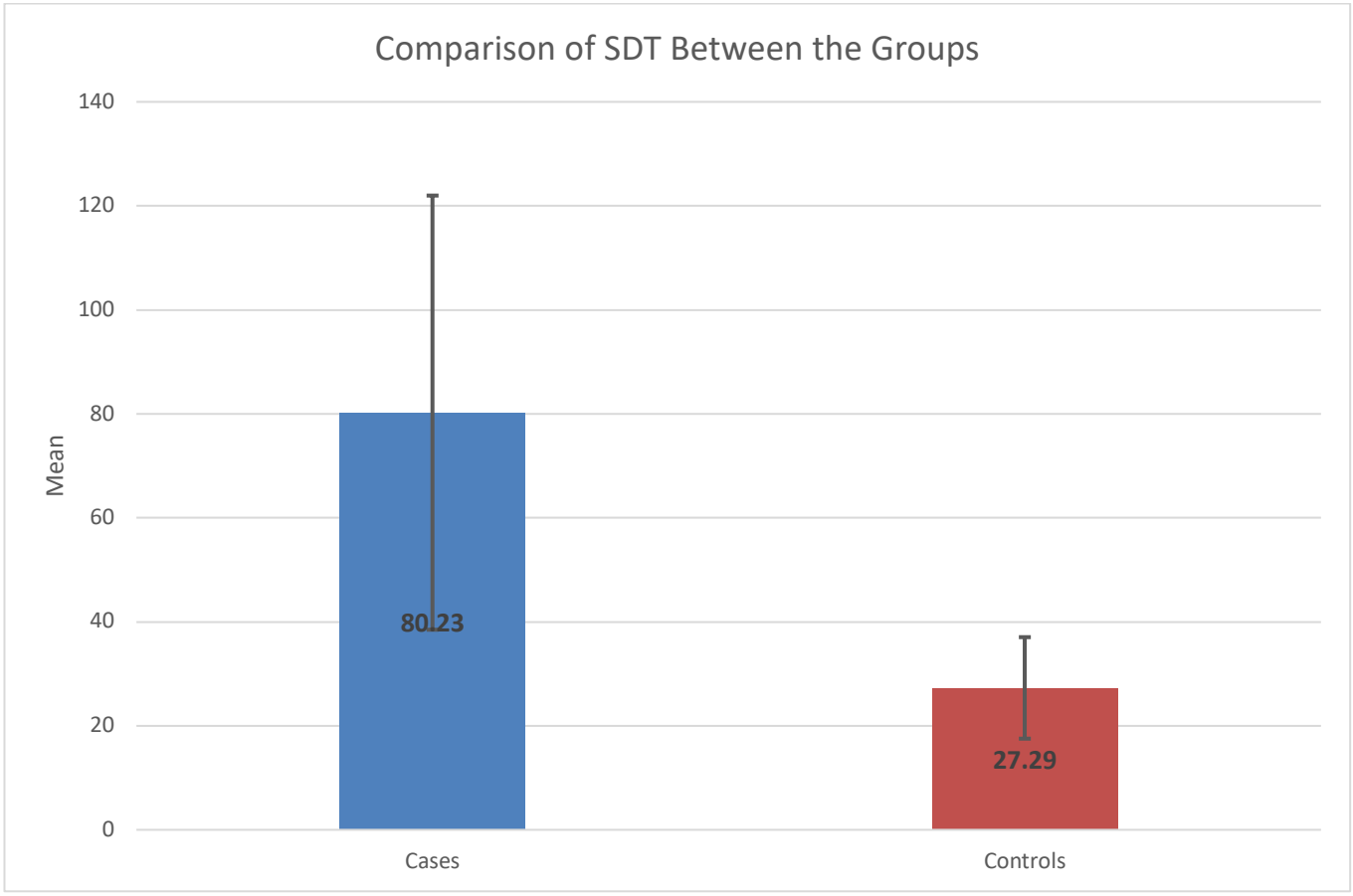


FIGURE :10. SDT GRAPH

Comparison of LTT Between the Groups

Groups	Mean	SD	t	P-value
Cases	172.68	93.44	-11.71	<0.001
Controls	50.12	19.06		

Table 13: The LTT comparison shows that cases had a markedly higher mean score (172.68 ± 93.44) than controls (50.12 ± 19.06). This difference was statistically significant with a t-value of -11.71 ($p<0.001$), suggesting that cases exhibited significantly worse performance in this cognitive assessment, likely due to underlying cognitive impairment.

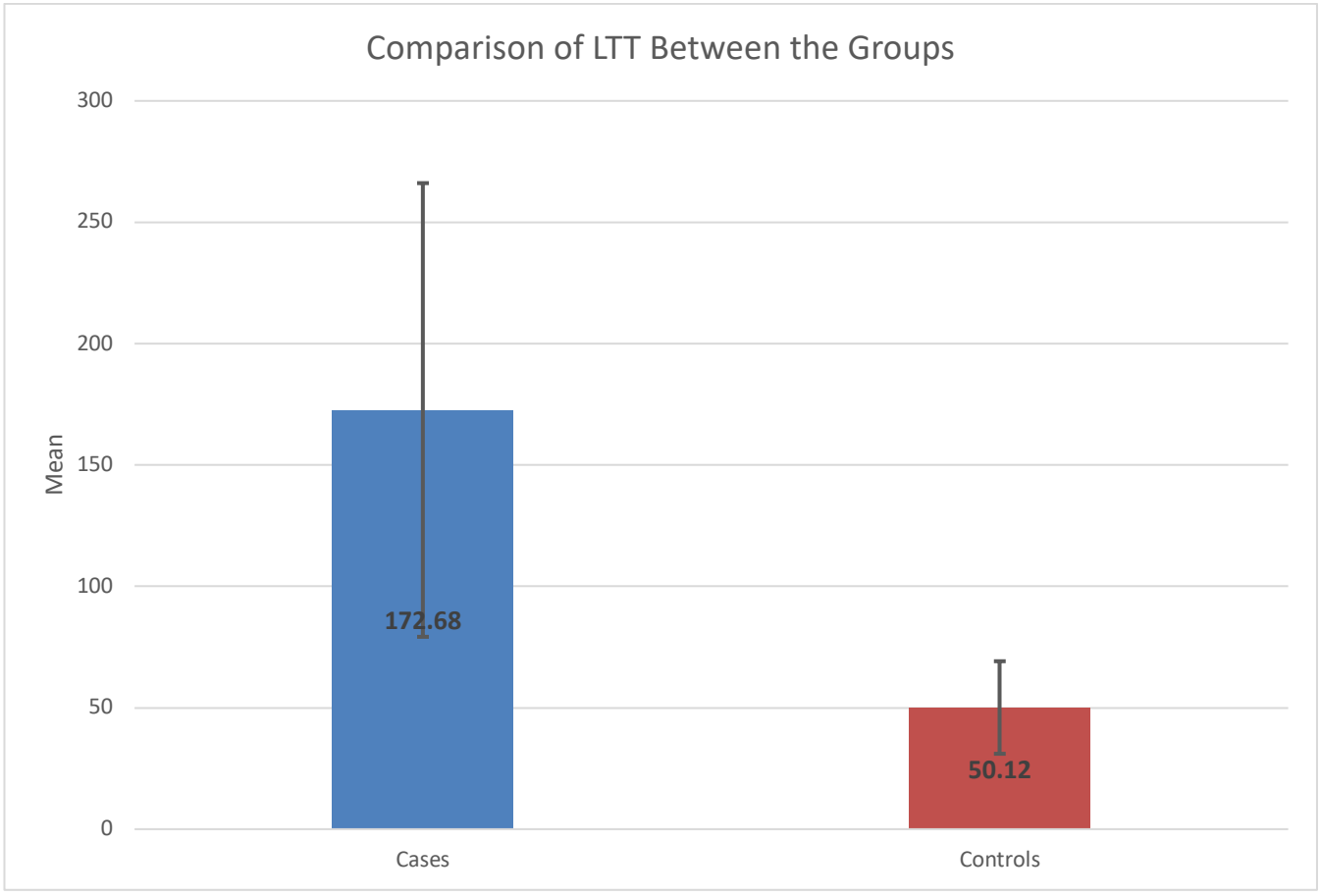


FIGURE 11: LTT GRAPH

Comparison of DST Between the Groups

Groups	Mean	SD	t	P-value
Cases	222.59	73.78	-15.84	<0.001
Controls	87.00	24.96		

Table 14: The DST scores also showed a significant difference between the groups, with cases scoring an average of 222.59 ± 73.78, compared to 87.00 ± 24.96 for controls. The t-test result (-15.84, $p<0.001$) indicates a highly significant difference, suggesting that DST is strongly associated with cognitive dysfunction in the cases group.

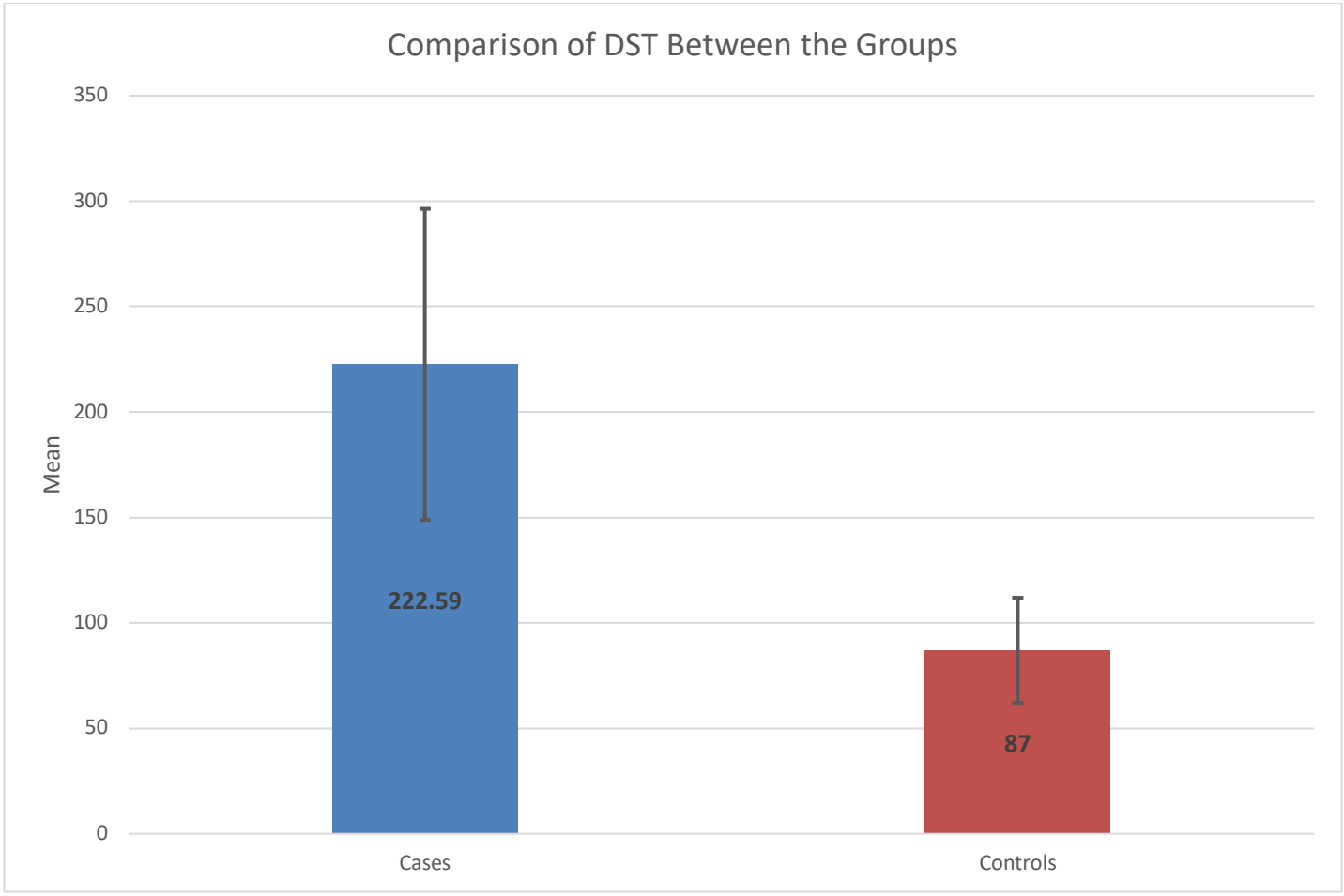


FIGURE 12 : DST GRAPH

: Comparison of PHES Between the Groups

Groups	Mean	SD	t	P-value
Cases	-4.40	3.89	14.92	<0.001
Controls	2.28	1.21		

Table 15: The PHES comparison demonstrated that cases had a significantly lower mean score (-4.40 ± 3.89) than controls (2.28 ± 1.21), indicating poorer cognitive performance among cases. The t-value of 14.92 and p-value <0.001 confirm the statistical significance of this difference, further supporting the role of PHES in distinguishing cases from controls based on cognitive function.

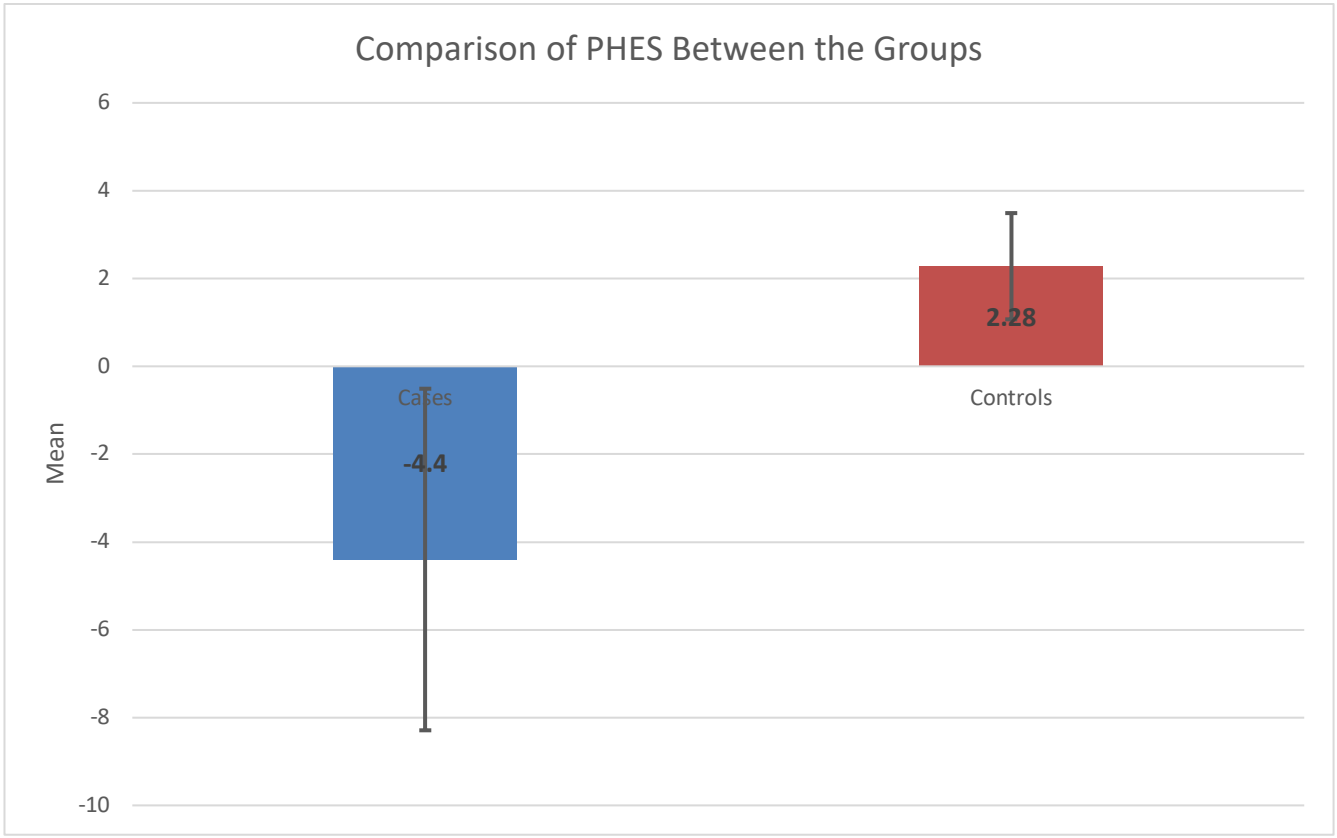


FIGURE 13: PHES GRAPH

DISCUSSION

DISCUSSION

MHE Detection: An Unmet Clinical Need

Minimal hepatic encephalopathy (MHE), a subclinical cognitive complication of cirrhosis, remains underdiagnosed due to the absence of routine screening and standardized tools. This study validates the Psychometric Hepatic Encephalopathy Score (PHES) as a pragmatic solution, identifying MHE in 37.35% of cirrhotic patients—a prevalence consistent with global reports (20–80%) and closely linked to worsening liver function (higher Child-Pugh scores). Notably, NCT-A and DST emerged as efficient screening alternatives, combining high sensitivity (77.42%) and specificity (90.15%) with brevity.

PHES Performance and Normative Adjustments

While age and education influenced individual test components (e.g., DST β=+3.883 for education), their impact was mitigated by regression-based adjustments, ensuring PHES reliability. Key observations:

- Healthy controls showed stable PHES scores across demographics, supporting standardized cutoffs (e.g., PHES < -4 for MHE).
- Contrary to Spanish studies citing gender effects, our cohort's performance was driven by liver disease severity, not sex or age.[1]

Ammonia Paradox and Pathophysiological Insights

Despite ammonia's established role in HE, this study found lower ammonia levels in MHE patients (33.52 vs. 40.00 μmol/L, p=0.013). This discordance suggests:

1. Non-ammonia mechanisms (e.g., systemic inflammation, gut dysbiosis) may contribute to MHE.
2. Single ammonia measurements lack sensitivity; chronic encephalopathy may require alternative biomarkers.

Clinical Utility of NCT-A and DST

- **NCT-A**: Discriminated MHE with 2.3× longer completion times in cases (127.31s vs. 54.48s, $p<0.001$).
- **DST**: Highly education-dependent but effective for rapid screening.
  Practical implication: In resource-limited settings, NCT-A alone could prioritize patients for full PHES testing.

Limitations and Future Directions

1. **Single-centre design**: External validation needed.
2. **Ammonia variability**: Serial measurements or alternative biomarkers (e.g., inflammatory cytokines) may clarify MHE drivers.
3. **Incomplete tests**: 3.61% of cases could not complete PHES, highlighting a need for ancillary tools (e.g., CFF) in severe cirrhosis.

CONCLUSION

1. Routine PHES screening should be integrated into cirrhosis care, especially for Child-Pugh B/C patients.
2. NCT-A and DST are viable for rapid clinics triage.
3. Ammonia-independent pathways warrant exploration in MHE pathogenesis.

This study reinforces PHES as the gold standard for MHE diagnosis while advocating for pragmatic adaptations to enhance early detection and intervention.

Key Strengths:

- Large sample (*n*=166) with age/education-adjusted analyses.
- Validated PHES against both healthy controls and cirrhosis-specific outcome.

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ANNEXURE I

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 880/2022-23 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology,** scrutinizes the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR DIAGNOSIS OF MINIMAL HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.MARAGARI MOUNIKA

NAME OF THE GUIDE: DR.MALLANNA S.MULIMANI, PROFESSOR, DEPT. OF MEDICINE.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA

MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103. Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.
BLDE (DU): Phone: +918352-262770, Fax: +918352-263303, Website: www.bldedu.ac.in, E-mail:office@bldedu.ac.in
College: Phone: +918352-262770, Fax: +918352-263019, E-mail: bmpmc.principal@bldedu.ac.in

ANNEXURE II

BLDE(DEEMED TO BE UNIVERSITY)
SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE,VIJAYAPURA-586103

INFORMED CONSENT FORM

TITLE OF THE PROJECT - :

PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR DIAGNOSIS OF MINIMAL HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER

P.G. GUIDE NAME - Dr. MALLANNA S MULIMANI

PROFESSOR , DEPARTMENT OF MEDICINE.

PRINCIPAL INVESTIGATOR- Dr. MARAGARI MOUNIKA

All aspects of this consent form are explained to the patient in the language understood by him/her.

INFORMED PART

PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in this study will help to patient's survival and better outcome.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. The researcher is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that researcher may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Dr. MARAGARI MOUNIKA Date

(Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. MARAGARI MOUNIKA has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

ANNEXURE – III

BLDE (DEEMED TO BE UNIVERSITY)

SHRI B.M. PATIL MEDICAL COLLEGE

VIJAYAPURA, KARNATAKA

SCHEME OF CASE TAKING

Informant :

NAME: CASE NO:

AGE: IP NO:

SEX: DOA:

RELIGION: DOD:

CHIEF COMPLAINTS:

HISTORY OF PRESENT ILLNESS:

PAST HISTORY:

PERSONAL HISTORY:

FAMILY HISTORY:

TREATMENT HISTORY:

GENERAL PHYSICAL EXAMINATION

VITALS

PR:

BP:

RR:

TEMP:

PALLOR:

ICTERUS:

CYANOSIS

CLUBBING

LYMPHADENOPATHY

EDEMA

ABDOMINAL GIRTH:

SYSTEMIC EXAMINATION

PER ABDOMEN:

CENTRAL NERVOUS SYSTEM:

HEPATIC ENCEPHALOPATHY

GRADING-

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM:

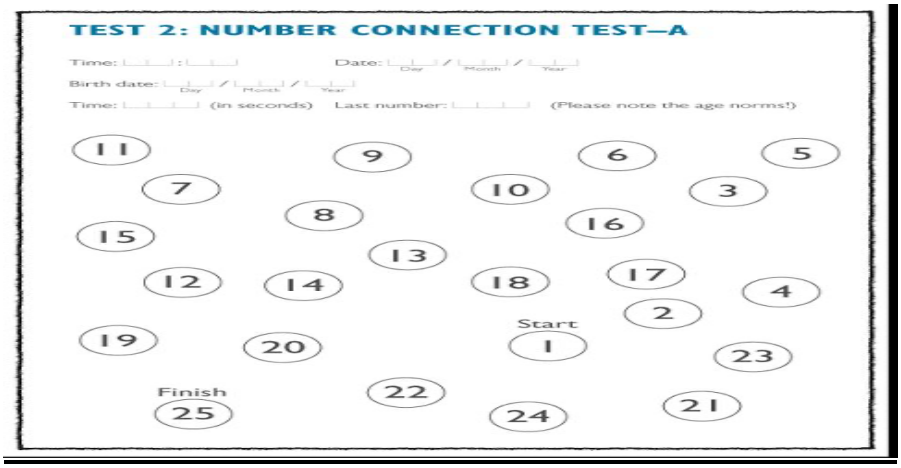
RADIOLOGICAL INVESTIGATION-

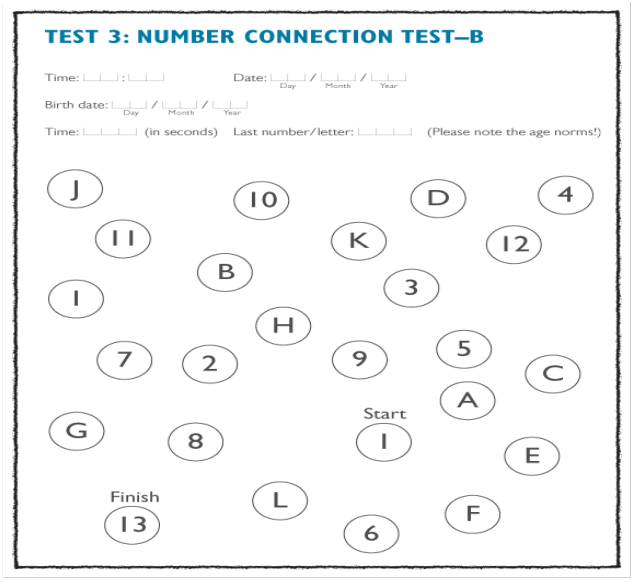
USG

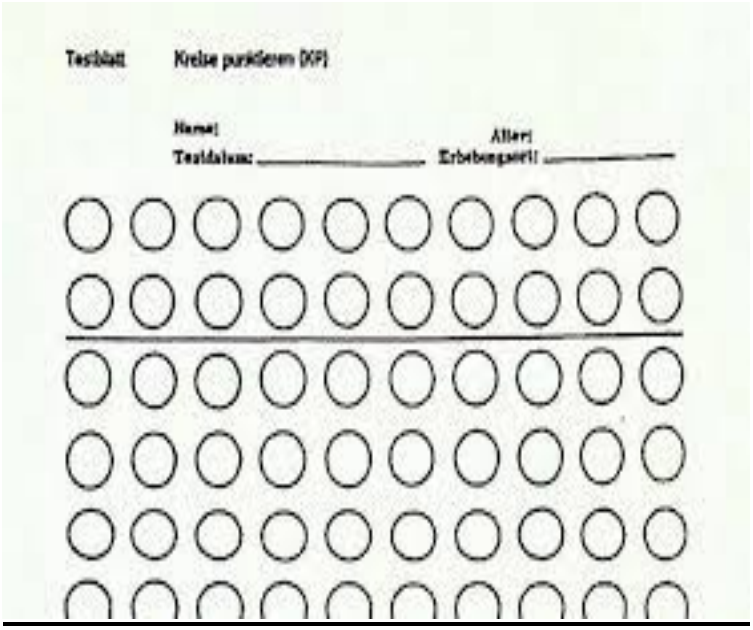
ECG-

PSYCHOMETRIC TESTS:

TOTAL PHES SCORE-





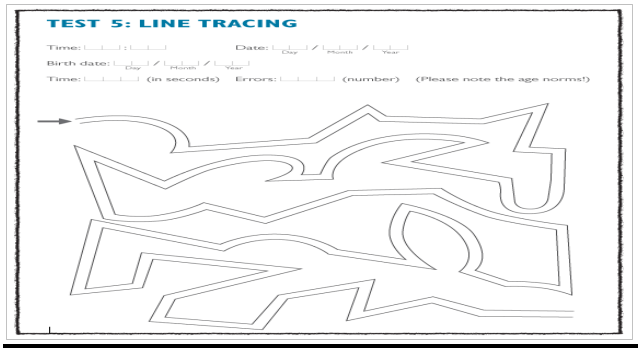


Psychomotor state
(digit-symbol
substitution test)

1	2	3	4	5	6	7	8	9
V	⊐	÷	Λ	X	⅂	⊏	⊤	⌐

2	1	3	1	2	1	3	1	4	2	4	2	5	1	4	3	5	2	6	2

__sec



BLOOD INVESTIGATIONS

CBC

1. HAEMOGLOBIN		
2. TLC		
3. NEUTROPHIL		
4. LYMPHOCYTE		
5. PLATELET COUNT		

RFT

S. UREA			
S. CREATININE			
S. SODIUM			
S. POTASSIUM			
S. CALCIUM			

LFT

T.B.				
CONJ/UNCON.				
SGOT				
SGPT				
ALBUMIN				
GLOBULIN				
ALP				

PT/INR

PT (T)			
PT (C)			
INR			

VIRAL MARKER

HIV	
HBsAg	
HCV	

CHILD PUGH SCORE

1. ASCITIC		
2. HE		
3. S. BILIRUBIN		
4. S. ALBUMIN		
5. PT OR INR		
CLASS		

CONCLUSION:

Date:-

Signature:-

ANNEXURE IV

MASTERCHART(CASES)

S.NO	NAME	AGE	SEX	IP NO	EDUCATION	S.AMMONIA	CTP	NCT A	NCT B	SDT	LTT	DST	PHES	
1	RUDRESH	48	MALE	341766	15	34	10	182	234	68	156	152	-7	MHE
2	HUSANAPPA	49	MALE	349290	7	18	9	156	184	56	142	184	-1	NO MHE
3	LAXMAN KANNUR	50	MALE	119905	3	67	10	230	284	90	236	260	-8	MHE
4	VISHAL	51	MALE	178019	5	37	8	210	296	72	210	250	-8	MHE
5	BHIMAPPA	52	MALE	164121	5	53	6	45	102	61	110	180	1	NO MHE
6	SANGU RAMANNA	60	MALE	341648	7	28	9	150	183	82	220	235	-6	MHE
7	RAMESH	45	MALE	341378	10	32	8	110	154	74	160	210	-5	MHE
8	MATHARABA SOMA	46	MALE	323829	10	28	9	170	194	72	230	250	-7	MHE
9	NEELAMMA	70	FEMALE	208362	3	44	12	200		87	260	310		NOT COMPLETED
10	MANJUNATH BASAVARAJ	31	MALE	301737	10	32	10	220	272	84	280	302	-9	MHE
11	MALAKANNA	65	MALE	401698	3	38	9	170	213	92	308	310	-9	MHE
12	JAIBHIM MALLAPPA	28	MALE	38815	15	24	10	190	243	98	310	320	-10	MHE
13	SIDDARAM SINGH	43	MALE	303192	12	28	8	102	160	76	210	270	-6	MHE
14	VEERESH LOLSAR	45	MALE	299965	10	48	10	160	194	84	260	300	-8	MHE
15	BASAPPA YALAGURADAPPA	39	MALE	305947	7	48	12	200	231	80	310	310	-8	MHE
16	SHEKAR SHASHIDAR	35	MALE	41117	10	22	8	110	124	110	190	250	-8	MHE
17	NAGARAJ BIRADAR	24	MALE	325238	12	28	8	140	168	150	250	270	-10	MHE
18	SHIVAND MALLAPPA	35	MALE	352838	10	32	10	200	234	130	320	340	-11	MHE
19	NILAMMA	80	FEMALE	401668	3	42	9	170		170	280	320		NOT COMPLETED
20	APPASHI	45	MALE	271793	7	34	9	220	243	110	290	310	-10	MHE
21	GUDALAL LALAHAMED	42	MALE	358739	7	32	9	130	156	100	310	320	-7	MHE
22	RAHUL ANIL	27	MALE	373712	10	28	10	160	130	110	250	270	-9	MHE
23	SHIVAJI TAMANNA	35	MALE	396505	7	34	9	160	140	130	280	320	-8	MHE
24	SHRIDHAR	53	MALE	390064	3	28	10	190	210	130	250	320	-8	MHE
25	NAGAPPA	41	MALE	166826	7	21	9	190	234	130	260	310	-10	MHE

26	RAJU PANDU	34	MALE	156670	10	22	12	230	253	160	270	320	-11	MHE
27	BASAVARAJ CHANDRASEKHAR	35	MALE	71690	10	32	12	250	284	190	360	380	-11	MHE
28	SOMANINGAPPA	68	MALE	409955	5	48	8	130	156	150	260	260	-8	MHE
29	SUNIL MALLIKARJUN	40	MALE	226693	5	9	8	150	160	130	260	310	-8	MHE
30	SHRISHAIL SIDDAPPA	50	MALE	327822	7	45	11	190	210	140	260	320	-10	MHE
31	SRIMANTH VASU	25	MALE	331979	10	28	6	70	112	120	190	200	-7	MHE
32	RAMESH BANAKANAHALLI	45	MALE	341378	7	31	8	200	230	200	230	260	-11	MHE
33	NAGAM BAIRAVADAGI	60	MALE	347978	5	28	7	50	78	110	200	220	-2	NO MHE
34	VIJAY SHANMUKHAPPA	44	MALE	345939	7	22	7	68	132	100	190	220	-4	NO MHE
35	SANGU BADIGER	60	MALE	341648	7	25	9	160	165	80	220	240	-5	NO MHE
36	MAHADEV SHARANAPPA	40	MALE	279617	10	32	12	220	254	190	340	350	-11	MHE
37	RAVI KHABU	42	MALE	275050	10	32	7	68	102	78	190	250	-3	NO MHE
38	SHIVA KUMAR BASAPPA	43	MALE	273285	7	54	11	190	213	130	260	260	-9	MHE
39	AJEET BASANNA	34	MALE	412974	7	21	8	84	113	70	250	270	-4	NO MHE
40	PRAMOD.S.PATI	46	MALE	134283	10	34	6	62	102	84	190	260	-4	NO MHE
41	BHARAT GOVIND	33	MALE	132453	3	32	8	65	108	70	200	220	-3	NO MHE
42	SHIVANAND VISHWANATH	30	MALE	134313	7	35	10	72	113	92	250	260	-5	NO MHE
43	ARJUN DOBHI	48	MALE	358444	10	17	8	68	112	84	200	250	-4	NO MHE
44	MAINU MAIBOOB	46	MALE	134307	12	35	12	150	173	130	310	340	-10	MHE
45	SHIVAPPA KALLAPPA	40	MALE	135091	15	38	7	62	108	70	190	200	-3	NO MHE
46	KRISHNAPPA	58	MALE	136457	3	36	8	82	112	80	200	190	-3	NO MHE
47	SHANTABAI	55	FEMALE	183354	5	32	8	68	104	80	200	190	-2	NO MHE
48	IRAVVA DUNDAPPA	55	FEMALE	279668	3	34	7	62	106	84	200	190	-2	NO MHE
49	NAYAN KUMAR	41	MALE	307122	5	38	8	84	112	72	204	200	-3	NO MHE
50	REVANASIDDA	65	MALE	185134	6	34	10	82	118	78	180	210	-2	NO MHE

50	REVANASIDDA	65	MALE	185134	6	34	10	82	118	78	180	210	-2	NO MHE
51	AYYAPPA I GUJERGOND	50	MALE	339734	3	36	8	68	124	84	190	190	-2	NO MHE
52	SHANKAR RATHOD	49	MALE	13773	7	32	6	110	150	36	71	167	-2	NO MHE
53	ABHIMANYU GOUNDI	56	MALE	14004	5	42	9	130	138	42	64	102	0	NO ME
54	LAXMI HIREMATH	80	FEMALE	17610	3	45	8	150		56				NOT COMPLETE
55	MAHESH HAANAL	32	MALE	17620	10	52	10	110	162	48	80	150	-4	NO MHC
56	SHIVAKANTAWWA KODATE	56	FEMALE	17900	3	54	10	132	165	48	92	193	-2	NO MHC
57	BHIMANNA YELLAPA	59	MALE	17472	7	56	10	140	153	56	80	165	1	NO MHC
58	LAKMAN NATIKAR	47	MALE	17622	12	46	9	121	143	47	68	142	-3	NO MHE
59	SRINATH RAM KAMBLE	45	MALE	17423	10	45	10	16	130	42	80	170	2	NO MH
60	BHAGANNA BABU GOUDA	35	MALE	15117	7	56	11	80	140	48	62	160	-2	NO MHE
61	BAGAPPA P KUDAGI	65	MALE	17421	3	24	8	153	220	48	70	240	-1	NO MHE
62	SANGAPPA LAYAPPA	60	MALE	18231	3	26	8	142	217	52	86	287	-3	NO MHE
63	MAHESH VEERABADHARAPPA	49	MALE	15984	12	56	11	130	142	48	80	158	-3	NO MHE
64	MALLAPA SANGAPPA	40	MALE	15471	10	43	9	116	160	45	80	170	-3	NO MHE
65	SADASHIV	45	MALE	17987	12	42	7	80	125	16	45	193	1	NO MH
66	GIRIMALLA HONKALI	48	MALE	16401	15	45	8	110	160	48	80	168	-3	NO MHE
67	SIDDARAM DHARMANNA	32	MALE	18433	15	58	11	65	120	18	24	86	1	NO MHE
68	NITHIN JAGADISH DAYAL	42	MALE	20050	10	34	7	150	125	56	32	142	-1	NO MHE
69	ANAND KHASE	45	MALE	19767	10	42	10	110	162	48	80	150	-3	NO MHE
70	SANTHOSH PUJARI	40	MALE	20385	12	32	9	132	142	48	92	156	-3	NO MHE

71	SOMANAGOUDA	40	MALE	18885	7	43	11	140	152	56	80	164	-3	NO MHE
72	VIKAS ROOPAKANTH	37	MALE	19114	7	65	10	121	162	47	68	176	-3	NO MHE
73	PARMANAND	40	MALE	18690	5	46	9	16	130	42	80	170	2	NO MHE
74	SHARANAPPA	60	MALE	18734	3	48	8	80	140	48	62	160	2	NO MHE
75	ALLABHAKASH	43	MALE	19370	7	43	7	128	134	48	70	132	-2	NO MHE
76	SARALABAI RAJPUT	53	MALE	19895	3	54	8	134	162	54	83	172	-2	NO MHE
77	GANGADHAR	42	MALE	20268	7	43	7	130	160	48	80	170	-3	NO MHE
78	LAXMAN SADASHIV	69	MALE	110222	3	42	8	116	172	45	80	185	1	NO MHE
79	SHARANAPPA NAGAREL	54	MALE	20251049	3	44	9	80	125	16	45	154	2	NO MHE
80	vijay harijan	40	MALE	25000338	10	36	8	110	160	48	80	72	-3	NO MHE
81	PARASAPPA BHAIRAPPA	45	MALE	18684	12	56	11	65	120	18	24	86	2	NO MHE
82	RAMU RATHOD	35	MALE	25001523	12	44	7	58	112	15	32	78	1	NO MHE
83	ADITYA SHASHIKANTH	31	MALE	25000336	12	46	8	62	108	22	34	72	1	NO MHE

CONTROLS:

s.no	NAME	AGE	SEX	IP NO	EDUCATION	CTP	NCT A	NCT B	SDT	LTT	DST	PHES	
1	PUTLABAI	35	FEMALE	159239	3	5	44	127	28	55	56	3	NO MHE
2	LAXMIBAI	37	FEMALE	176485	5	5	68	180	40	45	78	0	NO MHE
3	SHASHIKALA	30	FEMALE	169966	3	5	42	170	38	52	62	1	NO MHE
4	SANGARAJ	43	MALE	326765	10	5	52	134	40	68	74	0	NO MHE
5	RAFIK ABDUL	46	MALE	175224	10	5	52	126	52	72	84	1	NO MHE
6	GURULINGAMMA	60	FEMALE	177737	3	5	48	128	33	45	68	3	NO MHE
7	SUMAN	76	FEMALE	162443	3	5	52	132	32	62	68	3	NO MHE
8	BHIMARAJ	61	MALE	40329	7	5	48	143	35	62	58	3	NO MHE
9	ANIL MOTILAL	33	MALE	266629	3	5	58	123	38	65	68	2	NO MHE
10	BASAVARAJ	50	MALE	153297	7	5	44	102	36	68	78	3	NO MHE
11	GURUBASAPPA	61	MALE	148652	3	5	44	134	38	72	74	3	NO MHE
12	VITTAL SAYABANNA	75	MALE	79210	7	5	44	112	38	56	64	3	NO MHE
13	SURESH	55	MALE	164060	7	5	32	98	38	62	68	3	NO MHE
14	BABU AMARNASAB	33	MALE	1737	10	5	44	93	32	58	68	2	NO MHE
15	VAIBHAV PATIL	19	MALE	142112	10	5	36	87	32	62	68	-1	NO MHE
16	POORNIMA	21	FEMALE	332388	12	5	45	78	32	72	74	0	NO MHE
17	RAVI MALAPPA	28	MALE	168394	10	5	32	76	38	72	74	1	NO MHE
18	BHEERAPPA	78	MALE	165970	3	5	38	93	32	78	74	5	NO MHE
19	PRABHUGOUDA	60	MALE	186364	5	5	42	73	38	84	88	3	NO MHE
20	BONAMMA	40	FEMALE	175147	7	5	42	78	32	78	74	2	NO MHE
21	ARJUN	48	MALE	358444	7	5	38	82	32	68	64	3	NO MHE
22	GEETA SHIVARAJ	37	FEMALE	127616	10	5	33	87	38	78	84	1	NO MHE
23	FARHANA DURESHI	39	FEMALE	237542	10	5	34	92	28	82	94	2	NO MHE
24	KRISHNAPPA	75	MALE	186917	3	5	34	102	32	78	79	5	NO MHE
25	SIDDAMALPPA	65	MALE	172663	5	5	32	97	28	84	92	4	NO MHE

26	CHANDRASHEKAR	65	MALE	4910	3	5	28	104	32	82	84	4	NO MHE
27	SANGAMMA	33	FEMALE	185481	7	5	32	98	28	82	94	2	NO MHE
28	DABEBASHA	44	MALE	182172	5	5	32	102	28	68	72	2	NO MHE
29	NAGAPPA	29	MALE	164066	10	5	28	94	33	78	84	1	NO MHE
30	MALLIKARJUN	26	MALE	180472	10	5	72	84	32	84	98	-1	NO MHE
31	MALAPPA	65	MALE	112273	3	5	28	109	28	82	84	4	NO MHE
32	KALLAPPA MADAR	47	MALE	171422	5	5	33	78	23	61	84	3	NO MHE
33	NAGARATNA	36	MALE	166771	7	5	38	74	23	84	92	2	NO MHE
34	MALIN GARAY.M	32	MALE	175292	7	5	56	80	18	32	70	3	NO MHE
35	YUVARAJ	55	MALE	184554	5	5	70	130	38	28	150	3	NO MHE
36	YELLAPPA	61	MALE	179520	3	5	70	132	48	52	143	3	NO MHE
37	MALLAPPA	70	MALE	303135	5	5	70	102	38	62	132	4	NO MHE
38	ANIL KUMAR	48	MALE	139116	7	5	68	98	28	33	124	2	NO MHE
39	RAMESH	45	MALE	186329	7	5	68	92	22	38	112	2	NO MHE
40	IRAPPA	50	MALE	137099	7	5	72	122	32	42	118	2	NO MHE
41	YELLAPPA	65	MALE	186075	10	5	80	92	38	32	98	2	NO MHE
42	ASHOK	54	MALE	160486	7	5	62	78	39	42	92	3	NO MHE
43	YUSUFPATEL	25	MALE	185491	10	5	52	72	12	24	70	2	NO MHE
44	SHIVAMMA	50	MALE	18393	3	5	70	92	32	48	106	3	NO MHE
45	YALLAPPA	17	MALE	183954	7	5	52	80	12	30	62	1	NO MHE
46	VEER KUMAR	65	MALE	113801	5	5	65	98	28	40	142	3	NO MHE
47	KALLAPA	49	MALE	177323	5	5	68	82	22	38	130	3	NO MHE
48	JETTEPPA	74	MALE	179863	5	5	90	112	32	48	156	2	NO MHE
49	MAKTUMBI	44	MALE	264887	3	5	80	78	36	52	87	2	NO MHE
50	RENUKA	51	FEMALE	263725	5	5	65	82	24	42	98	3	NO MHE
51	GURUNATH	41	MALE	13493	4	5	62	80	18	34	80	3	NO MHE
52	RAKSHITA BAMMANAGI	19	FEMALE	11324	12	5	45	62	16	35	70	0	NO MHE
53	NINGANNA BASAPPA	40	MALE	15823	5	5	54	80	12	32	65	3	NOMHE
54	SANGAPPA SUSHILAWWA	40	MALE	15822	5	5	56	80	16	28	65	3	NO MHE
55	SHIVASHARAN	71	MALE	13796	5	5	80	102	32	45	118	4	NO MHE
56	PARVATI BADIGER	36	FEMALE	15283	10	5	50	70	16	28	72	3	NO MHE
57	AMAN KHAN	29	MALE	170990	12	5	48	68	12	28	80	2	NO MHE
58	SANGEETA HESASUR	21	FEMALE	15279	12	5	45	70	14	22	72	2	NO MHE

59	LAXMI PARASHURAM	21	FEMALE	14776	12	5	55	80	20	41	80	1	NO MHE
60	MALLIKARJUN VIRUPAKSHAPA	68	MALE	15453	3	5	92	102	34	43	94	3	NO MHE
61	SANGANNA KURI	43	MALE	14011	4	5	90	124	30	55	134	1	NO MHE
62	AKKAMAHADEVI	31	FEMALE	17091	12	5	62	80	22	36	80	2	NO MHE
63	SHAHAJABI	36	FEMALE	17552	10	5	68	80	28	38	80	2	NO MHE
64	RAMEJA BISTI	26	FEMALE	17177	12	5	56	80	12	28	65	1	NO MHE
65	SUJALAXMI	24	FEMALE	16896	12	5	45	68	12	22	65	1	NO MHE
66	MAHADEVI ANI	36	FEMALE	18055	10	5	40	80	11	31	55	2	NO MHE
67	MALLIKARJUN	38	MALE	18209	10	5	55	100	14	24	71	3	NO MHE
68	RAJU	52	MALE	15089	7	5	102	112	17	52	126	1	NO MHE
69	MALLIKARJUN HADPAD	35	MALE	18335	7	5	74	135	17	35	150	1	NO MHE
70	CHANDRU BAJU	60	MALE	17619	3	5	70	124	40	52	132	3	NO MHE
71	PARVATI BADIGER	48	MALE	18904	3	5	65	112	24	42	142	3	NO MHE
72	anita ravanasadiddappa	50	FEMALE	20417	3	5	62	80	18	34	80	3	NO MHE
73	shrishail basavaraj	66	MALE	17178	3	5	45	62	16	35	70	4	NO MHE
74	ambika subhashchandra	42	FEMALE	18364	5	5	54	80	12	32	65	3	NO MHE
75	maramma chandrappa	45	FEMALE	19085	5	5	56	80	16	28	65	3	NO MHE
76	bagamma chandrakanth	35	FEMALE	19058	3	5	80	102	32	45	80	2	NO MHE
77	jyothi dharappa	33	FEMALE	19191	3	5	50	70	16	28	72	3	NO MHE
78	laxmi chinnapauda birader	35	FEMALE	19348	3	5	48	68	12	28	80	3	NO MHE
79	mahantesh shanker	30	MALE	19778	5	5	45	70	14	22	72	3	NO MHE
80	lakkava jirageli	35	FEMALE	19088	3	5	55	80	20	41	80	3	NO MHE
81	eshwar sidraya	32	MALE	19603	10	5	68	98	34	43	92	1	NO MHE
82	shrishail bhairappa	24	MALE	20410	12	5	56	72	30	55	74	0	NO MHE
83	CHANASANGAYYA SIDDAYA	33	MALE	17788	12	5	62	80	22	36	80	2	NO MHE