" DIAGNOSTIC VALUE OF ALCOHOLIC LIVER DISEASE / NON ALCOHOLIC FATTY LIVER DISEASE INDEX (ANI) IN DIFFERENTIATING ALCOHOLIC LIVER DISEASE AND NON ALCOHOLIC FATTY LIVER DISEASE ONE YEAR BASED OBSERVATIONAL STUDY IN TERITARY CARE CENTRE"

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Dr. REKHA S PATIL
MD (GENERAL MEDICINE)
Professor and Head,
Department of General Medicine,
J. N. Medical College,
Nehru Nagar, Belagavi – 10
Professor & HOD
Dept. of Medicine
J. N. Medical College Belgaum
Date : 26/03/25
Place : Belagavi

Dr.(Mrs.) N.S. MAHANTSHETTI
MD (PAEDIATRICS)
Principal,
J. N. Medical College,
Nehru Nagar, Belagavi – 10
PRINCIPAL
Jawaharlal Nehru Medical College
BELAGAVI
Date : 26/03/25
Place : Belagavi

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Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 - 2471350 0831 - 2470759 www.jnmc.edu rincipal@jnmc.edu

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Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BG0122011
Postgraduate Student,
2022-23 Batch,
Department of General Medicine
J. N. Medical College, Belagavi.

ETHICAL CLEARANCE LETTER

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
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JNMC INSTITUTIONAL ETHICS COMMITTEE
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref No.MDC/JNMCIEC/ 77 **Date: 31/03/2023**

To,

REG NO. : BG0122011
PG Student in General Medicine
J. N. Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"DIAGNOSTIC VALUE OF ALCOHOLIC LIVER DISEASE/ NON ALCOHOLIC FATTY LIVER DISEASE INDEX (ANI) IN DIFFERENTIATING ALCOHOLIC LIVER DISEASE AND NONALCOHOLIC FATTY LIVER DISEASE ONE YEAR BASED OBSERVATIONAL STUDY IN TERITARY CARE CENTRE",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

(Dr. Smita Sonoli)
Member Secretary
JNMC Institutional Ethics Committee
J.N.Medical College, Belagavi.

(Dr. Harsha Hegde)
Chairman,
JNMC Institutional Ethics Committee
J.N.Medical College, Belagav

ABBREVIATIONS

ALD	:	Alcoholic Liver Disease
NAFLD	:	Non-Alcoholic Fatty Liver Disease
ANI	:	Alcoholic Liver Disease/Non-Alcoholic Fatty Liver Disease Index
ALT	:	Alanine Aminotransferase
AST	:	Aspartate Aminotransferase
AUC	:	Area Under the Curve
BMI	:	Body Mass Index
CAP	:	Controlled Attenuation Parameter
DM	:	Diabetes Mellitus
EASL	:	European Association for the Study of the Liver
HDL	:	High-Density Lipoprotein
HTN	:	Hypertension
KPa	:	Kilopascal
LDL	:	Low-Density Lipoprotein
NASH	:	Non-Alcoholic Steatohepatitis
ROC	:	Receiver Operating Characteristic
SGOT	:	Serum Glutamic Oxaloacetic Transaminase
SGPT	:	Serum Glutamic Pyruvic Transaminase
T2DM	:	Type 2 Diabetes Mellitus
USG	:	Ultrasonography
WHO	:	World Health Organization
AUROC	:	Area Under the Receiver Operating Characteristic
CDT	:	Carbohydrate-Deficient Transferrin

GGT	:	Gamma-Glutamyl Transferase
MCV	:	Mean Corpuscular Volume
MRI	:	Magnetic Resonance Imaging
PNPLA3	:	Patatin-like Phospholipase Domain-containing Protein 3
TG	:	Triglycerides
VLDL	:	Very Low-Density Lipoprotein

ABSTRACT

Introduction: Distinguishing between alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) poses a significant clinical challenge due to overlapping histopathological features, particularly when patient history regarding alcohol consumption is unreliable. The Alcoholic Liver Disease/Non-Alcoholic Fatty Liver Disease Index (ANI) has emerged as a promising non-invasive biomarker to differentiate between these conditions, potentially obviating the need for liver biopsy. This study aimed to evaluate the diagnostic accuracy of the ANI scoring system in distinguishing ALD from NAFLD in a tertiary care setting.

Methodology: This one-year observational study conducted at Kles Dr Prabhakar Kore Hospital & M.R.C, Belagavi included 100 patients (50 with ALD and 50 with NAFLD) diagnosed based on comprehensive clinical, biochemical, and imaging criteria. Demographic data, clinical characteristics, laboratory parameters, and imaging findings were recorded. ANI scores were calculated for all patients, and their discriminatory performance was assessed using ROC curve analysis.

Results: The ALD group consisted exclusively of males with significant alcohol consumption (>60 grams/day), while the NAFLD group showed a balanced gender distribution (54% females) and was associated with higher BMI and diabetes prevalence. Liver function tests revealed significantly higher SGOT levels (111.3±112.5 vs 47.16±48.7, $p<0.001$) and SGOT/SGPT ratios (2.1±1.1 vs 1.25±0.56, $p<0.001$) in ALD patients. The ANI score differed dramatically between groups: positive in ALD patients (7.08±4.6) and negative in NAFLD patients (-2.36±3.9), with high statistical significance ($p<0.001$). ROC curve analysis demonstrated excellent diagnostic accuracy of the ANI score with an AUC of 0.936. Fibroscan

assessment showed higher proportions of moderate fibrosis in ALD patients despite similar degrees of steatosis.

Conclusion: The ANI scoring system provides excellent discriminatory performance in differentiating ALD from NAFLD, with minimal overlap between the two groups. This non-invasive biomarker offers a reliable diagnostic tool for clinical practice, potentially reducing the need for invasive liver biopsies while guiding appropriate management strategies.

Keywords: Alcoholic liver disease; Non-alcoholic fatty liver disease; ANI score; Non-invasive biomarker; Liver fibrosis; Transaminases; SGOT/SGPT ratio; Fibroscan; Diagnostic accuracy

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF GRAPHS

INTRODUCTION

Chronic liver disease represents a significant global health burden, with Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD) emerging as predominant aetiologies. These conditions share remarkable similarities in their histopathological features, clinical presentations, and biochemical parameters, making differential diagnosis particularly challenging.[1] The distinction between ALD and NAFLD is crucial as their management strategies, disease progression, and prognosis differ significantly.[2]

NAFLD affects approximately 25% of the global population and is strongly associated with metabolic syndrome, obesity, and type 2 diabetes mellitus.[3] Conversely, ALD, driven by chronic alcohol consumption, affects an estimated 2-3% of the global population, with higher prevalence in regions with substantial alcohol consumption.[4] The overlap in clinical and biochemical presentations often leads to diagnostic uncertainty, particularly when patients may not accurately report their alcohol consumption patterns.[5] Traditional diagnostic approaches depends on reliability of history given by patients, imaging studies, and liver biopsy. However, these methods have inherent limitations namely patient history may be unreliable, imaging studies lack specificity in differentiation, and liver biopsy is an invasive with method and is associated with risks.[6] This diagnostic challenge has prompted the search for non-invasive biomarkers and scoring systems that could reliably distinguish between ALD and NAFLD.[7]

The Alcoholic Liver Disease/Non-Alcoholic Fatty Liver Disease Index (ANI) has emerged as a promising non-invasive tool for differentiation. This index incorporates readily available parameters including mean corpuscular volume (MCV),

aspartate amino transferase (AST), alanine amino transferase (ALT), and BMI by using formula, ANI = −58.5 + 0.637 (mean corpuscular volume) + 3.91 (aspartate transaminase/alanine transaminase) − 0.406 (body mass index) + 6.35 (if male sex).[8] The ANI score potentially offers a more objective approach to differentiation, reducing reliance on subjective patient histories.[9] This study aims to evaluate the diagnostic value of ANI in differentiating between ALD and NAFLD in a tertiary care setting over a one-year period. Understanding the utility and limitations of ANI could potentially streamline the diagnostic process, enable earlier appropriate interventions, and improve patient outcomes.[10]

AIMS AND OBJECTIVES

Objective:

1. To test the reliability of ANI scoring system as a non-invasive method to distinguish alcoholic liver disease (ALD) from non-alcoholic fatty liver disease (NAFLD)

REVIEW OF LITERATURE

FATTY LIVER DISEASES

Intrahepatic fat of at least 5% of liver weight is referred to as hepatic steatosis.[11] The general name for all of the different causes of steatosis is steatotic liver disease (SLD). A new nomenclature has been proposed to better describe the pathophysiology of fatty liver.

Previously known as nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD) is the histologic or imaging evidence of SLD without secondary sources of hepatic fat buildup, such as heavy alcohol use.[12]

Causes of Hepatic steatosis

Macrovesicular

- Excessive alcohol
- Hepatitis C
- Autoimmune hepatitis
- Parenteral nutrition
- Starvation
- Wilson's disease
- Lipodystrophy
- Abetalipoproteinemia
- Medications (amiodarone, methotrexate, tamoxifen, corticosteroids, antiretrovirals)

Microvesicular

- Acute fatty liver of pregnancy
- HELLP syndromea
- Reye's syndrome
- Inborn errors of metabolism
- Medications (valproate, antiretrovirals)

ALCOHOLIC FATTY LIVER DISEASES

With 3.3 million deaths in 2012, excessive alcohol use is a global health issue with significant social, economic, and clinical repercussions.[13] Decades of excessive drinking harm almost all of the body's organs. However, because the liver is the main site of ethanol metabolism, it suffers the earliest and most severe tissue damage from heavy drinking.[14]

Alcohol's Effects on Other Liver Cell Types

"The majority of the liver mass is made up of hepatocytes, whereas the remaining 15 to 30 percent is made up of nonparenchymal cells such as sinusoidal endothelial cells, hepatic stellate cells (HSCs), Kupffer cells (KCs), and liver-associated lymphocytes. Through direct cell-to-cell contact and soluble mediators, these nonparenchymal cells communicate with hepatocytes and with one another. Every type of liver cell has a distinct function in both causing and maintaining liver injury as well as in normal hepatic functioning."[14]

Spectrum of ALD

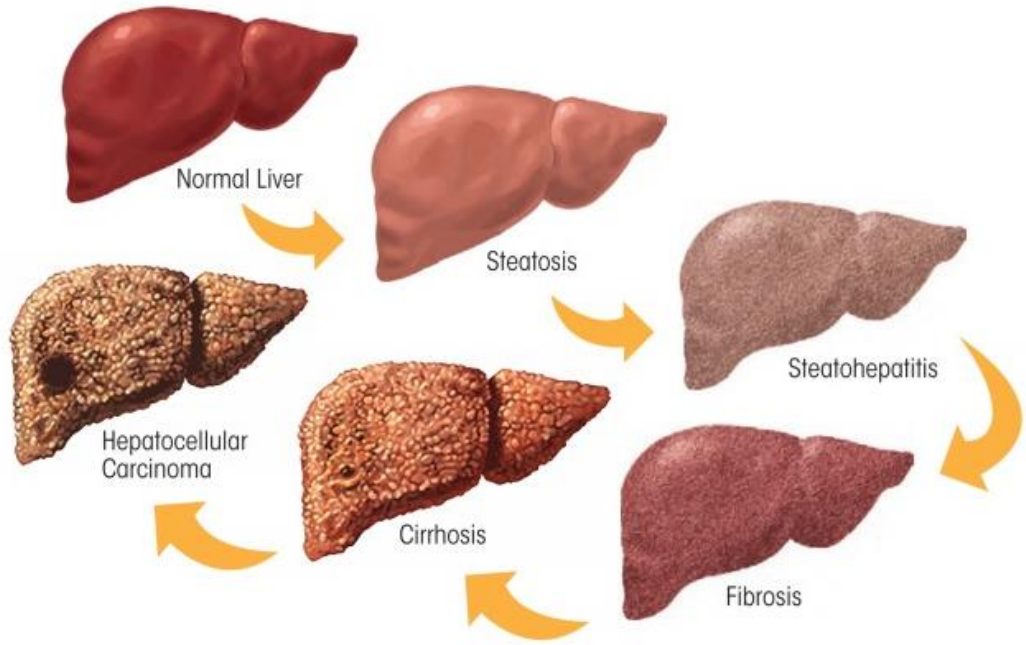
Hepatitis, fibrosis/cirrhosis, and fatty liver (i.e., steatosis) are the most common hepatic pathologies caused by excessive ethanol intake. More than 90% of

problem drinkers who have four to five standard drinks a day for decades develop steatosis, the earliest and most prevalent reaction.[15] The amount of alcoholic beverage that comprises around 0.5 fluid ounces, or 14 grammes, of pure alcohol is referred to as a standard drink. However, binge drinking—defined as consuming four to five drinks in two hours or less—also contributes to the development of steatosis.[16] In the past, steatosis was thought to be a harmless side effect of alcohol misuse. The hepatocytes that surround the liver's central vein (perivenular hepatocytes), mid-lobular hepatocytes, and hepatocytes that surround the hepatic portal vein (periportal hepatocytes) are the first to exhibit the deposition of fat, which is visible under a microscope as lipid droplets.[16] Steatosis is a treatable illness with a favourable prognosis if the affected person stops drinking. However, because fat probably indicates a higher risk for lipid peroxidation and oxidative damage, people with persistent steatosis are more vulnerable to fibrotic liver disease.[16]

The more severe, inflammatory form of liver damage known as alcoholic hepatitis is typified by the formation of tangled aggregates of insoluble proteins termed Mallory-Denk bodies within hepatocytes, neutrophilic infiltration, and enlarged, dying hepatocytes (also known as ballooning degeneration). The activation of KCs, the resident liver macrophages, is essential to the development of hepatitis.[16]

Abnormal levels of extracellular matrix proteins are deposited, primarily by activated HSCs, in fibrosis and its terminal or late stage, cirrhosis. Patients first have active pericellular fibrosis, which can lead to the late stage of hepatic scarring, cirrhosis. Hepatic fat is typically not noticeable in cirrhotic patients, but some level of hepatitis is probably always present in these patients. According to the World Health Organization's (2014) Global Status Report on Alcohol and Health, alcohol misuse was a contributing factor in half of all cirrhosis-related fatalities.[16]

Figure 1: Spectrum of alcoholic liver disease. A variety of liver lesions are caused by excessive ethanol consumption. More than 90% of problem drinkers who have four to five standard drinks a day develop fatty liver, also known as steatosis, the first and most prevalent reaction. Alcoholic liver disease can progress to cirrhosis, fibrosis, liver inflammation (steatohepatitis), and ultimately liver cancer (hepatocellular carcinoma) with persistent drinking.



Mechanisms Involved in Alcoholic Steatosis

Ethanol and acetaldehyde oxidations produce more NADH, which changes the cellular redox potential and promotes lipid production (i.e., lipogenesis), as was said in the section on ethanol metabolism that came before it. However, the liver's fast fat accumulation cannot be entirely explained by the ethanol-induced redox shift alone. The idea that ethanol-induced steatosis is multifactorial is now well supported by more recent research, as will be covered below.[16]

Alcohol Accelerates Hepatic Lipogenesis

Higher expression of lipogenic enzymes and cytokines, which are encoded by genes controlled by the transcription factors sterol regulatory element binding protein-1c (SREBP-1c) and early growth response-1 (Egr-1), leads to enhanced lipid synthesis.[17] SREBP-1c is a member of the transcription factor family that regulates the metabolism of cholesterol in the liver. Ethanol oxidation, on the other hand, short-circuits hepatic lipid metabolism in heavy drinkers, changing the liver's function from burning fat to storing it. Therefore, hepatic SREBP-1c is largely found in the ER and is comparatively inactive in the hepatocytes of abstinent individuals. Hepatic ethanol oxidation, on the other hand, causes SREBP-1c to move from the ER to the Golgi apparatus in binge drinkers.[18] There, it matures proteolytically to its active form, producing a transcriptionally active SREBP protein fragment that enters the nucleus and increases the expression of lipogenic genes. Gene expression in response to cellular stress is regulated by Egr-1. It attaches itself to areas of gene promoters related to steatosis and liver damage brought on by alcohol. The most prominent of these is the lipogenic cytokine tumour necrosis factor alpha (TNFα). Additionally, Egr-1 controls the expression of the SREBP-1c gene due to its early activation upon ethanol ingestion.[17,18]

Figure 2: Hepatic and extrahepatic mechanisms that contribute to the development of alcoholic fatty liver (i.e., steatosis).[17]

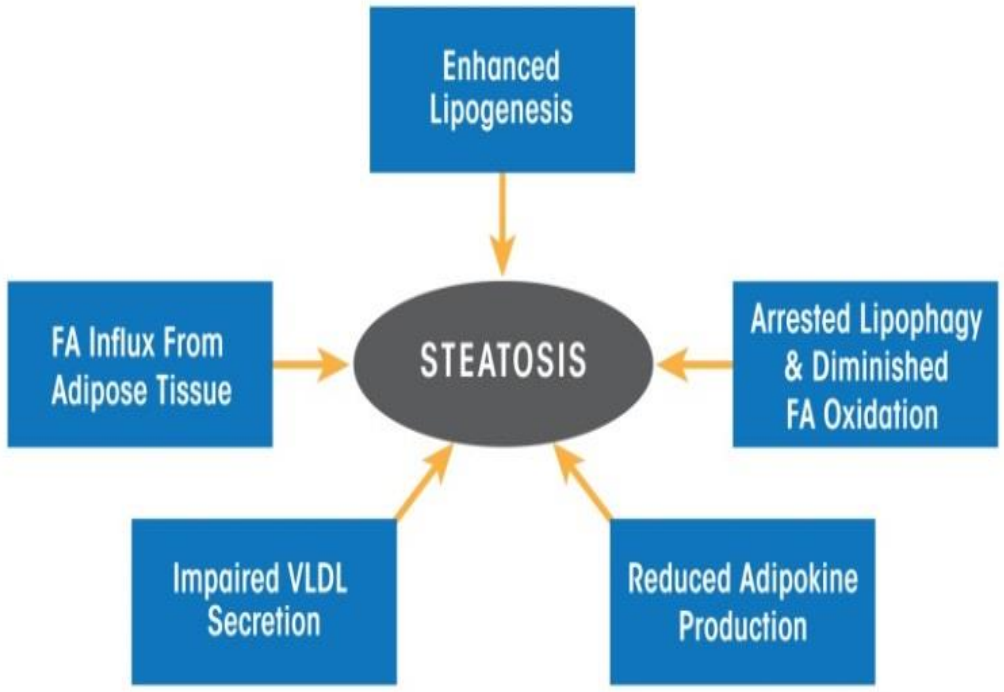


Figure 3: Proposed mechanism by which ethanol oxidation regulates early growth response-1 (Egr-1) and sterol regulatory element binding protein-1c (SREBP-1c) to enhance lipogenesis.[17]

Both cytochrome P450 2E1 (CYP2E1) and alcohol dehydrogenase (ADH) catalyse the oxidation of ethanol to acetaldehyde. By activating the Egr-1 promoter, this aldehyde increases the transcription of the Egr-1 gene, raising the amounts of Egr-1 mRNA and, ultimately, nuclear Egr-1 protein. Nuclear Egr-1 protein is thought to trigger ethanol-induced lipogenesis and fatty liver (i.e., steatosis) by controlling the transcription of SREBP-1c and tumour necrosis factor (TNF) genes.[17,18]

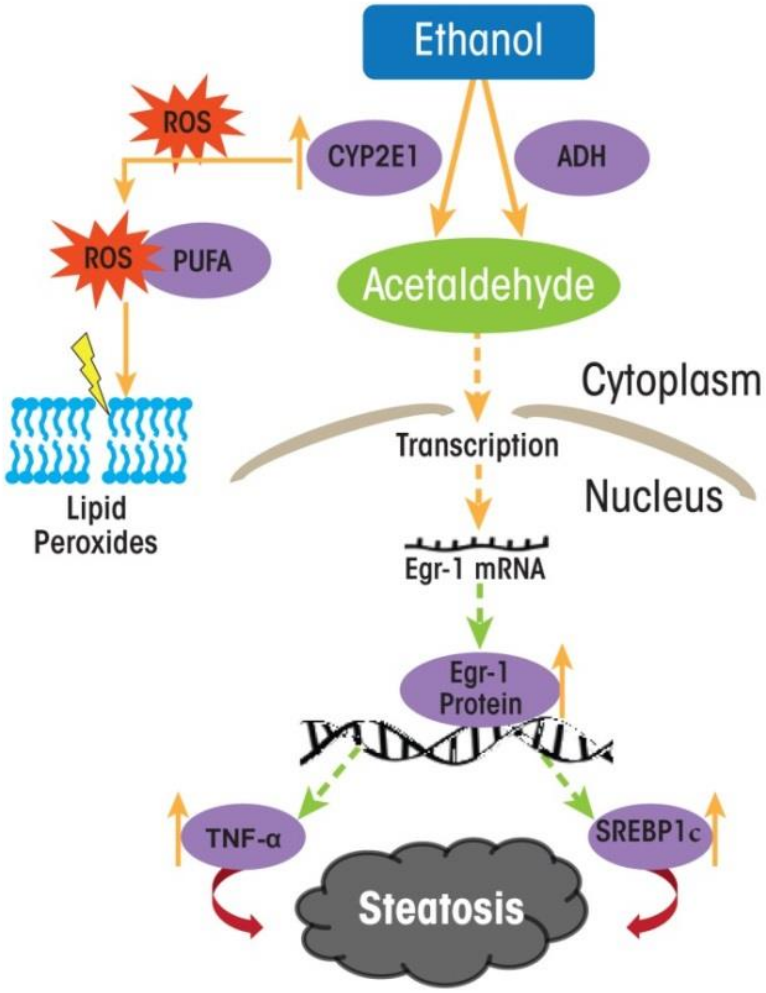


Figure 4: Pathogenesis of Alcoholic Hepatitis

Adipose tissue, or fat, plays a role in the development of steatosis in addition to increased hepatic lipogenesis.[19] Normally, adipose tissue serves as a significant energy store, storing extra calories from diet as fat. High-energy fat can therefore be used when needed to meet energy needs during periods of high calorie utilisation (e.g., activity) or low nutrition (e.g., fasting).[19] Ethanol use decreases adipose tissue mass via promoting fat breakdown (i.e., lipolysis) in adipose tissue, according to research conducted on mice fed alcohol continuously.[19] The liver absorbs the free fatty acids that are expelled from adipose tissue and converts them into triglycerides, which exacerbates the liver's fat buildup.[20] Additionally, fatty liver patients with

alcohol use disorder have significantly lower body weight, body mass index, and body-fat mass content than control participants, according to clinical investigations.[21]

Alcohol Decelerates Hepatic Lipid Breakdown

Lipid droplets, which contain the majority of the lipids in hepatocytes, must first be broken down in order to release the lipids for oxidation.[22] Lipophagy, a specific type of the intracellular process that breaks down cytoplasmic components (autophagy), is responsible for the breakdown of lipid droplets. Lipid droplets are taken up by autophagosomes, which are double-membrane-bound vacuoles, during lipophagy.[22] These vacuoles carry the cargo of lipid-droplets to lysosomes, where lipid-digesting enzymes (lipases) break them down, releasing free fatty acids that subsequently proceed through β-oxidation within mitochondria. Chronic ethanol usage is said to slow down autophagy rates, at least in part because ethanol is believed to result in defective lysosome biogenesis. This slows the digestion of lipid droplets in the steatotic liver by producing fewer, more faulty lysosomes.[22]

Furthermore, it is evident that excessive alcohol consumption lowers the rates of β-oxidation of fatty acids after they are released from lipid droplets. A number of factors contribute to the slowdown: First, mitochondrial β-oxidation is inhibited by the increased production of NADH by ethanol oxidation. Second, the peroxisome proliferator activated receptor alpha (PPAR-α), a transcription factor that works in tandem with the retinoid X receptor (RXR) and controls the expression of genes that control fatty-acid transport and oxidation, is rendered inactive by metabolically produced acetaldehyde.[22] By attaching to the transcription factor covalently, acetaldehyde probably renders PPAR-α inactive by preventing it from recognising and/or binding PPAR-α promoter regions. Third, mitochondrial depolarisation

brought on by acute and chronic ethanol oxidation reduces their capacity to produce energy (i.e., adenosine triphosphate [ATP] molecules) and causes their outer membranes to leak, which leads to ineffective fatty acid import and decreased β-oxidation rates.[23,24] Fourth, the hormone adiponectin, which is released by fat cells (i.e., adipocytes), is produced less when ethanol is consumed. According to one study, fatty-acid oxidation returns to normal when adiponectin is given to mice that are fed alcohol. Furthermore, adiponectin seems to decrease the cytokine TNFα synthesis, and there is evidence that TNFα may also control the production of adiponectin.[25]

Alcohol Causes Defective Hepatic Lipid Export[26,27]

It is commonly recognised that the liver only exports cholesterol and triglycerides as components of very low density lipoprotein (VLDL) particles; hence, any impairment in the production or export of VLDL particles leads to the buildup of fat in hepatocytes.[26,27] The presence of triglycerides, which comprise over half of the VLDL lipids, in cytoplasmic lipid droplets controls VLDL formation. The pool of triglycerides held in lipid droplets that first undergo lipolysis and subsequently re-esterify to form VLDL triglycerides accounts for up to 70% of the triglycerides found in VLDLs. It is unclear exactly how alcohol hinders the lipolysis of triglyceride reserves in lipid droplets for the assembly of VLDL and its subsequent secretion, despite previous observations linking altered VLDL secretion to the development of alcoholic steatosis.[26,27] However, research has demonstrated that decreased activity of a protein necessary for VLDL assembly and decreased synthesis of a VLDL ingredient are the two main causes of alcohol-impaired VLDL secretion.[26,27]

Mechanisms Involved in Alcoholic Hepatitis

About 30 to 40 percent of people who report persistent alcohol misuse develop alcoholic hepatitis. It is linked to a high short-term death rate and is the most severe type of ALD. Typical pathologic signs of hepatitis include fibrosis, infiltrating neutrophils, and ballooning degeneration of hepatocytes with Mallory-Denk bodies.[28] Macrophages, which are resident and invading immune cells that play a significant role in causing liver inflammation, are essential to the development of alcoholic hepatitis. Up to 15% of liver cells and 50% of all macrophages in the body are KCs, the resident macrophages in the liver.[29] As strong innate immune cells, they are found in the liver sinusoids and offer the initial line of defence. On the other hand, infiltrating macrophages are derived from the bone marrow as immature cells, and only in response to inflammation do they differentiate into macrophages in the liver.

The polarisation of macrophages, or their capacity to differentiate into either of two functional states—M1 (proinflammatory) or M2 (anti-inflammatory) macrophages—determines their capacity to control inflammation. Pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP) molecules, as well as circulating growth factors and cytokines, all influence the polarisation to either phenotype. The liver needs to be shielded from the development of an immune response to the innumerable antigens, infections, and toxic substances that it encounters through the portal circulation from the intestine. Because of this, KCs typically exhibit tolerogenic characteristics, which means that not all antigens elicit an immunological response from them. On the other hand, KCs may change to a proinflammatory M1 phenotype as a result of heavy alcohol consumption. Usually, a second insult—such as another chemical insult, dietary component, or viral infection—is necessary for ALD to develop from liver steatosis to

inflammation.[29] More significantly, depending on their capacity to either promote or inhibit proinflammatory alterations, KCs can control the course of inflammation. The intensity and stage of alcoholic hepatitis are linked to these consequences; in milder instances, KCs transition to the anti-inflammatory M2 phenotype, whereas in severe cases, they differentiate to the proinflammatory M1 phenotype.[29] As inflammatory mediators, KCs release a variety of proinflammatory cytokines, such as interleukins, TNFα, and chemokines, which draw inflammatory cells out of the bloodstream. Additionally, KCs are a rich source of ROS, which worsen oxidative stress in the liver.

What causes people with alcohol consumption disorder to exhibit KC activity? Endotoxin, commonly known as lipopolysaccharide (LPS), is a key component of Gram-negative bacteria's cell walls that moves from the gut lumen into the portal circulation and eventually reaches the liver. There are two primary ways that excessive ethanol consumption causes endotoxemia, according to mounting evidence: by promoting bacterial overgrowth and by raising intestinal permeability.[30] According to research on animals, the severity of liver illness is correlated with elevated amounts of endotoxins in the blood. Two different kinds of receptors on the KC surface—CD14 and toll-like receptor 4 (TLR4)—sense LPS.[30] Through the stimulation of CYP2E1 and decreased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, these receptors stimulate KCs to generate proinflammatory cytokines and encourage the creation of free radicals. Reactive oxygen and nitrogen species that are produced as a result encourage the release of proinflammatory cytokines, which raise the activation of inflammasomes in KCs and trigger the release of chemokines, which draw immune cells from the bloodstream to the liver. The innate immune system sensors known as inflammasomes control the activation of caspase-1 and cause

inflammation in response to toxic shocks (such as alcohol exposure), compounds produced from host proteins, and microbial or viral infections.[30]

Liver inflammation might be made worse by other reasons. The most notable of them are MAA adducts, which are generated in hepatocytes exposed to alcohol. Scavenger receptors on KCs absorb these adducts, which further stimulates the proinflammatory response. Additionally, because macrophages employ CYP2E1 to metabolise ethanol, alcohol consumption that causes oxidative stress triggers the production of proinflammatory cytokines, such as TNFα, in a macrophage-dependent manner. Hepatocytes are generally resistant to TNFα, but exposure to alcohol makes them more sensitive to the cytokine, which leads to apoptosis and death. KCs receive activation cues from the tiny vesicles (exosomes) that are released by dying hepatocytes. Inflammation is made worse when KCs engulf apoptotic hepatocytes, changing their phenotype to M1. Chemokines released in response to inflammation draw circulating neutrophils, T-cells, and macrophages—another source of oxidative stress—to the liver. These immune cells further encourage hepatocyte cell death and the continuation of alcoholic hepatitis by producing chemokines with direct cytotoxic effects and proinflammatory cytokines.[31,32]

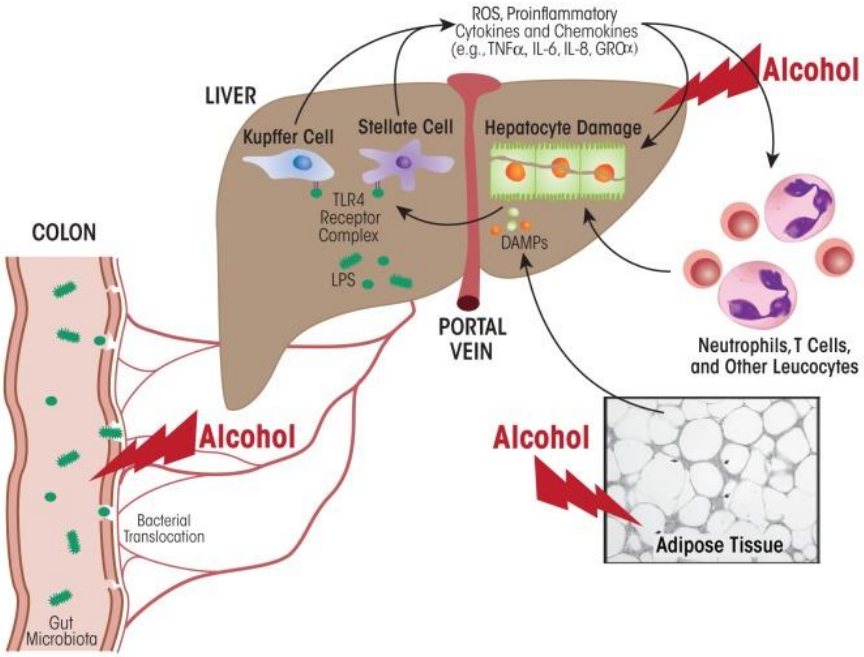
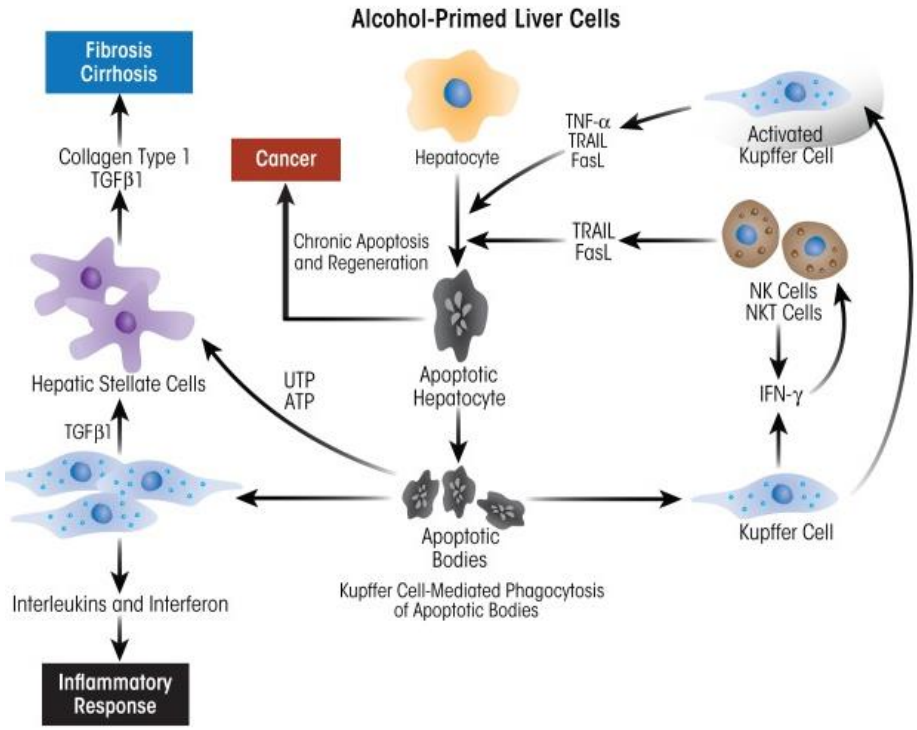


Figure 5: Schematic depiction of the role of Kupffer cells (KCs) and hepatic stellate cells (HSCs) in promoting alcohol-induced inflammatory changes and progression to fibrosis and cirrhosis.[31,32]



Mechanisms Involved in Fibrosis/Cirrhosis

The main contributors to the formation of fibrosis are HSCs. These cells often live in the Disse space as quiescent cells that store lipids (retinyl esters). HSCs go through a complicated activation phase after hepatic damage, and they are the main cause of the increased and erratic deposition of extracellular matrix components that define fibrosis. By releasing chemokines and proinflammatory cytokines and expressing adhesion molecules, activated HSCs also aid in the inflammatory response by coordinating the recruitment and activation of leukocytes.[33] The fibrogenic response is exacerbated by the leukocytes' subsequent attack and destruction of hepatocytes as well as their activation of quiescent and active HSCs.[33]

Hepatic fibrosis is a temporary and reversible wound-healing reaction that can return to normal in certain patients if they stop drinking alcohol. But if drinking persists, chronic inflammation and persistent fibrogenesis worsen, leading to the replacement of liver parenchyma by scar tissue, which seriously impairs the vascular architecture of the liver. The development of regenerating nodules of hepatic parenchyma encircled by fibrous septa is the primary pathological characteristic of cirrhosis. The development of cirrhosis advances from a compensated phase, when a portion of the liver is unharmed and functionally makes up for the damaged areas, to a decompensated phase, where the organ is completely encased in scar tissue. The latter is distinguished by the emergence of hepatic failure and/or portal hypertension.

Modifiers of ALD Risk

- Only over 35% of problem drinkers go on to have severe liver disease. This is due to the existence of modifiers that worsen, halt, or stop the progression of ALD disease, as mentioned below.

- Type of Beverage and Consumption Pattern. The type of beverage drank, as well as the quantity and frequency of drinking (such as binge drinking or outside mealtime), are the most significant factors influencing the course of liver disease. Males who consume 40 to 80 grammes of ethanol per day for 10 to 12 years, and females who consume 20 to 40 grammes per day, are generally at risk for more severe forms of ALD, such as cirrhosis, fibrosis, and alcoholic steatohepatitis.[34]

- Gender. According to epidemiologic data, women are more vulnerable than males to liver impairment caused by drinking. Because women have a lower percentage of body water than men of the same weight, they appear to have higher blood alcohol concentrations than men who consume the same amount of alcohol. Additionally, according to some accounts, women are less able than males to oxidise ethanol in the gut, a process known as first-pass metabolism. Women's livers are exposed to higher ethanol concentrations because of this deficiency, which permits larger amounts of ethanol to enter the portal circulation. Furthermore, females are more susceptible to the advancement of ALD than males due to gender-based differences in KC sensitivity to endotoxins and hepatic inflammatory responses.[35]

- Age. How ageing affects the course of ALD is not entirely understood. However, because older adults (those 65 and older) are more susceptible to and exhibit more severe ethanol-induced deficits than younger people, it is a predictor of ALD.[36]

- Ethnicity and race. The age at which various ALD subtypes manifest and their severity are significantly influenced by ethnicity. It's unclear why these disparities exist.[37]

- Genetics. The development and course of ALD are controlled by both genetic and epigenetic factors. Certain genetic markers (i.e., single-nucleotide polymorphisms) in genes encoding cytokines, antioxidant enzymes, and alcohol-metabolizing enzymes have been linked to the development of ALD by genome-wide association studies.[38] The most recent discovery of an independent risk factor for alcoholic cirrhosis was an allele of the triglyceride-degrading enzyme patatin-like phospholipase domain-containing protein 3 (PNPLA3 I148M).[38]

- Aspects of nutrition. One macronutrient and dietary modification for ALD is dietary fat. While dietary unsaturated fat that is richer in linoleic acid is said to encourage liver damage, dietary saturated fat appears to shield animals against alcohol-induced liver damage.[39] Substances. Hepatotoxicity is increased by the interaction of alcohol with other drugs, including illegal narcotics, over-the-counter pharmaceuticals, and prescription prescriptions. For instance, as previously mentioned, alcohol misuse can worsen the hepatotoxicity of paracetamol.

- Being overweight. According to population-based research, alcohol use and the risk of liver injury are significantly correlated among individuals with a high body mass index.[40]

- Smoking. Cigarette smoking is linked to an increased incidence of alcoholic cirrhosis in humans and can negatively impact specific liver functions.

- Infections with viruses. Alcohol abuse exacerbates the course of hepatitis B (HBV) and hepatitis C (HCV) viral infections, leading to cirrhosis, fibrosis, and even hepatocellular cancer. Although a number of common processes of alcohol-induced damage and viral infection have been proposed, the precise mechanisms underlying this fast disease progression remain unclear. Since over 170 million individuals worldwide suffer from viral infections like HCV or HBV, this topic will be covered in more detail in the section that follows.[41]

Non-alcoholic fatty liver disease (NAFLD)

Chronic liver disease is frequently caused by non-alcoholic fatty liver disease (NAFLD) all over the world. When no other causes of secondary hepatic fat accumulation (such as excessive alcohol consumption) can be found, NAFLD is a spectrum of diseases characterised by hepatic steatosis. The more severe end of the spectrum is non-alcoholic steatohepatitis (NASH), while the more benign disease is non-alcoholic fatty liver (NAFL). NAFLD can develop into cirrhosis and fibrosis.[42] Hepatic steatosis is found in NAFLD without any indication of inflammation, but in NASH, it is linked to lobular inflammation and apoptosis, which can result in cirrhosis and fibrosis.[43]

Prior to the middle of the last decade, NASH was generally regarded as a serious condition that primarily affected females who were obese, had a relatively benign prognosis, and were predictive risk factors for diabetes, heart disease, and stroke. It was also frequently linked to Type 2 Diabetes Mellitus (T2DM).[43] With a global frequency of 25%, the prevalence of liver disease (NAFLD) has increased significantly in Western nations. In Western industrialised nations, nonalcoholic fatty

liver disease (NAFLD) is on the rise, especially in those with metabolic syndrome, central obesity, type 2 diabetes, and dyslipidaemia.[44]

RISK FACTORS AND ETIOLOGY[45]

Metabolic syndrome and type 2 diabetes mellitus[45]

A person who has metabolic syndrome is more likely to develop type II diabetes and cardiovascular disease since it is a collection of cardiovascular risk factors. Three out of five of the following criteria must be present in order to meet the current diagnostic criteria: hyperglycemia (fasting glucose of 100 g/dL or higher), triglycerides of 150 mg/dL or higher, high-density lipoprotein cholesterol of less than 40 mg/dL in men and less than 50 mg/dL in women, hypertension (systolic blood pressure of 130 mmHg or greater or diastolic blood pressure of 85 mmHg or greater), and an increased waist circumference (as determined by population-specific data).[45] As was already established, as rates of metabolic syndrome have been rising, so too has the incidence of NAFLD. Indeed, it has been reported that the more metabolic syndrome criteria that are satisfied, the higher the incidence of NAFLD. Patients with type 2 diabetes mellitus (T2DM) had 80% more liver fat than non-diabetic patients (matched for age, sex, and body weight). [45]The frequency of NAFLD in T2DM patients may be far higher than reported in this patient population, as it has been demonstrated that patients with NAFLD can have normal liver function tests.[45] T2DM patients also have a two to four times higher risk of problems related to fatty liver and a very high risk of developing NASH.[45]

Ethnic differences

It has been demonstrated that Hispanic patients have the highest rate of NAFLD development. Intriguingly, NAFLD has been on the rise in the Asian population and is present in people with normal body mass indices. In a study conducted in the United States, the researchers discovered that African Americans had less steatosis than white people, whereas Asians and Hispanics had more NAFLD findings.[46] It has also been demonstrated that African Americans had a lower risk of liver failure, whereas Hispanics have a higher incidence of cirrhosis and steatohepatitis. Further genetic analysis using genome-wide association revealed that Hispanics with the homozygous PNPLA3 allele (patatin-like phospholipase domain-containing protein 3 rs738409) had a liver fat burden that was twice as high.[46] It has been demonstrated that the PNPLA3 gene family influences lipid metabolism, and individuals with this polymorphism have higher levels of inflammation, triglyceride storage, and hepatic fat. Actually, those who carry the mutation have more severe histologic characteristics of NAFLD due to the mutation of the PNPLA3 rs738409 gene, which codes for I148M.[46]

Gender and age

Regretfully, the literature has reached varying results about the role of gender in the development of NAFLD. While some research suggested a higher incidence in males, others suggested the opposite. According to reports, the prevalence of non-alcoholic fatty liver disease (NAFLD) rises with age, reaching over 40% in individuals over 60. In addition to NAFLD prevalence rising with age, patients 50 years of age and above also had higher incidences of NASH and cirrhosis than patients in younger age groups.[47]

Diet, smoking and life style

Diet, particularly a high-fat diet, has been considered a risk factor for the development of non-alcoholic fatty liver disease (NAFLD). It has been demonstrated that dietary changes can lower metabolic syndrome through calorie restriction and adjustment of dietary macronutrients, specifically fat, carbohydrate, or monounsaturated fatty acid enrichment. A higher chance of developing metabolic syndrome and eventual non-alcoholic fatty liver disease (NAFLD) is linked to diets that follow a Westernised pattern, such as those heavy in red meat intake, refined carbohydrates, pastries, and sugar-filled beverages.[48] A person is more likely to develop insulin resistance if they smoke. Furthermore, both passive and active smoke exposure are powerful independent predictors of metabolic syndrome, according to a study conducted on adolescents in the United States. Regarding lifestyle, studies have linked sedentary behaviour and fitness to an increased risk of NAFLD and NASH; the severity of NAFLD also increases with less physical activity.[48] According to the EASL-EASD-EASO Clinical Practice Guidelines for the Management of NAFLD, a thorough NAFLD screening examination should include a recommendation for the evaluation of physical activity habits.[48] In order to address obesity and insulin resistance, diet and exercise are also included in the NAFLD therapy plan. Numerous studies have assessed how a balanced diet and gradual weight loss affect the biologic characteristics of non-alcoholic fatty liver disease. Significant improvements in blood liver enzymes, lower hepatic fatty infiltration, decreased hepatic inflammation, and decreased levels of fibrosis have been observed with steady weight loss through diet, with or without exercise.[48] Additionally, exercise has a definite positive impact on hepatic fatty infiltration; this effect is especially noticeable when weight loss is minor or nonexistent and exercise levels are below those advised for managing obesity.[48]

Polycystic ovarian syndrome

Obesity and insulin resistance are two prevalent symptoms of polycystic ovary syndrome (PCOS), an endocrine condition that affects many women throughout their reproductive years. Women who have PCOS are therefore more likely to develop type 2 diabetes.[49] Insulin resistance exacerbates the hyperandrogenism that is common in women with PCOS by boosting ovarian androgen synthesis and lowering hepatic SHBG production, which raises the amounts of free androgens in the blood. Patients with PCOS are at risk of developing NAFLD because of the ensuing hyperandrogenism, which is linked to a more noticeable insulin resistance.[49]

Obstructive sleep apnea

Complete or partial airway obstruction brought on by pharyngeal collapse while you sleep is the hallmark of obstructive sleep apnoea (OSA). In recent years, there has been a growing correlation between OSA and cardiovascular disease, metabolic syndrome, and diabetes mellitus.[50] Obstructive sleep apnoea affects about 4% of the general population, but in obese people, that percentage rises to 35% to 45%.[50] The altered gas exchange (repeated hypoxemic and hypercapnic episodes), known as chronic intermittent hypoxia, is thought to be the pathogenic mechanism underlying this association.[50] This can result in oxidative stress, endothelial dysfunction, proinflammatory cytokines, metabolic dysregulation, and insulin resistance. It's interesting to note that OSA might be contributing to the progression of NAFLD from steatosis to NASH.[50]

Pathophysiology of NAFLD/NASH[51]

The process by which NASH develops is intricate and poorly understood. The pathogenesis of NAFLD and NASH has been extensively studied in recent years using animals, mostly focussing on the differences in dietary models (high fructose, high fat, or methionine/choline deficient diet (MCD)).[51] It has been proposed that NASH develops in two stages based on this body of research. Deposition of fat in the liver is the initial stage of this process, which will raise insulin resistance. This process's second phase consists of cellular and molecular alterations brought on by oxidative stress and the oxidation of fatty acids in the liver as a result of a number of variables, including cytokine damage, hyperinsulinemia, hepatic iron and/or lipid peroxidation, extracellular matrix variation, energy homeostasis, and immune system dysfunction. Insulin resistance develops through a complex mechanism.[51] Increased fat mass and adipocyte differentiation are important factors in the development of insulin resistance in the context of MS, as is the situation for many NASH patients.

There are two different forms of NAFLD. Insulin resistance is currently thought to be the main pathophysiological mechanism for the first kind of NAFLD, which has a limited association with metabolic syndrome.[51] Liver steatosis can result from viral diseases that are linked to the second kind of NAFLD. Infections such as hepatitis C and HIV may be the cause in this instance, but it is also linked to certain toxins, inherited or acquired metabolic diseases (e.g. lipodystrophy or cachexia or intestinal bypass surgery), and medications (total parenteral nutrition, glucocorticoids, tamoxifen, tetracycline, amiodaron, methotrexate, valproic acid, vinyl chloride).[51]

Symptoms and signs

While most NAFLD patients have no symptoms, others may report of hepatomegaly, acanthosis nigricans, lipomatosis, lethargy, and soreness in the right upper quadrant. End-stage liver disease might manifest in a considerable number of cirrhosis patients. NASH can be asymptomatic in 48–100% of cases, and it is frequently found after medical assessments for other causes. One study found that 25% of patients had splenomegaly at the time of diagnosis, despite the fact that clinical signs of chronic liver failure are uncommon in this cohort. [52]

Frequently, abnormal liver function tests like aminotransferases (ALT and AST) or an unintentional discovery of hepatic steatosis on radiologic abdominal findings lead to a diagnosis such as NASH or NAFLD.[52] A physical examination may reveal hepatomegaly, which is brought on by fatty infiltration of the liver.[52]

Laboratory findings

Serum indicators such as aminotransferases (AST, ALT) are mildly to moderately increased during laboratory testing. However, patients with NAFLD or associated disorders may have atypical AST and ALT levels. Stated differently, increased or normal AST and ALT levels do not indicate the presence of NAFLD. ALT elevations are more prevalent than AST elevations in NAFLD patients. Compared to ordinary steatosis, NASH typically has higher ALT levels. individuals with NAFLD frequently have raised serum ferritin levels, and 6–11% of individuals have increased transferrin saturation.[53]

Clotting factors and alkaline phosphatase (ALP) are other relevant markers. ALP can be abnormal in patients with non-alcoholic fatty liver disease (NAFLD) and can potentially be increased two to three times the upper limit of its normal value.

Furthermore, the diagnosis of NAFLD may benefit from further test results. Patients with chronic progressing illness may have elevated levels of both albumin and bilirubin. Laboratory assessments of clotting times may be abnormal in people with cirrhosis. Patients with cirrhosis typically have thrombocytopenia, a prolonged prothrombin time, and concurrent neutropenia.[53]

Imaging in NAFLD

Several imaging modalities can be used to support the diagnosis of liver diseases like NAFLD and NASH, however none of them are frequently employed to distinguish between the (histological) subtypes of NAFLD or NASH.[54] These liver illnesses can be identified by magnetic resonance imaging (MRI), abdominal ultrasonography (US), or computed tomography (CT) studies. Patients with NAFLD had higher fat signals on MRI, reduced hepatic attenuation on CT, and greater echogenicity on ultrasound.[54]

Ultrasound

Due to diffuse fatty infiltration, US frequently shows a bright liver or a hyperechoic texture. In identifying increasing fibrosis and steatosis, US has a sensitivity of 89 and a specificity of 93%. The US approach, on the other hand, is the most affordable and often utilised modality in clinical practice. Patients who are obese have lower US sensitivity. Steatosis is suggested by the US exhibiting hyperechogenic liver tissue in comparison to the spleen or kidney echogenicity.[55]But in these cases, the US's sensitivity is only 60–94%.[55]

Vibration-controlled transient Elastography (VCTE)

When assessing liver stiffness, VCTE is a non-invasive technique for ruling out advanced fibrosis.[51]

CT, MRI, and magnetic resonance spectroscopy (MRS)

Both imaging modalities can identify steatosis, but they are not sensitive enough to identify liver fibrosis or inflammation.

Unfortunately, MRS is (yet) not generally accessible and has a higher sensitivity to identify the previously stated disease processes.[51] Overall, the sensitivity of MRS, MRI, and CT to identify hepatic steatosis was 88%, 50%, and 33%, respectively. The three had respective specificities of 100, 83, and 63% for detecting hepatic steatosis.[51]

Histological findings in NAFLD

The gold standard for diagnosing NASH or NAFLD is a liver biopsy.[56] It is still debatable whether or not every patient with suspected NAFLD should get a liver biopsy. In patients with NAFLD, the general justifications for a liver biopsy either confirm or rule out the diagnosis. Although a liver biopsy is widely regarded as the gold standard for identifying non-alcoholic fatty liver disease (NAFLD), a preemptive diagnosis is primarily made based on the patient's imaging, test results, and medical history. A liver biopsy can be highly beneficial in determining the overall extent of hepatic damage as well as in individuals whose diagnosis is still ambiguous following non-invasive evaluations.[56]

Liver biopsy limitations include variability in sampling error, variable between and among observers, and risk and complications—issues with a pathological diagnosis that can result in incorrect staging and misdiagnosis. During the assessment of paired biopsies, numerous studies have demonstrated sampling variability and an unequal distribution of NASH histologic lesions.[56]

Patients with NAFLD can have their disease activity graded using the validated NAFLD Activity Score (NAS). Each of the NAS's components—steatosis (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2)—has a minimum and maximum score. The NAS does not cover fibrosis. Scores of 0 to 2 were assigned to cases that were primarily not diagnostic of NASH in the original study that developed the NAS; scores of 3 to 4 were distributed equally among those that were deemed not diagnostic, borderline, or positive for NASH; and scores of 5 to 8 were assigned to cases that were primarily diagnostic of NASH.[57]

DIFFERENTIATION OF ALD AND NFLD

Alcoholic Liver Disease

The severity and duration of alcohol misuse determine the clinical presentation of ALD. Patients range from those with no symptoms to those with severe cirrhosis. Acute alcoholic hepatitis may also be present. Laboratory biomarkers for chronic alcohol abuse include gamma-gluthamyl transferase (gamma-GT), mean corpuscular erythrocyte volume (MCV)[57], carbohydrate-deficient transferrin (%CDT), ethylglucuronide (EtG), and phosphatidylethanol (PEth). These biomarkers help distinguish between alcoholic and non-alcoholic causes of liver disease in patients. Thrombocytopenia, increased ESR, and macrocytic anaemia are further test indicators of AUD.

While helpful, accessory investigations are not conclusive. An elevated AST/ALT ratio is the most well-known anomaly. The upper limit of normal (ULN) is typically exceeded by fewer than 8 times for the AST and less than 5 times for the ALT. The degree of elevation and the severity of the ALD do not correlate. Usually, the AST has a greater degree of elevation than the ALT.[57] A hepatic shortage of pyridoxal 5′-phosphate, a co-factor for ALT activity, is the cause of this.[57]

The Amarapurkar team examined 36 NASH patients, with a mean age of 50.8 years. Of the patients, 30.5% had fibrosis, while 69.4% did not.[57] In 80.6% of the patients, they found statistical significance for AST, ALT levels, and the AST/ALT ratio between those with and without fibrosis using multiple regression and logistic regression analysis.[57] It is found that in the majority of situations, the AST/ALT ratio may be useful in identifying fibrosis in NASH patients who also have diabetes.

NASH cirrhosis frequently has an AST/ALT ratio greater than 1, which can occasionally be seen in NASH. An ALD is strongly suggested by a number larger than 2. Ninety percent of the 271 patients with biopsy-proven liver illness had an AST/ALT ratio > 2, and ninety-six percent of those with a ratio > 2.5 had ALD. Furthermore, gamma-gluthamyl transpeptidase (GGT) is frequently increased in ALD. Every patient with ALD exhibited GGT increases up to ten times the ULN, according to a report of 123 individuals with AUD. After eight weeks of abstinence, the elevated serum GGT level persisted.

Imaging tests can be used to identify hepatic parenchymal alterations, diagnose ALD, and correlate cytokines and chemokines both before and after detoxification.[57]

Zhang and his colleagues demonstrated that moderate to severe steatosis may be identified and measured using unenhanced computerised tomography (CT). However, it is not a reliable way to diagnose mild steatosis. Additionally, the authors advocate using dual energy CT to measure steatosis. The group also demonstrates that the most accurate imaging method for measuring liver steatosis is magnetic resonance imaging (MRI) proton-density fat fraction.

Alcoholic Fatty Liver Disease

Since most NAFLD patients have no symptoms, they might not even be aware that they have the disease. The physical examination results are comparable to those of ALD as previously mentioned. Both ALT and AST may be mildly to moderately elevated, but they may also be normal. Typically, the ratio of AST to ALT is less than one. There may also be an increase in serum ferritin or transferrin saturation. Advanced fibrosis and a higher NAFLD activity score are linked to serum ferritin levels that are more than 1.5 times the ULN.

Ultrasound may exhibit hyperechogenicity akin to ALD in imaging studies. In comparison to liver biopsy, a meta-analysis of 49 trials involving 4720 patients revealed an 85% sensitivity and a 94% specificity. However, those who are obese have reduced sensitivity. The sensitivity of CT and MRI is insufficient to identify fibrosis or inflammation. A quantitative measurement of hepatic fat can be obtained using magnetic resonance (MR) spectroscopy.

Because of the metabolic syndrome, NAFLD also affects other organ systems.

Cardiovascular disease and diabetes are among them. Furthermore, there is a link to diastolic dysfunction, and patients with both preserved and lowered ejection fraction heart failure have been shown to have greater in-hospital death rates in recent

years.

Liver Histology in ALD and NAFLD

Alcoholic Liver Disease

Macrovesicular steatosis, particularly in zone 3, is one of the early alterations in ALD. With neutrophils initially in zone 3, this steatosis may develop into steatohepatitis. Although they are present, Mallory-Denk bodies—eosinophilic aggregations inside the hepatic cytoplasm—can also be observed in NASH. According to a Veterans Administration research, 95% of people with cirrhosis and 76% of people with alcoholic hepatitis had MDB. With prolonged alcohol use, fibrosis can eventually appear, initially in zone 3, and then spread to the panlobular region. Regenerative nodules eventually show up, and this stage is believed to represent permanent cirrhosis. Both micronodular and macronodular cirrhosis are possible. Micronodular cirrhosis can occasionally develop into macronodular cirrhosis.

Non-Alcoholic Fatty Liver Disease[58]

When at least 5% of the hepatocytes are steatotic, NAFLD is detected. Iron accumulation in the liver is another possibility. Either steatosis, steatosis with portal or lobular inflammation, or steatosis with hepatocyte ballooning without inflammation can be present in NAFLD.[58] In addition to lobular inflammation and ballooning hepatocyte destruction, hepatic steatosis is necessary for the histologic diagnosis of NASH. Alcoholic steatohepatitis is comparable to this. There may also be hepatic siderosis and Mallory-Denk bodies.

It is difficult to distinguish NASH from other liver diseases, such as ALD, because they can coexist. 5.5% of patients of HCV hepatitis had steatohepatitis, according to a study of 3581 liver biopsies. The authors came to the conclusion that the prevalence of steatohepatitis in the general population is reflected in its existence.

Thus, NAFLD and other liver disorders, including ALD, frequently have comparable histological pictures. Due to the comparable clinical and histological features of ALD and NAFLD, a new nomenclature for fatty liver disease has been developed.[58]

It is challenging to distinguish ALD from NAFLD with confidence because of their similar pathological spectra, which range from basic steatosis to liver cirrhosis. The histology features listed below, however, aid in the differential diagnosis. Compared to ALD, NAFLD causes a higher degree of fatty liver cell degeneration. On the other hand, ALD exhibits a greater degree of inflammatory cell infiltration than NAFLD. Additionally, ALD is more likely than NAFLD to have venous or perivenular fibrosis, phlebosclerosis, and (less frequently) lymphocytic phlebitis.

Clinically, a patient's history of alcohol consumption, along with laboratory and imaging tests, is typically used to distinguish between ALD and NAFLD; however, the accuracy of these techniques may be low. Thus, clinical parameters have been used to create discriminant indices. For instance, a patient's gender, BMI, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, and mean corpuscular volume (MCV) are used to generate the ALD/NAFLD index (ANI).[59] With an area under the receiver operating characteristic curve (AUROC) of 0.983 (cut-off value, 0; sensitivity, 93.5%; specificity, 92.0%) in the derivation set and AUROCs of 0.974, 0.989, and 0.767 in the three validation sets, this index has

demonstrated a high level of diagnostic accuracy.[59] A recent validation study attested to the index's great accuracy. However, because individuals with end-stage liver disease often have elevated MCV and an elevated AST/ALT ratio, the ANI may be less accurate in these patients.[59] The ANI may not be applicable to other ethnic groups because it was developed using data sets primarily gathered from Caucasians, indicating the necessity for indices tailored to these ethnicities.[59]

ALD/NAFLD index[60]

The ALD/NAFLD index is a non-invasive scoring system used to assess liver disease severity. It combines several clinical parameters:

1. Aspartate aminotransferase (AST) levels
2. Alanine aminotransferase (ALT) levels
3. Mean corpuscular volume (MCV)
4. Body mass index (BMI)
5. Gender

Alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD), which can present similarly but need different therapies, can be distinguished with the use of this score. ALD is suggested by a higher score, whereas NAFLD is indicated by a lower score.The formula is:

54.5 + 0.74 × MCV - 27.96 × gender (male=1, female=0) + 0.25 × BMI + 0.37 × AST

Scores above 0 suggest ALD, while scores below 0 suggest NAFLD.

REVIEW OF RELATED ARTICLES

Roy A et al (2024)[61] examined how well the ANI performed in terms of differentiation within the SLD spectrum.[61] The study is cross-sectional. Of the 202

patients (47 years [interquartile range, IQR, 38 to 55], 23.75% were female, 77% were obese, 42.1% had diabetes, 38.1% had hypertension, and 28.7% used statins), 40.5% had ever consumed alcohol; 120 (59%), 50 (24.7%), and 32 (15.8%) had MASLD (ANI, -3.7 [IQR, -7 to -1.6]; MetALD, - 1.45 [IQR, -2.4 to 0.28]; and AALD, 0.71 [IQR, -1.3 to 4.8], respectively; P<0.05 for all).[61] For MASLD, the ANI's AUROC was 0.79 (IQR, 0.72 to 0.84; cut-off <-3.5), while for AALD, it was 0.80 (IQR, 0.74 to 0.86; cut-off >-1.49).[61] Gamma glutamyl transpeptidase (GGT) (AUROC=0.74 [IQR, 0.67 to 0.80]) and aspartate transaminase/alanine transaminase (AST/ALT) ratio (AUROC=0.75 [IQR, 0.69 to 0.81]) were both surpassed by the ANI.[61] Model performance was not enhanced by the addition of GGT (AUCdiff=0.004; P=0.33). They came to the conclusion that MASLD frequently has AC. In addition to outperforming the AST/ALT ratio or GGT, the ANI differentiates between MASLD and AALD, with distinct cut-offs within the intermediate zone indicating MetALD.[61]

Muralidhar P et al (2022)[62] 48 tertiary care hospital inpatients participated in a cross-sectional observational study. The index demonstrates great sensitivity (95.83%) and specificity (83.33%) for ALD patients, whose median ANI value is significantly higher than that of NAFLD patients (Median of ALD = 9.2485 vs. Median of NAFLD = -2.651) (P1.702). They came to the conclusion that, with a cut-off value of >1.702, the ANI scoring system demonstrated excellent sensitivity and specificity as an effective diagnostic tool in the Indian population. When it comes to distinguishing between patients with ALD and those with NAFLD, it performs better diagnostically than currently utilised serological indicators like AST/ALT and MCV, even though liver biopsy is still the gold standard.[62]

Wang J et al (2016)[63] This study sought to determine whether ANI in conjunction with γ-glutamyl transferase (GGT) would improve diagnosis accuracy in China and to confirm the validity of the alcoholic liver disease (ALD)/nonalcoholic

fatty liver disease (NAFLD) index (ANI) for differentiating ALD from NAFLD in patients with hepatic steatosis.[63] Compared to individuals with NAFLD, those with ALD had considerably greater ANI (7.11 ± 5.77 vs. –3.09 ± 3.89, $p < 0.001$). The sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC) of identified ALD cases were 87.1%, 92.5%, and 0.934 (95% CI), 0.879 to 0.969, respectively, with a cut-off value of –0.22.[63] The corresponding values were 75.29%, 72.94%, and 0.826 (95% CI, 0.752 to 0.885) for aspartate aminotransferase (AST)/alanine transaminase (ALT), 94.34%, 83.02%, and 0.814 (95% CI, 0.739 to 0.875), and 80.23%, 79.25%, and 0.815 (95% CI, 0.740 to 0.876) for mean corpuscular volume (MCV). Furthermore, the ANI AUROC demonstrated superior diagnostic performance and was considerably higher than the AST/ALT, MCV, or GGT AUROCs (all $p < 0.001$). ANI and GGT together demonstrated a higher AUROC than ANI alone (0.976 vs. 0.934, $p = 0.016$).[63] There was no statistically significant difference in AUROCs between AST/ALT, MCV, and GGT (all $p > 0.05$). ANI has a high degree of accuracy in differentiating between ALD and NAFLD; its efficacy increased when paired with GGT.

Cerović I et al (2013)[64] This study sought to determine whether ANI was a reliable noninvasive technique for differentiating between ALD and NAFLD.[64] Patients with ALD had considerably higher ANI than those with NAFLD ($P<0.01$). ANI's cutoff point is -0.66. While ANI less than -0.66 produces a higher chance of NAFLD with good specificity (96.7%) and sensitivity (84.1%), ANI greater than -0.66 implies ALD.[64] Patients with ALD had a lower BMI than those with NAFLD, but they had larger mean corpuscular volume and aspartate aminotransferase/alanine aminotransferase ratios ($P<0.01$).[64] They came to the conclusion that the ANI scoring system might be utilised to help prioritise patients for liver biopsy and estimate the alcoholic origin of steatosis or steatohepatitis. While ANI larger than -0.66 verifies

the alcoholic aetiology and does not rule out the participation of related factors to the development of fatty liver in a Serbian population, ANI less than -0.66 implies nonalcoholic fatty liver disease (NAFLD).[64]

MATERIALS AND METHODS

- **Study design:** Observational study
- **Study area:** Department of General Medicine, KLEs Dr Prabhakar Kore Hospital & M.R.C.,A Teritary Care Centre, Belagavi.
- **Study period:** Research study was conducted from January 2023 to December 2023. Below is the work plan.

Table 1: Work plan of the study with percentage of allocation of study time and duration in months

Work plan	% of allocation of study time	Duration in months
Understanding the problem, preparation of questionnaire.	5-10%	September 2022 to December 2022
Pilot study, Validation of questionnaire, data collection and manipulation	Upto 80%	January 2023 to December 2023
Analysis and interpretation	5-10%	January 2024 to March 2024
Dissertation write-up and submission	5-10%	April 2024 to June 2024

- **Sample size**:

The minimum sample size formula based on mean and standard deviation is

$$n = \frac{(Z_{1-\alpha/2}+z_{1-\beta})^2(s_1{}^2+s_2{}^2)}{(\overline{X}_1-\overline{X}_2)^2}$$

where zβ and zβ are associated with the test's power and significance level,

respectively. $z\alpha = 1.96$ and $z\beta = 0.84$ for 80% test power at the 5% level of significance.

The first group's mean BMI (23.9) and the second group's mean (26.1) are the parameters taken into account in the computation.

The first group's standard deviation (s1) is 3.59, and the second group's standard deviation (s2) is 3.90.

The sample size obtained with these values is 46.

The sample size was 50 to round off.

Each of the two groups had at least fifty cases.

- **Sampling method**: Universal sampling method

- **Inclusion criteria:**

- Patients with age more than 18 years and diagnosed with Fatty liver radiologically either by sonography or fibroscan are divided into ALD and NAFLD based on h/o alcohol consumption.

- The diagnosis of ALD was established based on a documented history of significant alcohol consumption (>60g/day in males and >40g/day in females for >5 years) along with clinical, biochemical, and radiological evidence of liver disease.

- NAFLD diagnosis was confirmed in patients with minimal or no alcohol consumption (<20g/day) who demonstrated evidence of hepatic steatosis on imaging in the absence of other causes of chronic liver disease.

- **Exclusion criteria:**

  - Patients less than 18 years of age.
  - Patients with radiologically proven fatty liver disease but with h/o equivocal (20 gm to 30gm) of alcohol intake.
  - Patients with CHRONIC LIVER DISEASES due to other aetiologies like
    1. Viral infections hepatitis by hepatitis A,B,C,D and E viruses
    2. Autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis.
    3. Drugs induced due to anabolic steroids. OCPs, acetaminophen etc

METHODOLOGY:

A hospital based, observational study was conducted at the Department of General Medicine, KLEs Dr Prabhakar Kore Hospital & M.R.C., Belagavi. The study protocol was approved by the Institutional Ethics Committee (MDC/JNMCIEC/77), and written informed consent was obtained from all participants prior to enrollment.

A total of 100 patients were enrolled in the study, divided equally into two groups: 50 patients with Alcoholic Liver Disease (ALD) and 50 patients with Non-Alcoholic Fatty Liver Disease (NAFLD).

Data Collection and Clinical Assessment

All participants underwent a comprehensive clinical evaluation including detailed history taking and physical examination. Anthropometric measurements including height, weight, body mass index (BMI), and waist circumference were recorded. A structured questionnaire was used to collect information about alcohol consumption patterns, dietary habits, physical activity, and comorbidities.

Laboratory Investigations

Blood samples were collected from all participants after an overnight fast of 12 hours. The following parameters were measured: complete blood count, liver function tests (including AST, ALT, ALP, GGT, total bilirubin, direct bilirubin, total protein, and albumin), lipid profile, fasting blood glucose, and HbA1c. All laboratory tests were performed using standardized methods in the hospital's central laboratory.

Calculation of ANI Score

The ANI score was calculated for each patient using the formula: ANI = −58.5 + 0.637 (mean corpuscular volume) + 3.91 (aspartate transaminase/alanine transaminase) − 0.406 (body mass index) + 6.35 (if male sex) . The results were expressed in standardised units with MCV in fL, AST and ALT in U/L and BMI in kg/m^2,.

Imaging Studies

All patients underwent abdominal ultrasonography performed by experienced radiologists who were blinded to the clinical data. Liver steatosis was graded according to standardised criteria using fibroscan.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation or median with interquartile range based on the distribution of data. Categorical variables were expressed as frequencies and percentages. The diagnostic performance of ANI was evaluated using receiver operating characteristic (ROC) curve analysis, and the area under the ROC curve (AUROC) was calculated. Sensitivity, specificity, positive predictive value, and

negative predictive value were determined at various cut-off points. A p-value <0.05 was considered statistically significant.

Quality Control and Data Management

All data was collected using standardized case report forms and entered into a secure electronic database. Regular quality checks were performed to ensure data accuracy and completeness. Any discrepancies were resolved by referring to the original medical records and through discussion with the investigating team.

RESULTS

The present study was conducted in the department of General Medicine at Kles Dr Prabhakar Kore Hospital & M.R.C, A Teritary.Care Centre, Belagavi from January 2023 to December 2023 to test the reliability of ANI scoring system as a non-invasive method to distinguish alcoholic liver disease (ALD) from non-alcoholic fatty liver disease (NAFLD).

Total of 100 patients with 5o in each group were included in the study:

- **Alcoholic liver disease**:50 patients
- **Non-alcoholic fatty liver disease:** 50 patients

Following were the results of the study:

Table 1: Distribution of age among groups

Age (in years)	Groups		p-value
	ALD	NAFLD	
18-20	0	2 (4%)	0.46
21-40	14 (28%)	15 (30%)	
41-60	26 (52%)	26 (52%)	
>60	10 (20%)	7 (14%)	
Total	**50 (100%)**	**50 (100%)**	

Table 1 and graph 1 shows the age distribution among the ALD and NAFLD groups. Most patients in both groups were in the 41-60 years age range (52% in each group), followed by 21-40 years (28% in ALD, 30% in NAFLD). There were no patients aged 18-20 years in the ALD group, while the NAFLD group had 2 patients (4%) in this age range. The elderly population (>60 years) comprised 20% of ALD patients and 14% of NAFLD patients. The p-value of 0.46 indicates no statistically significant difference in age distribution between the two groups.

Graph 1: Distribution of age among groups

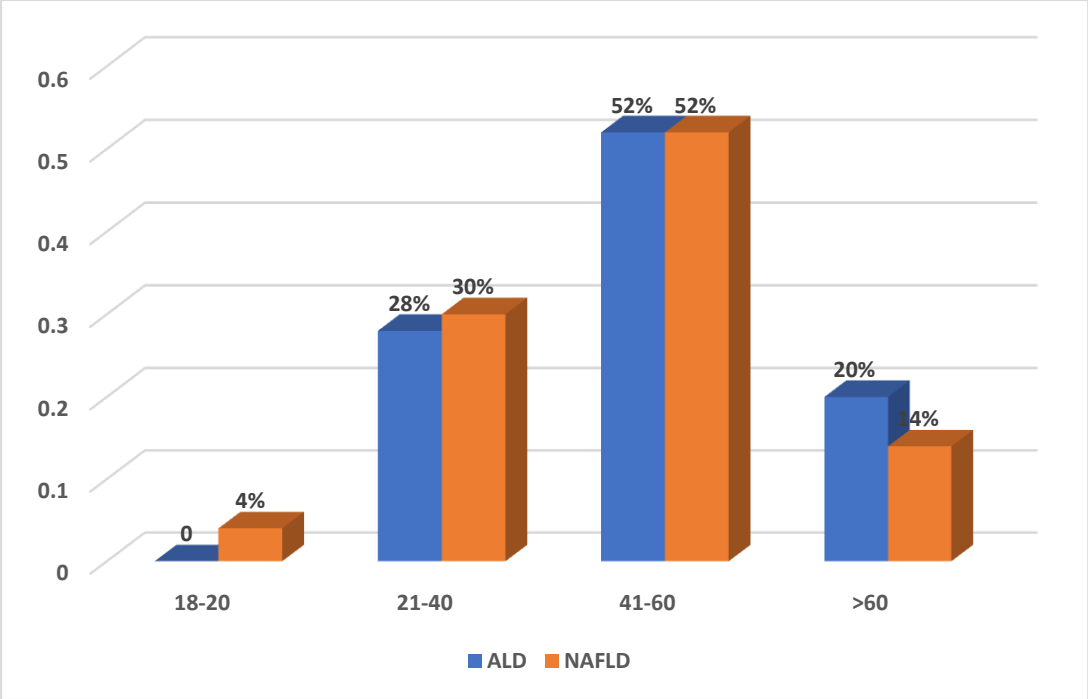


Table 2: Distribution of gender among groups

Gender	Groups		p-value
	ALD	NAFLD	
Female	0	27 (54%)	**<0.001**
Male	50 (100%)	23 (46%)	
Total	**50 (100%)**	**50 (100%)**	

Table 2 and graph 2 demonstrates a highly significant gender distribution difference between the groups (p<0.001). The ALD group consisted entirely of males (100%), whereas the NAFLD group had a more balanced gender distribution with 54% females and 46% males.

Graph 2: Distribution of gender among groups

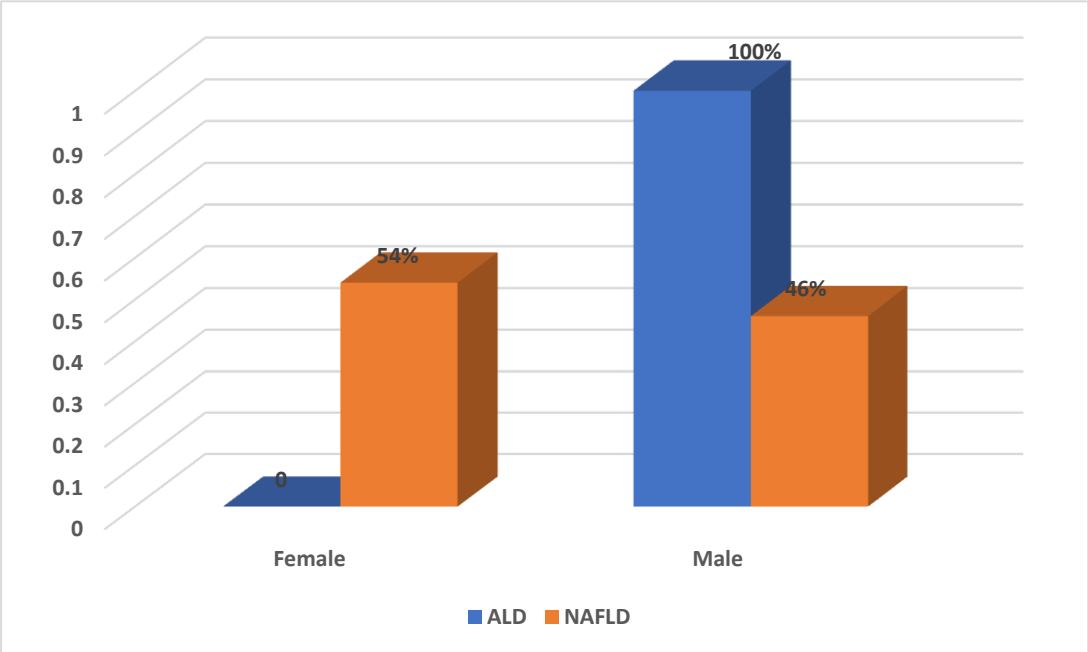


Table 3: Distribution of co-morbidities among groups

Co-morbidities	Groups		p-value
	ALD	NAFLD	
DM	15 (30%)	29 (58%)	**0.005**
HTN	21 (42%)	16 (32%)	0.3
Dyslipidemia	17 (34%)	24 (48%)	0.19

Table 3 and graph 3 presents the distribution of co-morbidities among both groups. Diabetes mellitus (DM) was significantly more prevalent in the NAFLD group (58%) compared to the ALD group (30%), with a p-value of 0.005. Hypertension (HTN) was more common in the ALD group (42%) than in the NAFLD group (32%), but this difference was not statistically significant (p=0.3). Similarly, dyslipidemia was more frequent in the NAFLD group (48%) compared to the ALD group (34%), though this difference did not reach statistical significance (p=0.19).

Graph 3: Distribution of co-morbidities among groups

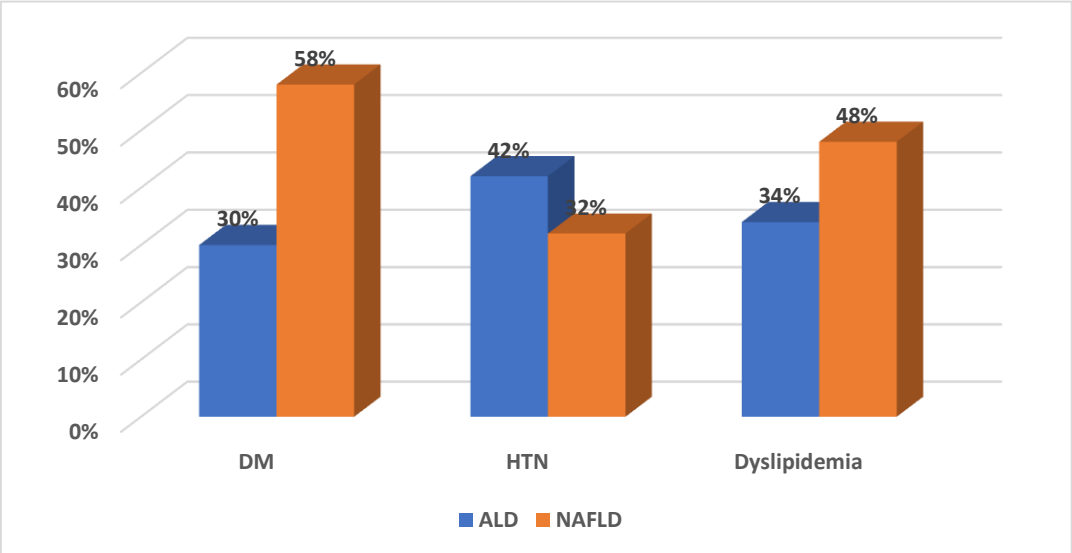


Table 4: Distribution of alcohol consumption among groups

Alcohol consumption	Groups		p-value
	ALD	NAFLD	
None	0	45 (90%)	**<0.001**
Casual	0	5 (10%)	
>60 gms/day	14 (28%)	0	
>70 gms/day	12 (24%)	0	
>75 gms/day	2 (4%)	0	
>80 gms /day	10 (20%)	0	
>90 gms/day	6 (12%)	0	
>100 gms/day	6 (12%)	0	

Table 4 and graph 4 details alcohol consumption patterns, showing a highly significant difference between groups ($p<0.001$). As expected, all ALD patients consumed significant amounts of alcohol (>60 grams/day), with the largest proportion (28%) consuming >60 grams/day. In contrast, 90% of NAFLD patients reported no alcohol consumption, while the remaining 10% were casual drinkers. This confirms appropriate patient classification in the study.

Graph 4: Distribution of alcohol consumption among groups

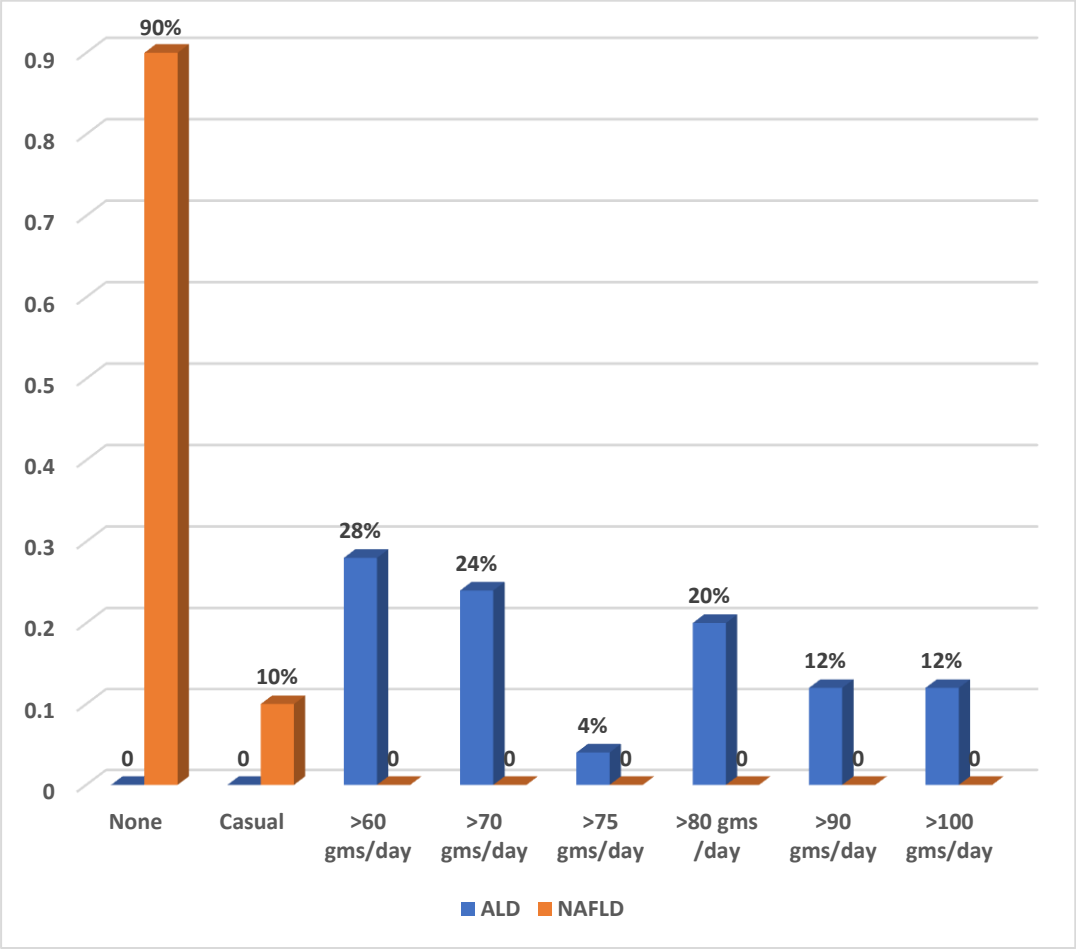


Table 5: Distribution of BMI among groups

BMI	Groups		p-value
	ALD	NAFLD	
<18.5	2 (4%)	1 (2%)	**0.03**
18.5-24.9	26 (52%)	14 (28%)	
25-29.9	17 (34%)	20 (40%)	
>30	5 (10%)	15 (30%)	
Total	**50 (100%)**	**50 (100%)**	

Table 5 and graph 5 illustrates BMI distribution, revealing a statistically significant difference between groups (p=0.03). The NAFLD group had a higher proportion of obese patients (BMI >30) at 30% compared to only 10% in the ALD group. Conversely, normal BMI (18.5-24.9) was more common in the ALD group (52%) versus the NAFLD group (28%).

Graph 5: Distribution of BMI among groups

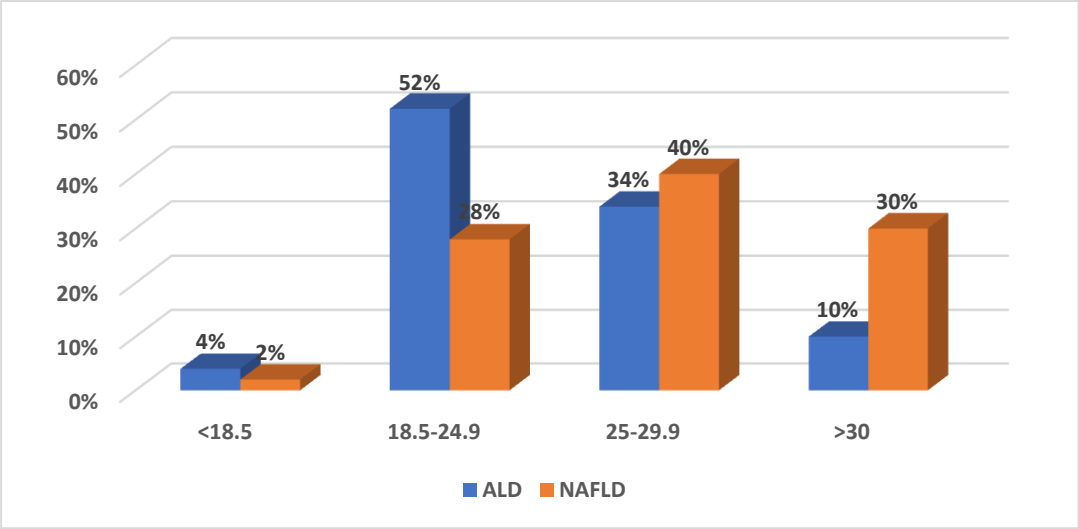


Table 6: Distribution of USG among groups

USG	Groups		p-value
	ALD	NAFLD	
Fatty liver	50 (100%)	48 (96%)	0.15
Hepatomegaly with fatty infiltration	0	2 (4%)	
Total	**50 (100%)**	**50 (100%)**	

Table 6 and graph 6 compares ultrasonography (USG) findings, showing that all ALD patients (100%) and most NAFLD patients (96%) had fatty liver on imaging. A small proportion (4%) of NAFLD patients had hepatomegaly with fatty infiltration. The p-value of 0.15 indicates no statistically significant difference in ultrasonographic findings between the groups.

Graph 6: Distribution of USG among groups

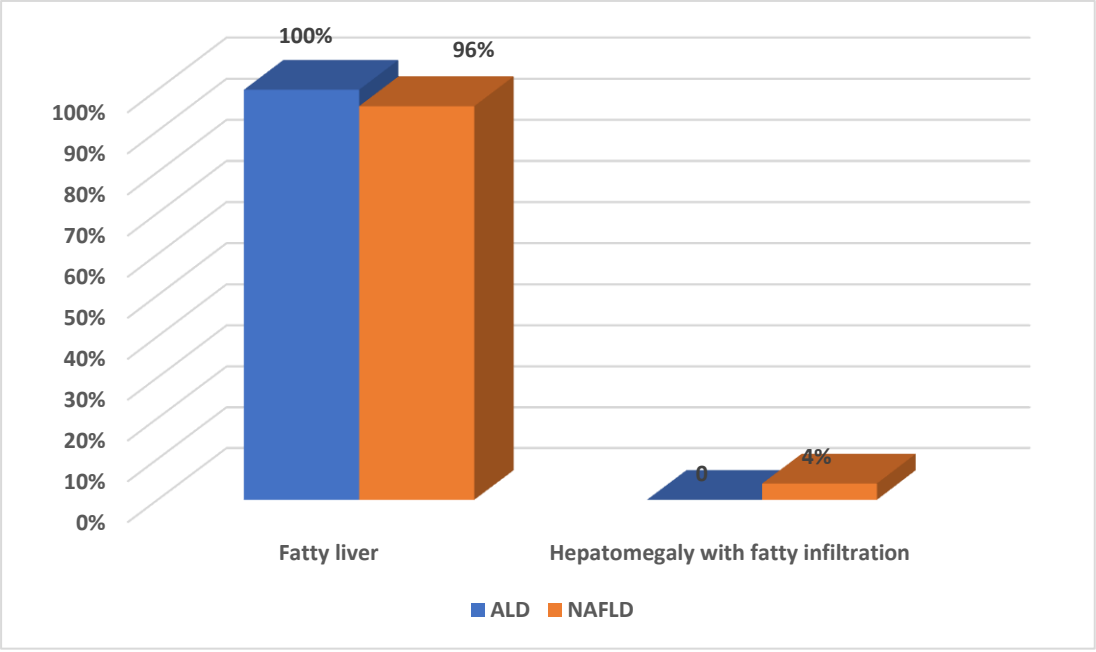


Table 7: Distribution of liver function test among groups

Liver function test	Groups		p-value
	ALD	NAFLD	
SGPT	51.6±33.9	38.7±30.8	**0.05**
SGOT	111.3±112.5	47.16±48.7	**<0.001**
SGOT/SGPT	2.1±1.1	1.25±0.56	**<0.001**
ANI score	7.08±4.6	-2.36±3.9	**<0.001**

Table 7 and graph 7 presents liver function test results, demonstrating several significant differences. The SGPT levels were higher in the ALD group (51.6±33.9) compared to the NAFLD group (38.7±30.8), with borderline significance (p=0.05). SGOT levels were markedly elevated in the ALD group (111.3±112.5) versus the NAFLD group (47.16±48.7), showing high statistical significance (p<0.001). The SGOT/SGPT ratio was significantly higher in the ALD group (2.1±1.1) compared to the NAFLD group (1.25±0.56), with p<0.001. Most notably, the ANI score showed a dramatic difference between groups: positive in ALD patients (7.08±4.6) and negative in NAFLD patients (-2.36±3.9), with high statistical significance (p<0.001).

Graph 7: Distribution of liver function test among groups

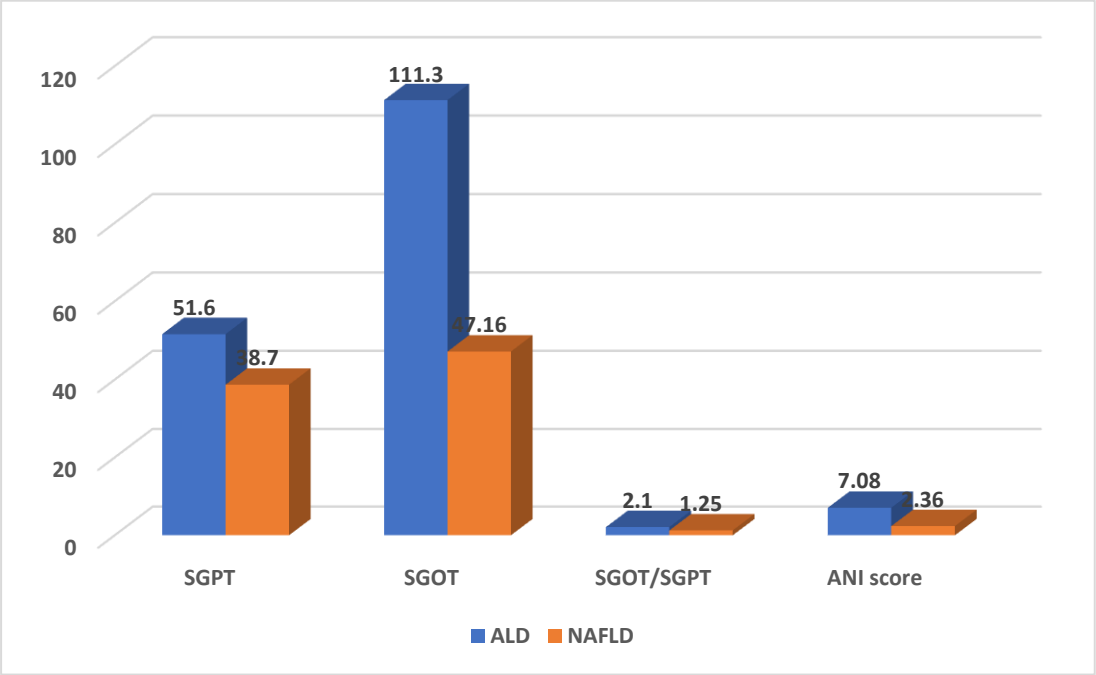


Table 8: Distribution of lipid profile among groups

Lipid profile	Groups		p-value
	ALD	NAFLD	
Total cholesterol	126.2±28	136.5±29.2	0.44
LDL	66.5±14.9	86.2±26.7	0.08
HDL	30.5±12.1	34.3±8.7	0.41
Triglycerides	124.7±56.4	146.8±76.3	0.5

Table 8 and graph 8 shows the lipid profile comparison between groups. Although NAFLD patients had slightly higher mean values for total cholesterol (136.5±29.2 vs 126.2±28), LDL (86.2±26.7 vs 66.5±14.9), HDL (34.3±8.7 vs 30.5±12.1), and triglycerides (146.8±76.3 vs 124.7±56.4) compared to ALD patients, none of these differences reached statistical significance (p-values ranging from 0.08 to 0.5).

Graph 8: Distribution of lipid profile among groups

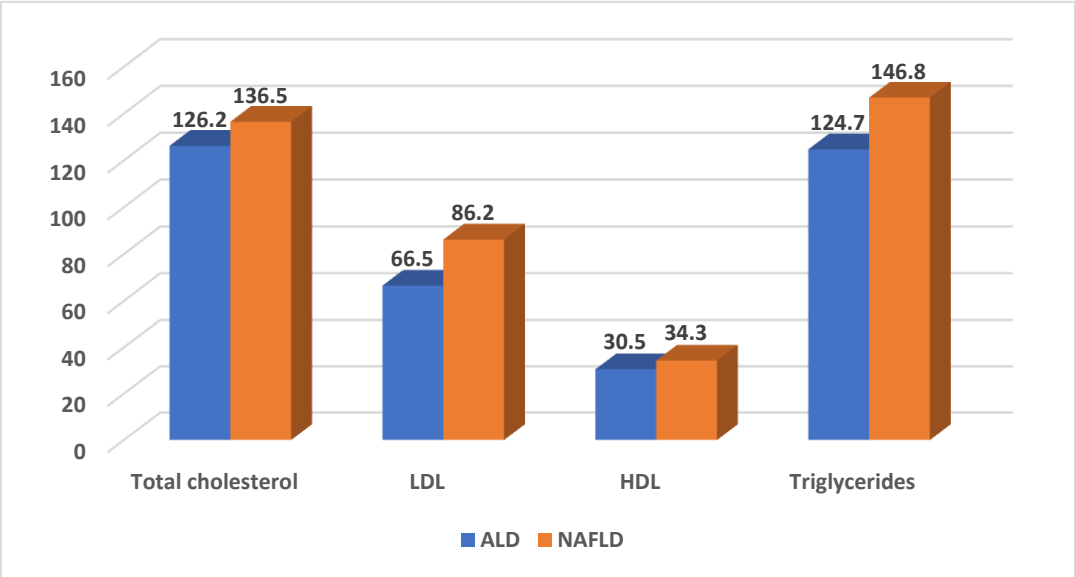


Table 9: Distribution of Fibroscan K among groups

Fibroscan K (Kpa)	Groups		p-value
	ALD	NAFLD	
2-7	18 (36%)	29 (58%)	**0.03**
7-14	32 (64%)	21 (42%)	
>14	-	-	
Total	**50 (100%)**	**50 (100%)**	

Table 9 and graph 9 compares Fibroscan K values (liver stiffness measurement in kPa), showing a significant difference between groups (p=0.03). The ALD group had a higher proportion of patients with moderate fibrosis (7-14 kPa) at 64% compared to 42% in the NAFLD group. Conversely, more NAFLD patients (58%) had minimal fibrosis (2-7 kPa) compared to ALD patients (36%). No patients in either group had severe fibrosis (>14 kPa).

Graph 9: Distribution of Fibroscan K among groups

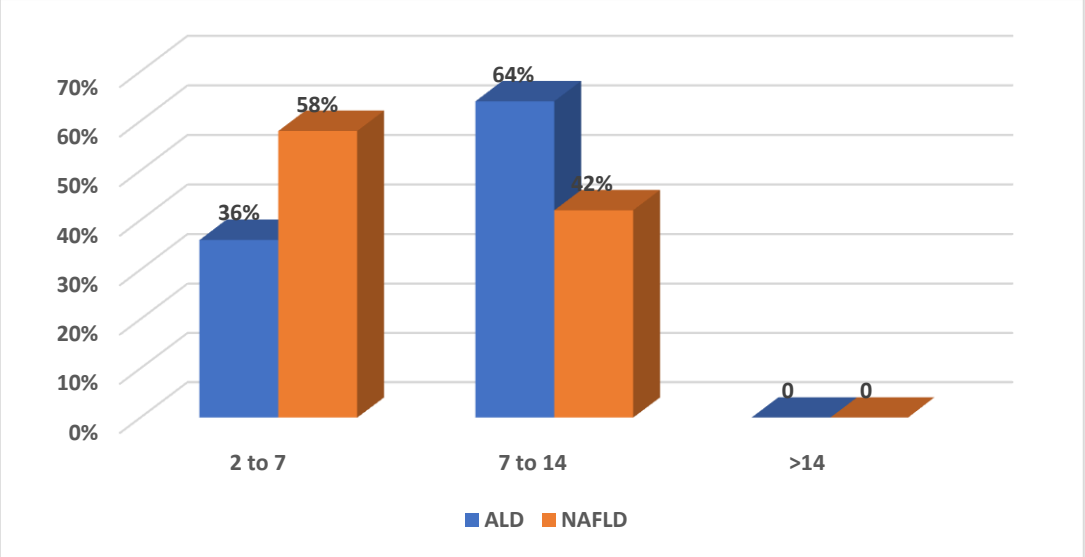


Table 10: Distribution of Fibroscan CAP among groups

Fibroscan CAP (Db/m)	Groups		p-value
	ALD	NAFLD	
100-200	-	-	0.18
201-300	39 (78%)	33 (66%)	
>300	11 (22%)	17 (34%)	
Total	**50 (100%)**	**50 (100%)**	

Table 10 and graph 10 presents Fibroscan CAP values (Controlled Attenuation Parameter, measuring steatosis in dB/m). While the NAFLD group had a higher proportion of patients with severe steatosis (>300 dB/m) at 34% compared to 22% in the ALD group, this difference was not statistically significant (p=0.18). Most patients in both groups had moderate steatosis (201-300 dB/m): 78% in ALD and 66% in NAFLD.

Graph 10: Distribution of Fibroscan CAP among groups

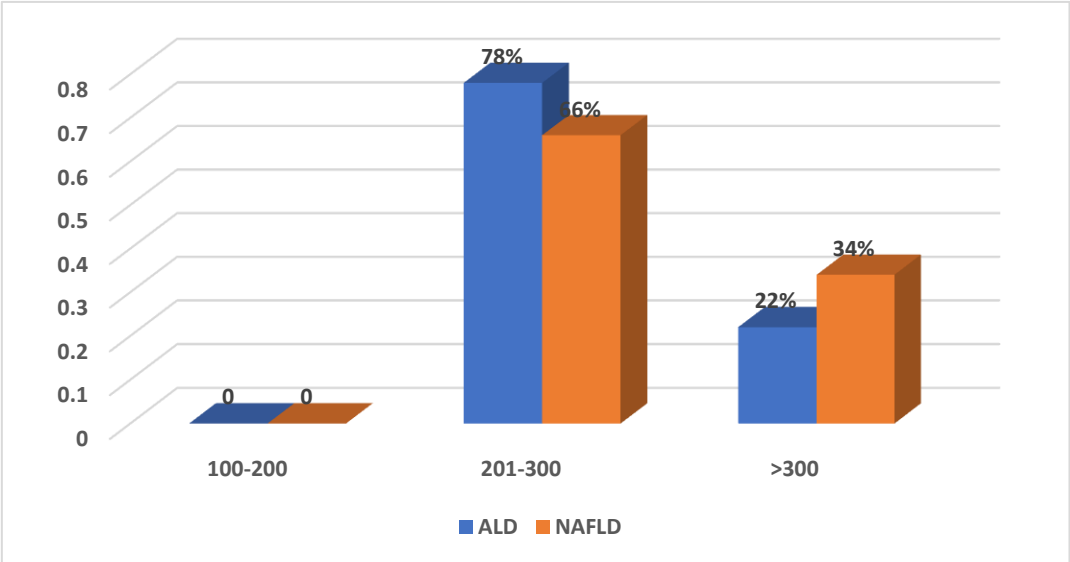
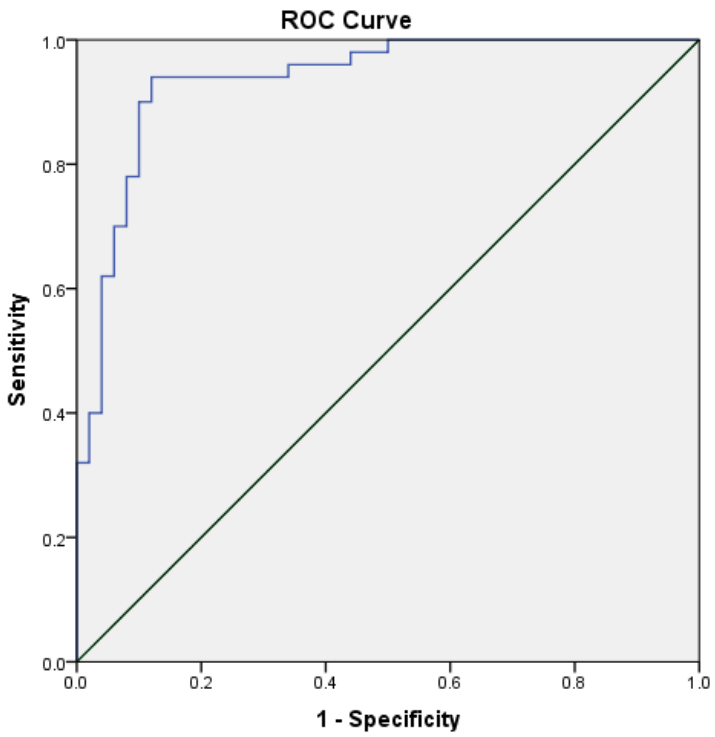


Table 11: ROC curve analysis of ANI score in ALD patients

ANI score	
AUC	0.936

Table 11 demonstrates the ROC curve analysis of the ANI score in diagnosing ALD, showing an impressive Area Under the Curve (AUC) of 0.936. This indicates excellent diagnostic accuracy of the ANI score in differentiating ALD from NAFLD, supporting the main hypothesis of the study.

Graph 11: ROC curve analysis of ANI score in ALD patients



DISCUSSION

Liver diseases represent a significant global health burden, with fatty liver disease emerging as one of the most prevalent hepatic disorders worldwide. The spectrum of fatty liver disease encompasses two major categories: alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), which share similar histopathological features but differ markedly in etiology, pathogenesis, and management approaches. Distinguishing between these two entities in clinical practice remains challenging, particularly when patient history regarding alcohol consumption is unreliable or incomplete. Traditional biochemical markers and imaging modalities often provide insufficient discriminatory power between ALD and NAFLD, necessitating the development of more accurate non-invasive diagnostic tools. The Alcoholic Liver Disease/Non-Alcoholic Fatty Liver Disease Index (ANI) represents a promising biomarker-based approach to differentiate between these conditions, potentially obviating the need for invasive liver biopsies. This study was conducted to evaluate the diagnostic accuracy of the ANI scoring system in distinguishing ALD from NAFLD in a tertiary care setting in Belagavi, India. The following discussion contextualizes our findings within the existing literature and explores their implications for clinical practice and future research.

Demographic Characteristics and Risk Factor Profile

Age and Gender Distribution

In our study, the age distribution was comparable between the ALD and NAFLD groups, with the majority of patients in both cohorts (52%) falling within the 41-60 years age range. This finding aligns with the typical age distribution reported in several epidemiological studies of fatty liver disease. Rehm et al. observed that the

peak incidence of ALD typically occurs in the fourth to fifth decades of life, reflecting the cumulative effect of alcohol consumption over time.^65^ Similarly, Wong et al. reported that NAFLD prevalence increases with age, reaching its zenith in middle age (40-60 years).[66]

However, our study demonstrated a striking gender disparity between the two groups, with ALD patients being exclusively male (100%), whereas the NAFLD group exhibited a more balanced gender distribution (54% females, 46% males). This pronounced gender difference is consistent with observations by Torruellas et al., who attributed this pattern to several factors including higher alcohol consumption rates among men, gender-based differences in alcohol metabolism, and potentially protective effects of estrogen against alcoholic liver injury in women.[67] Likewise, Younossi et al. noted that while NAFLD affects both genders, certain risk profiles and prevalence patterns differ between males and females, with postmenopausal women showing increased vulnerability to NAFLD compared to premenopausal women, suggesting hormonal influences on disease development.[68]

Interestingly, Naveau et al., in their original validation study of the ANI scoring system, reported a similar gender disparity, with a male predominance in the ALD group (76.9%) compared to the NAFLD group (42.1%).[69] Our finding of 100% male predominance in the ALD group represents an even more extreme gender skew, which may reflect regional and cultural differences in alcohol consumption patterns in the Indian subcontinent compared to Western countries.

Alcohol Consumption Patterns

As expected, alcohol consumption patterns differed significantly between the two groups ($p<0.001$), with all ALD patients consuming substantial amounts of

alcohol (>60 grams/day) and 90% of NAFLD patients reporting no alcohol consumption. This clear delineation confirms appropriate patient classification in our study. The threshold of 60 grams/day used in our study is consistent with established criteria for defining significant alcohol consumption associated with liver injury. Lackner et al. established that alcohol consumption exceeding 60 grams/day in men and 40 grams/day in women for 5 years or more significantly increases the risk of developing ALD.[70]

In our ALD cohort, we observed a range of alcohol consumption levels, with 28% consuming >60 grams/day, 24% consuming >70 grams/day, and 24% consuming >80 grams/day or more. This pattern aligns with findings by Askgaard et al., who demonstrated a dose-response relationship between alcohol intake and liver disease progression, with higher consumption levels associated with more advanced liver injury.[71] The relatively high proportion of patients consuming extremely high amounts of alcohol (>90-100 grams/day) in our study (24% combined) may contribute to the more pronounced liver enzyme abnormalities observed in our ALD cohort.

Body Mass Index (BMI)

Our study revealed significant differences in BMI distribution between the ALD and NAFLD groups (p=0.03), with NAFLD patients exhibiting higher rates of obesity (30% with BMI >30) compared to ALD patients (10% with BMI >30). Conversely, normal BMI (18.5-24.9) was more prevalent in the ALD group (52%) versus the NAFLD group (28%). These findings corroborate the established relationship between NAFLD and obesity documented by numerous studies. Loomba and Sanyal reported that obesity is present in 30-100% of NAFLD patients, with the

risk of NAFLD increasing exponentially with higher BMI values.[72]

The relationship between BMI and ALD is more complex. While moderate alcohol consumption may not significantly impact BMI, heavy chronic alcohol use can lead to malnutrition and lower BMI in some patients, as observed by Addolorato et al.[73] However, the interaction between alcohol consumption and obesity merits attention. Hart et al. demonstrated that the combination of alcohol consumption and obesity synergistically increases the risk of liver-related mortality, suggesting potential mechanistic overlaps in liver injury pathways.[74]

The BMI differences observed in our study population reflect these established patterns and emphasize the distinct risk factor profiles of ALD and NAFLD, despite their histopathological similarities. These differences in body habitus may also influence the interpretation of clinical findings, including ultrasonographic assessment of hepatic steatosis.

Comorbidity Profile

The distribution of comorbidities between ALD and NAFLD groups in our study revealed notable differences, particularly regarding diabetes mellitus (DM), which was significantly more prevalent in the NAFLD group (58%) compared to the ALD group (30%) ($p=0.005$). This finding aligns with the well-established association between NAFLD and metabolic syndrome components. Lonardo et al. described NAFLD as the hepatic manifestation of metabolic syndrome, with insulin resistance serving as a key pathophysiological mechanism underlying both conditions.[75] The bidirectional relationship between type 2 diabetes and NAFLD has been extensively documented, with each condition increasing the risk and severity of the other, as demonstrated in a large meta-analysis by Mantovani et al.[76]

While hypertension was more common in the ALD group (42%) than in the NAFLD group (32%), this difference did not reach statistical significance (p=0.3). This observation partially contrasts with findings by VanWagner et al., who reported higher prevalence of hypertension in NAFLD patients, potentially related to insulin resistance and endothelial dysfunction.[77] The higher prevalence of hypertension in our ALD cohort may reflect alcohol's well-documented effect on blood pressure, as described by Rehm et al., who found that chronic heavy alcohol consumption increases the risk of hypertension in a dose-dependent manner.[78]

Dyslipidemia, another component of metabolic syndrome, was more frequent in our NAFLD group (48%) compared to the ALD group (34%), though this difference did not reach statistical significance (p=0.19). This trend is consistent with observations by Chatrath et al., who described characteristic dyslipidemic patterns in NAFLD, including hypertriglyceridemia, low HDL-cholesterol, and increased small, dense LDL particles.[79]The non-significant difference in our study may reflect the complex effects of alcohol on lipid metabolism, as moderate alcohol consumption has been associated with increased HDL cholesterol, while heavy drinking may promote hypertriglyceridemia, as reported by Whitfield et al.[80]

The comorbidity profiles observed in our study not only support the appropriate classification of patients but also highlight the distinct pathophysiological mechanisms underlying ALD and NAFLD, with metabolic derangements playing a more prominent role in the latter.

Liver Function Tests and ANI Score

Transaminase Patterns

Our study demonstrated significant differences in liver enzyme patterns between ALD and NAFLD groups. SGPT (ALT) levels were higher in the ALD group (51.6±33.9 U/L) compared to the NAFLD group (38.7±30.8 U/L), with borderline statistical significance ($p=0.05$). More strikingly, SGOT (AST) levels were markedly elevated in the ALD group (111.3±112.5 U/L) versus the NAFLD group (47.16±48.7 U/L), showing high statistical significance ($p<0.001$).

These findings corroborate the characteristic transaminase patterns described in the literature. Malnick et al. observed that AST elevations typically predominate in ALD, whereas ALT elevations are often more pronounced in NAFLD.[81] The molecular basis for this pattern was elucidated by Nyblom et al., who attributed it to alcohol-induced mitochondrial injury and pyridoxine deficiency, which disproportionately affect AST levels.[82]

The wide standard deviation in AST values in our ALD group (112.5 U/L) suggests considerable heterogeneity in disease severity, consistent with observations by Sorbi et al., who noted that AST levels may fluctuate substantially in ALD depending on the pattern of alcohol consumption, presence of alcoholic hepatitis, and degree of fibrosis.[83]

AST/ALT Ratio

The AST/ALT (SGOT/SGPT) ratio was significantly higher in our ALD group (2.1±1.1) compared to the NAFLD group (1.25±0.56), with $p<0.001$. This finding is consistent with the traditional threshold of 2.0 for the AST/ALT ratio as a

discriminator between ALD and NAFLD, as initially proposed by Cohen and Kaplan.[84] However, the mean ratio in our NAFLD group (1.25) was higher than that reported in some studies, such as that by Botros and Sikaris, who found mean AST/ALT ratios closer to 0.8 in NAFLD patients.[85] This difference might reflect selection bias in our tertiary care setting, with potentially more advanced NAFLD cases being referred for evaluation.

It is noteworthy that while the AST/ALT ratio has been widely used as a simple biomarker to distinguish between ALD and NAFLD, its performance as a standalone discriminator has limitations. Jung KS et al. reported significant overlap in AST/ALT ratios between ALD and NAFLD patients, particularly in those with advanced fibrosis.[86] These limitations underscore the value of more comprehensive scoring systems like ANI, which incorporate multiple parameters for enhanced diagnostic accuracy.

ANI Score Performance

The most notable finding of our study was the dramatic difference in ANI scores between groups: positive in ALD patients (7.08±4.6) and negative in NAFLD patients (-2.36±3.9), with high statistical significance ($p<0.001$). The ROC curve analysis demonstrated excellent diagnostic accuracy of the ANI score in differentiating ALD from NAFLD, with an impressive Area Under the Curve (AUC) of 0.936.

This robust performance is comparable to that reported in the original validation study by Naveau et al., who documented an AUC of 0.941 for the ANI score in distinguishing ALD from NAFLD.[69] Our findings also align with those of Trépo et al., who evaluated the ANI score in a large cohort of patients with biopsy-

proven ALD and NAFLD, reporting an AUC of 0.926.[87]The consistency of our results with these international studies, despite potential differences in patient populations and healthcare settings, supports the reliability and generalizability of the ANI scoring system.

The relatively wide standard deviation in ANI scores in both our ALD and NAFLD groups reflects the heterogeneity of these conditions, as noted by Mueller et al., who found that the performance of non-invasive biomarkers may vary depending on the stage of liver disease and presence of confounding factors.[88] Nevertheless, the minimal overlap between ANI score distributions in our two groups highlights its value as a practical clinical tool.

Interestingly, our study found a slightly better discriminatory performance of the ANI score (AUC 0.936) compared to the AST/ALT ratio alone, supporting the concept that multiparametric indices offer enhanced diagnostic accuracy over single biomarkers. This observation is consistent with findings by Hanley et al., who demonstrated that combining multiple biomarkers improves the diagnostic performance for liver diseases.[89]

The excellent performance of the ANI score in our cohort may be partly attributed to the clear clinical distinction between our ALD and NAFLD groups, particularly regarding alcohol consumption patterns and gender distribution. This highlights the potential utility of the ANI score in straightforward clinical scenarios, though its performance in more complex cases, such as those with concurrent alcohol use and metabolic syndrome, warrants further investigation.

Lipid Profile Analysis

Our study found that NAFLD patients had slightly higher mean values for total cholesterol (136.5±29.2 vs 126.2±28 mg/dL), LDL (86.2±26.7 vs 66.5±14.9 mg/dL), HDL (34.3±8.7 vs 30.5±12.1 mg/dL), and triglycerides (146.8±76.3 vs 124.7±56.4 mg/dL) compared to ALD patients. However, none of these differences reached statistical significance (p-values ranging from 0.08 to 0.5).

These findings partially align with the characteristic dyslipidemic patterns associated with NAFLD described by Chatrath et al., typically featuring elevated triglycerides, low HDL, and increased small, dense LDL particles.[79] However, the relatively modest lipid abnormalities in our NAFLD cohort may reflect confounding factors such as concurrent medication use (particularly statins) or dietary modifications following diagnosis.

The lipid profile in ALD presents a more complex picture, influenced by both direct effects of alcohol on lipid metabolism and the impact of alcohol-induced liver injury. Baraona and Lieber described the dual effect of alcohol on lipid metabolism: while moderate alcohol consumption may increase HDL levels and reduce cardiovascular risk, heavy chronic drinking promotes hepatic lipogenesis and hypertriglyceridemia.[90] The relatively low lipid levels in our ALD cohort could reflect the impact of advanced liver disease on synthetic function, as suggested by Chrostek et al., who observed that cholesterol levels may decline with progression of alcoholic liver disease.[91]

Notably, the HDL levels were low in both our ALD (30.5±12.1 mg/dL) and NAFLD (34.3±8.7 mg/dL) groups, diverging from the pattern of alcohol-associated HDL elevation described in some studies. This observation aligns with findings by

Lucey et al., who noted that the HDL-raising effect of alcohol is attenuated or reversed in the setting of established alcoholic liver disease.[92]

While lipid abnormalities are recognized features of both conditions, our results suggest that standard lipid profiles may offer limited discriminatory value between ALD and NAFLD in clinical practice. This underscores the importance of more specific biomarkers like the ANI score for accurate differentiation of these entities.

Ultrasonographic and Elastographic Findings

Ultrasonography (USG) Findings

Our ultrasonographic evaluation revealed fatty liver in all ALD patients (100%) and most NAFLD patients (96%), with a small proportion (4%) of NAFLD patients showing hepatomegaly with fatty infiltration. The p-value of 0.15 indicates no statistically significant difference in ultrasonographic findings between the groups.

These findings are consistent with observations by Hernaez et al., who reported in a meta-analysis that conventional ultrasonography has high sensitivity (84.8%) and specificity (93.6%) for detecting moderate-to-severe hepatic steatosis but cannot reliably distinguish between ALD and NAFLD.[93] The nearly universal detection of fatty liver in our cohorts reflects the study design, which specifically enrolled patients with established fatty liver disease based on clinical, biochemical, and imaging criteria.

The slight variation in ultrasonographic patterns between our groups, with a small proportion of NAFLD patients showing hepatomegaly with fatty infiltration, aligns with observations by Strauss et al., who noted that hepatomegaly may be more

prominent in certain phenotypes of NAFLD, particularly those associated with severe insulin resistance.[94] However, the non-significant difference (p=0.15) suggests limited utility of conventional ultrasonography for differentiating between ALD and NAFLD.

Fibroscan Findings

Our elastographic assessment revealed significant differences in liver stiffness measurements (Fibroscan K) between groups (p=0.03). The ALD group had a higher proportion of patients with moderate fibrosis (7-14 kPa) at 64% compared to 42% in the NAFLD group. Conversely, more NAFLD patients (58%) had minimal fibrosis (2-7 kPa) compared to ALD patients (36%). No patients in either group had severe fibrosis (>14 kPa).

These findings are consistent with observations by Mueller et al., who reported that for a given degree of steatosis, ALD patients typically exhibit higher liver stiffness values compared to NAFLD patients.[95] This pattern may reflect differences in the pathogenesis of fibrosis between the two conditions, with alcohol directly stimulating hepatic stellate cells and promoting pro-inflammatory cytokine production, as described by Tsukamoto et al.[96]

The absence of severe fibrosis (>14 kPa) in our cohorts suggests that we primarily enrolled patients with early to intermediate stages of liver disease, which is typically when the differential diagnosis between ALD and NAFLD is most clinically challenging and relevant. This case mix is appropriate for evaluating the performance of non-invasive diagnostic tools like the ANI score, as patients with advanced cirrhosis often present with more distinctive clinical features regardless of etiology.

Regarding steatosis quantification, Fibroscan CAP (Controlled Attenuation Parameter) values showed that while the NAFLD group had a higher proportion of patients with severe steatosis (>300 dB/m) at 34% compared to 22% in the ALD group, this difference was not statistically significant (p=0.18). Most patients in both groups had moderate steatosis (201-300 dB/m): 78% in ALD and 66% in NAFLD.

These CAP findings align with observations by de Lédinghen et al., who demonstrated that CAP values correlate well with histological steatosis grade but do not reliably distinguish between different etiologies of fatty liver.[97] The trend toward higher CAP values in our NAFLD cohort is consistent with findings by Karlas et al., who reported that for a given BMI, NAFLD patients typically exhibit higher degrees of steatosis compared to ALD patients.[98]

The combination of higher fibrosis (Fibroscan K) in the ALD group despite lower steatosis (CAP) compared to the NAFLD group is noteworthy and suggests differing pathophysiological mechanisms. This pattern aligns with observations by Roulot et al., who noted that alcohol appears to promote fibrosis progression more aggressively than metabolic factors, even with less severe steatosis.[99]

Clinical Implications and Future Directions

The excellent performance of the ANI score in our study (AUC 0.936) suggests its potential utility as a non-invasive tool for differentiating ALD from NAFLD in clinical practice. This discrimination has important implications for patient management, as highlighted by European Association for the Study of the Liver (EASL) guidelines, which emphasize distinct therapeutic approaches for these two conditions.[100]

For ALD patients, alcohol abstinence remains the cornerstone of management, with specific pharmacotherapies for alcohol use disorder and alcoholic hepatitis playing crucial roles. In contrast, NAFLD management focuses on addressing components of metabolic syndrome through lifestyle modifications, weight loss, and targeted pharmacological interventions. Accurately distinguishing between these conditions is therefore essential for implementing appropriate therapeutic strategies.

Beyond its diagnostic utility, the ANI score may also have prognostic implications. Trépo et al. observed that higher ANI scores in ALD patients correlated with more severe histological findings and poorer clinical outcomes.[87] This suggests potential value of the ANI score not only for diagnosis but also for risk stratification and monitoring disease progression.

The integration of the ANI score with other non-invasive assessment tools may further enhance diagnostic accuracy. Boursier et al. demonstrated that combining different non-invasive markers could improve the detection and staging of liver fibrosis.[101]Future research could explore whether incorporating the ANI score into multiparametric algorithms alongside elastography, serum fibrosis markers, and clinical parameters might yield even greater diagnostic precision.

Several limitations of our study warrant acknowledgment. First, the gold standard for diagnosing and differentiating ALD and NAFLD remains liver biopsy, which was not performed in our cohort due to ethical and practical considerations. However, our strict inclusion criteria and comprehensive clinical, biochemical, and imaging assessment likely ensured accurate classification of patients. Second, the pronounced gender disparity in our ALD group (100% male) may limit the generalizability of our findings to female patients with alcohol-related liver disease.

Third, our study was conducted at a single tertiary care center, and the findings may not fully translate to different healthcare settings or patient populations.

Future studies should address these limitations by validating the ANI score in more diverse populations, including multicenter designs and broader demographic profiles. Additionally, investigating the performance of the ANI score in patients with dual pathology (concurrent significant alcohol use and metabolic syndrome) would be valuable, as this represents a growing clinical challenge. Longitudinal studies evaluating the predictive value of the ANI score for clinical outcomes would also enhance its clinical utility.

Conclusion

Our study demonstrated that the ANI scoring system provides excellent discriminatory performance in differentiating ALD from NAFLD, with an impressive AUC of 0.936. This finding supports the utility of the ANI score as a reliable non-invasive tool in clinical practice, potentially reducing the need for invasive liver biopsies. The clear separation of ANI scores between ALD patients (positive values) and NAFLD patients (negative values) offers a practical framework for clinical decision-making.

Additionally, our findings highlighted distinct clinical, biochemical, and elastographic profiles between ALD and NAFLD patients, contributing to the growing body of evidence on the unique features of these conditions despite their histopathological similarities. The significant differences in gender distribution, comorbidity profiles, transaminase patterns, and fibrosis measurements underscore the importance of comprehensive assessment in the evaluation of fatty liver disease.

The excellent performance of the ANI score in our Indian patient cohort suggests its applicability across diverse populations and healthcare settings. Implementation of this non-invasive biomarker-based approach could streamline the diagnostic process, guide appropriate therapeutic interventions, and ultimately improve outcomes for patients with fatty liver disease.

CONCLUSION

The present study demonstrates that the ANI scoring system serves as a reliable and effective non-invasive tool for differentiating alcoholic liver disease from non-alcoholic fatty liver disease. With an impressive AUC of 0.936 in ROC curve analysis, the ANI score showed excellent diagnostic accuracy in distinguishing between these two etiologies of fatty liver disease, which often present with overlapping clinical and histological features.

Our findings revealed significant differences in ANI scores between ALD patients (7.08±4.6) and NAFLD patients (-2.36±3.9), with minimal overlap between the two groups. This clear separation confirms that positive ANI values strongly indicate ALD, while negative values are highly suggestive of NAFLD. Such discriminatory power has important clinical implications, potentially reducing the need for invasive liver biopsies while guiding appropriate management strategies for these distinct conditions.

The study also highlighted significant differences in demographic, clinical, and biochemical profiles between ALD and NAFLD patients. The ALD group consisted exclusively of males with significant alcohol consumption, whereas the NAFLD group showed a more balanced gender distribution and was associated with obesity and diabetes. Liver enzyme patterns differed significantly, with ALD patients showing higher AST levels and AST/ALT ratios compared to NAFLD patients, reflecting different underlying pathophysiological mechanisms.

Elastographic assessment revealed a higher prevalence of moderate fibrosis in ALD patients despite similar degrees of steatosis, suggesting that alcohol may promote more aggressive fibrosis progression compared to metabolic factors. The

integration of these clinical, biochemical, and elastographic parameters with the ANI score provides a comprehensive framework for evaluating patients with fatty liver disease in clinical practice.

Based on our findings, we recommend that the ANI scoring system be incorporated into routine clinical assessment of patients with suspected fatty liver disease. This approach would facilitate more accurate etiological diagnosis, avoid unnecessary invasive procedures, and enable early implementation of targeted therapeutic interventions. Future research should focus on validating these findings in larger, more diverse populations and investigating the prognostic implications of the ANI score for long-term clinical outcomes.

SUMMARY

INTRODUCTION

Distinguishing between alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) poses a significant clinical challenge due to overlapping histopathological features, particularly when patient history regarding alcohol consumption is unreliable. The Alcoholic Liver Disease/Non-Alcoholic Fatty Liver Disease Index (ANI) has emerged as a promising non-invasive biomarker to differentiate between these conditions, potentially obviating the need for liver biopsy. This study aimed to evaluate the diagnostic accuracy of the ANI scoring system in distinguishing ALD from NAFLD in a tertiary care setting.

AIMS AND OBJECTIVES

Objective:

1. To test the reliability of ANI scoring system as a non-invasive method to distinguish alcoholic liver disease (ALD) from non-alcoholic fatty liver disease (NAFLD)

MATERIAL AND METHODS

This one-year observational study conducted at Kles Dr Prabhakar Kore Hospital & M.R.C, Belagavi included 100 patients (50 with ALD and 50 with NAFLD) diagnosed based on comprehensive clinical, biochemical, and imaging criteria. Demographic data, clinical characteristics, laboratory parameters, and imaging findings were recorded. ANI scores were calculated for all patients, and their discriminatory performance was assessed using ROC curve analysis.

RESULTS

- The age distribution was comparable between groups, with most patients in the 41-60 years range (52% in each group). A significant gender disparity was observed, with the ALD group consisting entirely of males (100%), while the NAFLD group had a more balanced distribution (54% females, 46% males).

- All ALD patients consumed significant amounts of alcohol (>60 grams/day), while 90% of NAFLD patients reported no alcohol consumption. The NAFLD group showed higher rates of obesity (BMI >30) at 30% compared to 10% in the ALD group, and diabetes was significantly more prevalent in NAFLD patients (58% vs 30%).

- Liver function tests revealed higher SGPT levels in the ALD group (51.6±33.9 vs 38.7±30.8, $p=0.05$) and markedly elevated SGOT levels (111.3±112.5 vs 47.16±48.7, $p<0.001$). The SGOT/SGPT ratio was significantly higher in ALD patients (2.1±1.1 vs 1.25±0.56, $p<0.001$). Most notably, the ANI score showed a dramatic difference between groups: positive in ALD patients (7.08±4.6) and negative in NAFLD patients (-2.36±3.9), with ROC curve analysis demonstrating excellent diagnostic performance (AUC=0.936).

- Fibroscan assessment showed that ALD patients had higher proportions of moderate fibrosis (7-14 kPa) at 64% compared to 42% in NAFLD patients, though steatosis severity (measured by CAP values) was slightly higher in the NAFLD group. These findings confirm that the ANI scoring system provides excellent discrimination between ALD and NAFLD, offering a reliable non-invasive diagnostic tool for clinical practice.

CONCLUSION:

The ANI scoring system provides excellent discriminatory performance in differentiating ALD from NAFLD, with minimal overlap between the two groups. This non-invasive biomarker offers a reliable diagnostic tool for clinical practice, potentially reducing the need for invasive liver biopsies while guiding appropriate management strategies.

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ANNEXURES

ANNEXURE – I - INFORMED CONSENT FORM

DIAGNOSTIC VALUE OF ALCOHOLIC LIVER DISEASE / NON ALCOHOLIC FATTY LIVER DISEASE INDEX (ANI) IN DIFFERENTIATING ALCOHOLIC LIVER DISEASE AND NON ALCOHOLIC FATTY LIVER DISEASE ONE YEAR BASED OBSERVATIONAL STUDY IN TERITARY CARE CENTRE

Name of Student/Principal Investigator: _____

Name of Guide/Co Investigators: _____

- **Introduction:** Fatty liver disease (FLD) is a common disease, and can be further subdivided according to its cause into either alcoholic fatty liver disease (a type of alcoholic liver disease [ALD]) or non alcoholic fatty liver disease (NAFLD)]. ALD and NAFLD are serious threats to the health of people worldwide. In clinical practice, it is crucial to distinguishing alcohol basis from non alcoholic basis of hepatic steatosis, as the diagnosis relates to the selection of treatment, priority for liver transplantation and organ allocation. A liver biopsy is considered the "gold standard" to establish the diagnosis, but it is an invasive procedure accompanied by certain risks and deficiencies and therefore has limited clinical application. So Dunn et.al,developed a new diagnostic model called the ALD/NAFLD index (ANI), to distinguish ALD from NAFLD..
- **Need for the study :**The purpose of this study was to verify the reliability of ANI as a non invasive approach to the differential diagnosis of ALD and NAFLD. The

goal is to provide a reliable and convenient tool for the clinician to differentiate diagnoses of ALD and NAFLD

- **Explanation of procedure:** All the patients fulfilling the inclusion and exclusion criteria and willing to participate in the study are included, the protocol of the study is explained and the informed consent is taken, venous blood samples are taken at the time of admission and height and weight are checked and gender is noted down at the time of admission
- **Withdrawal from participation in the study:** Participation in this study in voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.
- **Possible benefits from participating in the study:** You will not get any benefits by participating in this study. This is to evaluate the diagnostic value of non invasive procedure which will help to reduce the burden of invasive procedure that helps in the interest of large population.
- **Possible risks from participating in the study:** There are no risks involved in participating in this study.
- **Privacy and confidentiality:** The information collected from you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.
- **Financial incentives:** You will not receive any payment for participating in this study.

- **Cost of investigations** done during the course of study will be paid by the **principal investigator.**
- **Authorization for publication of aggregated data:** Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups. However, your identity will never be revealed.
- **Questions:**

  If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

  Legal rights: By signing this consent form, we are not waving any of your legal rights

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "**DIAGNOSTIC VALUE OF ALCOHOLIC LIVER DISEASE / NON ALCOHOLIC FATTY LIVER DISEASE INDEX (ANI) IN DIFFERENTIATING ALCOHOLIC LIVER DISEASE AND NON ALCOHOLIC FATTY LIVER DISEASE ONE YEAR BASED OBSERVATIONAL STUDY IN TERITARY CARE CENTRE** ". My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE – II- PROFORMA

DIAGNOSTIC VALUE OF ALCOHOLIC LIVER DISEASE / NON ALCOHOLIC FATTY LIVER DISEASE INDEX (ANI) IN DIFFERENTIATING ALCOHOLIC LIVER DISEASE AND NON ALCOHOLIC FATTY LIVER DISEASE ONE YEAR BASED OBSERVATIONAL STUDY IN TERITARY CARE CENTRE

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

HISTORY OF PRESENT ILLNESS :

PAST HISTORY :

Co-morbidities

DM		HTN		IHD		CKD		CLD		CVA		Malignancy	
Others													

Drug history:

Personal history:

Family history:

PHYSICAL EXAMINATION:

WEIGHT :

HEIGHT:

BODY MASS INDEX:

GENERAL CONDITION:

PALLOR		CLUBBING	
ICTERUS		PEDAL EDEMA	
CYANOSIS		LYMPHADENOPATHY	

VITALS:

TEMPERATURE		R.R	
P.R		B.P	

SYSTEMIC EXAMINATION:

R. S:

C.V.S:

C.N.S:

P.A:

LAB PARAMETERS AT ADMISSION:

HEMOGRAM	**LIVER FUNCTION TESTS**
1. MEAN CORPUSCULAR VOLUME (MCV)	1. ALANINE AMINO TRANSFERASE(ALT) 2. ASPARTATE AMINO TRANSFERASE(AST)

FORMULA USED TO CALUCULATE ANI SCORE :

−58.5+0.637(MCV)+3.91(AST/ALT)−0.406(BMI)+6.35 for male gender

ANNEXURE III – MASTER CHART

SL NO	PATIENT UHID	AGE	SEX	OCCUPATION	DM	HTN	DYSLIPIDEMA	OTHERS	ALCOHOL H/O	WEIGHT	HEIGHT	BMI	PR	BP	USG A+P	FIBROSCAN K	FIBROSCAN CAP	DIAGNOSIS	MCV	ALT/SGPT	AST/SGOT	ANI SCORE	HBA1C	S.CHOLE	S.LDL	S.HDL	S.TGS
1	10026705	52	FEMALE	HOUSE WIFE	YES	NO	YES	NIL	NO	73	151	32	76	140/90	HEPATOMEGALY WITH FATTY INFILTRATON	7.4	252	NAFLD	95.1	32	51	-4.68	8.09	213	88	70	124
2	10040506	30	MALE	EMPLOYEE	NO	NO	NO	NIL	NO	67	178	21.1	96	110/70	FATTY LIVER	5.6	257	NAFLD	90.9	32	17	-0.03	8.15	143	87	60	97
3	10046815	53	MALE	BUSSINESS	YES	YES	YES	NIL	NO	92	167	33	86	130/90	FATTY LIVER	5.6	282	NAFLD	93.8	30	39	-0.71	8.45	201	88	34	108
4	10050440	70	FEMALE	HOUSE WIFE	NO	NO	NO	NIL	NO	60	156	24.7	66	140/90	FATTY LIVER	7.1	270	NAFLD	83.6	11	28	0.02	6.44	205	64	63	110
5	10050537	33	FEMALE	HOUSE WIFE	NO	NO	NO	NIL	NO	51	152	22.1	86	110/70	FATTY LIVER	7.5	290	NAFLD	73.6	19	24	-3.93	5.46	125	103	63	97
6	10051760	40	MALE	CLERK	YES	NO	NO	NIL	NO	88	170	30.4	96	140/80	FATTY LIVER	8.6	301	NAFLD	75.6	14	40	-3.93	6.5	149	124	60	111
7	10052290	63	MALE	RETD.	YES	YES	YES	NIL	NO	74	165	27.2	100	130/70	HEPATOMEGALY WITH FATTY INFILTRATON	4.9	297	NAFLD	90.9	27	33	0.19	8.16	139	112	66	106
8	10052825	29	MALE	STUDENT	NO	NO	NO	NIL	NO	69	172	23.3	88	120/80	FATTY LIVER	6.2	310	NAFLD	88.8	22	15	-0.34	7.05	140	120	37	99
9	10058104	55	MALE	BUSSINESS	YES	NO	YES	NIL	OCCASIONAL	96	169	33.6	78	130/100	FATTY LIVER	10	304	NAFLD	74.7	15	23	-1.35	7.91	222	69	35	109
10	10059182	66	MALE	BUSSINESS	YES	YES	YES	NIL	OCCASIONAL	76	158	30.4	98	110/80	FATTY LIVER	10	295	NAFLD	93.8	71	54	-0.144	5.57	133	75	55	88
11	10060193	34	MALE	S.ENGINEER	NO	NO	YES	NIL	NO	69	165	25.3	70	130/90	FATTY LIVER	3.4	333	NAFLD	87.1	38	34	0.55	6.2	130	148	55	111
12	10062620	58	FEMALE	HOUSE WIFE	YES	YES	NO	NIL	NO	59	156	24.2	64	110/90	FATTY LIVER	9.8	315	NAFLD	92.1	69	143	-1.55	7.59	139	149	51	113
13	10062885	43	FEMALE	EMPLOYEE	YES	NO	NO	NIL	NO	75	156	30.8	88	110/70	FATTY LIVER	7	309	NAFLD	72.6	40	29	-7.06	7.36	195	159	43	133
14	10042191	35	MALE	BUSSINESS	NO	NO	NO	NIL	NO	65	165	23.9	98	140/90	FATTY LIVER	4.8	309	NAFLD	89.1	76	76	0.66	6.48	226	124	44	131
15	10043228	52	MALE	BUSSINESS	YES	YES	YES	NIL	NO	91	169	31.9	92	150/90	FATTY LIVER	6.6	292	NAFLD	74.9	41	36	-3.06	6.88	214	137	62	138
16	7521165	55	MALE	EMPLOYEE	YES	YES	YES	OSA	NO	101	170	34.9	78	130/80	FATTY LIVER	4.9	289	NAFLD	75	28	32	-2.76	8.09	167	113	62	114
17	10069874	47	FEMALE	HOUSE WIFE	NO	NO	NO	NIL	NO	62	155	25.8	66	100/70	FATTY LIVER	6.5	356	NAFLD	89.5	24	22	-6.78	5.29	145	149	40	111
18	10031154	18	FEMALE	STUDENT	NO	NO	NO	NIL	NO	50	150	22.2	98	110/70	FATTY LIVER	6.3	258	NAFLD	92.2	141	302	-0.4	8.95	142	106	47	98
19	10030757	48	FEMALE	HOUSE WIFE	NO	NO	NO	NIL	NO	58	150	25.8	88	120/90	FATTY LIVER	7.1	248	NAFLD	94.4	18	16	-5.36	7.28	154	82	45	94
20	10088124	46	MALE	BUSSINESS	YES	YES	YES	NIL	OCCASIONAL	99	158	35.1	96	150/100	FATTY LIVER	3.6	296	NAFLD	95.7	28	27	-1.66	6.66	194	124	59	126
21	10091426	60	MALE	BUSSINESS	YES	YES	YES	NIL	OCCASIONAL	110	180	26	76	140/100	FATTY LIVER	4.5	338	NAFLD	85.6	15	23	-1.35	7.4	136	72	27	255
22	10090101	44	MALE	EMPLOYEE	NO	NO	NO	NIL	NO	76	165	27.9	88	110/90	FATTY LIVER	7.5	277	NAFLD	94.2	60	86	2.13	4.3	91	59	28	53
23	10086565	61	FEMALE	HOUSE WIFE	YES	NO	NO	NIL	NO	71	160	27.7	76	130/90	FATTY LIVER	4	256	NAFLD	85.9	17	17	-7.23	6.7	169	82	60	104
24	10084792	60	FEMALE	HOUSE WIFE	YES	YES	YES	NIL	NO	80	150	31.1	78	150/90	FATTY LIVER	6.9	249	NAFLD	94.4	62	106	-4.3	6.55	211	86	62	120
25	10083377	29	MALE	STUDENT	NO	NO	NO	NIL	NO	90	178	28.4	90	140/90	FATTY LIVER	3.5	249	NAFLD	79.5	26	23	-1.61	7.9	146	85	36	145
26	10080870	51	MALE	BUSSINESS	YES	YES	YES	NIL	NO	83	168	29.4	88	110/70	FATTY LIVER	6.4	258	NAFLD	92.5	139	121	-1.76	5.4	237	142	58	146
27	10048001	52	FEMALE	HOUSE WIFE	YES	NO	NO	NIL	NO	65	160	25.4	96	140/90	FATTY LIVER	3.4	260	NAFLD	109.7	25	69	7.59	7.12	210	101	40	117
28	10054299	20	MALE	STUDENT	NO	NO	NO	NIL	NO	105	175	34.3	86	150/100	FATTY LIVER	6.7	249	NAFLD	83.3	29	27	-3.83	8.99	223	113	42	126
29	7456426	37	FEMALE	HOUSE WIFE	YES	YES	YES	NIL	NO	110	168	31	88	150/110	FATTY LIVER	9.2	339	NAFLD	107.9	18	28	-6.209	8.9	138	153	42	111
30	7421504	38	MALE	EMPLOYEE	NO	NO	NO	NIL	NO	62	168	22	62	110/80	FATTY LIVER	5.3	267	NAFLD	76.9	72	50	0.23	8.43	142	147	45	111

31	10069868	37	MALE	EMPLOYEE	YES	NO	YES	NIL	NO	89	173	29.7	98	130/90	FATTY LIVER	4.6	315	NAFLD	92	21	26	-0.763	6.82	157	91	52	100
32	10030206	21	MALE	STUDENT	NO	NO	NO	NIL	NO	48	165	17.6	68	120/90	FATTY LIVER	9.5	249	NAFLD	82.1	145	168	3.839	8.1	147	119	57	107
33	7232799	40	FEMALE	HOUSE WIFE	NO	NO	YES	NIL	NO	49	162	18.7	76	130/90	FATTY LIVER	10	313	NAFLD	99.5	30	56	9.019	5.57	166	116	36	106
34	10081165	56	MALE	HOUSE WIFE	NO	NO	YES	NIL	NO	61	165	22.4	68	140/90	FATTY LIVER	5.3	249	NAFLD	85.4	23	48	5.52	5.2	123	86	64	91
35	6725031	51	FEMALE	EMPLOYEE	YES	NO	YES	NIL	NO	69	152	29.9	86	140/90	FATTY LIVER	7.8	302	NAFLD	96	54	34	-7.026	8.76	200	157	54	137
36	7405212	56	MALE	FARMER	YES	YES	YES	NIL	NO	60	160	23.4	84	150/90	FATTY LIVER	4.8	269	NAFLD	86	12	24	4.77	6.71	166	128	37	110
37	5861105	36	FEMALE	HOUSE WIFE	YES	NO	YES	NIL	NO	96	188	27.2	98	110/90	FATTY LIVER	7.6	344	NAFLD	96	28	21	-5.459	6.89	147	142	41	110
38	4219262	62	FEMALE	HOUSE WIFE	YES	YES	YES	NIL	NO	78	154	32.9	96	110/90	FATTY LIVER	7	274	NAFLD	94	22	20	-8.425	6.18	152	79	67	99
39	7339406	47	FEMALE	HOUSE WIFE	YES	YES	YES	NIL	NO	64	142	31.7	86	130/90	FATTY LIVER	6.2	263	NAFLD	86	16	33	-4.702	7.23	159	152	40	117
40	10054184	61	FEMALE	HOUSE WIFE	YES	NO	NO	NIL	NO	65	148	29.7	78	140/90	FATTY LIVER	5.3	295	NAFLD	90	32	28	-8.533	5.77	145	145	62	118
41	6301101	76	FEMALE	HOUSE WIFE	NO	NO	NO	NIL	NO	76	174	25.8	68	130/90	FATTY LIVER	8.6	287	NAFLD	76	30	26	-6.982	5.33	123	137	42	100
42	4141439	51	MALE	EMPLOYEE	NO	NO	NO	NIL	NO	79	165	29	98	140/90	FATTY LIVER	3.8	262	NAFLD	80	28	28	-1.41	8.07	217	121	49	129
43	7322707	60	FEMALE	HOUSE WIFE	YES	YES	YES	NIL	NO	77	151	33.8	76	130/80	FATTY LIVER	8.8	273	NAFLD	96	24	34	-5.369	8.98	139	139	36	105
44	7159938	42	FEMALE	HOUSE WIFE	NO	NO	NO	NIL	NO	51	146	23.9	78	120/80	FATTY LIVER	6.2	268	NAFLD	96	37	50	-1.768	5.21	179	68	30	93
45	10066145	57	FEMALE	HOUSE WIFE	NO	NO	NO	NIL	NO	62	158	24.8	86	130/90	FATTY LIVER	7.9	303	NAFLD	89	41	37	-6.436	5.03	132	106	62	100
46	10066656	55	FEMALE	EMPLOYEE	NO	NO	NO	NIL	NO	55	156	22.6	76	140/80	FATTY LIVER	6.1	297	NAFLD	90	28	26	-5.441	5.82	140	140	55	112
47	7505642	43	FEMALE	BUSSINESS	YES	NO	YES	NIL	NO	59	151	25.9	86	130/90	FATTY LIVER	9.2	284	NAFLD	96	16	16	-3.95	8.04	178	86	42	102
48	6094968	34	FEMALE	EMPLOYEE	NO	NO	NO	NIL	NO	74	160	28.9	72	130/90	FATTY LIVER	7.7	353	NAFLD	98	42	33	-4.735	7.07	159	122	60	114
49	7117605	56	FEMALE	HOUSE WIFE	YES	YES	YES	NIL	NO	65	151	28.5	88	140/90	FATTY LIVER	7.3	288	NAFLD	86.6	25	26	-7.233	6.48	179	59	65	101
50	10037544	49	MALE	FARMER	NO	YES	NO	NIL	>90 GMS/DAY	72	172	24.3	96	150/90	FATTY LIVER	3.8	264	ALD	96	18	77	10.86	8.08	131	110	41	94
51	10044263	60	MALE	EMPLOYEE	NO	NO	NO	NIL	>80 GMS/DAY	58	168	20.5	88	140/90	FATTY LIVER	5.6	253	ALD	91.4	108	137	1.12	6.39	144	98	51	98
52	10046356	50	MALE	BUSSINESS	NO	NO	NO	NIL	>100 GMS/DAY	60	165	22	90	130/80	FATTY LIVER	7.3	309	ALD	91.1	34	93	8.217	8.6	221	150	52	141
53	2682453	52	MALE	EMPLOYEE	YES	YES	YES	NIL	>75 GMS/DAY	88	174	29.1	78	110/70	FATTY LIVER	7.6	285	ALD	106.8	73	64	5.074	6.9	226	79	59	121
54	10047635	38	MALE	EMPLOYEE	NO	NO	NO	NIL	>80GMS/DAY	62	176	20	96	130/90	FATTY LIVER	7.2	334	ALD	78.4	53	206	10.06	7.44	152	82	38	91
55	10046943	52	MALE	BUSSINESS	NO	YES	NO	NIL	>66GMS/DAY	70	170	24.2	86	140/90	FATTY LIVER	6.6	259	ALD	93.2	52	135	7.54	5.82	129	105	46	93
56	10047949	42	MALE	BUSSINESS	YES	YES	YES	NIL	>80GMS/DAY	85	165	31.2	88	150/100	FATTY LIVER	9.8	308	ALD	107.6	32	46	6.414	5.19	230	78	34	114
57	10048811	30	MALE	EMPLOYEE	NO	NO	NO	NIL	>75 GMS/DAY	46	175	15	78	140/90	FATTY LIVER	8.6	309	ALD	94.4	115	480	13.62	5.7	121	157	46	108
58	10049797	70	MALE	BUSSINESS	YES	YES	YES	NIL	>100GMS/DAY	75	175	24.5	98	150/100	FATTY LIVER	7.5	309	ALD	85.1	30	44	2.29	5.71	153	60	62	92
59	10053921	60	MALE	EMPLOYEE	NO	YES	NO	NIL	>100GMS/DAY	70	161	27	78	150/100	FATTY LIVER	9.8	274	ALD	100.9	23	48	9.321	8.17	123	75	61	86
60	10054807	57	MALE	BUSSINESS	NO	NO	NO	NIL	>60GMS/DAY	57	156	23.4	86	130/90	FATTY LIVER	7.8	305	ALD	103.7	25	65	14.27	6.38	176	50	58	95
61	10056024	42	MALE	BUSSINESS	NO	YES	NO	NIL	>70 GMS/DAY	76	170	26.3	76	140/110	FATTY LIVER	7.5	300	ALD	104.1	16	32	10.6	5.96	165	73	43	94
62	10055808	42	MALE	BUSSINESS	NO	NO	NO	NIL	>90GMS/DAY	84	180	25.9	88	140/90	FATTY LIVER	4.5	289	ALD	70.6	9	19	4.19	7.96	191	155	34	127
63	10058495	57	MALE	EMPLOYEE	NO	NO	NO	NIL	>100 GMS/DAY	58	165	21.3	76	130/90	FATTY LIVER	6.8	257	ALD	104.6	17	58	16.543	7.54	229	82	39	117
64	10057305	44	MALE	EMPLOYEE	NO	NO	NO	NIL	>80 GMS/DAY	69	170	23.9	66	130/70	FATTY LIVER	10	263	ALD	107.9	62	167	14.289	6.95	200	142	46	129
65	10062130	52	MALE	FARMER	NO	YES	YES	NIL	>90GMS/DAY	75	178	23.7	88	130/90	FATTY LIVER	7.5	296	ALD	99	119	185	3.806	8.51	239	62	31	111
66	10063073	44	MALE	EMPLOYEE	NO	NO	NO	NIL	>60GMS/DAY	56	158	22.4	96	140/90	FATTY LIVER	10	262	ALD	115	153	644	16.09	8.25	151	96	53	100
67	10041459	45	MALE	EMPLOYEE	NO	NO	NO	NIL	>70 GMS/DAY	77	170	26.6	100	150/100	FATTY LIVER	10	287	ALD	101.8	52	84	8.123	5.84	146	81	60	96
68	10041708	33	MALE	BUSSINESS	NO	NO	NO	NIL	>60GMS/DAY	69	165	25.3	76	140/90	FATTY LIVER	7.5	294	ALD	94.4	47	154	9.44	8.57	122	136	48	102
69	10042273	36	MALE	BUSSINESS	NO	NO	NO	NIL	>90GMS/DAY	55	160	21.5	78	130/80	FATTY LIVER	6.8	331	ALD	102	28	87	9.45	7.13	129	133	43	102
70	10042383	35	MALE	EMPLOYEE	NO	NO	NO	NIL	>70 GMS/DAY	76	175	24.8	98	140/90	FATTY LIVER	6.2	264	ALD	133.2	62	199	15.12	8.5	139	82	42	88
71	10075709	50	MALE	BUSSINESS	YES	YES	YES	NIL	>70 GMS/DAY	77	176	26.6	86	150/110	FATTY LIVER	9.6	259	ALD	94.7	61	72	4.385	6.28	235	109	42	129
72	10075075	34	MALE	EMPLOYEE	NO	NO	NO	NIL	>60 GMS/DAY	70	176	22.6	88	140/90	FATTY LIVER	7.3	276	ALD	102.8	62	118	11.6	8.84	162	79	58	99
73	10075697	42	MALE	EMPLOYEE	NO	YES	YES	NIL	>90 GMS/DAY	89	165	32.7	78	150/90	FATTY LIVER	7.5	265	ALD	98.3	54	91	3.78	5.3	129	72	36	79
74	10076460	48	MALE	BUSSINESS	NO	NO	NO	NIL	>70 GMS/DAY	55	168	19.5	68	130/90	FATTY LIVER	4.3	270	ALD	115.5	53	142	16.02	7.88	234	160	42	145
75	10074192	24	MALE	STUDENT	NO	NO	NO	NIL	>60GMS/DAY	53	168	18.8	98	140/100	FATTY LIVER	10	400	ALD	99.6	51	61	6.931	8.52	168	132	48	116
76	10077218	49	MALE	BUSSINESS	YES	YES	YES	NIL	>70 GMS/DAY	42	150	18.7	98	110/70	FATTY LIVER	8.8	376	ALD	93.3	29	31	3.87	7.23	152	62	66	93
77	10065573	45	MALE	EMPLOYEE	NO	NO	NO	NIL	>60GMS/DAY	52	170	18	68	110/70	FATTY LIVER	6.7	267	ALD	93	49	83	6.486	8.89	163	79	38	93

78	10066010	32	MALE	STUDENT	NO	NO	NO	NIL	>60GMS/DAY	68	174	22.5	98	120/90	FATTY LIVER	10	280	ALD	98.8	141	151	5.838	8.16	180	70	40	97
79	10067594	48	MALE	FARMER	YES	YES	YES	NIL	>90 GMS/DAY	73	173	24.4	82	140/80	FATTY LIVER	4.8	300	ALD	103	47	32	9.297	6.03	227	81	40	116
80	10069229	26	MALE	STUDENT	NO	NO	NO	NIL	>60GMS/DAY	61	165	22.4	68	130/90	FATTY LIVER	7.5	258	ALD	105	93	309	5.665	6.89	238	72	52	121
81	10068756	62	MALE	FARMER	NO	NO	NO	NIL	>100GMS/DAY	75	173	25.1	98	150/110	FATTY LIVER	7.6	315	ALD	106.6	47	139	14.43	5.49	123	145	42	103
82	10070649	63	MALE	FARMER	YES	YES	YES	NIL	>70 GMS/DAY	77	165	28.3	86	140/80	FATTY LIVER	7.5	269	ALD	92.4	21	64	6.949	8.19	142	80	59	93
83	10071396	40	MALE	EMPLOYEE	NO	NO	NO	NIL	>60 GMS/DAY	65	172	22	78	130/90	FATTY LIVER	7.5	285	ALD	108.1	30	181	5.17	6.78	122	148	61	110
84	10031831	30	MALE	STUDENT	NO	NO	NO	NIL	>70GMS/DAY	55	170	19	76	120/80	FATTY LIVER	10	274	ALD	97.6	96	81	5.606	7.68	235	81	37	118
85	10031685	71	MALE	FARMER	YES	YES	YES	NIL	>90 GMS/DAY	71	166	25.8	98	140/100	FATTY LIVER	7.5	289	ALD	76.5	23	114	7.709	8.05	231	56	43	110
86	10035145	32	MALE	EMPLOYEE	NO	NO	NO	NIL	>100 GMS/DAY	77	171	26.3	78	130/90	FATTY LIVER	8.3	286	ALD	112	72	109	8.703	5.89	150	102	41	98
87	10034450	53	MALE	FARMER	YES	YES	NO	NIL	>80 GMS/DAY	73	160	28.5	90	140/90	FATTY LIVER	8.7	303	ALD	94.6	23	39	3.169	7.93	194	160	70	141
88	10033779	58	MALE	FARMER	NO	NO	NO	NIL	>70 GMS/DAY	69	170	23.9	98	110/90	FATTY LIVER	4.5	296	ALD	88.9	37	76	4.782	5.8	235	150	65	150
89	10031353	45	MALE	BUSSINESS	NO	YES	NO	NIL	>80 GMS/DAY	65	168	23	76	130/90	FATTY LIVER	3.8	280	ALD	95.7	92	143	5.55	8.02	146	119	35	100
90	10088436	62	MALE	FARMER	NO	YES	NO	NIL	>60GMS/DAY	69	165	25.5	82	140/90	FATTY LIVER	9.5	289	ALD	99.2	17	23	6.089	7.26	166	153	49	123
91	10087183	66	MALE	FARMER	YES	YES	YES	NIL	>70 GMS/DAY	78	165	28.7	66	140/80	FATTY LIVER	7.2	262	ALD	88.2	16	37	3.844	5.66	199	136	65	133
92	10087394	67	MALE	RETD.	YES	YES	YES	NIL	>80 GMS/DAY	70	164	26	80	130/90	FATTY LIVER	3.8	278	ALD	85.1	31	48	1.952	7.67	171	59	68	99
93	10090103	44	MALE	EMPLOYEE	NO	NO	NO	NIL	>60 GMS/DAY	76	165	27.9	68	120/90	FATTY LIVER	7.6	277	ALD	94.2	60	86	2.132	4.3	91	59	28	53
94	10085520	48	MALE	FARMER	YES	YES	YES	NIL	>70 GMS/DAY	80	160	31.3	98	150/90	FATTY LIVER	4.1	264	ALD	101.7	24	37	5.994	6.98	214	79	39	111
95	10082364	52	MALE	BUSSINESS	NO	NO	NO	NIL	>80 GMS/DAY	51	165	18.7	96	140/90	FATTY LIVER	5.5	249	ALD	89.8	19	54	9.974	7.56	203	64	51	106
96	10049049	32	MALE	BUSSINESS	NO	NO	NO	NIL	>80 GMS/DAY	63	173	21	66	110/90	FATTY LIVER	7.5	249	ALD	101	74	185	5.225	7.84	140	145	56	114
97	7402188	31	MALE	STUDENT	NO	NO	NO	NIL	>60 GMS/DAY	68	180	21	96	130/90	FATTY LIVER	5.4	280	ALD	96	80	48	2.822	6.91	136	58	38	77
98	10053005	68	MALE	RETD.	YES	YES	YES	NIL	>80 GMS/DAY	77	170	26.6	78	140/90	FATTY LIVER	6.6	289	ALD	86	24	21	-0.924	8.5	175	150	53	126
99	7427807	63	MALE	FARMER	YES	YES	YES	NIL	>70 GMS/DAY	80	159	31.6	88	150/90	FATTY LIVER	5.1	289	ALD	77	19	23	-1.642	5.47	190	79	48	106
100	7429946	71	MALE	FARMER	YES	NO	YES	NIL	>60 GMS/DAY	91	174	30.1	96	130/90	FATTY LIVER	5.2	268	ALD	92	26	21	-2.609	5.37	191	151	45	129