"AST TO PLATELET RATIO INDEX (APRI) IN PATIENTS WITH METABOLIC SYNDROME AND ITS RELATION WITH CARDIOVASCULAR RISK"

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ABSTRACT

Introduction

Metabolic syndrome (MetS) encompasses central obesity, elevated triglycerides, reduced HDL cholesterol, high blood sugar, high blood pressure, and insulin resistance, increasing the risk of atherosclerotic cardiovascular disease (ASCVD) and MAFLD. This study investigates the role of the Aspartate Aminotransferase to Platelet Ratio Index (APRI) in predicting cardiovascular risk in subjects with and without MetS.

Aims

1. Compare APRI scores between MetS and non-MetS subjects, and various factors influencing APRI.
2. Analyze APRI's role in predicting cardiovascular risk using the Framingham Risk Score and ASCVD score in MetS subjects.

Materials and Methods

This cross-sectional study included 68 subjects, equally divided between MetS and non-MetS groups. Demographic data, medical history, anthropometric measurements and biochemical markers were collected in a standard proforma. APRI, ASCVD, FRS scores calculated. Data tabulated in Masterchart. Statistical analyses were performed using Chi-square tests, t-tests, Mann-Whitney U tests, Spearman’s rank correlation tests. A p-value of ≤ 0.05 was considered significant.

Results

Subjects with MetS had significantly higher APRI (0.6 ± 0.38) scores compared to those in the non-Metabolic Syndrome group (0.24 ± 0.11) (p-value < 0.001). Elevated APRI scores in MetS subjects was linked to higher cardiovascular risk, as indicated by the Framingham Risk Score (p-value< 0.0034) and ASCVD (p-value < 0.0030) score. Elevated APRI scores showed correlation to metabolic syndrome criteria ie waist circumference (p-value < 0.001), diabetes (p-value < 0.0165), HBA1c (p-value < 0.0159) SBP (p-value < 0.0134) and negatively correlates to HDL level (p-value < 0.0065).

Conclusion

Individuals with MetS had significantly higher APRI values compared to those without Mets. Elevated APRI scores are significantly associated with increased cardiovascular risk in MetS patients especially in age group 60-69 and females. Higher APRI is also associated with each component of MetS, increased waist circumference, elevated glycemia, elevated SBP, and Low HDL. Leading to stronger correlations between CVR and APRI when Components of Metabolic Syndrome are present. APRI can be used as a valuable non-invasive routine marker for cardiovascular risk prediction in MetS,

Keywords

APRI, Metabolic syndrome, Cardiovascular risk.

LIST OF ABBREVIATIONS

MetS	Metabolic syndrome
APRI	AST to Platelet Ratio Index
ASCVD	Atherosclerotic cardiovascular disease
FRS	Framinghams Risk score
MASLD	Metabolic dysfunction-associated steatotic liver disease
NAFLD	Non-Alcoholic Fatty Liver Disease
IDF	International Diabetes Federation
WHO	World Health Organization
NCEP: ATP-III	National Cholesterol Education Program ATP III Guidelines
EGIR(1999)	The European group for the study of insulin resistance
WC	Waist Circumference
TG	Triglycerides
HDL	high-density lipoprotein
BMI	Body mass index
T2DM	type 2 diabetes mellitus
GLUT4	Glucose transporter type 4
PI3K-Akt	phosphoinositide 3-kinase pathway and the mitogen-activated protein kinase
enos	endothelial nitric oxide synthase
MAP kinase	Mitogen-activated protein kinase
SOS	son of sevenless
VCAM-1 -	vascular cell adhesion molecule 1

ET-1	endothelin-1
eNOS	endothelial nitric oxide synthase
Akt1	alpha serine/threonine-protein kinase
TNF α	Tumor Necrosis Factor α
IL-6	Interleukin-6
VLDL	Very low-density lipoproteins
FFA	free fatty acids
IGF	insulin like growth factor
IRS	insulin receptor substrate
JNK	Janus Kinase
IKK	inhibitor of nuclear factor-κB (IκB) kinase
MODY	maturity-onset diabetes of the young
GCK	Glucokinase
HNF	Hepatocyte nuclear factors
MetALD	Metabolic Dysfunction- and Alcohol-Associated Liver Disease
PPAR-α	peroxisome proliferator-activated receptor
MASH	metabolic-associated steatohepatitis
NPC1L1	Niemann-Pick C1-like 1

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Metabolic syndrome, often referred to as insulin resistance syndrome or syndrome X, encompasses a collection of metabolic irregularities that heighten the risk of developing atherosclerotic cardiovascular disease (ASCVD) and diabetes mellitus. The core features of metabolic syndrome comprise central obesity, elevated triglyceride levels, reduced levels of high-density lipoprotein cholesterol, high blood sugar, and high blood pressure, along with insulin resistance. [3]

Diagnosis of metabolic syndrome typically involves measuring waist circumference, which is a crucial criterion. This syndrome is identified as a chronic, low-grade inflammatory state, driven by amplified production of chemokines, adipokines, and cytokines, coupled with atypical immune cell activation. These inflammatory processes are linked to the development of Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as Non-Alcoholic Fatty Liver Disease (NAFLD).

Visceral obesity, the significant component of metabolic syndrome, is marked by a systemic low-grade inflammation that significantly contributes to the onset of MASLD. This condition is often associated with liver fibrosis. The chronic inflammation, together with heightened insulin resistance and various other health complications, leads to the major consequences of metabolic syndrome, including atherosclerotic plaque formation, Metabolic Associated Steatotic Liver Disease (MASLD). [1]

The EPIC study has underscored the significance of waist circumference as a non-aggressive technique to conjecture excessive visceral adipose tissue and foresee the menace of cardiovascular-related mortality. The accumulation of visceral fat is

pivotal in metabolic syndrome (MetS) complications, substantially elevating cardiovascular risk.

In recent times, non-invasive serum markers have gained recognition as effective and user-friendly tools for predicting liver fibrosis. Various studies have explored the utility of the NAFLD score (NFS) and the AST to Platelet Ratio Index (APRI score) in assessing the impact of MetS in patients without hepatitis. These studies aim to understand whether liver fibrosis is associated with cardiovascular disease. However, the relationship amongst these scores and MetS remains inadequately defined[2]

AIMS AND OBJECTIVES

- A cross-sectional study, Comparing APRI score in metabolic syndrome and non-metabolic syndrome subjects and its association with various factors.
- In the present study we plan to analyse the role of APRI score in predicting the cardiovascular risk using the FRAMINGHAMS SCORE and ASCVD score in metabolic syndrome subjects.

REVIEW OF LITERATURE

Metabolic Syndrome is a collection of cardiovascular disease risk features that upsurge the likelihood for developing type 2 diabetes mellitus. This condition was originally termed "syndrome X" in 1988. A key feature of metabolic syndrome is insulin resistance.

Criterion for Diagnosis:

1. International Diabetes Federation (IDF) .[7]

2. World Health Organization (WHO) Standards/Criteria[8]

3. National Cholesterol Education Program ATP III Guidelines (NCEP: ATP-III) [9,10]

Nomenclature

The following are some alternative terms for metabolic syndrome:

1. Syndrome X
2. Metabolic syndrome
3. X Pluri metabolic syndrome
4. Insulin resistance syndrome
5. "deadly quartet,"
6. Hyper tri-glyceridemic waist
7. Reaven's Syndrome

HISTORY OF METABOLIC SYNDROME

The concept of interconnected metabolic disturbances emerged around 80 years ago, initially identified as a combination of gout, hypertension, hyperglycaemia[4].

Although the risk factors for diabetes had been recognized since at least the 1920s, the term "metabolic syndrome" was not coined until the late 1950s and gained more frequent use in the late 1970s.

In 1947, Dr. Jean Vague from Marseilles discovered that upper body weight gain is linked to an increased risk of diabetes, atherosclerosis, gout, and kidney stones[11]. Later,Avogadro, Crepaldi, and their colleagues later demonstrated that a low-calorie, low-carbohydrate diet could treat diabetes, hypercholesterolemia, and significant hypertriglyceridemia in moderately obese individuals[12].

In the late 1970s, Gerald B. Phillips identified glucose intolerance, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, and hypertension as risk factors for myocardial infarction[13], noting that aging, obesity, and other conditions were linked to this "constellation of anomalies"[12]

Gerald Reaven brought renewed attention to "syndrome X" in 1988, describes it as a condition characterized by high blood pressure, glucose intolerance, elevated triglyceride levels, and low levels of high-density lipoprotein (HDL) cholesterol[14]. However, the association between hypertension, hyperglycemia, and gout was first noted by Kylin in 1923, long before the term "metabolic syndrome" was widely used[15].

World Health Organization coined the term "metabolic syndrome" in 1998 to standardize the description of what was previously known as insulin resistance syndrome. The new term was adopted for the reason that it was recognized insulin resistance was not the sole basis of all the symptoms associated with the syndrome.

Definitions

	NCEP: ATP-III (2005 revision)[9,10]	**WHO (1998)[8]**	**EGIR (1999)[16]**	**IDF (2005)[7]**
Absolutely required	None	IR [IFG, IGT, T_2DM Or other evidence of IR]	Hyperinsulinemia (plasma insulin > 75^{th} percentile	Central obesity (wc:>94cms(male); >80cms (female)
Criteria	Any three of the five criteria	IR or "diabetes plus two of the five criteria below"	Hyperinsulinemia "plus two of the four criteria below"	Obesity plus two of the four criteria below
Obesity	Waist circumference: >40inches[M]; >35 inches[F]	Waist/hip ratio: >0.90[M]; >0.85[F] or BMI>30kg/m^2	WC >94cms[M]; >80cms[F]	Central obesity already required
Hyperglycemia	Fasting glucose>100mg/dl or on treatment	Insulin resistance already required	Insulin resistance already required	Fasting glucose>100mg/dl
Dyslipidemia	TG>150mg/dl or on treatment	TG>150mg/dl or HDL-C <35mg/dl[M]; <39mg/dl[F]	TG>177mg/dl or HDL-C <39mg/dl	TG>150mg/dl or on treatment
Dyslipidemia (second, separate criteria)	HDL-C <40 mg/dl[M]; <50mg/dl[F]; or on treatment.	-	-	HDL-C <40 mg/dl[M]; <50mg/dl[F]; or on treatment.
Other	>130mmHg systolic or >85mmHg diastolic or on treatment	>140/90mmHg	>140/90mmHg or on treatment	>130mmHg systolic or >85mmHg diastolic or on treatment
Other criteria	-	microalbuminuria	-	-

Table A: DEFINITIONS OF METABOLIC SYNDROME

IDF Metabolic Syndrome Worldwide Definition

The International Diabetes Federation (IDF) has established specific standards to define metabolic syndrome (MetS). According to the IDF, the criteria are:

- Waist Circumference (WC): Greater than 90* cm in males or greater than 80* cm in females.
- Systolic Arterial Pressure: 130 mmHg or higher, or diastolic blood pressure of 85 mmHg or higher, or currently on medication for hypertension.
- Fasting Plasma Glucose: 100 mg/dL or higher, or on medication for elevated glucose.
- Triglycerides (TG): 150 mg/dL or higher, or on medication for elevated triglycerides; high-density lipoprotein (HDL) concentration less than 40 mg/dL in males or less than 50 mg/dL in females, or on medication for dyslipidemia.

An increased waist circumference along with the presence of two or more of the other criteria results in a diagnosis of MetS as per this definition.

*IDF values for Indian Asians.

Epidemiology

Approximately one-fourth of the global grown-up population, or about a billion grown-ups, are estimated to have MetS[17].

"The occurrence of metabolic syndrome tends to increase with age. In the United States, about 34% of male and 35% of female are affected, according to data from the National Health and Nutrition Examination Survey (NHANES) III"[18-19].

Obesity rates have risen with industrialization, and this trend is expected to persist, leading to a significant increase in the prevalence of metabolic syndrome, juvenile obesity is becoming more common and severe, resulting in the earlier appearance of metabolic syndrome symptoms in younger people[20].

South Asians, including migrants to wealthy republics in Western Europe or the USA, often exhibit a elevated percentage of body fat at lesser BMI values, increased waist-to-hip ratio (WHR) or waist circumference, and reduced lean mass compared to other ethnic groups. A notable characteristic of Asian Indians is high body fat, even at BMI values not classified as obese, resulting in a phenotype marked by a high body fat to BMI ratio, high WC or WHR, and a smaller amount of lean mass, predominantly in the lower limbs[21].

"Hoskote et al. reviewed the "thrifty gene" theory, which explains the raised levels of insulin resistance and its consequences among Indians in contrast to Europoid and other Caucasian populations"[22] . Historically, Indians have been primarily vegetarian, with an economy centred on agriculture, leading to a diet with lower energy density. Conversely, Europeans have traditionally consumed a meat-based diet with higher energy density due to severe winters and lower agricultural output.

Indian populations frequently faced food shortages and energy deprivation during famines and floods, leading to the "thrifty genotype." This genotype favoured efficient energy storage through ages of abundance to be exploited during scarcity.

These genomic revisions, advantageous in an energy-run-down state, become detrimental when dietary energy intake is elevated and physical activity is low, as seen with industrialization and economic affluence. Consequently, the thrifty gene continues to promote energy storage, resulting in overweight, particularly central obesity[22].This also supports the "Barker's hypothesis," which conditions that kids born with low birth weight incline to stock more energy as fat, leading to the development of type 2 diabetes (T2DM) in adulthood[23]. Indians may be metabolically diverse from Europeans due to the thrifty gene and other unknown factors[22].

In India, MetS and insulin resistance are prevalent. Studies show that in urban Indian residents, the age-adjusted prevalence of metabolic syndrome is around 25%, with approximately 31% in women and 18.5% in men[24]. Comparatively, an international study estimated that about 13–15% of India's adult population has MetS, with ladies being further affected (approximately 8–9% amid men and 18–19% amid ladies) [25].The pervasiveness of MetS increases with age.

Mid-aged Armed Forces employees in India, despite their fitness levels, exhibit a prevalence of MetS between 6.2% and 8.5%. Key findings from studies by Bhalwar et al. include:

- Significant clustering of MetS risk factors among those with fasting hyperinsulinemia.
- Predictors: increasing age, low physical activity, and higher BMI[26].
- Risk factors: age over 45, lack of exercise, non-vegetarian diet, and tobacco use.

Relation to predictability of diabetes and cardiovascular disease

"Metabolic syndrome is associated with a heightened risk of both diabetes and cardiovascular disease." Numerous studies have shown that metabolic syndrome can predict future diabetes.

"The DECODE study, which examined European men and women, found that non-diabetic individuals with metabolic syndrome had a significantly increased risk of death from all causes and cardiovascular disease. The hazard ratios for all-cause and cardiovascular disease mortality were 1.44 and 2.26 in men, and 1.38 and 2.78 in women, respectively, after adjusting for age, blood cholesterol levels, and smoking"[28].

"The INTERHEART study's findings are crucial. This study examined cardiovascular risk factors in nearly 30,000 people from 52 countries across all inhabited continents. The results identified several key risk factors for myocardial infarction: abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, low consumption of fruits and vegetables, high alcohol intake, and irregular physical activity. These factors were consistently significant across sexes, ages, and regions"[29].

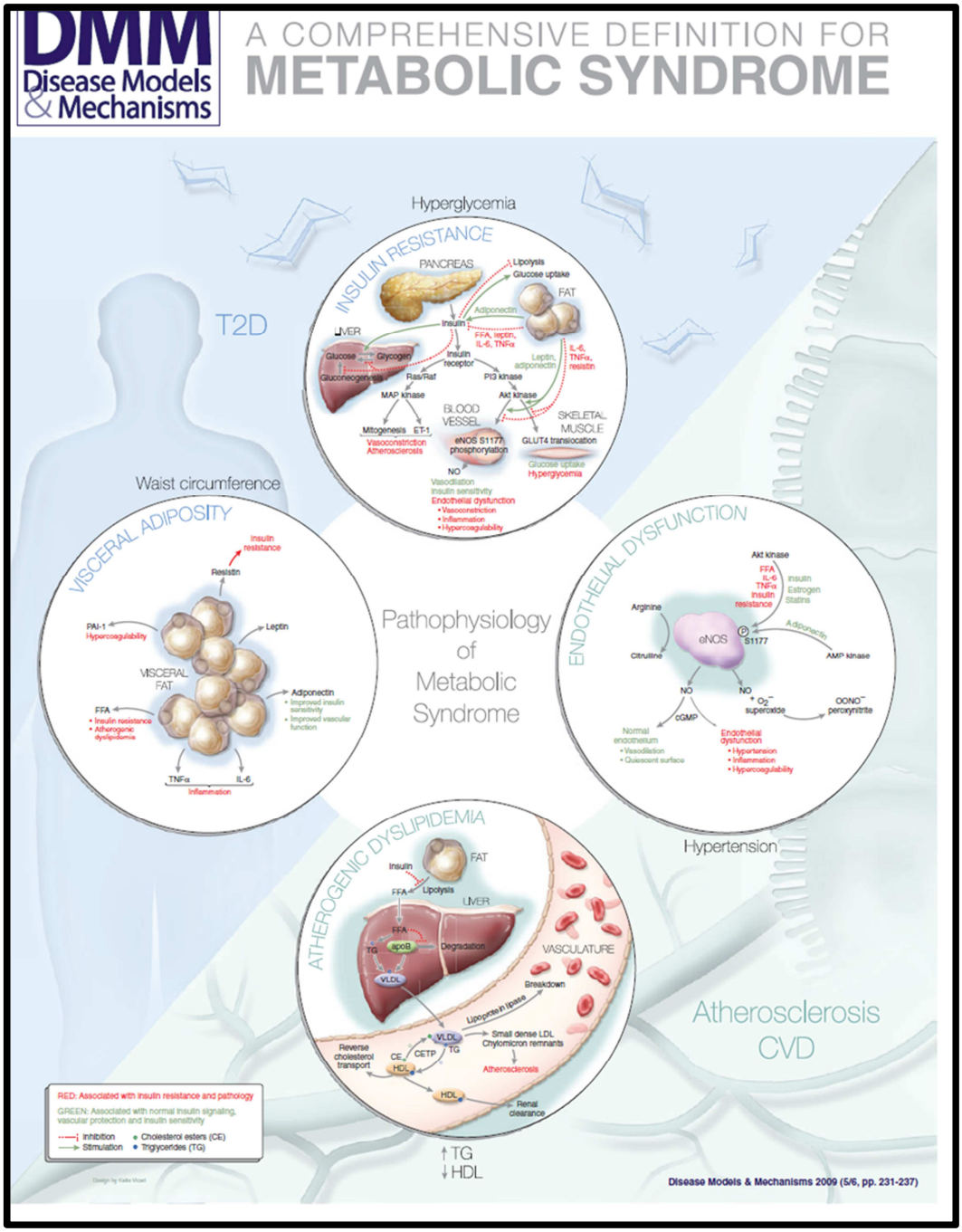

FIGURE I: Various Pathophysiological Mechanisms of Metabolic Syndrome

Mechanisms underlying the metabolic Syndrome

Insulin resistance

"Insulin, formed via the pancreas in retort to high blood sugar, helps regulate glucose use in different tissues like skeletal muscle, liver, and adipose tissue. In skeletal muscle and adipose tissue, insulin promotes glucose acceptance by moving the GLUT4 glucose transporter to the cell surface." It also stimulates conversion of glucose into glycogen and inhibits its breakdown in skeletal muscle and liver. In the liver, insulin reduces the production of glucose, preventing an excess release into circulation. In adipose tissue, insulin prevents fat breakdown and enhances glucose take-up.

"The combined effect is increased glucose uptake, reduced blood sugar levels, and the conversion of glucose into storage forms like glycogen or fat (Kim et al., 2006) [30]. In insulin resistance, however, cells in adipose tissue, muscle, and liver did not retort properly to insulin, leading to high blood glucose levels". This problem is made worse by disrupted feedback mechanisms**.**

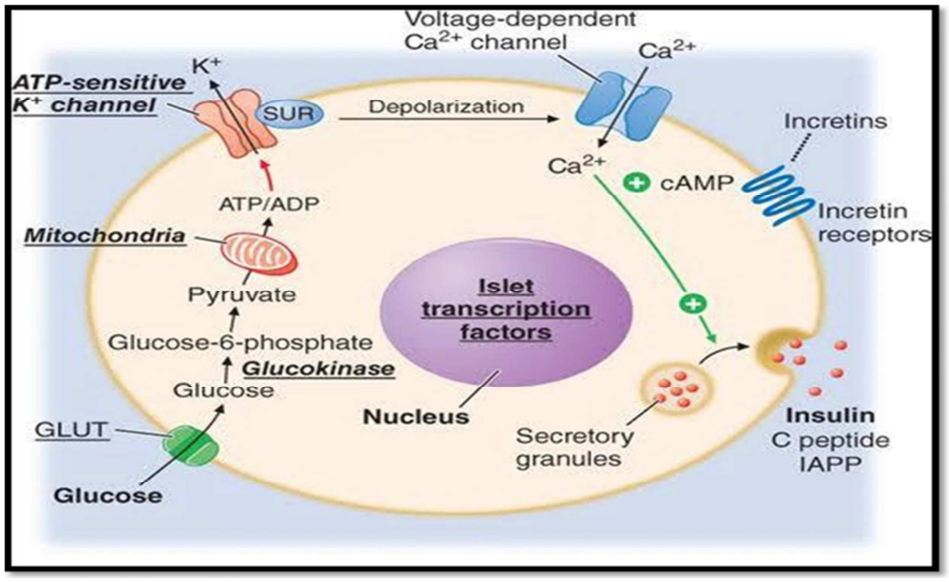

FIGURE II : Glucose sensing and insulin release from pancreas

When insulin binds to its receptor, a ligand-activated tyrosine kinase, it initiates signaling pathways that regulate glucose metabolism. This binding causes the receptor to phosphorylate downstream substrates, activating “the phosphoinositide 3-kinase pathway and the mitogen-activated protein kinase pathway. The phosphorylation of insulin receptor substrates activates PI3K,” which subsequently activates 3-phosphoinositide-dependent protein kinase 1 and Akt kinase.

“The PI3K-Akt pathway plays a key role in the metabolic properties of insulin. In vascular endothelial cells, Akt kinase activates endothelial nitric oxide synthase (eNOS), while in skeletal muscle and adipose tissue, it promotes the translocation of the GLUT4 glucose transporter to the cell surface, thereby increasing glucose take-up.”

The MAP kinase pathway is activated when tyrosine phosphorylation of the SHC protein triggers the GTP exchange factor SOS. “This pathway contributes to the production of endothelin-1 (ET-1), which causes vasoconstriction, and the countenance of vascular cell adhesion molecules like VCAM-1 and E-selectin, promoting leukocyte-endothelial interactions and stimulating the development and division of vascular smooth muscle cells.”

In insulin resistance, the PI3K-Akt pathway is disrupted, but the MAP kinase pathway remains unaffected. This disruption reduces endothelial nitric oxide (NO) production, leading to endothelial dysfunction, and decreases GLUT4 translocation, resulting in lower glucose uptake in skeletal muscle and fat. Meanwhile, the MAP kinase pathway continues to function, producing ET-1, expressing adhesion molecules, and stimulating vascular smooth muscle cells. These changes contribute to vascular abnormalities and an increased risk of atherosclerosis.

Insulin enhances local blood flow in tissues by activating endothelial nitric oxide synthase (eNOS), leading to dual primary results (Kim et al., 2006; Jonk et al., 2007) [30,31]. First, it triggers capillary recruitment within minutes. Then, over 30 minutes to 2 hours, it causes dilation of larger resistance vessels, improving overall perfusion. These results contribute to vasodilation and enhance the distribution of glucose and insulin to tissues. Insulin's vascular actions link glucose homeostasis with blood flow, aiding glucose metabolism at physiological insulin levels. Pharmacologically inhibiting nitric oxide (NO) production can decrease glucose disposal by 40%.

Excessive circulating fatty acids play a significant role in developing insulin resistance. When these fatty acids reach insulin-sensitive tissues, they contribute to insulin resistance by increasing substrate availability and altering downstream signalling. Inside muscles, fatty acids can hinder the activation of protein kinase C. Furthermore, the accumulation of acyl CoAs or their derivatives like ceramide can diminish Akt1 activation.

Insulin-mediated glucose disposal rates can vary significantly among individuals, influenced by factors such as body fat, fitness levels, and genetics. Insulin resistance occurs when peripheral tissues like skeletal muscle, fat, and liver become less responsive towards insulin. This condition is a strong predictor of T2DM, with hyperinsulinemia often indicating insulin resistance.

Visceral adiposity

Visceral obesity leads to decreased insulin-mediated glucose uptake, closely linking it to insulin resistance. This connection is mediated by adipokines produced by adipose tissue, which influence the interplay between metabolism and vascular function (Kershaw and Flier, 2004). Key adipokines involved are:

- **Tumor Necrosis Factor α** and **Interleukin-6:** These proinflammatory adipokines lead to vascular dysfunction and insulin resistance.
- **Renin-Angiotensin System:** Activation in adipose tissue causes high blood pressure and insulin resistance.
- **Adiponectin:** A defensive adipokine that enhances insulin sensitivity and energy metabolism. Its values are reduced in conditions like obesity, T2DM, and metabolic syndrome.

Atherogenic dyslipidemia

Atherogenic dyslipidemia, marked by high plasma TG levels, low HDL cholesterol levels, and increased small dense LDL particles, is closely associated with insulin resistance and visceral obesity (Semenkovich, 2006) [32]. Insulin resistance leads to this condition through several mechanisms:

- **Increased Lipolysis:** Normally, insulin overwhelms lipolysis in adipocytes. Diminished insulin signalling upsurges lipolysis, raising free fatty acid (FFA) levels. These FFAs are used in the liver to synthesize TGs and alleviate the creation of apoB, the primary protein in very-low-density lipoprotein particles, ensuing in increased VLDL construction.

- **Increased VLDL Production:** Insulin typically breaks down apoB via PI3K-dependent pathways. In insulin resistance, this degradation is reduced, directly increasing VLDL production.

- **Decreased VLDL Clearance:** Insulin regulates lipoprotein lipase, the enzyme responsible for VLDL clearance. Insulin resistance reduces this enzyme's activity, leading to both increased VLDL production and decreased VLDL clearance.

"VLDL is processed into remnant lipoproteins and small dense LDL, both of which endorse atheroma formation. TGs in VLDL are relocated to HDL by cholesterol ester transfer protein in exchange for cholesteryl esters, creating TG-enriched HDL and cholesteryl ester-enriched VLDL particles. TG-enhanced HDL is cleared more hastily from circulation, leaving scarcer HDL elements for reverse cholesterol transference from the vasculature."

Endothelial dysfunction

Endothelial disfunction is a key alleyway linking various cardiovascular risk factors to the advance of atherosclerosis (Gimbrone et al., 2000; Huang, 2005; Kim et al., 2006) [33,34,30]. Endothelial cells contour the internal lining of blood vessels, performing essential mechanical and biological roles. They respond to physiological and pathological stimuli by producing vasoactive substances such as nitric oxide (NO), prostacyclin, and endothelin's.

The endothelium's expression of cell adhesion molecules controls communications with circulating leukocytes and monocytes, affecting inflammation, besides platelets, impacting haemostasis and thrombosis. It also modulates the response of the vascular smooth muscle layer, contributing towards the creation of

intimal layers all through atherosclerotic plaque growth. While standard endothelial function defends these processes, endothelial dysfunction plays a vital role in the pathogenesis of atherosclerotic lesions.

Insulin resistance leads to endothelial dysfunction by decreasing Akt kinase activity, which reduces the phosphorylation and activity of eNOS. Since eNOS phosphorylation at S1177 is crucial, aimed at insulin's hemodynamic activities, this results in reduced blood flow to skeletal muscle. This reduction creates a sequence where endothelial dysfunction further degrades insulin resistance. Additionally, insulin-mediated endothelin-1 (ET-1) appearance and the mitogenic effects on vascular smooth muscle remain unaffected by insulin resistance, additional contributory to endothelial dysfunction [34,35].

Visceral adiposeness roots endothelial dysfunction by affecting eNOS phosphorylation through resistin, IL-6, and TNFα. TNFα not only inhibits IRS-1 activation but also activates NADPH oxidase, leading to increased superoxide production. Additionally, TNFα stimulates lipolysis, resulting in the release of free fatty acids (FFA) [36].

Metabolic Syndrome and Inflammation

The metabolic and immune systems are crucial for survival, with immune response and metabolic regulation being deeply interconnected. Proper function in one system relies on the other, creating a fundamental homeostatic mechanism. Dysfunction in this interface can lead to chronic metabolic ailments like obesity, type 2 diabetes, and cardiovascular ailment. These conditions represent the most significant peril to global human healthiness and welfare.

Traditionally, inflammation is the body's main response to injuries, marked by swelling, redness, pain, and fever (tumor, rubor, dolor, and calor) [37]. This interim reaction is critical for tissue repair, involving complex signals among various cells and organs. However, long-standing inflammation can be harmful. In obesity and diabetes, while similar inflammatory mediators are present, the classic signs of inflammation are often missing. This has led to the concept of 'metaflammation'—a term for metabolically triggered, low-grade chronic inflammation[38].

One of the utmost perilous processes for existence is the capability to endure periods of famishment. This capability favors energy efficiency, leading to the storing of excess calories during times when sustenance is scarce. However, when there is a constant surplus of food, this advantageous metabolic trait can result in excessive adiposity and its associated health issues [(39,40)].

Adipose tissue and the liver have a unique structure where metabolic cells (adipocytes or hepatocytes) are positioned near immune cells (Kupffer cells or macrophages) and are connected to an extensive web of blood vessels (Fig. 2). This setup allows for ongoing communications amongst immune and metabolic responses and facilitates communication with other organs such as pancreatic islets and muscles. This close interaction is crucial in the development of metabolic diseases, particularly obesity and type 2 diabetes [(41,42)].

Chronic disruptions in metabolic balance from malnutrition or overnutrition lead to abnormal immune responses. Modern diets and sedentary lifestyles contribute to metabolic overload. Historically beneficial traits, combined with nutrient and pathogen response interactions, have increased chronic metabolic ailments globally. Targeting the origin of these disease clusters may offer effective prevention or treatment strategies.

"TNF-α is a pro-inflammatory cytokine that triggers various signaling pathways, together with those that inhibit insulin action. In obese mouse models, the absence of TNF-α improves insulin sensitivity and glucose homeostasis, indicating its crucial role in obesity[43,44]. TNF-α is also overexpressed in the adipose and muscle tissues of obese humans, and when administered exogenously, it primes to insulin resistance"[45-48]

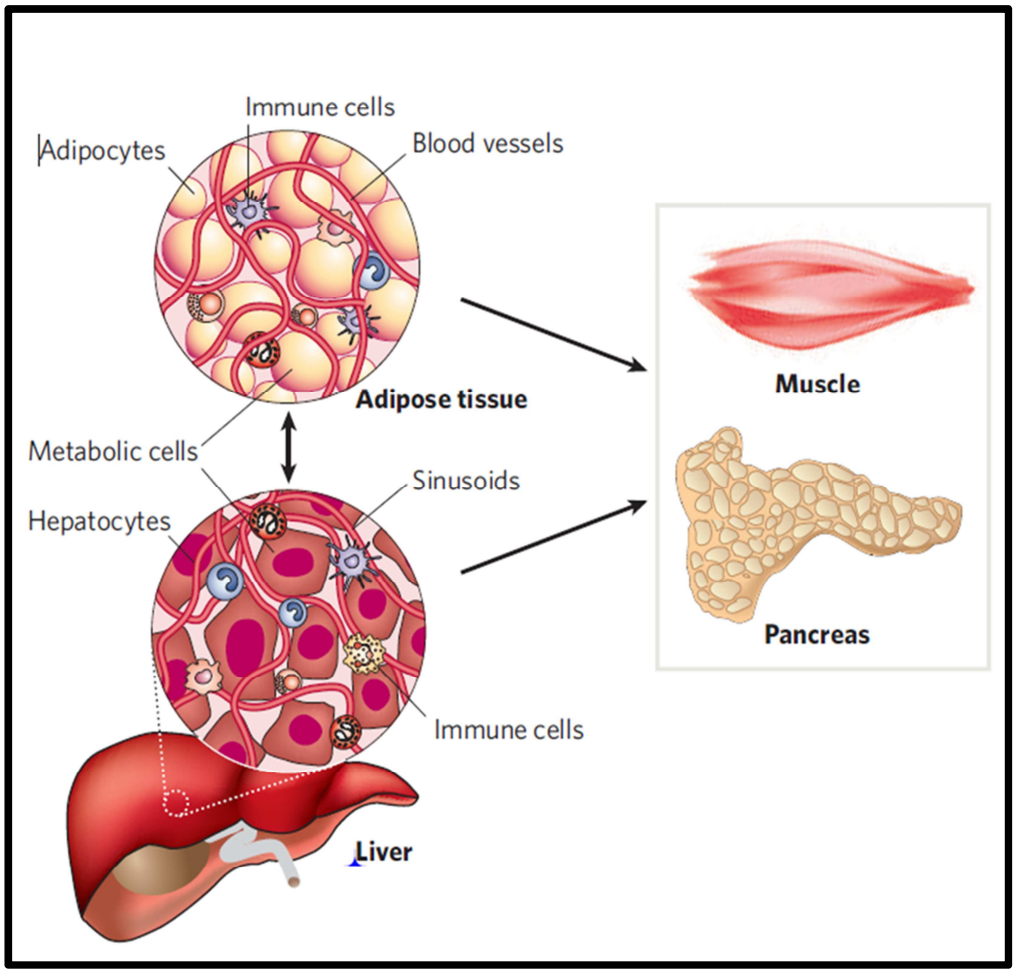

FIGURE III: "Architectural association and juxtaposition of prime metabolic (hepatocyte and adipocyte) and immune (macrophages , Kupffer cells , lymphocytes and dendritic cells) cells in adipose tissue and liver."

Although early studies couldn't definitively establish TNF-α's role in human insulin resistance[49], the extensive use of anti-TNF-α treatments in inflammatory ailments like rheumatoid arthritis has shown clear secondary benefits, auxiliary to the role of TNF-α in systemic insulin sensitivity in humans [50,51].

"Research indicates that, besides TNF-α, many other inflammatory mediators and cytokines are overexpressed in adipose and other tissues in both mouse models of obesity and humans. However, the precise role of each inflammatory mediator remains unclear, even in controlled experimental models.[41]."

Obesity and Inflammation

The inflammatory response associated with obesity primarily originates and persists in adipose tissue, though it can extend to other critical metabolic sites such as the liver[41]. Recent research highlights the unique characteristics of adipocytes and central adipose tissue as pivotal in generating inflammatory responses and mediators. Besides their traditional roles in energy regulation and metabolic homeostasis, adipose tissue is essential for the collaboration between adipocytes and additional immune system effectors**.** (FIGURE-3)

Adipocytes share many similarities with immune cells such as T cells, macrophages, and dendritic cells. These include functions like complement activation, making of inflammatory mediators, pathogen sensing, and phagocytic capabilities [41,42]. Studying the interface between metabolism and inflammation can reveal how cells involved in metabolism or immunity, like adipocytes and macrophages, share response mechanisms.

Adipose tissue illustrates the close functional and structural relationship between metabolic and immune cells (FIGURE-3). This concept also applies to other

vital metabolic organs, especially the liver, which significantly influences the inflammatory processes linked to obesity.

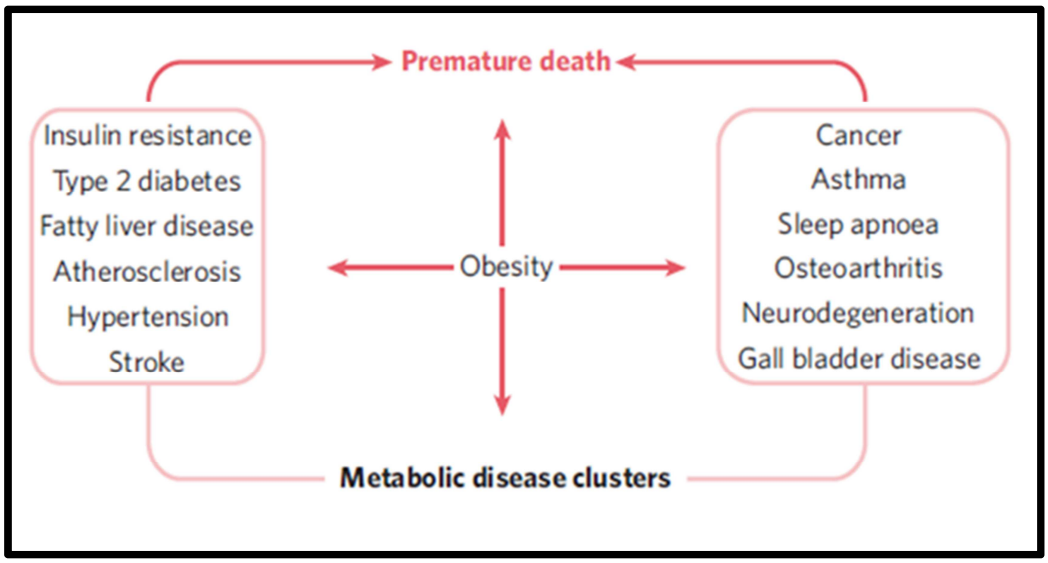

Figure IV: Obesity and Related Disorders

"Obesity is considered to be a vital feature that rises the hazard for a immense collection of ailments, with noteworthy morbidity and mortality. In general, the mechanistic foundation of the relation among obesity and the illnesses listed on the right is poorly understood compared with that of those listed on the left."

Inflammatory signalling and insulin action

Inflammatory signals in obesity interfere with insulin action by disrupting the insulin signalling pathway. Insulin and IGF receptors use insulin receptor substrate (IRS) proteins for signalling. In obesity, insulin usually causes tyrosine phosphorylation of IRS proteins, a step often impaired in insulin resistance. TNF-α disrupts this process by promoting serine phosphorylation of IRS-1, which interferes with insulin signalling.

Kinases such as JNK, IKK, and PKC play a crucial role in phosphorylating IRS-1 at serine residues, thereby impairing its insulin signaling capability and contributing to insulin resistance [52,53,54]. These kinases are activated by stressors like cytokines, free fatty acids, and endoplasmic reticulum stress, which are common in obesity [41,52,55]. JNK activity notably increases in metabolic tissues such as adipose and liver during obesity, leading to insulin resistance. When JNK is inhibited in obese mice, there is a significant improvement in insulin sensitivity and systemic glucose homeostasis [56.57,58].

IKK-β is a vital kinase in the development of insulin resistance. Mice with reduced IKK-β activity show fractional safety against obesity-brought insulin resistance, and inhibiting this kinase enhances insulin action [59,60]. The activity of IKK-β in the liver significantly influences systemic metabolism. Furthermore, myeloid-specific deletion of IKK-β also provides fractional protection contrary to insulin resistance, underscoring its role in systemic metabolic regulation [61,62].

Protein kinase C (PKC) interacts with inflammatory and metabolic pathways, responding to lipid signals and contributing to insulin resistance. Targeting kinases like JNK and IKK-β could improve insulin sensitivity and effectively treat diabetes. [63,64].

DYSLIPIDEMIA

Metabolic syndrome features elevated TG and reduced HDL-C; a condition known as dyslipidemia[65]. Excess liver fat promotes the development and release of very low-density lipoprotein (VLDL) particles, increasing triglycerides, apo B, and small LDL particles in the serum. As blood triglyceride levels rise, more VLDL triglycerides are exchanged for HDL cholesterol esters, altering HDL-cholesterol

levels. Total cholesterol alone may not accurately predict low HDL or high triglycerides[27].

HYPERTRIGLYCERIDEMIA

Increased non-esterified fatty acids (NEFAs) lead to a rise in hepatic lipids, indicating fatty liver[66]. In an insulin-resistant state, higher transport of peripheral free fatty acids to the liver boosts hepatic triglyceride (TG) synthesis, encouraging the formation and release of VLDL containing TG. Typically, insulin suppresses the liver's ability to produce VLDL particles by reducing their assembly and production[67]. When insulin is unable to function properly, serum triglyceride levels increase[68]. Hypertriglyceridemia increases cholesterol ester transfer protein, which converts cholesterol esters into triglyceride-rich lipoproteins.

Clinical importance and uses:

Triglycerides are lipids consisting of a glycerol molecule linked to three fatty acid chains, which can vary in length and composition, being either saturated or unsaturated. These chains, made of carbon and hydrogen atoms, have single or double bonds based on their saturation. The combination of different chains results in a heterogeneous structure.

"Normal findings in adult and elderly individuals are as follows" [66]:

- Male - 40-160 mg/dL or 0.45-1.81 mmol/L (SI units)
- Female - 35-135 mg/dL or 0.40-1.52 mmol/L (SI units)

Values of possible medical urgency[66]

A fasting triglyceride level of over 400 mg/dL may indicate medical urgency.

LOW HDL CHOLESTEROL

Metabolic syndrome often leads to decreased HDL cholesterol levels. Hepatic lipase uses HDL particles as substrates when triglycerides build up on them, causing rapid degradation of HDL[69]. Cholesteryl ester transfer protein mediates this process, and abnormal lipoprotein lipase activity can further reduce HDL cholesterol levels. Innate immunity activation plays a key role in insulin resistance and dyslipidemia in metabolic syndrome. Animal studies show it alters lipoproteins, enzymes, transfer proteins, and receptors, producing more atherogenic particles. Inflammation increases lipase production, lowering HDL's lipid content and speeding up its catabolism.

Atherogenic dyslipidemia is marked by low HDL levels and other symptoms. Low HDL is a strong risk predictor, comparable to high total apo B lipoprotein levels. Researchers believe HDL significantly influences atherogenesis through enhanced reverse cholesterol transport, anti-inflammatory properties, and protection against LDL alteration. HDL levels also indicate other lipid and nonlipid risk factors.

Clinical importance:

High-density lipoprotein cholesterol is crucial for assessing coronary and other vascular pathology risks. Normal HDL-C levels are[69]**:**

- Male: >45 mg/dL or >0.75 mmol/L (SI units)
- Female: >55 mg/dL or >0.91 mmol/L (SI units)

HDL-C levels can increase due to:

- Hyperalphalipoproteinaemia
- Regular physical activity or exercise
- Chronic liver disease
- Weight loss

Conditions Leading to Decreased HDL-C Levels:

- Obesity
- Uncontrolled diabetes mellitus
- Hepatocellular disease
- Cholestasis
- Chronic renal failure
- Metabolic syndrome
- Malnutrition
- Sedentary lifestyle
- Cigarette smoking
- Familial abetalipoproteinemia
- Beta-blocker therapy (short-term effect)

SMALL DENSE LDL PARTICLES

In metabolic disorder, LDL particles tend to be smaller and denser. These small, compact LDL particles are more likely to cause atherosclerosis[70], linking insulin resistance with cardiovascular disease. Hepatic lipase breaks down the triglycerides in LDL particles, reducing their size, and an abundance of triglycerides enhances this process[71].

People with metabolic syndrome often have higher levels of oxidized LDL, which increases the risk of atherothrombotic coronary disease[72]. Smaller LDL particles are more atherogenic[73] and typically indicate a higher number of LDL particles overall[74].

Measuring LDL+VLDL cholesterol (non-HDL cholesterol) or total apoB provides an approximate count of atherogenic particles in the blood. People with metabolic syndrome frequently have raised levels of LDL+VLDL cholesterol and total apoB. Evaluating these parameters and using them as therapeutic objectives should be prioritized for those with metabolic syndrome[75].

Clinical Importance and Uses:

Normal blood test findings for low-density lipoprotein cholesterol (LDL-C) are[72]:

- Adults: < 130 mg/dL
- Children: < 110 mg/dL

LDL-C is a major contributor to the development of atherosclerotic heart disease.

To prevent atherosclerotic plaque formation, LDL levels should be between 50-70 mg/dL. Higher levels increase the peril of coronary artery disease, as highlighted by the Framingham Heart Study, which first showed the link between total cholesterol and coronary artery disease (CAD) [76]

Lipoproteins

Lipoproteins are complexes of proteins in addition to lipids indispensable for transporting lipid-soluble vitamins, lipids, and cholesterol. They feature a hydrophobic core of triglycerides and cholesteryl esters, surrounded by a hydrophilic layer of phospholipids, unesterified cholesterol, and proteins(pH-6.2).

Types and Characteristics of Lipoproteins

Plasma lipoproteins are categorized by their density into five main groups:

- **Chylomicrons**
- **Very low-density lipoproteins (VLDL)**
- **Intermediate-density lipoproteins (IDL)**
- **Low-density lipoproteins (LDL)**
- **High-density lipoproteins (HDL)**

HDL is the smallest and densest lipoprotein, while chylomicrons and VLDL are the largest and least dense.

Apolipoproteins, which bind to lipoproteins, are crucial for their formation, shape, and function. HDL particles include apoprotein A1, produced in the liver and intestines. APO B 48 and APO B 100 can detect VLDL, IDL, and LDL.

RISK FACTORS

GENETICS

Excessive food consumption and physical inactivity have been linked to the evolution of metabolic genes, leading to the emergence of metabolic syndrome, a concept known as the "thrifty genotype theory." Family studies suggest that metabolic syndrome symptoms are highly heritable. However, creating a genetic profile to predict complex diseases like metabolic syndrome or atherosclerosis remains a challenge**.**

Concept of genes predisposing to metabolic syndrome

Severe insulin resistance (IR) results from mutations in PPAR genes, impairing protein function (Savage et al., 20030)[77]. Hypertension and dyslipidemia are also influenced by genetic factors. The calpain 10 gene. (song et al) [78] is crucial for cellular protein modification and breakdown. Variations in the calpain gene affect the onset of type 2 diabetes. Variations in SUR and Kir6.2 genes are hazard factors for type 2 diabetes. Mutations in the HNF1-alpha gene and modifications to the GCK or HNF-4 alpha genes can cause maturity-onset diabetes of the young (MODY) [77].

Table B : Biomarkers of Inflammation [79]

Category	Biomarkers	Biological Effect
Adipokines	Leptin Adiponectin	Insulin sensitivity regulation. Ability to calm inflammation. Glucose intolerance, glucose regulation impairment.
Inflammatory Markers	Interleukin-6, tumour necrosis factor alpha type 2 receptor, and C-reactive protein Interleukin 8	Endothelium dysfunction Thrombosis caused by atherosclerotic, insulin resistance.
Chemokines		Epithelial adhesion to neutrophils
Haemostatic markers	Inhibitor 1 of Plasminogen Activated Protein	The expression of cell adhesion molecules is increased. Resistance to insulin.

OVERWEIGHT / OBESITY

Central adiposity, or increased waist circumference, highlights the strong link between waist size and overall fat accumulation, significantly contributing to the prevalence of metabolic syndrome. Notably, even those who are not overweight can develop insulin resistance and metabolic syndrome.

Sedentary Lifestyle

A sedentary lifestyle increases the risk of cardiovascular disease and mortality. Inactivity is linked to central obesity, low HDL cholesterol, high TG, blood pressure, and blood sugar. People inactive for over four hours daily are twice as likely to develop metabolic syndrome compared to those inactive for less than an hour daily.

NAFLD/ MASLD

For many years, being overweight or obese has been linked to liver issues like hepatic steatosis, hepatocyte injury, inflammation, and fibrosis. In 1980, Jurgen Ludwig recognized this condition as "non-alcoholic steatohepatitis"[80]

Later, the term non-alcoholic fatty liver disease (NAFLD) was introduced to cover the spectrum from steatosis to steatohepatitis, including subtypes NAFL and NASH.

The updated term is now MASLD (Metabolic Associated Steatotic Liver Disease), under the broader category of Steatotic Liver Disease.

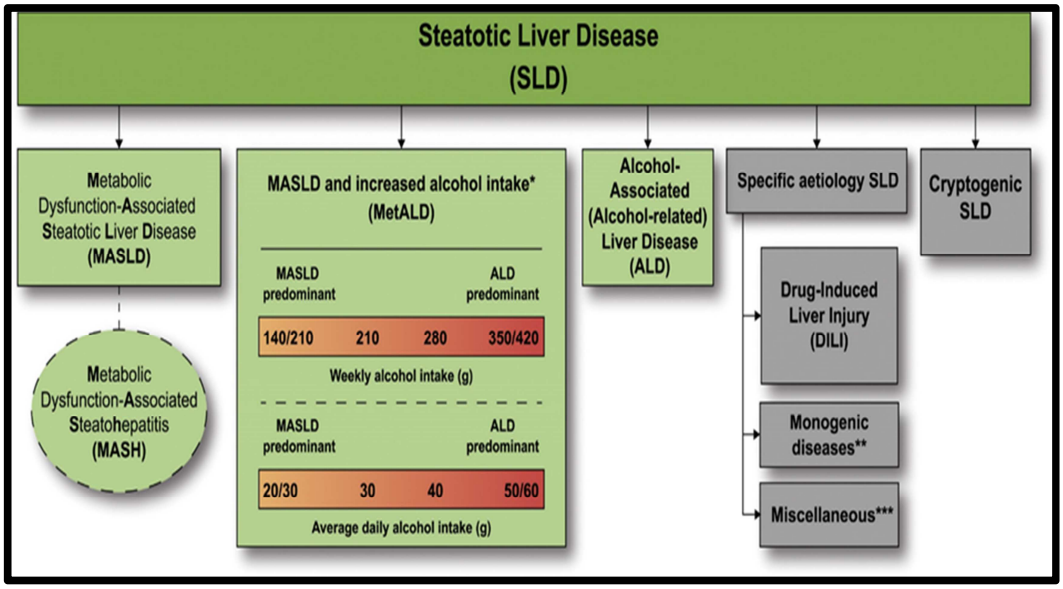

FIGURE V: Spectrum of steatotic Liver Disease

Steatotic liver disease is further classified by

Metabolic dysfunction-associated steatotic liver disease (MASLD) – Patients with MASLD alone have fatty liver (>5 percent hepatic steatosis) and at least one risk factor for cardiometabolic dysfunction, such as dyslipidemia or obesity. They have no other causes of steatotic liver disease and minimal or no alcohol consumption (less than 20 g daily for females and less than 30 g daily for males).

This condition was formerly known as nonalcoholic fatty liver disease (NAFLD).

MASLD with Metabolic Dysfunction-Associated Steatohepatitis (MASH)-Patients with MASH exhibit histologic evidence of inflammation and hepatocellular injury, such as ballooning of hepatocytes, with or without fibrosis.

This condition was previously known as nonalcoholic steatohepatitis (NASH).

MASH Cirrhosis

Patients with MASH cirrhosis have cirrhosis along with current or past histologic evidence of MASH or a history of MASLD.

Metabolic Dysfunction- and Alcohol-Associated Liver Disease (MetALD)

MetALD occurs in patients with liver steatosis, at least one metabolic risk factor, and a history of moderate alcohol consumption (20 to 50 g daily for females, 30 to 60 g daily for males). This condition recognizes that steatotic liver disease can involve both metabolic dysfunction and alcohol. The specified alcohol intake delineates a spectrum between MASLD-predominant and alcohol-predominant disease[82]

Diagnosis of MASLD

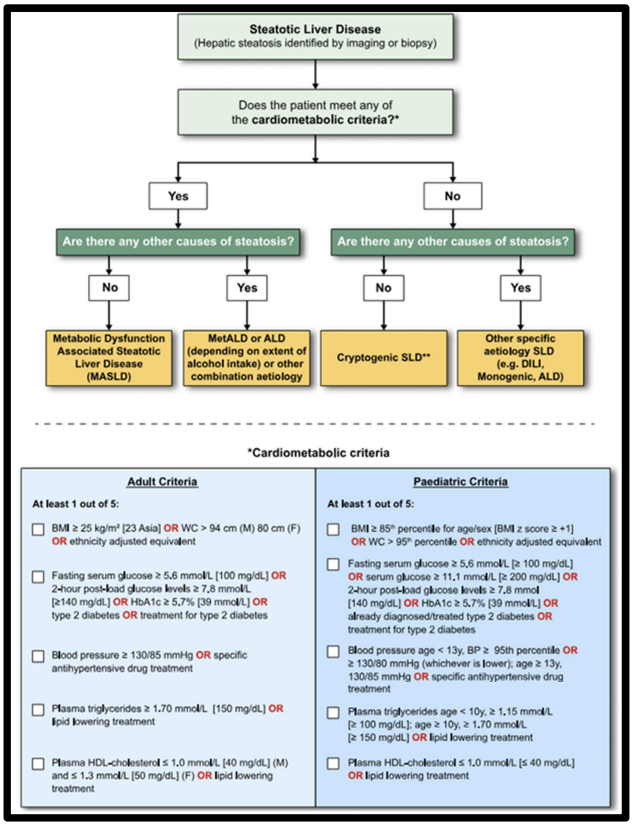

FIGURE VI: MASLD Diagnostic Criteria

MASLD Diagnostic Criteria

"In the presence of hepatic steatosis, the identification of any cardiometabolic risk factors (CMRF) leads to a diagnosis of MASLD, provided there are no other causes of hepatic steatosis. If other drivers of steatosis are found, it suggests a combination etiology. For alcohol-related cases, the condition is termed MetALD or ALD, depending on the extent of alcohol intake."

If there are no overt cardiometabolic criteria, other potential causes must be excluded. If none are found, the condition is termed cryptogenic SLD, although it might also be considered possible MASLD and benefit from periodic reassessment. In cases of advanced fibrosis or cirrhosis, steatosis might be absent, requiring clinical judgment based on CMRFs and the exclusion of other causes.

Metabolic Abnormalities That Persuade MASLD and Epidemiology

Metabolic syndrome features are common in patients with MASLD, and these components also heighten the risk of developing MASLD[83]. Key risk factors include obesity, type 2 diabetes, hypertension, and dyslipidemia (elevated triglycerides and low HDL-C levels)[83].

Obesity is the utmost prevalent and well-recognized risk factor for MASLD.

A meta-analysis was conducted to determine whether central obesity is related with MASLD, altering for general obesity. This investigation, encompassing twenty studies, found significant pooled odds ratios (OR) for waist circumference (WC) and body mass index (BMI) of 2.34 (95% CI, 1.83 to 3.00) and 2.85 (95% CI, 1.60 to 5.08), respectively[84].

Even though MASLD, MASH, and MASH with progressive fibrosis are meticulously linked to type 2 diabetes, their universal occurrence rates have not been well documented. A meta-analysis of 80 studies from 20 nations estimated the prevalence of these conditions in affected people with type 2 diabetes[85]. It found the global prevalence of MASLD to be 55.5% (95% CI, 47.3 to 63.7) and the prevalence of MASH to be 37.3% (95% CI, 24.7 to 50.0) [85].

Evidence increasingly connects MASLD to high blood pressure. A meta-analysis of 11 studies evaluated this association[86].Hypertension significantly increased the risk of developing MASLD (HR, 1.63; 95% CI, 1.41 to 1.88) [86]. Conversely, MASLD significantly increased the incidence of high blood pressure (HR, 1.55; 95% CI, 1.29 to 1.87) [86]. This suggests a bidirectional affiliation amid MASLD and high blood pressure, autonomous of conventional cardiometabolic hazard factors.

Dyslipidaemia, characterized by raised serum triglyceride (TG) levels and low serum high-density lipoprotein cholesterol (HDL-C) levels, is common in patients with MASLD. The prevalence of MASLD in persons with dyslipidemia appearing in lipid clinics is projected to be 50%[87].

Pathogenesis

"Metabolic syndrome and its components—obesity, impaired glucose metabolism, high blood pressure, and dyslipidemia—are closely linked to insulin resistance. The pathogenesis of MASLD remains largely unidentified. Sanyal, A.J. et al. confirmed that peripheral insulin resistance is present in both MASLD and MASH patients using a hyper-insulinemic euglycemic clamp.[88]. Numerous studies have

indicated that defects in the insulin signaling pathway, especially those connected with insulin receptor substrate-2 (IRS-2), play a crucial role in insulin resistance[89]."

"In rat studies, those with MASLD showed insulin resistance, with increased fasting blood glucose and insulin levels, more epididymal fat, significant hepatic steatosis, inflammation, and reduced IRS-2 mRNA and protein levels compared to controls.[90]. Treatment with the insulin sensitizer pioglitazone resulted in noteworthy recovery, including up-regulated IRS-2 mRNA and protein levels[90], suggesting that insulin resistance may significantly contribute to the development of MASLD."

Visceral adipose tissue accumulation increases the production of inflammatory cytokines like TNF-α, IL-6, and IL-1β, while reducing adiponectin production. This imbalance promotes systemic insulin resistance.[91] The metabolism of free fatty acids (FFAs) is changed in insulin resistance[92]. Lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL) are critical enzymes for triglyceride (TG) and fatty acid (FA) metabolism, with LPL hydrolyzing extracellular TG in lipoproteins and HSL hydrolyzing intracellular TG in adipocytes[93].

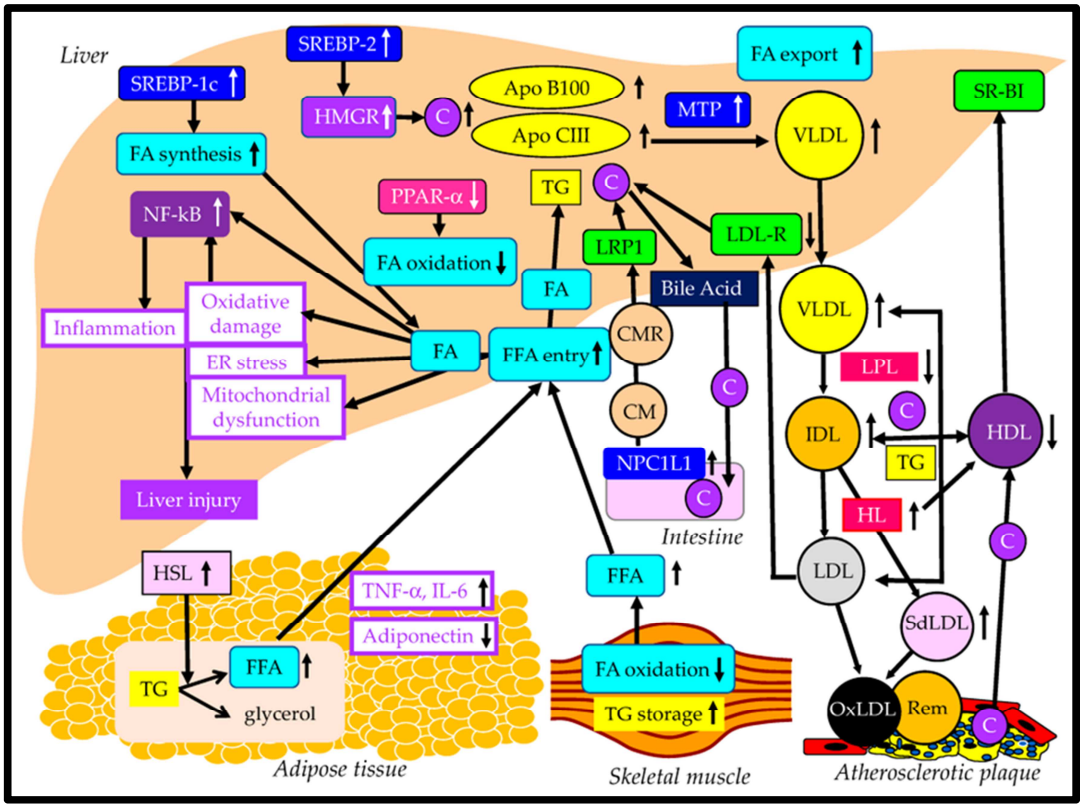

FIGURE VII: Abnormal lipid metabolism

"The abnormal lipid metabolism possibly induced by insulin resistance and its association with the development of MASLD. Black and white arrows pointing upward and downward indicate an increase or decrease in expression or activity, respectively. Solid black lines indicate the flow of substances and the effects of each metabolic event"

Insulin resistance increases the activity of hormone-sensitive lipase (HSL) in adipose tissue, which hydrolyzes triglycerides (TG) into free fatty acids (FFAs) [94]. This causes excess TG storage within skeletal muscle[93] and reduces fatty acid (FA) oxidation, leading to elevated serum FFA levels due to augmented release from adipose tissue and diminished use in muscle. Elevated FFAs entering the liver result in the overproduction of very-low-density lipoprotein (VLDL). Insulin resistance also decreases apo B100 degradation[95], while increasing apo CIII production[96] and

microsomal TG transfer protein (MTP) expression, further enhancing VLDL production.

Sterol regulatory element binding protein 1c expression rises, boosting FA synthesis[97]. Hepatic fatty acid (FA) metabolism involves FA uptake, VLDL secretion, synthesis by SREBP-1c, and β-oxidation. FA accumulation marks metabolic-associated fatty liver disease (MASLD). Insulin resistance increases VLDL1 secretion, causing VLDL1 buildup, LDL peroxidation, and reduced antioxidant status in MASLD.

Animal studies indicate that overproduction of VLDL is associated with hepatic oxidative stress, inflammation, and insulin resistance. Mutations in the MTP gene can lead to progressive MASLD by reducing MTP activity, resulting in triglyceride accumulation, endoplasmic reticulum stress, and inflammation. Conversely, increased MTP expression can protect against MASLD.

Fatty acid (FA) oxidation principally happens in mitochondria, with some oxidation beginning within peroxisomes[97]. In obesity, ω-oxidation by cytochrome P450 enzymes produces large amounts of reactive oxygen species (ROS) [98]. Carnitine palmitoyl-transferase 1 (CPT-1) is essential for fatty acid (FA) entry into mitochondria and is regulated by peroxisome proliferator-activated receptor (PPAR)-α,[(99-102)]. The expression of PPAR-α is negatively correlated with visceral adiposity and insulin resistance[103].

Overexpression of apo CIII leads to MASLD-like features, including augmented liver lipid content, inflammation, and diminished antioxidant capacity[104]. Augmented apo CIII significantly contributes to liver inflammation and cell death. Free fatty acids (FFAs) worsen hepatic insulin resistance by generating lipotoxic

intermediates like diacylglycerols, which cause endoplasmic reticulum stress and reactive oxygen species (ROS) formation—key aspects in metabolic-associated steatohepatitis (MASH) [105,106].

Other lipid species, such as toxic phospholipids[107] and cholesterol, have been implicated in MASH. Insulin resistance activates SREBP-2, increasing cholesterol biosynthesis[108] and leading to inflammation and cell death due to elevated free cholesterol and cholesterol esters[108].

The Association of MASLD with ASCVD

"A retrospective examination of 619 patients diagnosed with MASLD indicated that cardiovascular (CV) events (38.3%), non-liver malignancy (18.7%), and complications of liver cirrhosis (7.8%) were the utmost common sources of death. This highlights that CV events are the utmost critical determining factor of mortality in MASLD patients"[109]. A meta-analysis found that MASLD is significantly linked with an increased risk of developing cardiovascular disease (CVD) (odds ratio (OR), 2.05; 95% confidence interval (95%CI), 1.81 to 2.31; $p < 0.0001$) [110].

Nevertheless, MASH is associated with heightened liver-related mortality (OR for MASH, 5.71; 95%CI, 2.31 to 14.13; OR for MASH with progressive fibrosis, 10.06; 95%CI, 4.35 to 23.25) however not cardiovascular mortality (OR, 0.91; 95%CI, 0.42 to 1.98). Hence, patients with MASLD are considered a hazard cluster for both CVD and the development of MASH.

A large multicenter retrospective study found that the BMIs of individuals with MASLD remained suggestively higher than those without MASLD ($p < 0.01$). The prevalence of MASLD increased linearly with BMI:

- BMI < 23 kg/m²: 10.5%
- BMI ≥ 23 kg/m² and <25 kg/m²: 37.9%
- BMI ≥ 25 kg/m² and <28 kg/m²: 58.4%
- BMI ≥ 28 kg/m²: 84.2%[111]

This suggests a 7.4–11.4% rise in MASLD prevalence per 1 kg/m² increase in BMI. The prevalence of MASLD also displayed a direct upsurge with higher serum triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) levels

Suggested Mechanisms

1. Insulin Resistance and VLDL Generation:

- When insulin resistance occurs, it boosts the production of VLDL while diminishing its breakdown in the bloodstream. This phenomenon stems from insulin resistance's negative impact on enzymes such as lipoprotein lipase (LPL) and hepatic lipase (HL).

2. Lipoprotein Effects:

- Insulin resistance results in reduced levels of HDL and increased levels of small-dense LDL (SdLDL) and remnant lipoproteins, which are highly atherogenic[112].
- Decreased activity of LPL leads to elevated VLDL and intermediate-density lipoprotein (IDL) [113-115] levels, alongside decreased HDL levels.
- Increased activity of HL, associated with insulin resistance, may elevate SdLDL and other atherogenic lipoproteins.

3. HDL Function:

- HDL facilitates reverse cholesterol transport, a process that counteracts atherosclerosis[116]. Diminished HDL levels contribute to atherogenic conditions.
- Lower HDL levels might be partly due to augmented clearance by HL.

4. Characteristics of Small-Dense LDL (SdLDL):

- SdLDL is less effectively recognized by LDL receptors, leading to prolonged circulation in the bloodstream. Its propensity for oxidation and adhesion to endothelial walls promotes atherosclerosis[116].

5. Remnant Lipoprotein Features:

- Remnant lipoproteins, having undergone intravascular modification[117], contain more cholesterol than nascent VLDL[118]. These highly atherogenic particles are readily taken up by macrophages without requiring oxidative alteration[119].

6. Role of LDL Receptor and Insulin:

- Insulin influences the expression and function of LDL receptors. Insulin resistance suppresses LDL receptor activity, resulting in elevated LDL-C levels[120].

7. Niemann-Pick C1-like 1 (NPC1L1) and LDL Receptor-Related Protein 1 (LRP1):

- NPC1L1 is pivotal in intestinal cholesterol absorption, its higher expression correlating with increased chylomicron cholesterol[121].
- LRP1 aids in the clearance of chylomicron remnants from circulation and helps prevent atherosclerosis by removing cholesterol-rich lipoproteins[122].

8. Atherosclerosis Progression:

- Retention and modification of cholesterol-rich, apo B-containing lipoproteins within arterial walls contribute to atherosclerosis development[123].

These condensed points capture the intricate connections among insulin resistance, lipoprotein metabolism, and atherosclerosis.

Therapeutic Approaches for MASLD and Metabolic Syndrome

Enhancing weight loss and ameliorating atherogenic lipoproteins are pivotal for enhancing the prediction of MASLD (Metabolic Associated Steatotic Liver Disease) patients. Consequently, lifestyle adjustments such as dietary modifications and physical activity, alongside surgical procedures aimed at reducing body weight, represent promising therapeutic avenues for MASLD.

Lifestyle Modification

Dietary Adjustments

Achieving weight loss through lifestyle modification stands as a fundamental therapeutic measure for MASLD. Several dietary strategies:

- **Low Carbohydrate Diets**: These diets help reduce body weight and hepatic fat. However, a meta-analysis found no significant difference between low-carb and low-fat diets on liver health in MASLD patients[124].
- **Mediterranean and Hypocaloric Diets**: Eight RCTs have shown that diets rich in unsaturated fats improve liver fat and enzyme levels in MASLD patients.[125]. A meta-analysis showed that calorie-limited diets significantly improve ALT, hepatic steatosis, and liver stiffness. [126]There is a dose-response

correlation where greater calorie restriction leads to more significant improvements in liver function and weight reduction.

- **Intermittent Fasting**: This dietary regimen has garnered attention for its efficacy in weight management and ameliorating cardiovascular and metabolic risks[127]Meta-analyses have shown significant improvements in body weight, BMI, ALT, and AST levels in MASLD patients undergoing intermittent fasting [128].

Physical Activity

Increased physical exertion, irrespective of dietary alterations, markedly diminishes intrahepatic lipid content and enhances ALT and AST levels[129]. Meta-analyses have indicated that exercise alone can reduce visceral, subcutaneous, and intrahepatic fat, while also improving hepatic insulin sensitivity[130].

Combined Diet and Exercise

Combining diet and exercise yields better improvements in MASLD than either alone. A meta-analysis revealed that a ≥5% body weight reduction improves hepatic steatosis, and a ≥7% reduction enhances the NAFLD activity score.[131] The combination of exercise and dietary interventions has been found to lower ALT levels and improve the NAFLD activity score more effectively than either intervention alone[132].

Pharmacological Interventions for MASLD

Anti-MASH Candidate Drugs

Several drugs targeting Peroxisome Proliferator-Activated Receptor (PPAR) subtypes (PPARα/δ/γ) show promise due to their capacity to regulate systemic lipid metabolism and inflammation[133].

Pemafibrate

1. Effects on Liver Function

- Liver Enzymes and Fibrosis: Pemafibrate, acting as a selective PPARα modulator, significantly reduces serum levels of AST, ALT, and GGT while elevating serum albumin. It also diminishes hepatic steatosis and fibrosis indexes[134].

2. Mechanisms of Action

- Pemafibrate improves MASLD by promoting the browning of white adipose tissue[135], thereby enhancing energy expenditure and reducing systemic insulin resistance[136]. It stimuates fatty acid oxidation in muscle and liver, reducing triglyceride storage and VLDL production. [137]. Additionally, its activation of AMPK through increased adiponectin production aids in reducing fatty acid[138] and cholesterol synthesis[139], inflammation[140], and oxidative stress[141].

3. Vasculoprotective Effects

- Pemafibrate lowers triglyceride synthesis[142] and VLDL levels[143] while increasing HDL levels and reducing small-dense LDL and remnant lipoproteins[116]. It facilitates cholesterol efflux from macrophages[144], exhibits anti-inflammatory effects[116], and inhibits vascular smooth muscle cell proliferation, potentially mitigating cardiovascular events in patients with atherogenic dyslipidemia[145].

SGLT2 Inhibitors (SGLT2is)

1. Effects on Liver Function

- SGLT2is notably reduce serum AST and ALT levels[146,147] and improve the FIB-4 index[148]. They also diminish liver stiffness and steatosis as assessed by transient elastography and other non-invasive methods[149-151].

2. Mechanisms of Action

- SGLT2is decrease plasma glucose levels by attenuating renal glucose reabsorption[152], resulting in weight reduction and improved coronary risk factors[153]. They enhance fatty acid oxidation, reduce hepatic fat, and decrease inflammation and oxidative stress. SGLT2is also improve insulin resistance and lipid metabolism by increasing the glucagon-to-insulin ratio and activating hormone-sensitive lipase.

3. Vasculoprotective Effects

- SGLT2is decrease HbA1c, body weight, and systolic blood pressure[154], and elevate HDL-C while reducing TG levels[155,156]. They enhance endothelial function[157], diminish oxidative stress and inflammation, and notably lower major adverse cardiovascular events in individuals with type 2 diabetes[158]

GLP-1RAs in MASLD Treatment

1. Effects of GLP-1RAs on Liver Enzymes, Hepatic Steatosis, and Fibrosis

- After 12 months of dulaglutide therapy, there's a significant improvement in serum GGT levels and NAFLD activity score among type 2 diabetes patients[159].

- Meta-analyses reveal that GLP-1RAs enhance liver enzymes[160], liver histology scores for steatosis and fibrosis[161], and decrease liver fat content measured by MRI[162].

2. Mechanisms for MASLD Treatment Using GLP-1RAs

- GLP-1RAs boost pancreatic insulin release while reducing glucagon, delaying gastric emptying, and suppressing postprandial hyperglycemia and appetite, thereby leading to reduced energy intake and body weight[(163-165)].
- GLP-1 acts as a satiation signal primarily through vagal afferents[166].
- Higher insulin and lower glucagon levels decrease hormone-sensitive lipase activity, reducing triglyceride breakdown and fatty acid release, which lowers fatty acid influx into the liver.
- GLP-1RAs reduce inflammation and oxidative stress, as shown by lower CRP and TNF-α levels and higher adiponectin. This activates AMPK, improving MASLD symptoms. [167].

3. Vasculoprotective Effects of GLP-1RAs

- GLP-1RAs decrease systolic blood pressure, body weight, and hemoglobin A1c levels[168].
- -They ameliorate atherogenic postprandial hyperlipidemia[169] and enhance endothelial function[170], providing cardioprotective benefits.
- -Meta-analyses suggest that GLP-1RA therapy significantly reduces the risk of major adverse cardiovascular events , extended MACEs, all-cause mortality, and cardiovascular mortality[171].

4. Comparison of SGLT2is and GLP-1RAs for MASLD

- Reviews and analyses indicate that semaglutide, liraglutide, and dapagliflozin are effective treatments for MASLD, with semaglutide exhibiting a therapeutic edge[172].
- GLP-1RAs notably reduce visceral fat and triglyceride levels compared to SGLT2is[173].
- -While PPAR agonists and GLP-1RAs enhance histological aspects of MASH, SGLT2is reduce liver fat content[174].

5. Combination Therapy Using SGLT2is and GLP-1RAs

- Administration of dulaglutide alongside SGLT2is for 12 months significantly improves serum GGT levels and NAFLD activity scores[175] and a potential decline in the FIB-4 index.

Combination Therapy of SGLT2is and Pemafibrate

- Pemafibrate alone reduces AST, ALT, and GGT levels while increasing albumin in hypertriglyceridemia patients.
- The combined therapy of pemafibrate and SGLT2is holds promise in improving AST levels and the AST/ALT ratio, indicating potential benefits for advanced liver fibrosis.

Conclusion

- Effective management of MASLD involves a comprehensive approach encompassing lifestyle modifications, pharmacological interventions, and surgical procedures.

- Foundational strategies such as diet and exercise are crucial, while bariatric surgery and intragastric balloons offer significant benefits for patients requiring more intensive interventions.
- Combining these approaches can lead to substantial improvements in liver health and overall prognosis for MASLD patients.

Linking MASLD and ASCVD

The etiopathogenesis, risk factors, and diagnostic criteria for MASLD, ASCVD, and Metabolic syndrome exhibit significant similarities, intertwining as a complex network where one disease can exacerbate another. Notably, cardiovascular disease (CVD) emerges as the primary cause of mortality in patients with NASH, particularly those without advanced cirrhosis. Conversely, significant hepatic-related morbidity and mortality are closely associated with NASH-cirrhosis.

"In a meta-analysis by Mantovani et al., encompassing 5,802,226 adults from 36 longitudinal studies with a median follow-up of 6.5 years, NAFLD was linked with a moderately elevated risk of fatal or non-fatal CVD events. Notably, this risk significantly escalated with the severity of NAFLD, particularly in relation to fibrosis stage, irrespective of confounding metabolic factors.[180]"

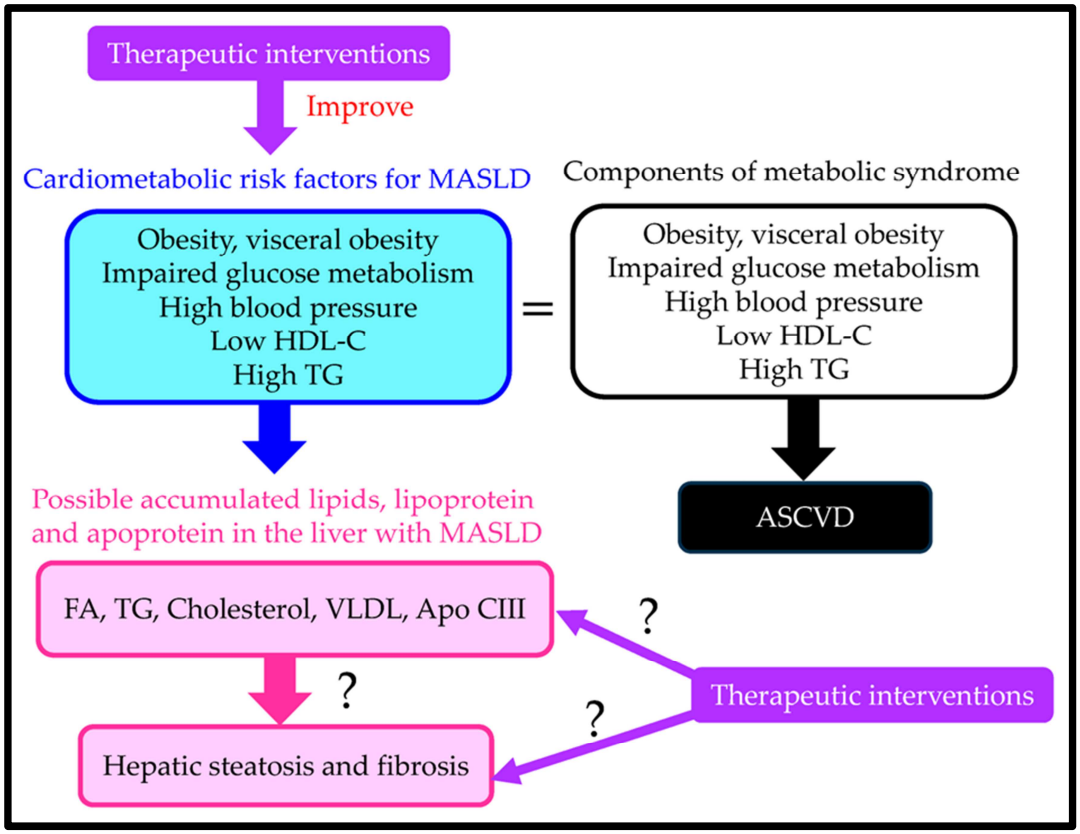

FIGURE VIII: Linking ASCVD with Metabolic Syndrome

Hence, therapeutic approaches targeting equally liver fibrosis and ASCVD are imperative intended for effectively treating MASLD. Interferences that ameliorate cardiometabolic hazard factors may confer benefits for improving MASLD outcomes. However, the precise effects of such therapeutic measures on lipid, lipoprotein, and apoprotein buildup in the liver, as well as hepatic steatosis and fibrosis, require further elucidation. Additionally, the specific lipid factor vital for MASLD development remains principally unidentified, warranting future research in this area.

A study by Alkhouri et al. found that lipid ratios increase progressively from patients with normal biopsies to those with simple steatosis and then to those with NASH. This rise in lipid ratios positively correlates with the NAFLD activity score (NAS) and its individual histological features[181]. The study highlights the link

between the severity of liver injury and inflammation with increased cardiovascular risk and an atherogenic lipid profile. These findings suggest that liver inflammation may contribute to the development of atherosclerosis, emphasizing the connection between different histologic subtypes.

Role of Fibrosis and Markers

Progressive liver fibrosis stands as the primary cause of organ failure in chronic liver diseases, including MASLD. Advanced fibrosis can culminate in cirrhosis, leading to liver failure, portal hypertension, and hepatocellular carcinoma.

Fibrosis manifests diverse spatial patterns and arises from various prevalent mechanisms based on underlying causes of parenchymal damage.

Early detection of fibrosis is crucial for initiating anti-fibrotic therapies capable of halting or reversing this process.

Notably, fibrosis serves as a robust predictor of liver-related outcomes and cardiovascular disease in patients with NAFLD.

However, detecting liver fibrosis poses challenges, as affected individuals often lack specific clinical manifestations or laboratory findings. Liver biopsy, the gold standard for confirming fibrosis stage, is invasive and costly, with potential complications. Hence, there is a pressing need for reliable, non-invasive diagnostic methods to identify fibrosis in patients with MASLD.

Several noninvasive scoring systems, including the fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), and AST/platelet ratio index (APRI), have been developed to stratify fibrosis stage.

Origin of APRI

Originating from a study by Wai et al. in 2003, the APRI was devised based on platelet count, AST level, and ALP level as independent predictors of significant fibrosis and cirrhosis in treatment-naïve chronic Hepatitis C patients[182]. The APRI demonstrates simplicity and comparable accuracy in predicting fibrosis and cirrhosis, offering a valuable tool for non-invasive fibrosis assessment in patients with MASLD.

The aspartate aminotransferase to platelet ratio index (APRI) is a diagnostic tool designed to assess liver fibrosis and cirrhosis, particularly useful in regions with limited access to advanced medical resources. It utilizes the inverse relationship between the stage of liver fibrosis and the levels of AST (aspartate aminotransferase) and platelet count.

APRI Formula

The APRI is calculated with the following formula:

$$\text{APRI} = \frac{\text{AST level (/ULN)}}{\text{Platelet counts } (10^9/\text{L})} \times 100$$

FIGURE IX : APRI FORMULA

Studies and Performance

1. Meta-Analysis by Lin et al. (2011)[183]

- **Context**: Examined APRI's effectiveness in predicting fibrosis in HCV-infected patients.
- **Results**: Demonstrated moderate diagnostic utility. Although less accurate than some other noninvasive methods, it remains the preferred choice in resource-limited areas.

2. Study by Khan DA, Fatima-Tuz-Zuhra et al.[184]

- **Sample**: 120 patients.
- **Fibrosis Breakdown**:
    - No fibrosis (F0): 8.3%
    - Portal fibrosis (F1): 38%
    - Septal fibrosis (F2): 28%
    - Bridging fibrosis (F3): 18%
    - Cirrhosis (F4): 8%
- **Findings**:
    - Significant fibrosis (AUC = 0.82) at cut-offs of 0.5 and 1.5:
        - NPV: 78%
        - PPV: 72%
        - Sensitivity: 66%
        - Specificity: 83%
    - Advanced fibrosis (AUC = 0.87) at cut-offs of 0.90 and 1.75:
        - NPV: 95% (at 0.90)
        - PPV: 78% (at 1.75)
    - Correctly identified significant fibrosis in 48% of cases and advanced fibrosis in 66%.

3. Study by Jain P, Tripathi BK et al.[185]

- **Sample**: 51 patients (17.64% Hepatitis B, 13.72% Hepatitis C, 49.01% chronic alcoholics).
- **Findings**:
    - Accurately classified 96.1% of cirrhosis cases.
    - AUC: 0.973 at a cut-off of 0.65.
    - NPV and PPV: 96% and 96.1%.
    - Sensitivity and Specificity: 96% and 96.1%.

4. Study by Johannessen, A., Stockdale, A.J., Henrion, M.Y.R. et al.[186]

- **Context**: Assessed non-invasive fibrosis markers for chronic hepatitis B in Africa.
- **Findings**:
    - Using transient elastography as a reference:
        - WHO-recommended cirrhosis threshold (>2.0): Sensitivity: 16.5%.
        - Optimized thresholds:
        - Rule-in (>0.65): Sensitivity: 56.2%, Specificity: 90%.
        - Rule-out (<0.36): Sensitivity: 80.6%, Specificity: 64.3%.
    - Conclusion: The WHO threshold is too high for sub-Saharan Africa; suggested improved thresholds for better diagnostic accuracy.

Conclusion

APRI is a simple and cost-effective tool for assessing liver fibrosis and cirrhosis, especially beneficial in areas with limited healthcare resources. Although not as precise as some other non-invasive methods, its simplicity and accessibility make it a valuable diagnostic tool. The studies reviewed indicate its moderate to high accuracy and suggest potential improvements in threshold values to enhance its effectiveness in different populations.

Comparision with Other Non invasive Markers

A meta-analysis revealed that the accuracy of serological biomarkers varies based on the level of liver fibrosis. "For any level of fibrosis, all models demonstrated reasonable precision. For substantial fibrosis, the FibroMeter, FibroTest, and NFS replicas showed high accuracy, whereas APRI, FIB-4, and the BARD score displayed moderate meticulousness. When assessing advanced fibrosis, the ELF, FibroMeter, FIB-4, and NFS models exhibited high accuracy, while the BARD score, FibroTest, and APRI indicated moderate accuracy. In the case of cirrhosis, only FIB-4 showed high meticulousness, while APRI and NFS had moderate diagnostic accuracy.[187]"

The APRI consistently showed reasonable diagnostic precision for all degrees of liver fibrosis severity, from early stages to cirrhosis. This finding aligns with prior meta-analyses indicating moderate accuracy for APRI in evaluating advanced fibrosis. However, some studies have stated discrepancies in its effectiveness for anticipating liver fibrosis. "Due to these conflicting results, the MASLD practice guidelines from the AASLD, American College of Gastroenterology, and American Gastroenterological Association recommend using the FIB-4 or NFS score to find patients with MASLD at stage 3 or 4 fibrosis.[188]"

Cardiac Risk Scores

ASCVD Score

The ASCVD Risk Score is an essential tool intended for evaluating the 10-year risk of atherosclerotic cardiovascular events, such as myocardial infarction or stroke, in individuals without prior cardiovascular disease[189].

Developed from extensive longitudinal studies like the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) Study, the algorithm incorporates traditional cardiovascular risk factors, including:

1. Age
2. Sex
3. Race
4. Total cholesterol
5. HDL cholesterol
6. Blood pressure
7. Diabetes status
8. Smoking status

The ASCVD Risk Score is integrated into various clinical guidelines, such as those from the American College of Cardiology (ACC) and the American Heart Association (AHA), which recommend its use in adults aged 40 to 75 years for primary prevention strategies.

The score aids clinicians in decision-making regarding the initiation of statin therapy, lifestyle modifications, and other interventions aimed at reducing

cardiovascular risk. It also enhances patient-clinician communication, facilitating discussions about risk factors and preventive measures.[190]

Despite its widespread use, the ASCVD Risk Score has limitations. Critics argue that it may overestimate risk in certain populations, such as those with a lower baseline risk. Additionally, the reliance on traditional risk factors may not account for emerging biomarkers and genetic factors contributing to cardiovascular risk. Further research is necessary to refine the score and incorporate these novel risk predictors.

Framingham Risk Score

The Framingham Risk Score (FRS) is a widely used tool intended to predict the 10-year risk of developing coronary heart disease. It originates from the extensive Framingham Heart Study, which began in 1948.[191] The FRS calculates an individual's risk profile based on several cardiovascular risk factors:

- Age
- Sex
- Blood pressure
- Total cholesterol
- HDL cholesterol
- Smoking status
- Diabetes status

Developed by analyzing data from this cohort, the FRS is recommended by guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) for assessing cardiovascular risk in adults. The score helps determine the need for interventions such as lifestyle changes, medication, and ongoing risk factor monitoring.

However, the FRS has limitations[192]. It was initially calibrated primarily for smokers and focused on a predominantly white population, which limits its generalizability to other groups.

Connecting ASCVD, FRS, and APRI

In a study by Stefano Ballestri and Alessandro Mantovani on liver fibrosis in non-alcoholic fatty liver disease (NAFLD) patients, they explored the non-invasive evaluation of liver fibrosis and its correlation with cardiovascular disease and mortality, they found APRI to be a reliable marker to rule out liver Fibrosis , indicate that combining APRI with other non-invasive tests can improve diagnostic accuracy and provide better stratification of cardiovascular risk in NAFLD patients and found good connection between APRI and cardiovascular risk besides suggested that the integration of APRI with other non-invasive techniques enhances the overall prediction of cardiovascular risk and mortality, aiding in better clinical decision-making for NAFLD patients[194].

In research conducted by Özgür Sert A. et al., it was found that there is a notable correlation between the Aspartate Aminotransferase to Platelet Ratio Index (APRI) and carotid intima-media thickness (IMT) in obese adolescents diagnosed with Non-Alcoholic Fatty Liver Disease (NAFLD). The study indicated that a higher APRI score in these adolescents might be indicative of a heightened cardiovascular risk profile[194].

A meta-analysis by Yi et al reviewed nine studies including 155,382 NAFLD patients. It found that higher APRI scores are allied with an amplified risk of cardiovascular illness in unadjusted models. However, the adjusted models showed the association was significant for the NAFLD fibrosis score but not for APRI .[195]

In a study by carlos de mattias et al, in mixed group of individuals with and without metabolic syndrome (MetS), the Aspartate Aminotransferase to Platelet Ratio Index (APRI) shows a significant correlation with cardiovascular risk (CVR). When the APRI is greater than 0.5, there is a marked increase in CVR for both men and women, with a particularly notable rise in females. This increase in CVR is pronounced in older patients but is significantly higher among younger and premenopausal women, reaching risk levels typically seen in men.[196] Elevated APRI in MetS patients is associated with the highest CVR levels, underscoring the importance of liver fibrosis as a critical predictor of cardiovascular disease in individuals with both conditions. Overall, our findings emphasize the utility of APRI as a straightforward and reliable score for predicting CVR in metabolic patients. [196]

Finney et al. (2023) provide a detailed examination of the relationship between NAFLD and atherosclerotic cardiovascular disease (ASCVD) and the biomarkers of NAFLD, highlighting the pathophysiological mechanisms that link these two conditions. According to their research, NAFLD is not only a marker of metabolic risk but also an active contributor to the development and progression of ASCVD. The article underscores that inflammation, insulin resistance, and lipid abnormalities are central to the pathogenesis of both NAFLD and ASCVD, creating a vicious cycle that exacerbates cardiovascular risk.[197]

The above study also identifies the need for further research, as despite substantial evidence indicating a link between hepatic biomarkers and cardiovascular disease (CVD), further research is necessary, as some studies do not demonstrate a significant connection. If this relationship remains strong and consistently reproducible, non-alcoholic fatty liver disease (NAFLD) and its biomarkers could play an important role in imminent cardiovascular risk prediction. They might serve

as risk-enhancing factors or be integrated into new cardiovascular risk prediction models.

Our study, aims to explore this lacunae and study the link between non-invasive liver fibrosis scores, and Cardiovascular risk and patients with metabolic syndrome.

MATERIALS AND METHODS

Study Design: A cross sectional study in a tertiary care Hospital

Source of Data: Inpatient and out patient department at KLE Prabhakar Kore charitable hospital will be the source.

Study Period: 1 year from January 2023 to December 2023

Sample Size: sample size at 95% confidence interval 20% allowable error and 10% attrition

$n= (Z_{1-\alpha/2} + Z_{1-\beta/2})^2 (SD1^2+ SD2^2) / (\underline{x}_1- \underline{x2})^2$

$n = (1.96+0.85)^2 \times (0.60^2 + 0.43^2) / (32.38-32.02)^2$

n= 33.2

n= 33

minimum required sample size = 33 x 2 = 64

Sampling technique: Written informed consent will be taken from all the participants at the time of admission.

1.1 Inclusion Criteria: International Diabetes Federation(IDF) DEFINITION:

(IDF) established the following criteria to define the MetS: i.e.

- Waist circumference (WC) > 90 cm* in males or > 80 cm* in females
- Systolic Arterial Pressure (SAP) ≥ 130 mmHg or diastolic blood pressure ≥ 85 mm Hg or on drug treatment for hypertension)

- Fasting plasma glucose (FPG) ≥ 100 mg/dL (or drug treatment for elevated glucose)
- Triglycerides (TG) ≥ 150 mg/dL (or drug treatment for elevated triglycerides); high density lipoprotein (HDL) concentration < 40 mg/dL in males or < 50 mg/dL in females (or drug treatment for dyslipidemia).

Increased values of WC and the contemporary presence of two or more other criteria leads, according to the aforementioned definition, to the diagnosis of MetS.

*IDF values for Indian Asians.

Exclusion Criteria:

- Chronic alcoholic
- Cardio vascular diseases (k/c/o heart failure, k/c/o coronary arterial disease, k/c/o acute arrhythmias)
- k/c/o Liver diseases
- Diagnosed Secondary hypertension
- h/o chronic systemic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis**)**
- h/o neoplastic diseases with recent onset (less than 10 years) and/or under chemotherapy including failure.

Ethical consideration

The study received approval from the institutional human ethics committee. Informed written consent was obtained from all participants, and only those who signed the consent form were included in the study.

Study protocol:

Cases at KLE Dr.Prabhakar Kore charitable hospital and medical research center, Belagavi will be screened and those who fulfill the inclusion and exclusion criteria will be recruited for the study with the approval of the ethical committee written informed consent will be taken from all the participants enrolled for the study their data collected and AST to Platelet ratio index will be calculated by further ASCVD and Framingham risk score calculator will be used to stratify CVR.

$$APRI = \frac{\frac{AST\ level}{AST\ upper\ limit\ of\ normal}}{Platelet\ count\ in\ (10^9\ per\ litre)}$$

Figure X : FRS calculator

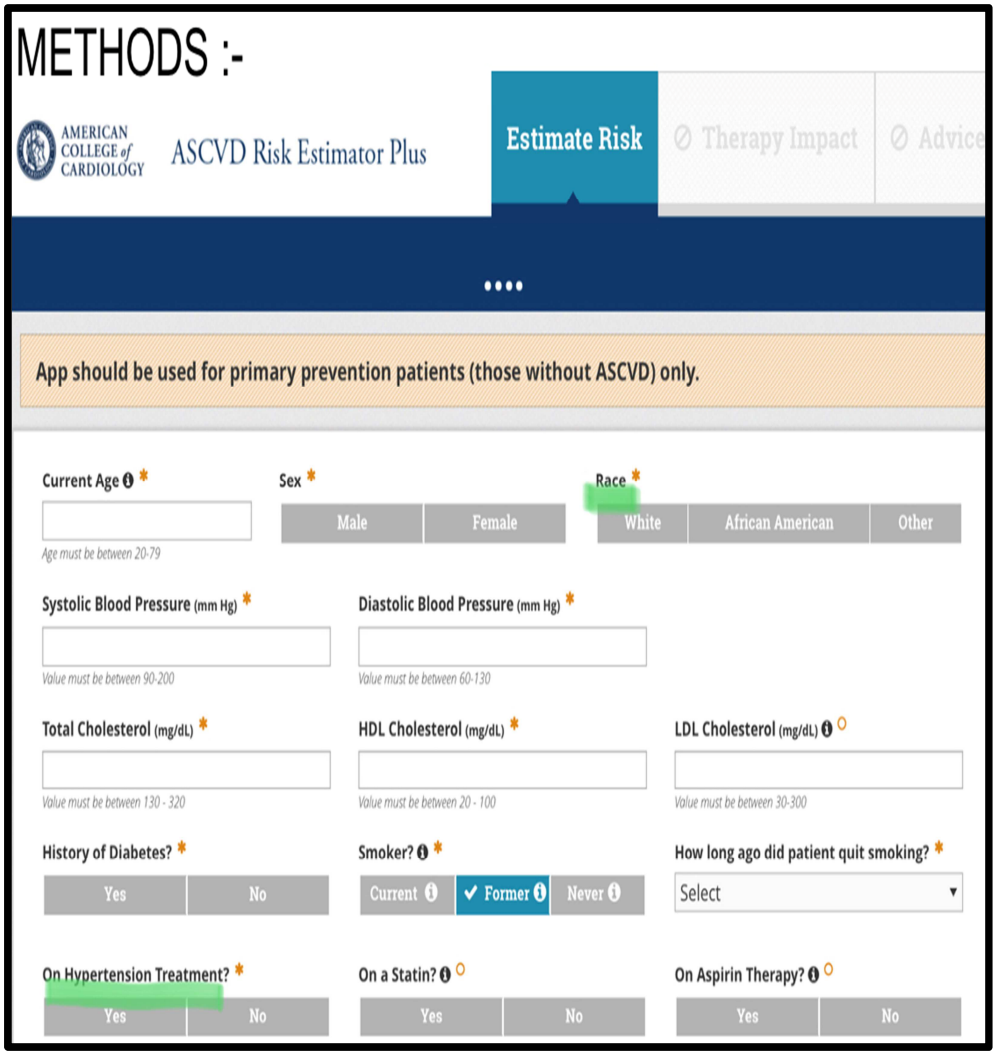

Figure XI : ASCVD calculator

Data collection procedure: ***one year cross sectional study an informed consent will be obtained from the patients

*in-patient and out-patient individuals with metabolic syndrome will be identified.

Detailed history and examination would be done.

History including = age, sex, h/o smoking, h/o diabetes, h/o hypertension treatment, on treatment with drugs like statin or aspirin?

Examination including = systolic and diastolic blood pressure

Anthropometrical measurements of the patients including

Waist circumference (a tape measure just above the hipbones)

Height

Weight

Bmi

Calf circumference

Will be taken

Investigations

CBC

MR

LFT

HBA1C

LIPID PROFILE

FBS

PPBS

Calculation of cardiovascular risk by ASCVD and FRS

Statistical analysis: Data is analyzed using statistical software R version 4.4.0. and Microsoft Excel. Categorical variables given in the form of frequency tables. Continuous variables given in Mean ± SD / Median (Min, Max) form. Chi square test is used to check the association of categorical variables with groups. Normality of

variable is checked by Shapiro Wilk test and QQ plot. If data follows normal distribution, parametric tests will be used. Otherwise, non-parametric tests will be used. Two sample t test is used to compare the means of variables over groups. Mann Whitney U test is used to compare the distribution of variables over groups. Spearman's rank correlation test is used to check the correlation of variables. Kruskal Wallis test is used to compare the distribution of APRI values over cardiovascular risk by using Framingham Risk Score and ASCVD. Dunn test is used as post hoc analysis. P-value less than or equal to 0.05 indicates statistical significance.

RESULTS

Data contains measurements on 68 subjects. The following table gives the distribution of subjects according to Metabolic syndrome.

Table 1: Distribution of subjects according to Metabolic syndrome.

Metabolic syndrome	Number of subjects (%)
No	34 (50%)
Yes	34 (50%)

Out of the total subjects, 34 (50%) subjects were identified as having Metabolic syndrome, while the remaining 34 (50%) subjects did not exhibit Metabolic syndrome.

Table 2: Comparison of demographic variables between Metabolic syndrome and Non metabolic syndrome Patients

Variables	Sub Category	Metabolic syndrome		Total	p-value
		No	Yes		
Age	<50	9 (26.47%)	4 (11.76%)	13 (19.12%)	0.4501[C]
	50-59	10 (29.41%)	14 (41.18%)	24 (35.29%)	
	60-69	9 (26.47%)	10 (29.41%)	19 (27.94%)	
	≥70	6 (17.65%)	6 (17.65%)	12 (17.65%)	
	Mean ± SD Median (Min, Max)	56.97 ± 8.65 56 (40, 70)	58.62 ± 9.31 59 (36, 76)	57.79 ± 8.96 58.5 (36, 76)	0.4527[t]
Race	Indian	34 (100%)	34 (100%)	68 (100%)	1[C]
Sex	Female	15 (44.12%)	13 (38.24%)	28 (41.18%)	0.6222[C]
	Male	19 (55.88%)	21 (61.76%)	40 (58.82%)	

Abbreviation: C – Chi square test, t – Two sample t test.

In terms of age distribution, the majority of subjects are aged between 50 and 59, with 41.18% of Metabolic Syndrome cases in this range, compared to 29.41% without it. The mean ages are similar, 56.97 ± 8.65 years for those without Metabolic Syndrome and 58.62 ± 9.31 years for those with it. From Chi square test and two sample t test, it is observed that there is no significant difference in age over Metabolic Syndrome.

All subjects are of Indian race, making race comparison irrelevant (p-value = 1).

Among the subjects with Metabolic Syndrome, 38.24% were females, while 44.12% of those without Metabolic Syndrome were females. From Chi Square test, it is observed that there is no significant difference in sex distribution between the groups.

Table 3: Comparison of Medical history of Metabolic syndrome and Non metabolic syndrome Patients

Variables	Sub Category	Metabolic syndrome		Total	p-value
		No	Yes		
Diabetes	Absent	34 (100%)	3 (8.82%)	37 (54.41%)	**< 0.001^{C*}**
	Present	0	31 (91.18%)	31 (45.59%)	
Hypertension	Absent	34 (100%)	19 (55.88%)	53 (77.94%)	**< 0.001^{C*}**
	Present	0	15 (44.12%)	15 (22.06%)	
Hypothyroidism	Absent	34 (100%)	32 (94.12%)	66 (97.06%)	0.5052^{MC}
	Present	0	2 (5.88%)	2 (2.94%)	
BPH	Absent	34 (100%)	33 (97.06%)	67 (98.53%)	0.9999^{MC}
	Present	0	1 (2.94%)	1 (1.47%)	
On OHA/ Insulin	No	34 (100%)	3 (8.82%)	37 (54.41%)	**< 0.001^{C*}**
	Yes	0	31 (91.18%)	31 (45.59%)	
On Antihypertensives	No	34 (100%)	21 (61.76%)	46 (67.65%)	**< 0.001^{C*}**
	Yes	0	13 (38.24%)	22 (32.35%)	
On Statin	No	34 (100%)	28 (82.35%)	62 (91.18%)	**0.0295^{MC*}**
	Yes	0	6 (17.65%)	6 (8.82%)	
On Aspirin	No	34 (100%)	29 (85.29%)	63 (92.65%)	0.0550^{MC}
	Yes	0	5 (14.71%)	5 (7.35%)	
Smoker	No	32 (94.12%)	28 (82.35%)	60 (88.24%)	0.2769^{MC}
	Yes	2 (5.88%)	6 (17.65%)	8 (11.76%)	
Alcoholic	No	34 (100%)	33 (97.06%)	67 (98.53%)	0.9999^{MC}
	Yes	0	1 (2.94%)	1 (1.47%)	

*Abbreviation: C – Chi square test, MC – Chi square test with Monte Carlo simulation, * indicates statistical significance.*

Among subjects with Metabolic Syndrome, 91.18% have diabetes, compared to 0% in non-Metabolic Syndrome group (p-value < 0.001). Additionally, 44.12% had hypertension compared to 0% in non-Metabolic Syndrome group (p-value < 0.001). The use of antihypertensive is higher among those with Metabolic Syndrome (38.24%) compared to those without (0%) (p-value < 0.001). The use of statins is also significantly higher in subjects with Metabolic Syndrome (17.65%) versus those without 0% (p-value = 0.0295)

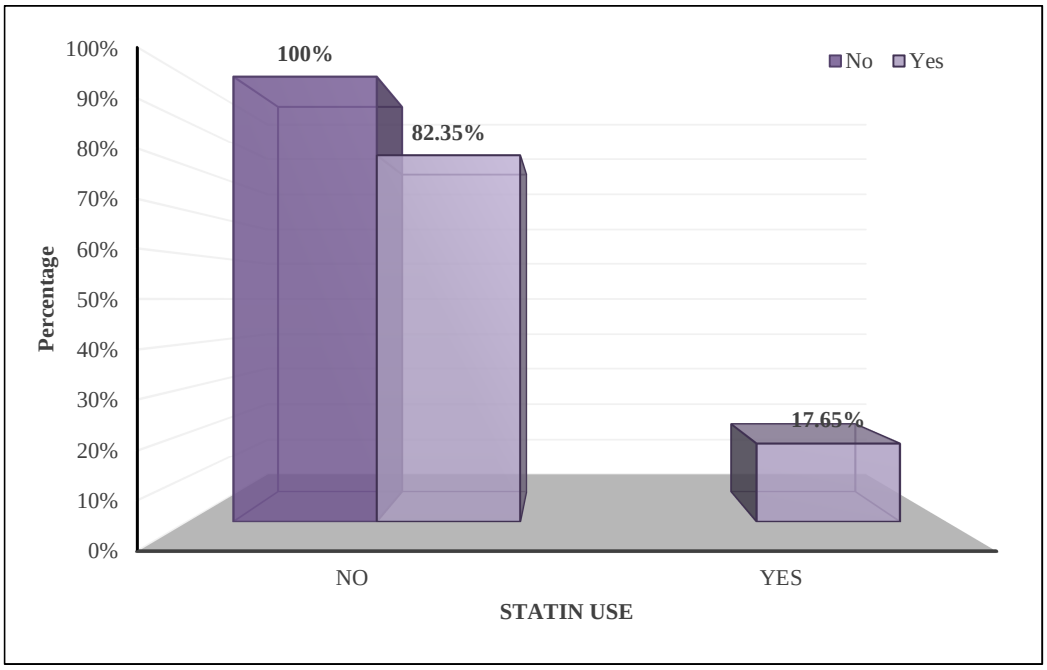

FIGURE 1: Distribution of statin use over metabolic syndrome.

Table 4: Comparison of Anthropometric Measurements of Metabolic syndrome and Non Metabolic syndrome Patients

Variables	Metabolic syndrome		Total	p-value
	No	Yes		
Hip circumference (cm)	81.36 ± 5.32 82 (72, 90)	95.9 ± 15.93 91.5 (81, 152)	88.63 ± 13.88 86.5 (72, 152)	**< 0.001^{MW}***
Height (cm)	167.5 ± 8.07 168 (152, 186)	163.28 ± 10.4 165 (132, 186)	165.39 ± 9.48 166 (132, 186)	0.0657^{t}
Weight (Kg)	67.35 ± 8.08 66 (55, 85)	77.06 ± 13.56 75 (56, 110)	72.21 ± 12.11 70 (55, 110)	**0.0022^{MW}***
BMI Kg/m2	23.27 ± 1.35 23.64 (20.2, 25.95)	28.88 ± 4.15 27.7 (21.1, 39.44)	26.07 ± 4.17 24.94 (20.2, 39.44)	**< 0.001^{MW}***

*Abbreviation: MW – Mann Whitney U test, t -Two sample t test, * indicates statistical significance.*

Individuals with Metabolic Syndrome have a significantly larger hip circumference (p-value < 0.001), higher weight (p-value =0.0022), and higher body mass index (BMI) (p-value < 0.001) compared to those without the syndrome.

Table 5: Comparison of Blood pressure of Metabolic syndrome and Non Metabolic Syndrome Patients

Variables	Metabolic syndrome		Total	p-value
	No	Yes		
SBP	120.94 ± 7.02 122 (100, 132)	127.35 ± 8.89 128 (110, 146)	124.15 ± 8.58 122 (100, 146)	**0.0041^{MW}***
DBP	78.24 ± 6.05 79 (70, 90)	83.62 ± 7.06 86 (70, 92)	80.93 ± 7.06 80 (70, 92)	**0.0014^{MW}***

*Abbreviation: MW – Mann Whitney U test, * indicates statistical significance.*

The difference in systolic blood pressure (SBP) between the two groups is statistically significant (p-value = 0.0041). Similarly, there is a significant difference in diastolic blood pressure (DBP), with those with Metabolic Syndrome having higher DBP compared to those without (p-value = 0.0014).

Table 6: Comparison of Laboratory Parameters Of Metabolic Syndrome and Non Metabolic syndrome.

Variables	Metabolic syndrome		Total	p-value
	No	Yes		
Haemoglobin (g/dl)	13.15 ± 2.33 12.9 (9.6, 18.2)	12.48 ± 2.1 12.25 (9.5, 17.1)	12.81 ± 2.22 12.6 (9.5, 18.2)	0.2074^{MW}
TLC(x103/µl)	10.96 ± 5.83 9.05 (4.2, 30.8)	10.56 ± 3.64 10.3 (3.9, 19.7)	10.76 ± 4.83 9.9 (3.9, 30.8)	0.5478^{MW}
Platelets(x103/µl)	317.32 ± 116.06 305.5 (115, 657)	235.18 ± 92.73 203.5 (118, 487)	276.25 ± 112.17 245.5 (115, 657)	**$< 0.001^{MW}$***
Urea(mg/dl)	22.49 ± 10.47 20.05 (6.46, 46.3)	27.92 ± 17.11 22.4 (10, 87)	25.21 ± 14.34 21.6 (6.46, 87)	0.1812^{MW}
Creatinine (mg/dl)	0.84 ± 0.18 0.84 (0.46, 1.25)	0.98 ± 0.48 0.88 (0.41, 2.7)	0.91 ± 0.37 0.86 (0.41, 2.7)	0.4041^{MW}
Total Bilirubin (mg/dl)	0.88 ± 0.63 0.86 (0.11, 2.88)	0.67 ± 0.31 0.58 (0.22, 1.57)	0.77 ± 0.5 0.68 (0.11, 2.88)	0.3639^{MW}
Direct Bilirubin(mg/dl)	0.39 ± 0.27 0.35 (0.06, 1)	0.28 ± 0.15 0.23 (0.09, 0.64)	0.34 ± 0.23 0.29 (0.06, 1)	0.2220^{MW}
Total Protein(g/dl)	6.88 ± 0.61 6.65 (6, 8.1)	6.75 ± 0.91 7 (4.2, 8.3)	6.81 ± 0.77 6.85 (4.2, 8.3)	0.5127^{t}
Albumin(g/dl)	3.81 ± 0.51 3.8 (2.8, 5)	3.77 ± 0.65 3.9 (2.2, 4.7)	3.79 ± 0.58 3.8 (2.2, 5)	0.7719^{t}
Globulin (g/dl)	3.04 ± 0.49 3 (2, 4.1)	3.02 ± 0.52 3 (1.9, 4.2)	3.03 ± 0.5 3 (1.9, 4.2)	0.8670^{t}

ALT (SGPT) (U/l)	19.94 ± 10.13 17.5 (10, 49)	28 ± 17.1 25.5 (11, 100)	23.97 ± 14.53 21.5 (10, 100)	**0.0092^{MW}***
AST (SGOT) (U/l)	28.53 ± 12.8 27.5 (11, 76)	35.32 ± 27.7 27 (10, 127)	31.93 ± 21.69 27.5 (10, 127)	0.9120^{MW}
ALK. Phosphatase (U/l)	79.09 ± 22.76 81 (16, 139)	100.68 ± 27.43 98 (63, 188)	89.88 ± 27.27 88 (16, 188)	**< 0.001^{MW}***
Cholesterol (mg/dl)	154.15 ± 39.65 147.5 (68, 230)	147.68 ± 47.27 134.5 (52, 230)	150.91 ± 43.42 144.5 (52, 230)	0.5430^{t}
LDL (mg/dl)	100.35 ± 36.88 99 (20, 165)	95.71 ± 42.87 88.5 (23, 179)	98.03 ± 39.76 95 (20, 179)	0.6334^{t}
HDL (mg/dl)	42.35 ± 14.11 42 (11, 74)	30.88 ± 10.57 30 (11, 50)	36.62 ± 13.65 38 (11, 74)	**< 0.001^{t}***
TG (mg/dl)	120.03 ± 48.27 119 (42, 288)	137.76 ± 54.57 136 (42, 271)	128.9 ± 51.91 121 (42, 288)	0.1977^{MW}
LDL/HDL RATIO	2.58 ± 1.06 2.42 (0.73, 5)	3.56 ± 2.21 3 (0.77, 11.07)	3.07 ± 1.79 2.7 (0.73, 11.07)	0.0753^{MW}
HbA1c (%	5.74 ± 0.6 5.6 (5, 8.1)	8.03 ± 1.77 8.05 (5.4, 13.4)	6.89 ± 1.75 6.1 (5, 13.4)	**< 0.001^{MW}***
FBS (mg/dl)	100.53 ± 18.66 98 (72, 164)	162.94 ± 57.93 141 (90, 321)	131.74 ± 53.04 120 (72, 321)	**< 0.001^{MW}***

*Abbreviation: MW – Mann Whitney U test, t - Two sample t test, * indicates statistical significance.*

Individuals with Metabolic Syndrome have significantly lower platelet counts (p-value < 0.001), higher ALT (p-value = 0.0092), higher alkaline phosphate (p-value = 0.0453) and lower HDL (p-value < 0.001), compared to those without the syndrome.

Additionally, they exhibit higher levels of HbA1c (p-value < 0.001), and fasting blood sugar (FBS) (p-value < 0.001) compared to subjects without Metabolic Syndrome. However, no significant differences are observed in parameters such as hemoglobin, total leukocyte count, urea, creatinine, total bilirubin, direct bilirubin, total protein, albumin, globulin, cholesterol, LDL, TG and LDL/HDL ratio between the two groups.

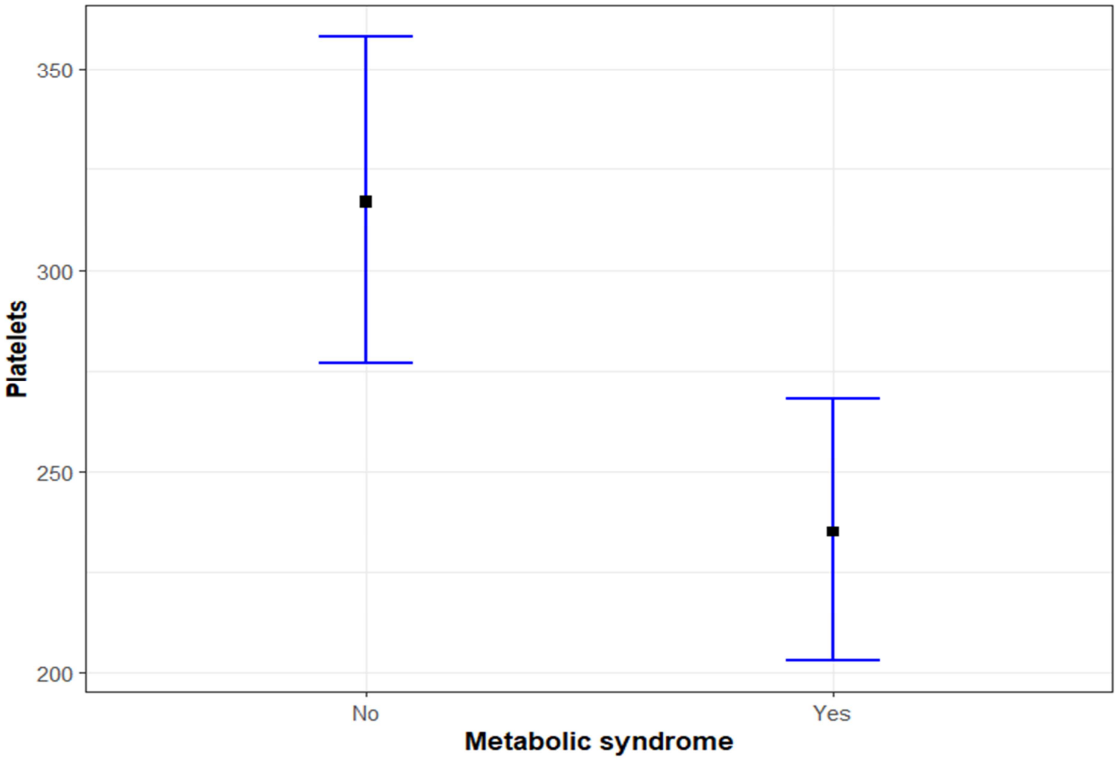

Figure 2: Mean plot of platelets in Metabolic syndrome and Non Metabolic syndrome subjects

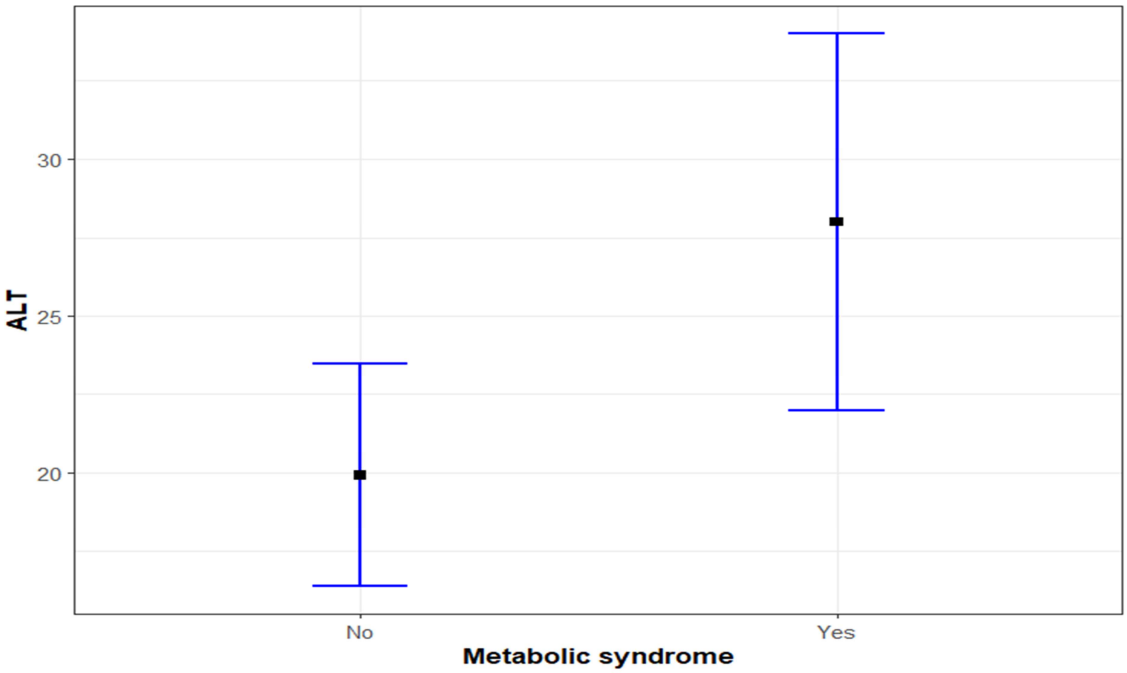

Figure 3: Mean plot of ALT in metabolic syndrome and Non Metabolic syndrome subjects

Table 7: Comparison of Additional tests between Metabolic syndrome and Non Metabolic syndrome Patients

Variables	Sub Category	Metabolic syndrome		Total	p-value
		No	Yes		
Monofilament	Loss of sensation	0	8 (23.53%)	8 (11.76%)	**0.0070^{MC}***
	Normal	34 (100%)	26 (76.47%)	60 (88.24%)	
ECG	LVH	0	4 (11.76%)	4 (5.88%)	**< 0.001^{MC}***
	Non-specific changes	0	4 (11.76%)	4 (5.88%)	
	Non-specific changes, LVH	0	1 (2.94%)	1 (1.47%)	
	Non-specific t wave changes	0	1 (2.94%)	1 (1.47%)	
	Normal	34 (100%)	24 (70.59%)	58 (85.29%)	

*Abbreviation: MC – Chi square test with Monte Carlo simulation, MW – Mann Whitney U test, * indicates statistical significance.*

Loss of sensation, assessed using a monofilament test, is significantly more prevalent among individuals with Metabolic Syndrome compared to those without (p-value=0.0070). Similarly, abnormalities on ECG are significantly more frequent in subjects with Metabolic Syndrome (p-value < 0.001).

Table 8: Comparison of APRI of Metabolic syndrome and Non metabolic syndrome Patients

APRI	Metabolic syndrome		Total	p-value
	No	Yes		
High likelihood of fibrosis	0	2 (5.88%)	2 (2.94%)	**< 0.001^{MC}***
Intermediate likelihood of fibrosis	3 (8.82%)	20 (58.82%)	23 (33.82%)	
Low likelihood of fibrosis	31 (91.18%)	12 (35.29%)	43 (63.24%)	
Mean ± SD	0.24 ± 0.11	0.6 ± 0.38	0.42 ± 0.33	**< 0.001^{MW}***
Median (Min, Max)	0.2 (0.1, 0.5)	0.5 (0.2, 1.6)	0.3 (0.1, 1.6)	

*Abbreviation: MC – Chi square test with Monte Carlo simulation, MW – Mann Whitney U test, * indicates statistical significance.*

Individuals with Metabolic Syndrome showed higher proportions of intermediate and high likelihood of fibrosis compared to those without, with a mean APRI score of 0.6 ± 0.38 in the Metabolic Syndrome group compared to 0.24 ± 0.11 in the non-Metabolic Syndrome group (p-value < 0.001).

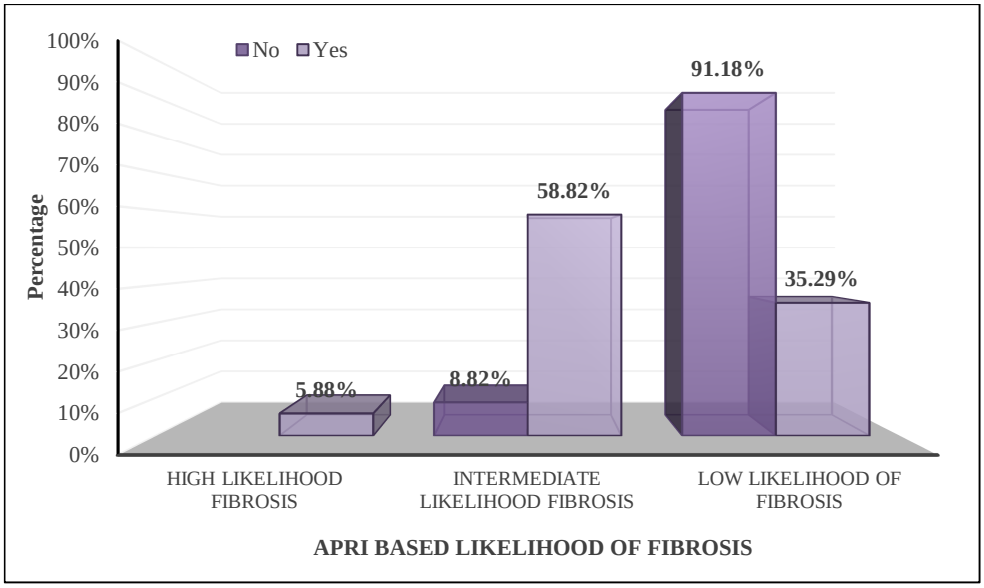

Figure 4: Distribution of APRI based likelihood of fibrosis in metabolic syndrome and Non metabolic Syndrome Subjects

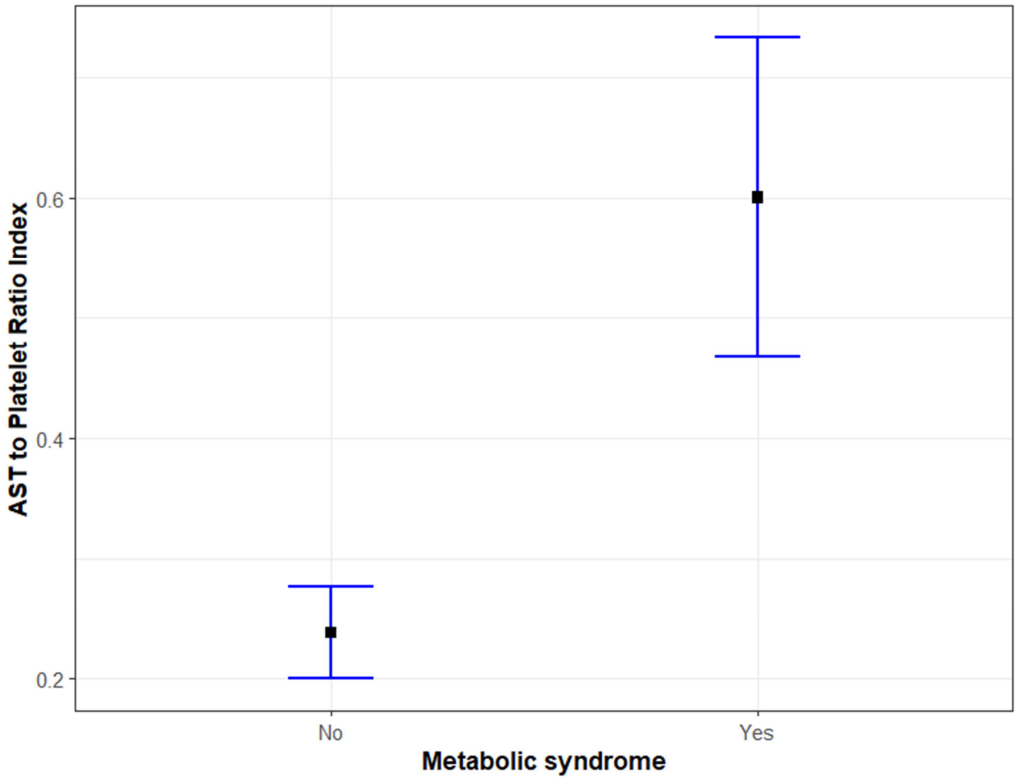

Figure 5: Mean plot of APRI in Metabolic syndrome and Non Metabolic Syndrome Patients.

Table 9: Comparison of Cardiovascular Risk Scores of Metabolic syndrome and Non-Metabolic syndrome Patients

Variables	Sub Category	Metabolic syndrome		Total	p-value
		No	Yes		
ASCVD	Borderline risk	5 (14.71%)	7 (20.59%)	12 (17.65%)	**< 0.001[MC]***
	High risk	1 (2.94%)	11 (32.35%)	12 (17.65%)	
	Intermediate risk	7 (20.59%)	13 (38.24%)	20 (29.41%)	
	Low risk	21 (61.76%)	3 (8.82%)	24 (35.29%)	
	Mean ± SD Median (Min, Max)	5.81 ± 5.61 3.1 (0.6, 22.7)	15.44 ± 9.9 13.7 (1.5, 38.5)	10.62 ± 9.35 7 (0.6, 38.5)	**< 0.001[MW]***
FRS	High risk	2 (5.88%)	11 (32.35%)	13 (19.12%)	**< 0.001[MC]***
	Intermediate risk	4 (11.76%)	14 (41.18%)	18 (26.47%)	
	Low risk	28 (82.35%)	9 (26.47%)	37 (54.41%)	
	Mean ± SD Median (Min, Max)	7.55 ± 7.03 5.55 (0.8, 32.78)	16.68 ± 12.22 12 (0.1, 57.4)	12.11 ± 10.91 8.75 (0.1, 57.4)	**< 0.001[MW]***

*Abbreviation: MC – Chi square test with Monte Carlo simulation, MW – Mann Whitney U test, * indicates statistical significance.*

For the ASCVD risk scores, individuals with Metabolic Syndrome were more likely to fall into higher risk categories. Specifically, 32.35% of individuals with Metabolic Syndrome were classified as high risk, compared to only 2.94% without Metabolic Syndrome. Similarly, a larger proportion of those with Metabolic Syndrome were in the intermediate risk category (38.24% vs. 20.59%). Conversely, a majority of individuals without Metabolic Syndrome were in the low-risk category (61.76% vs. 8.82%). The mean ASCVD risk score was significantly higher in the Metabolic Syndrome group (15.44 ± 9.9) compared to those without (5.81 ± 5.61) indicating statistical significance (p-value < 0.001).

The FRS scores also showed significant differences. A higher percentage of individuals with Metabolic Syndrome were in the high-risk category (32.35% vs. 5.88%) and intermediate risk category (41.18% vs. 11.76%) compared to those without Metabolic Syndrome. Conversely, a greater proportion of individuals without Metabolic Syndrome were in the low-risk category (82.35% vs. 26.47%). The mean FRS was significantly higher in the Metabolic Syndrome group (16.68 ± 12.22) compared to those without (7.55 ± 7.03) (p-value < 0.001).

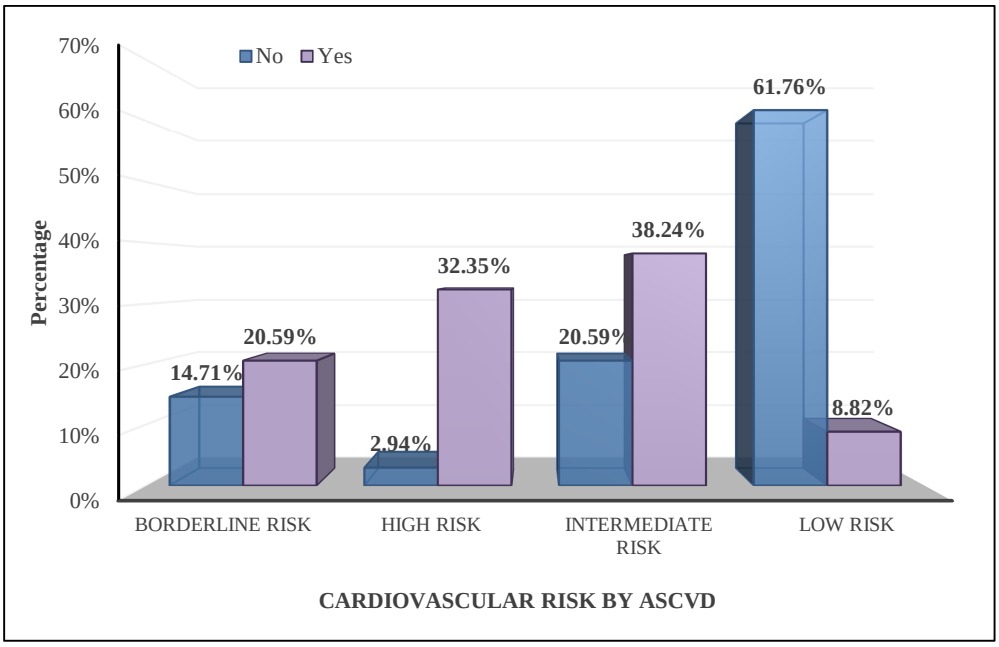

Figure 6 : Distribution of cardiovascular risk by ASCVD categories in metabolic syndrome and Non Metabolic syndrome Subjects.

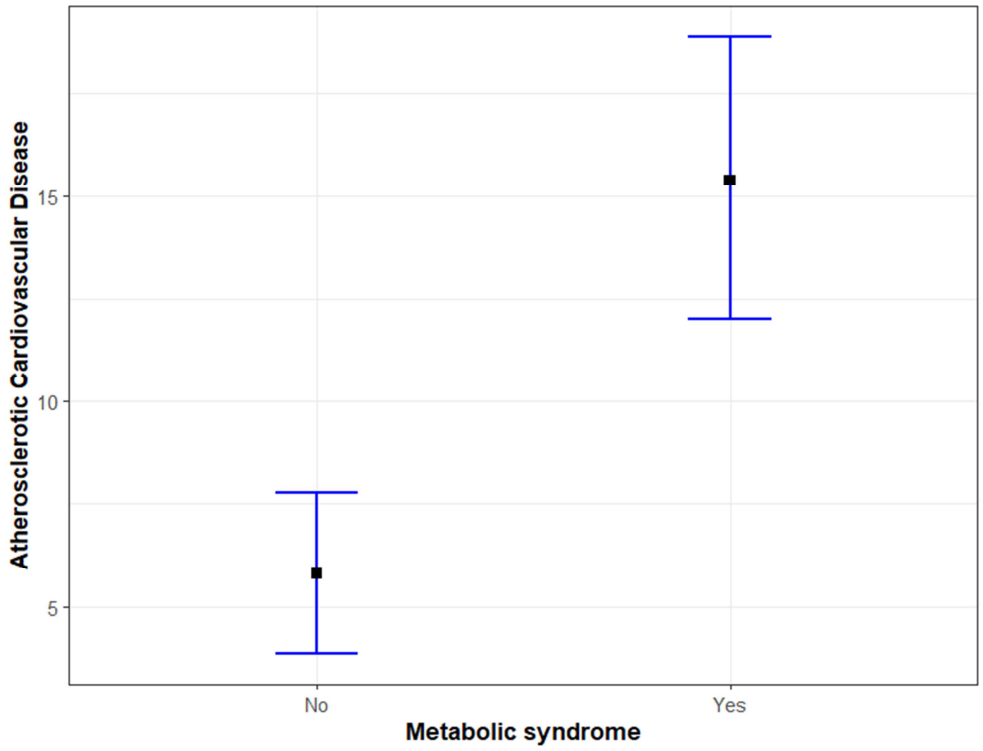

Figure 7: Mean plot of ASCVD of metabolic syndrome and Non metabolic syndrome patients

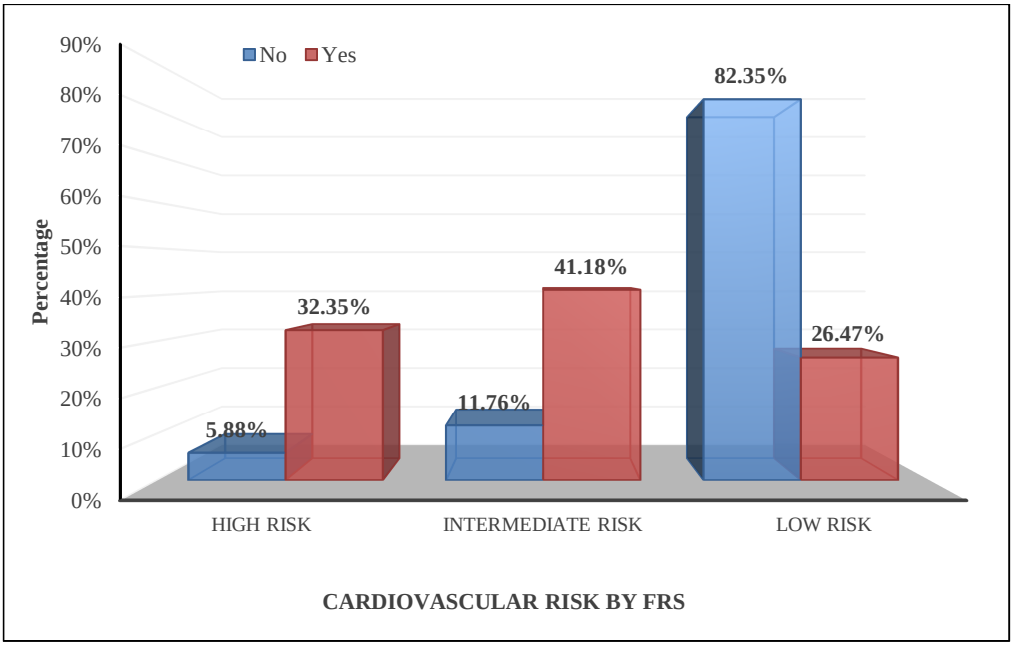

Figure 8: Distribution of cardiovascular risk by FRS of metabolic syndrome and Non metabolic syndrome subjects

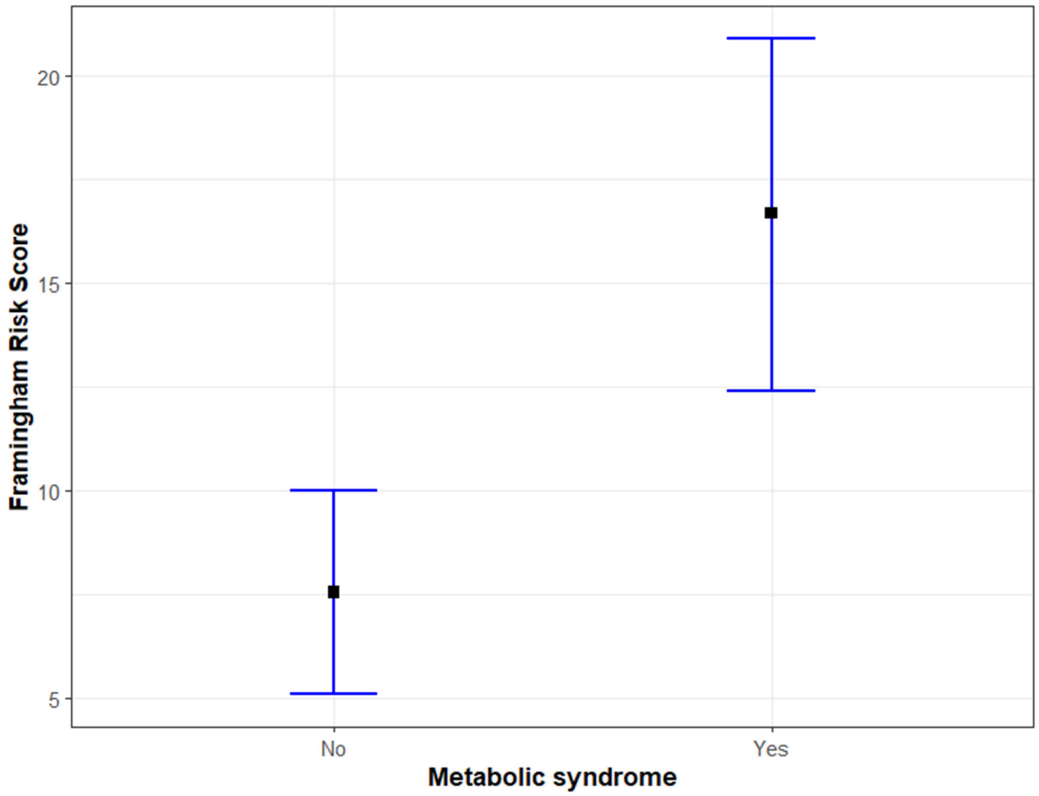

Figure 9: Mean plot of FRS of metabolic syndrome and Non Metabolic syndrome Subjects.

Table 10: Correlation of APRI with FRS according to Metabolic syndrome.

Metabolic syndrome	Correlation coefficient	p-value [SP]
Yes	0.4887	**0.0034***
No	0.2928	0.0929

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance.*

For individuals with Metabolic Syndrome, there is a significant positive correlation between APRI and FRS, with a correlation coefficient of 0.4887 and a p-value of 0.0034. This suggests that higher APRI scores are associated with higher cardiovascular risk scores.

In contrast, for individuals without Metabolic Syndrome, the correlation between APRI and FRS is weaker and not statistically significant, with a correlation coefficient of 0.2928 and a p-value of 0.0929.

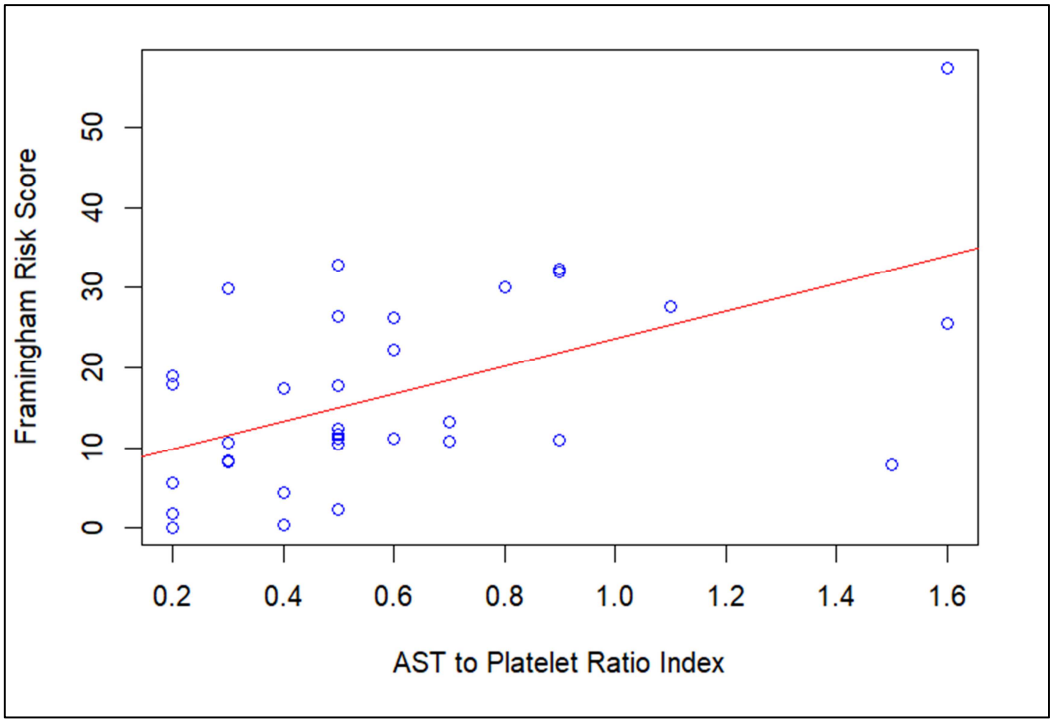

Figure 10: Scatter plot of Framingham Risk Score with APRI values in subjects with Metabolic Syndrome.

Table 11: Correlation of APRI with FRS according to Metabolic syndrome and age group.

Metabolic syndrome	Age Group	Correlation coefficient	p-value [SP]
Yes	<50	0.8	0.2
	50-59	0.2587	0.3719
	60-69	0.8186	**0.0038***
	≥70	-0.0290	0.9565
No	<50	0.3986	0.2879
	50-59	0.5698	0.0855
	60-69	0.3379	0.3738
	≥70	0.6002	0.2078

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance.*

For those with Metabolic Syndrome, the correlation is significant and strong in the 60-69 age group (correlation coefficient 0.8186, p-value = 0.0038), indicating a strong association between higher APRI scores and increased cardiovascular risk. In younger age groups (<50 and 50-59), the correlations are positive but not statistically significant. For individuals without Metabolic Syndrome, all age groups show weak and non-significant correlations, suggesting no meaningful relationship between APRI and FRS in these populations.

The following table gives the correlation of APRI with FRS according to Metabolic syndrome and sex.

Table 12: Correlation of APRI with FRS according to Metabolic syndrome and sex.

Metabolic syndrome	Sex	Correlation coefficient	p-value [SP]
Yes	Female	0.5963	**0.0315***
	Male	0.3503	0.1195
No	Female	0.3005	0.2765
	Male	-0.0585	0.8119

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance.*

In females with Metabolic Syndrome, there is a significant positive correlation (correlation coefficient of 0.5963, p-value = 0.0315), indicating that higher APRI scores are associated with higher cardiovascular risk. However, in males with Metabolic Syndrome, the correlation is weaker and not statistically significant (correlation coefficient of 0.3503, p-value = 0.1195). For individuals without Metabolic Syndrome, both females and males show weak and non-significant correlations (females: correlation coefficient of 0.3005, p-value = 0.2765; males: correlation coefficient of -0.0585, p-value = 0.8119).

Table 13: Comparison of APRI and cardiovascular risk by using Framingham Risk Score.

Metabolic syndrome	Cardiovascular risk by using Framingham Risk Score			p-value
	High risk	Intermediate risk	Low risk	
Yes	0.85 ± 0.43 0.8 (0.3, 1.6)	0.5 ± 0.19 0.5 (0.2, 0.9)	0.44 ± 0.41 0.3 (0.2, 1.5)	**0.0056^{K}***
No	0.25 ± 0.07 0.25 (0.2, 0.3)	0.28 ± 0.1 0.25 (0.2, 0.4)	0.23 ± 0.12 0.2 (0.1, 0.5)	0.5496^{K}
Total	0.76 ± 0.46 0.6 (0.2, 1.6)	0.45 ± 0.2 0.5 (0.2, 0.9)	0.28 ± 0.24 0.2 (0.1, 1.5)	**< 0.001^{K}***

*Abbreviation: K – Kruskal Wallis test, * indicates statistical significance.*

For individuals with metabolic syndrome, APRI values are notably higher in those at high cardiovascular risk (0.85 ± 0.43) compared to those at intermediate (0.5 ± 0.19) and low risk (0.44 ± 0.41), (p-value = 0.0056). From pairwise comparisons, it is observed that there is significant difference between low and high risk (p-value=0.0045).

In individuals without metabolic syndrome, there was no significant difference in APRI values cardiovascular risk (p-value = 0.5496).

Overall, the total sample reveals APRI values of 0.76 ± 0.46 for high, 0.45 ± 0.2 for intermediate, and 0.28 ± 0.24 for low-risk groups, with a highly significant difference (p-value < 0.001). Further from pairwise comparison, it is observed that, there are significant differences between low and high-risk groups (p-value < 0.001) as well as low risk and intermediate risk groups (p-value = 0.0055).

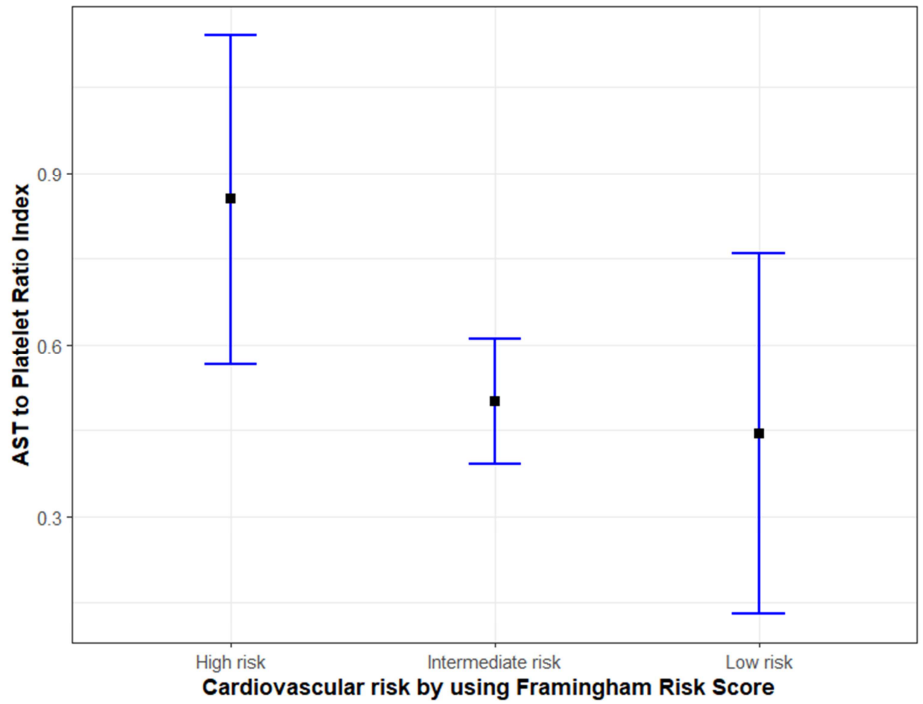

Figure 11: Mean plot of APRI over cardiovascular risk by using Framingham Risk Score in subjects with Metabolic syndrome.

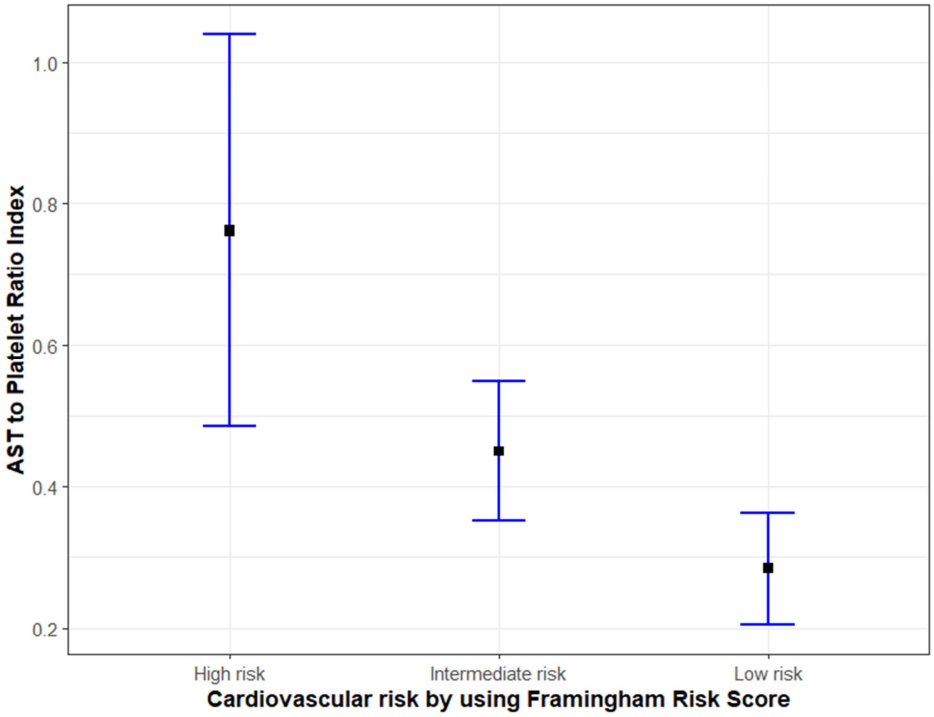

Figure 12: Mean plot of APRI and cardiovascular risk by using Framingham Risk Score for combined Metabolic and Non Metabolic subjects.

Table 14: Correlation of APRI with ASCVD according to Metabolic syndrome.

Metabolic syndrome	Correlation coefficient	p-value [SP]
Yes	0.4932	**0.0030***
No	0.3019	0.0827

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance.*

For individuals with Metabolic Syndrome, there is a significant positive correlation (correlation coefficient 0.4932, p-value = 0.0030), indicating that higher APRI scores are significantly associated with higher ASCVD risk scores. In individuals without Metabolic Syndrome, there is a weaker positive and non-significant correlation (correlation coefficient 0.3019, p-value = 0.0827).

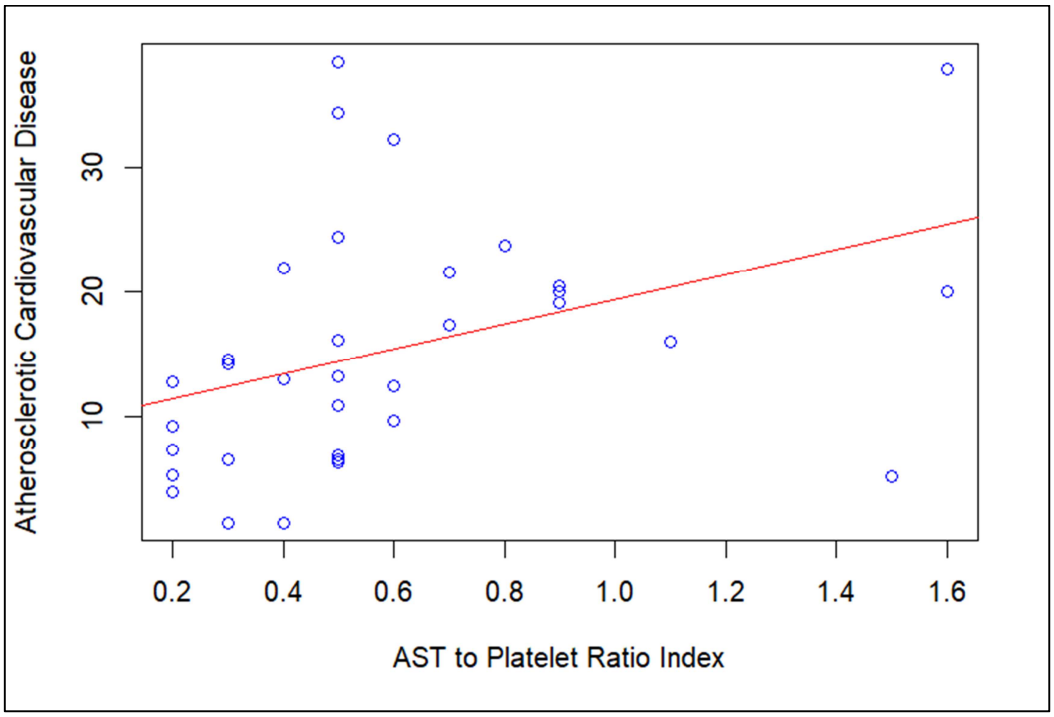

Figure 13: Scatter plot of ASCVD with APRI values in subjects with Metabolic Syndrome.

Table 15: Correlation of APRI with ASCVD according to Metabolic syndrome and age group.

Metabolic syndrome	Age Group	Correlation coefficient	p-value [SP]
Yes	<50	0.3162	0.6838
	50-59	0.2071	0.4774
	60-69	0.4493	0.1927
	≥70	0.4928	0.3206
No	<50	0.4392	0.2369
	50-59	0.1899	0.5992
	60-69	0.3466	0.3609
	≥70	0.3381	0.5122

Abbreviation: SP – Spearman's rank correlation test.

Among individuals with and without Metabolic Syndrome, there is no significant correlation between APRI and ASCVD across different age groups. This implies that the association between fibrosis likelihood and cardiovascular risk, as measured by APRI and ASCVD respectively, does not vary significantly across different age groups in individuals both with and without Metabolic Syndrome.

Table 16: Correlation of APRI with ASCVD according to Metabolic syndrome and sex.

Metabolic syndrome	Sex	Correlation coefficient	p-value [SP]
Yes	Female	0.6556	**0.0150***
	Male	0.4008	0.0718
No	Female	-0.0288	0.9190
	Male	0.2132	0.3807

*Abbreviation: SP – Spearman's rank correlation test, * indicates statistical significance.*

Among individuals with Metabolic Syndrome, females show a strong and significant positive correlation (correlation coefficient 0.6556, p-value = 0.0150), indicating that higher APRI scores are significantly associated with higher ASCVD risk. In males with Metabolic Syndrome, the correlation is positive but not statistically significant (correlation coefficient 0.4008, p-value = 0.0718). For those without Metabolic Syndrome, both females and males exhibit weak and non-significant correlations .

Table 17: Comparison of APRI and ASCVD in Metabolic syndrome and Non Metabolic Syndrome Patients

Metabolic syndrome	ASCVD				p-value
	Borderline risk	**High risk**	**Intermediate risk**	**Low risk**	
Yes	0.53 ± 0.45 0.5 (0.2, 1.5)	0.82 ± 0.42 0.7 (0.4, 1.6)	0.52 ± 0.27 0.5 (0.2, 1.1)	0.3 ± 0.1 0.3 (0.2, 0.4)	**0.0286^{K}***
No	0.32 ± 0.11 0.3 (0.2, 0.5)	0.3	0.23 ± 0.1 0.2 (0.1, 0.4)	0.22 ± 0.11 0.2 (0.1, 0.5)	0.1301^{K}
Total	0.44 ± 0.36 0.3 (0.2, 1.5)	0.78 ± 0.43 0.65 (0.3, 1.6)	0.42 ± 0.26 0.35 (0.1, 1.1)	0.23 ± 0.11 0.2 (0.1, 0.5)	**< 0.001^{K}***

*Abbreviation: K – Kruskal Wallis test, * indicates statistical significance.*

For individuals with Metabolic Syndrome, there is a statistically significant difference in APRI values across ASCVD risk categories (p-value = 0.0286). Specifically, those categorized as high risk for ASCVD have the highest mean APRI value (0.82 ± 0.42), followed by those with borderline risk (0.53 ± 0.45), intermediate risk (0.52 ± 0.27), and low risk (0.3 ± 0.1). Further from pairwise comparison, it is observed that there is significant difference between low risk and high-risk groups (p-value= 0.0448).

In contrast, for individuals without Metabolic Syndrome, the difference in APRI values across ASCVD risk categories is not statistically significant (p-value = 0.1301).

Overall, the total sample reveals a notable difference in APRI levels across ASCVD risk categories (p-value < 0.001). Further from pairwise comparison, it is observed that, there is significant difference between low risk and high-risk group (p-value < 0.001), low risk and intermediate risk group (p-value = 0.0328).

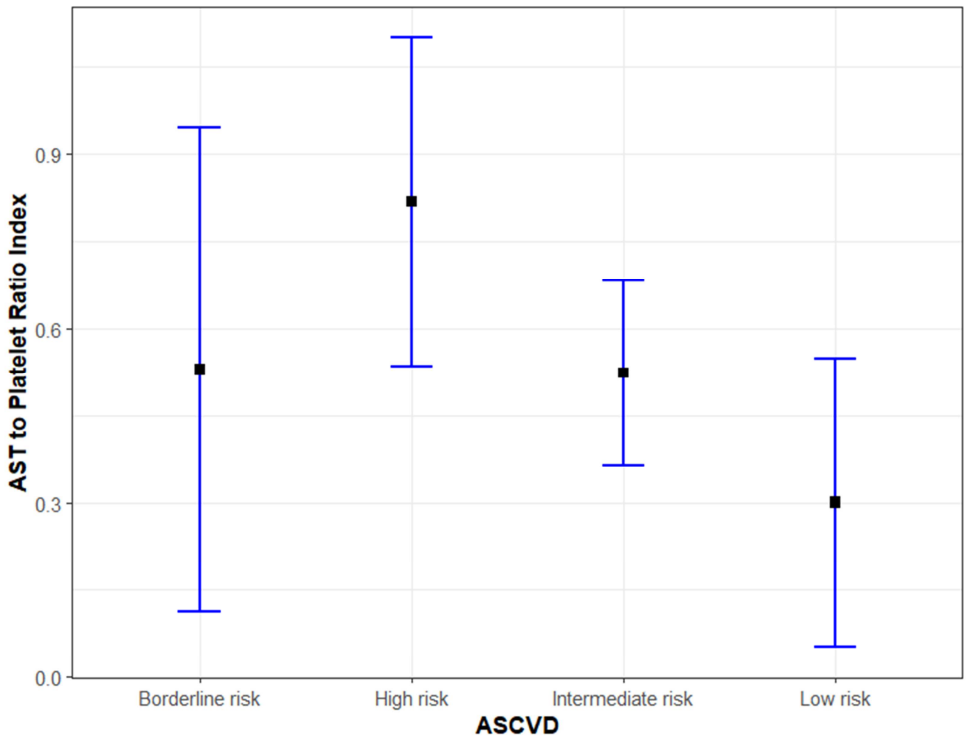

Figure 14: Mean plot of APRI and ASCVD in subjects with Metabolic syndrome.

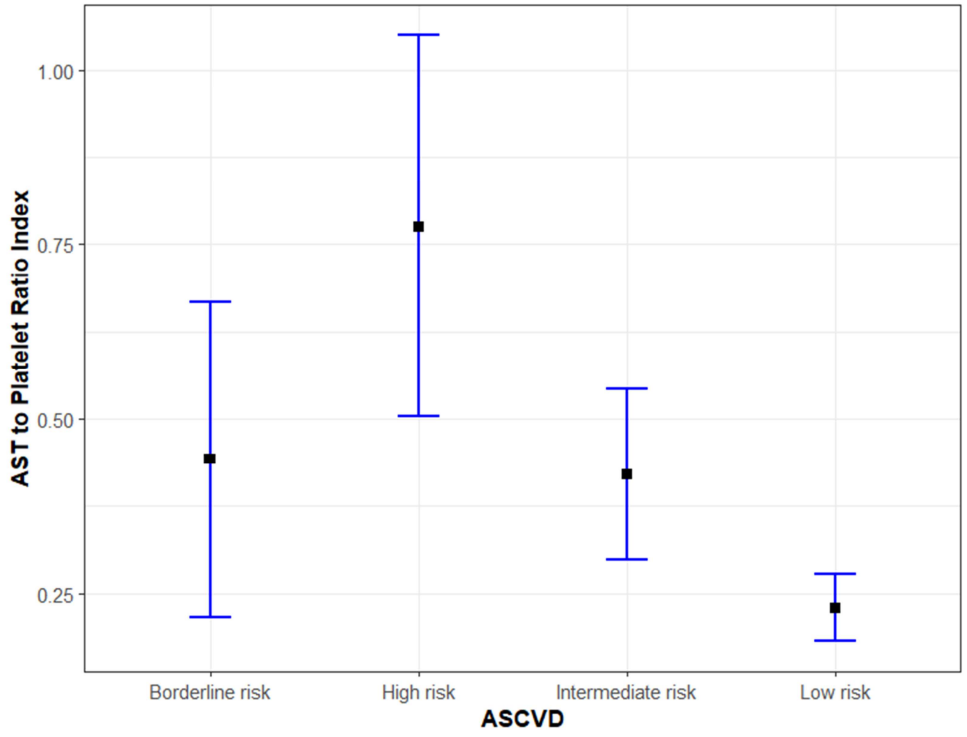

Figure 15: Mean plot of APRI and ASCVD for combined Metabolic and Non Metabolic subjects .

Table 18: Correlation of APRI with age according to Metabolic syndrome.

Variables	Metabolic syndrome		Non-Metabolic syndrome	
	Correlation coefficient	**p-value**	**Correlation coefficient**	**p-value**
Age (years)	0.1428	0.4204	0.1508	0.3947

*Abbreviation: SP – Spearman's rank correlation coefficient, * indicates statistical significance.*

For individuals with metabolic syndrome, there is a positive correlation between age and APRI, with a correlation coefficient of 0.1428. However, this correlation is not statistically significant at the conventional level (p-value = 0.4204).

Similarly, for individuals without metabolic syndrome, there is also a positive correlation between age and APRI, with a correlation coefficient of 0.1508. However, this correlation is not statistically significant (p-value = 0.3947).

Table 19: Comparison of APRI with sex in Metabolic syndrome and Non Metabolic syndrome subjects

Sex	Metabolic syndrome		Non-Metabolic syndrome	
	Mean ± SD **Median (Min, Max)**	**p-value**	**Mean ± SD** **Median (Min, Max)**	**p-value**
Female	0.53 ± 0.39 0.5 (0.2, 1.6)	0.2980[MW]	0.18 ± 0.07 0.2 (0.1, 0.3)	**0.0049[MW]***
Male	0.64 ± 0.38 0.5 (0.2, 1.6)		0.28 ± 0.12 0.3 (0.1, 0.5)	

*Abbreviation: MW – Mann Whitney U test, * indicates statistical significance.*

In individuals with metabolic syndrome, there are notable differences in APRI levels based on gender. Males tend to have higher APRI levels compared to females, though this difference is not statistically significant.

In individuals without metabolic syndrome, higher APRI levels is observed in males compared to females. From Mann Whitney U test, it is observed that this difference is statistically significant (p-value = 0.0049).

Table 20: Comparison of APRI with comorbidities in Metabolic syndrome group.

Variables	Sub Category	Metabolic syndrome	
		Mean ± SD **Median (Min, Max)**	**p-value**
Diabetes	Absent	0.23 ± 0.06 0.2 (0.2, 2.3)	**0.0165^{MW}***
	Present	0.64 ± 0.38 0.5 (0.2, 1.6)	
Hypertension	Absent	0.66 ± 0.46 0.5 (0.2, 1.6)	0.8194^{MW}
	Present	0.53 ± 0.23 0.5 (0.2, 1.1)	

*Abbreviation: MW – Mann Whitney U test, * indicates statistical significance.*

For individuals with metabolic syndrome, the mean APRI values are significantly higher in those with diabetes compared to those without diabetes (0.64 ± 0.38 vs. 0.23 ± 0.06, p-value = 0.0165). Regarding hypertension, there is no significant difference in mean APRI values between individuals with and without hypertension in metabolic syndrome group (0.66 ± 0.46 vs. 0.53 ± 0.23, p-value = 0.8194).

Table 21: Correlation of APRI with anthropometry variables according to Metabolic syndrome.

Variables	Metabolic syndrome		Non-Metabolic syndrome	
	Correlation coefficient	**p-value**	**Correlation coefficient**	**p-value**
Waist circumference (cm)	0.7355	**< 0.001***	0.1749	0.3225
Height (cm)	0.2421	0.1678	0.2583	0.1402
Weight (Kg)	0.6365	**< 0.001***	0.1756	0.3204
BMI Kg/m2	0.6164	**< 0.001***	-0.0659	0.7111

*Abbreviation: SP – Spearman's rank correlation coefficient, * indicates statistical significance.*

In individuals with metabolic syndrome, there are strong positive correlations between APRI and waist circumference (correlation coefficient = 0.7355, p-value < 0.001), weight (correlation coefficient = 0.6365, p-value < 0.001), and BMI (correlation coefficient = 0.6164, p-value < 0.001). Similarly, in individuals without metabolic syndrome, there are no significant correlations between APRI with hip circumference, weight, and BMI.

In contrast, height does not show a significant correlation with APRI in individuals with metabolic syndrome and without metabolic syndrome.

Table 22: Correlation of APRI with Blood pressure according to Metabolic syndrome.

Variables	Metabolic syndrome		Non-Metabolic syndrome	
	Correlation coefficient	**p-value**	**Correlation coefficient**	**p-value**
SBP	0.4199	**0.0134***	-0.04916	0.7825
DBP	-0.0723	0.6845	0.1629	0.3574

*Abbreviation: SP – Spearman's rank correlation coefficient, * indicates statistical significance.*

In individuals with metabolic syndrome, there is a significant positive correlation between SBP and APRI, with a correlation coefficient of 0.4199 (p-value = 0.0134). However, there is no significant correlation between DBP and APRI in individuals with metabolic syndrome.

In individuals without metabolic syndrome, neither SBP nor DBP shows a significant correlation with APRI.

Table 23: Correlation of APRI with laboratory parameters in Metabolic syndrome and Non metabolic syndrome Patients.

Variables	Metabolic syndrome		Non-Metabolic syndrome	
	Correlation coefficient	**p-value**	**Correlation coefficient**	**p-value**
Haemoglobin (g/dl)	-0.0573	0.7474	0.5292	**0.0015***
TLC(x103/µl)	0.2505	0.1530	0.0083	0.9628
Urea(mg/dl)	-0.0053	0.9761	0.0754	0.6718
Creatinine (mg/dl)	0.1873	0.2888	0.2486	0.1562
Total Bilirubin (mg/dl)	0.3468	**0.0445***	0.3140	0.0705
Direct Bilirubin(mg/dl)	0.1897	0.2827	0.2862	0.1008
Total Protein(g/dl)	-0.1085	0.5415	0.1041	0.5581
Albumin(g/dl)	-0.2110	0.2310	0.0487	0.7843
Globulin (g/dl)	0.0317	0.8589	0.1468	0.4075
ALT (SGPT) (U/l)	0.2501	0.1538	0.4369	**0.0098***
ALK. Phosphatase (U/l)	-0.0810	0.6596	0.2381	0.1751
Cholesterol (mg/dl)	0.3923	**0.0217***	-0.2343	0.1823
LDL (mg/dl)	-0.0949	0.5935	-0.1280	0.4706
HDL (mg/dl)	-0.4577	**0.0065***	0.0023	0.9898
TG (mg/dl)	0.0234	0.8953	0.0476	0.7891
LDL/HDL RATIO	0.0783	0.6598	-0.0687	0.6996
HbA1c (%	0.4106	**0.0159***	0.0369	0.8359
FBS (mg/dl)	-0.1610	0.3630	0.3003	0.0845

*Abbreviation: SP – Spearman's rank correlation coefficient, * indicates statistical significance.*

In individuals with Metabolic syndrome, significant positive correlations were observed between APRI and total bilirubin (correlation coefficient = 0.3468, p-value = 0.0445), cholesterol (correlation coefficient = 0.3923, p-value = 0.0217) and HbA1c (correlation coefficient = 0.4106, p-value = 0.0159), while HDL showed a significant negative correlation (correlation coefficient = -0.4577, p-value = 0.0065).

In contrast, for individuals without Metabolic syndrome, significant positive correlations were found between APRI and hemoglobin (correlation coefficient = 0.5292, p-value = 0.0015), ALT (correlation coefficient = 0.4369, p-value = 0.0098) and AST (correlation coefficient = 0.6088, p-value < 0.001), with a significant negative correlation observed with platelets (correlation coefficient = -0.5066, p-value = 0.0022).

DISCUSSION

"The metabolic syndrome (MetS, Syndrome X, Insulin resistance syndrome, IRS) is a constellation of several cardiovascular risk factors promoting atherosclerotic cardiovascular disease (ASCVD). It consists of an atherogenic dyslipidemia (i.e. elevated triglycerides, low high density lipoprotein cholesterol (HDL-C)), elevation of blood pressure and glucose, prothrombotic and proinflammatory states. Metabolic syndrome is a complex web of metabolic factors that are associated with a 2-fold risk of CVD and a 5-fold risk of diabetes. Asian Indians are at a high risk of developing diabetes and CVD as the number of cases are consistently increasing."

This study was done to assess the APRI in metabolic and non metabolic syndrome patients, its correlation with various factors, and its correlation with ASCVD and FRS scores to stratify Cardiovascular risk.

Our study done on a sample of 68 patients, out of the total which, 34 (50%) were Metabolic Syndrome subjects, and 34(50%) were Non-Metabolic Syndrome subjects (controls).

In terms of age distribution in our study, the majority of subjects are aged between 50 and 59. The mean ages are similar, 58.62 ± 9.31 years for Metabolic Syndrome subjects and 56.97 ± 8.65 years in Non-metabolic syndrome subjects. In a study by Carlo De Matteis, Marica Cariello et al mean ages were 61.31± 0.52 in the metabolic syndrome group and 52.58±0.59 in the Non metabolic syndrome group[1]. The age group were similar in our study and the other studies.

Among the subjects with Metabolic Syndrome, 38.24% were females and 61.76% were males, while 44.12% of the Non Metabolic Syndrome subjects were females and 55.88% males. It is observed that there is no significant difference in sex

distribution between the groups. In a study by Carlo De Matteis, Marica Cariello et al there were 48% females and 42% males in the metabolic syndrome group and 50% females in the Non-Metabolic syndrome group[196]. Similar to our study with no significant difference in sex distribution between the two groups.

In our study on comparing the diabetic parameters, all individuals with metabolic syndrome had a significantly higher prevalence of diabetes (91.18%). Due to increased prevalence of diabetics in the metabolic syndrome group, the use of OHA (77.4%) and insulin(22.5%) is significantly higher among those with Metabolic Syndrome (91.18%). When comparing the related Lab values both HBA1c(8.03 ± 1.77) and FBS(162 ± 57.93) in Metabolic syndrome subjects show comparatively higher values with significance (p value < 0.001) as compared to Non-Metabolic Syndrome group . In the study by Carlo De Matteis, Marica Cariello et, the metabolic syndrome group subjects had significantly high levels of Blood glucose (121.4 ± 2.02) and HBA1c (7.1% ± 0.8) [196]. This study does not mention the exact number of diabetics. The mean HBA1c level was found to be 8.9±2.1% among Indian diabetics in a study by Unnikrishnan et al.[198] In our study population there was increased prevalence of uncontrolled diabetics.

In our present study, significantly high number of subjects in metabolic syndrome group had hypertension (44.12%) compared to non-Metabolic Syndrome group (0%). The use of antihypertensive is higher among those with Metabolic Syndrome for treating the same. In comparing the Blood Pressure measurements both SBP and DBP had significantly higher values (p-value = 0.0041) in the Metabolic syndrome group with SBP (127.35 ± 8.89) and 83.62 ± 7.06) compared to Non-metabolic syndrome group(120.94 ± 7.02 and 78.24 ± 6.05). In the study by Carlo De Matteis, Marica Cariello et al, there was a significant difference ($p<0.05$) of SBP and

DBP in-between Metabolic syndrome group (134± 0.9 and 81.4 ± 0.73) and Non-Metabolic syndrome group (124.0 ± 0.28 and 76.9 ± 0.27)[196]. Both studies show higher SBP and DBP in Metabolic Syndrome subjects.

In comparing anthropometric measures, in our study, individuals in the Metabolic Syndrome group have a significantly larger hip circumference (p-value < 0.001), higher weight (p-value =0.0022), and higher body mass index (BMI) (p-value < 0.001) compared to those in the Non-Metabolic syndrome group. In the study by Carlo De Matteis, Marica Cariello et al they found similar characteristics with higher weight (p<0.05), hip circumference (p<0.05) and BMI(p<0.05) among MetS patients[196]. Our study had more significant difference between the weight of metabolic syndrome patients and non metabolic syndrome patients due to prevelance of both undernutrition and obesity among adults in india.[199] (Kalra, Sanjay et al)

Variable	our Study – MetS Yes (Mean ± SD)	our Study - Non-MetS (Mean ± SD)	our Study p-value	Carlos de-Study - MetS Yes (Mean ± SD)	Carlos de-Non-MetS (Mean ± SD)	Carlos de-study (p-value)
BMI (Kg/m²)	28.88 ± 4.15	23.27 ± 1.35	**<0.001**	29.1 ± 4.3	24.5 ± 3.2	**<0.001**
Weight (Kg)	77.06 ± 13.56	67.35 ± 8.08	**0.0022**	83.21 ± 1.32	76.89 ± 0.71	**<0.05**
Waist Circumference (cm)	95.9 ± 15.93	81.36 ± 5.32	**<0.001**	102.3 ± 12.5	88.7 ± 10.2	**<0.001**

Table I: comparison of baseline anthropometric characteristics of both studies

In our study, Individuals with Metabolic Syndrome have significantly lower HDL (p-value < 0.001), compared to those in the Non Metabolic syndrome group. Additionally, they exhibit higher levels of LDL (137.76 ± 54) in metabolic syndrome subjects and (120.03 ± 48) in subjects without metabolic syndrome. Though not

statistically significant. The use of statins is also significantly higher in subjects with Metabolic Syndrome (17.65%) versus those in Non Metabolic syndrome group. In the study by Carlo De Matteis, Marica Cariello et al the metabolic syndrome group showed significantly higher values of TG ($p<0.05$) and significantly lower values of HDL($p<0.05$)[196]. In a study by Udgire & Karnik they showed that Hypertriglyceridemia was present in 67.8% of patients with metabolic syndrome whereas in patients without metabolic syndrome it was present in 33.1%. HDL was found low in 82.5% of patients with metabolic syndrome while it was low in 38.4% of patients without metabolic syndrome in Indian context[200]. This study shows similar findings to our study.

On Comparison of other Laboratory Parameters, In our study, Individuals in Metabolic Syndrome group have significantly lower platelet counts (p-value < 0.001), higher ALT (p-value = 0.0092), higher alkaline phosphate (p-value=0.0453, compared to those without the syndrome.

In study by carlo de mattias, et al in MetS patients, Platelet count was not significantly different between the two groups. Liver markers such as aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and were found significantly higher in MetS patients[196]. Both the studies show similar findings.

APRI RISK SCORE IN METABOLIC SYNDROME

In our study, on comparing APRI among metabolic syndrome and non-metabolic syndrome groups, individuals in the Metabolic Syndrome group showed higher proportions of intermediate and high likelihood of fibrosis compared to those non-metabolic syndrome groups with a mean APRI score of 0.6 ± 0.38 in the

Metabolic Syndrome group compared to 0.24 ± 0.11 in the non-Metabolic Syndrome group (p-value < 0.001).

Similarly in the study by Carlo De Matteis, Marica Cariello et al where they found a significant increase in subjects with APRI > 0.5 (the intermediate and high risk of fibrosis groups) in MetS subjects compared to Non MetS subjects. The mean APRI score of in Metabolic syndrome subjects was 0.62 ± 0.02 and in Non Mets subjects was 0.3 ± 0.01[196]. This study shows similar findings to our study on comparison of groups and Values of APRI.

The presence of elevated APRI in these patients highlights a deeper link between liver health and metabolic disorders, emphasizing the role of liver fibrosis and systemic inflammation in exacerbating cardiovascular risk. Elevated APRI reflects not only liver fibrosis but also systemic inflammation. Chronic low-grade inflammation is a hallmark of MetS and contributes to the pathogenesis of its components, including insulin resistance and atherogenic dyslipidaemia.

APRI comparision with various components of metabolic syndrome

In our study in individuals in the metabolic syndrome group, the mean APRI values are significantly higher in diabetic patients compared to non-diabetics (0.64 ± 0.38 vs. 0.23 ± 0.06, p-value = 0.0165). In the study by Carlo De Matteis, Marica Cariello et al concluded that elevated glycemia was identified as a major determinant of increased APRI levels ($p<0.01$), underscoring the link between APRI and diabetes, in metabolic syndrome patients[196]. In another study by S Ludgate, J Steen et al in Dublin, on diabetic patients with abnormal LFT's the researchers showed that APRI may have a role in screening diabetic patients for advanced liver disease, with 77.3% of patients with liver imaging performed and an abnormal APRI score having

advanced fibrosis, with limited sample size of 33 patients with abnormal APRI.[201] In an alternative study by Amit Kumar Das, Anuj Sharma et al in Bihar, India. On a subset of 80 Obese type 2 diabetics concluded that APRI identified significant fibrosis ($p<0.0001$) better in diabetics, validating the use of APRI in diabetics in our study, and confirming increased prevalence of Liver fibrosis in Diabetics.[202]

In relation to Hypertension, in our study there is no significant difference in mean APRI values between individuals with and without hypertension in metabolic syndrome group (0.66 ± 0.46 vs. 0.53 ± 0.23, p-value = 0.8194). In individuals with metabolic syndrome, there is a significant positive correlation between SBP and APRI, with a correlation coefficient of 0.4199 (p-value = 0.0134). However, there is no significant correlation between DBP and APRI in individuals with metabolic syndrome.

In the study by Carlo De Matteis, Marica Cariello et al they found no significant differences in APRI levels specifically in patients with increased blood pressure[196]. These findings are similar to our study. In a Chinese study by Xiong, Shengjun; Yin et al they conclude that APRI is significantly associated with the risk of cardiovascular disease in hypertensive patients, but does not mention any positive correlation between hypertension and APRI[203]. In another study by Koo, D.-J., Lee et al APRI was significantly associated with systolic blood pressure (SBP) and diastolic blood pressure (DBP)[204]. This relationship is variable and will need further studies.

In correlating with Anthropometric measures, In our study, in individuals with metabolic syndrome, there are strong positive correlations between APRI and Waist circumference (correlation coefficient = 0.7355, p-value < 0.001), weight (correlation coefficient = 0.6365, p-value < 0.001), and BMI (correlation coefficient = 0.6164, p-value < 0.001). In the study by Carlo De Matteis, Marica Cariello et al they inferred

similar characteristics that APRI increased in overweight patients (0.34 ± 0.05) as well as in obese subjects (0.35 ± 0.07) compared to healthy subjects (0.3 ± 0.06). Furthermore, they observed a significant up-regulation of APRI levels in patients with elevated WC ($p<0.05$).[196]

In a study by Yen YH, Kuo FY, in vietnam among CHC patients, they observed that the performance of APRI was better in obese patients[205]. In a related study by Yejin Kim, Yoosoo Chang et al in a large cohort of Koreans with NAFLD, they found that 5454 subjects with low APRI progressed to intermediate or high APRI with increase in weight quartiles and concluded , weight gain(change in BMI) was positively associated with APRI progression, whereas weight loss was negatively associated[206]. These findings also are similar to our study.

APRI correlation	Our study (p)	Carlos de mattias et al study
Waist circumference	**< 0.001**	<**0.05**
Diabetes	**0.0165**	**<0.01**
HTN	Not significant	Not significant
Dyslipidemia (Low HDL)	**< 0.001**	**<0.05**

Table II : Correlation of APRI with metabolic syndrome paramets in MetS patients

CARDIOVASCULAR RISK SCORES AND METABOLIC SYNDROME

In our study, the FRS scores also showed significant differences. A higher percentage of individuals with Metabolic Syndrome were in the high-risk category (32.35% vs. 5.88%) and intermediate risk category (41.18% vs. 11.76%) compared to Non Metabolic Syndrome group. Conversely, a greater proportion of individuals in

Non Metabolic Syndrome group were in the low-risk category (82.35% vs. 26.47%). The mean FRS was significantly higher in the Metabolic Syndrome group (16.68 ± 12.22) compared to the Non-Metabolic syndrome group (7.55 ± 7.03) (p-value < 0.001).

For the ASCVD risk scores, individuals with Metabolic Syndrome were more likely to fall into higher risk categories. Specifically, 32.35% of individuals with Metabolic Syndrome were classified as high risk, compared to only 2.94% in the Non Metabolic Syndrome group. Similarly, a larger proportion of those with Metabolic Syndrome were in the intermediate risk category (38.24% vs. 20.59%). Conversely, a majority of individuals in Non Metabolic Syndrome group were in the low-risk category (61.76% vs. 8.82%). The mean ASCVD risk score was significantly higher in the Metabolic Syndrome group (15.44 ± 9.9) compared to Non Metabolic Syndrome group (5.81 ± 5.61) indicating statistical significance (p-value < 0.001).

In the study by Carlos de mattias the patients with metabolic syndrome showed significantly high (p value< 0.05) Framingham risk scores with Mets Yes patients having mean scores of 32.91 ± 1.91 with Mets No patients having mean scores of 13.43 ± 1.43 [196]. In another study by Stefano ballestri, alessandro Mantovani et al , which was done in Italy to compare Non invasive markers and CVR in 107 patients who were diagnosed as NAFLD, patients with NAFLD were more likely to be overweight/obese, had a higher prevalence of diabetes and metabolic syndrome, as well as higher values of CVR scores (SCORE, Framingham risk score (FRS), Progetto CUORE)[193]. These findings are similar to our study.

Correlation of APRI with FRS and ASCVD

In our study, APRI and FRS have a substantial positive correlation (p-value = 0.0034) for persons with Metabolic Syndrome, there is also a significant positive correlation between ASCVD and APRI (p-value = 0.0030) in persons with Metabolic Syndrome, indicating that higher APRI scores are significantly associated with higher risk of CVD.

Similarly in the study by Carlo De Matteis, Marica Cariello et al the researchers found a significant and positive correlation(r=0.8) between APRI and CVR by FRS ($p<0.01$), with high statistical relevance in Mets Patients compared to Non mets patients[196]. In the study by Stefano ballestri, alessandro Mantovani et al the done on Italian population and using Italian CVR scores and FRS found moderate to strong correlation (coefficient 0.407 p = <0.001) between APRI and CVR (FRS, SCORE and PROGETTO CUORE) in NAFLD patients, in the same study all other non invasive markers (FIB 4, AAR, forns) showed positive and significant correlation with all 3 CVR scores[193].

In the study by Xiong, Shengjun; Yin et al in hypertensive patients, they found that LFSs were associated with CVD and high levels of LFSs significantly increase the probability of CVD in hypertensive population[208].

In the study by Hai Nguyen Ngoc Dang, Thang Viet Luong in Vietnam on MAFLD patients, they concluded that Patients with MAFLD predominantly face high or very high CV risks, with elevated liver fibrosis associated with increased 10-year estimated CVD risk.[209] The FIB-4 score which also contains AST and Platelets along with ALT and age, exhibits promising predictive value for identifying MAFLD

patients at very high risk of CV disease. This can act as future direction of research from our study.

In a study by Hui-Hui Liu, Ye-Xuan Cao et al in post Elective Percutaneous Coronary Intervention patients found that High LFSs levels might be useful for predicting adverse prognosis in patients with stable coronary artery disease following PCI[210], suggesting the possibility of the application of LFSs in the risk stratification before elective PCI

For those with Metabolic Syndrome, in our study age groups <50 and 50-59 and 60-69 show positive correlation, the correlation is significant and strong in the 60-69 age group (correlation coefficient 0.8186, p-value = 0.0038) between APRI and FRS, indicating a strong association between higher APRI scores and increased cardiovascular risk in this age group. In the study by Carlo De Matteis, Marica Cariello et al the researchers found a significant increase in CVR and APRI in age ranges 18-30 and also 31 -50 showing 2 fold increase in CVR.[196]The difference in age can be a attributed to Indian race which according to a study by Kundu J, Kundu S et al indicates that the overall self-reported prevalence of diagnosed CVDs was 29.4% for older adults age 45 and above in India. Age was associated with an increased risk of CVD,[211]also that our study population lacked subjects in the age group 18-30.

In females with Metabolic Syndrome, there is a significant positive correlation (correlation coefficient of 0.5963, p-value = 0.0315) between APRI and FRS, indicating that higher APRI scores are associated with higher cardiovascular risk. However, in males with Metabolic Syndrome, the correlation is weaker and not statistically significant (correlation coefficient of 0.3503, p-value = 0.1195). according to a study by Kundu J, Kundu S et al female older adults more likely to have CVDs than males [211]. Women are protected during reproductive age by the

cardioprotective effects of Estrogen as our mean study population was 58.62 ± 9.31 this effect would have been lost.

In the study by Carlo De Matteis, Marica Cariello et al they had findings that particularly in patients with a diagnosis of MetS, the difference in CVR between men and women decreases when APRI levels rise. Remarkably, they demonstrated that CVR in MetS Women with APRI > 0.5 essentially attain the same value as men in the MetS with APRI > 0.5 group [196].

In a meta-analysis by Mottillo, S, Filion, et al they had an observation that point estimates for cardiovascular risk were consistently higher in women with metabolic syndrome compared with men with metabolic syndrome, especially for all-cause mortality [212].our study and above Italian study and the meta analysis report increased CVR in females with metabolic syndrome.

STRENGTHS OF STUDY

- Our study used commonly available lab parameters i.e. AST and Platelet, and combined them to use a proven Marker of APRI, which is a Non-Invasive Marker of liver fibrosis and links it to CVR in metabolic syndrome group of patients.
- Study used two risk scores for CVR (FRS and ASCVD), leading to stronger association and to minimize Racial differences. Hardly, any other studies use ASCVD.

LIMITATIONS OF THE STUDY

- The relatively small sample size may limit the generalizability of the findings. Larger studies are needed to confirm these results.
- The study's cross-sectional nature precludes causal inferences. Longitudinal studies are necessary to establish causality and examine the temporal relationship between APRI and cardiovascular risk.
- No uniform distribution of age groups among our study sample.

CONCLUSIONS

- Individuals with MetS had significantly higher APRI values compared to those without MetS.
- In patients with metabolic syndrome, higher APRI values were associated with increased CVR, as assessed by both the Framingham Risk Score (FRS) and ASCVD scores.
- Significant differences were found among groups with APRI showing increased CVR in age group of 60-69 and among females of the metabolic syndrome group.
- Higher APRI values correlated with components of metabolic syndrome such as increased waist circumference, elevated glycemia, elevated systolic blood pressure, and Low HDL. Leading to stronger correlations between CVR and APRI when Components of Metabolic Syndrome are present.
- The study findings, suggest the use of APRI as a simple non-invasive routine marker for calculating cardiovascular risk in patients with Metabolic Syndrome.

SUMMARY

This study investigates the role of the Aspartate Aminotransferase to Platelet Ratio Index (APRI) in predicting cardiovascular risk in patients with metabolic syndrome (MetS). Metabolic syndrome, characterized by central obesity, elevated triglycerides, reduced HDL cholesterol, high blood pressure, and insulin resistance, is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD) and MAFLD.

The primary objectives were to compare APRI scores between MetS and non-MetS subjects and analyze the role of APRI in predicting cardiovascular risk using the Framingham Risk Score and ASCVD score in MetS subjects and figure out various factors affecting APRI.

A cross-sectional study was conducted with 68 subjects divided equally between those with and without MetS. Demographic data, anthropometric measurements, medical history, and biochemical markers were collected, and APRI was calculated. Statistical analyses included Chi-square tests, t-tests, Mann-Whitney U tests, Spearman's rank correlation tests, and Kruskal-Wallis tests. A p-value of ≤ 0.05 was considered significant.

- The results revealed that in baseline characteristics, the mean ages are similar, 58.62 ± 9.31 years for Metabolic Syndrome subjects and 56.97 ± 8.65 years in non-metabolic syndrome subjects, with no significant difference among gender distribution.
- In anthropometric measures Individuals with Metabolic Syndrome had a significantly larger hip circumference (p-value < 0.001), higher weight (p-

value =0.0022), and higher body mass index (BMI) (p-value < 0.001) compared to those in non metabolic syndrome group.

- Individuals with Metabolic Syndrome had significantly lower platelet counts (p-value < 0.001), higher ALT (p-value = 0.0092), higher alkaline phosphate (p-value = 0.0453) and lower HDL (p-value < 0.001), compared to non metabolic syndrome subjects. Additionally, they exhibit higher levels of HbA1c (p-value < 0.001), and fasting blood sugar (FBS) (p-value < 0.001) and higher SBP and DBP values compared to subjects without Metabolic Syndrome.
- Subjects with MetS had significantly higher APRI scores than those without MetS. Individuals with Metabolic Syndrome showed higher proportions of intermediate and high likelihood of fibrosis(>1.0) compared to those without, with a mean APRI score of 0.6 ± 0.38 in the Metabolic Syndrome group compared to 0.24 ± 0.11 in the non-Metabolic Syndrome group (p-value < 0.001).
- In Metabolic Syndrome subjects, there is a significant positive correlation between APRI with FRS and ASCVD risk scores. This suggests that higher APRI scores are associated with higher cardiovascular risk.
- In Metabolic Syndrome subjects, the correlation between APRI and FRS is significant and strong in the 60-69 age group (p-value = 0.0038), indicating a strong association between higher APRI scores and increased cardiovascular risk in this age group.
- Among females of the metabolic syndrome group, Greater significance was found in the correlation between APRI with FRS and ASCVD. Indicating women with higher APRI have higher cardiovascular risk compared to men.

- Higher APRI is associated with each individual component of metabolic syndrome such as increased waist circumference, Diabetes, SBP and dyslipidaemia. Highlighting the contribution of each individual component of metabolic syndrome to higher APRI and higher cardiovascular risk.

The study findings, suggest the use of APRI as a simple non-invasive marker for calculating cardiovascular risk in patients with Metabolic Syndrome.

Future research should explore the utility of APRI in larger and more diverse populations to validate these findings and refine cardiovascular risk prediction models.

BIBLIOGRAPHY

1. Satapathy, S. K. & Sanyal, A. J. Epidemiology and natural history of nonalcoholic fatty liver disease. Semin. Liver Dis. 35, 221–235.
2. https:// doi. org/ 10. 1055/s- 0035- 15629 43 (2015).
3. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988 Dec 1;37(12):1595-607.
4. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama. 2002 Jan 16;287(3):356-9.
5. Joshi SR. Metabolic syndrome-emerging clusters of the Indian phenotype. J Assoc Physicians India. 2003. Available from: https://www.researchgate.net/profile/Shashank-Joshi-8/publication/10568117_Metabolic_syndrome_-_Emerging_clusters_of_the_Indian_phenotype/links/00b495386fb5ceee35000000/Metabolic-syndrome-Emerging-clusters-of-the-Indian-phenotype.pdf
6. Wasir JS, Misra A, Vikram NK, Pandey RM, Gupta R. Comparison of definitions of the metabolic syndrome in adult Asian Indians. J Assoc Physicians India. 2008. Available from: https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=42ffb7639510a802fa83bb3d3ac1a9796b7609d3
7. Ineternational diabetes federation .worldwide definition of the metabolic syndrome. Available at www.idf.org/webdata/docs/idf_metabolic syndrome definition.pdf.

8. Abate N, Chandalia M, Snell PG, Grundy SM. Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men. The Journal of Clinical Endocrinology & Metabolism. 2004 Jun 1;89(6):27[5]0-5.

9. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama. 2002 Jan 16;287(3):356-9.

10. Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. The Journal of Clinical Endocrinology & Metabolism. 2001 Nov 1;86(11):5366-71.

11. Vague J. The degree of masculine differentiation of obesities: A factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. Am J Clin Nutr. 1956;4:20–34.

12. Avogaro P, Crepaldi G, Enzi G, Tiengo A (1967). "Associazione di iperlipemia, diabete mellito e obesita' di medio grado" [Association of hyperlipemia, diabetes mellitus and middle-degree obesity]. Acta Diabetologica Latina (in Italian). 4(4): 572–90. doi:10.1007/BF01544100. S2CID 25839940.

13. Phillips GB (July 1978). "Sex hormones, risk factors and cardiovascular disease". The American Journal of Medicine. 65 (1): 7–11. doi:10.1016/0002-9343(78)90685-X

14. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988 Dec 1;37(12):1595-607.

15. Kylin E (1923). "[Studies of the hypertension-hyperglycemia-hyperuricemia syndrome]". Zentralbl Inn Med (in German). 44: 105–27.

16. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR) Diabet Med. 1999;16:442–3

17. Saklayen M.G. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018 Feb 26;20:12. (published online). PMCID: PMC5866840; PMID: 29480368.

18. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama. 2002 Jan 16;287(3):356-9.

19. Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes. 2010;2(3):180-193. Available from: https:/onlinelibrary.wiley.com/doi/pdfdirect/10.1111/j.17530407.2010.00078.x

20. INTERNATIONAL JOURNAL OF PAEDIATRIC RESEARCH 2006.

21. Mohanan P.P. Metabolic syndrome in Indian population: public health implication. Hypertens J. 2016;2:1–6.

22. Bhalwar R. Metabolic syndrome: The Indian public health perspective. Med J Armed Forces India. 2020 Jan;76(1):8-16. doi: 10.1016/j.mjafi.2019.12.001. Epub 2020 Jan 13. PMID: 32020962; PMCID: PMC6994803.

23. Edwards, M. (2019). The Barker Hypothesis. In: Preedy, V., Patel, V. (eds) Handbook of Famine, Starvation, and Nutrient Deprivation. Springer, Cham. https://doi.org/10.1007/978-3-319-55387-0_71

24. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, Fujimoto WY. Visceral adiposity is an independent predictor of incident hypertension in Japanese Americans. Annals of internal medicine. 2004 Jun 15;140(12):992-1000.

25. Eckel R.H., Grundy S.M., Zimmet P.Z. The metabolic syndrome. Lancet. 2005;365:1415–1428.

26. Bhalwar R., Ohri V.C., Somani B.L., Kasthuri A.S. Differentials and determinants of syndrome 'X' and its role as coronary risk among healthy middle aged Indian army personnel. MJAFI (Med J Armed Forces India) 2006;62:146–152

27. Bhalwar R. Armed Forces Medical Research Committee (AFMRC) Project No: 3743/2007. Project Sanctioned under Aegis of DRDO and DGAFMS. 2012. A multi-centric study to uncover the real load of metabolic syndrome and its associated risk factors among army personnel. Report submitted in 2011 and presented as Best AFMRC Project in February.

28. DECODE Study Group. Does diagnosis of the metabolic syndrome detect further men at high risk of cardiovascular death beyond those identified by a conventional cardiovascular risk score? The DECODE Study. Eur J Cardiovasc Prev Rehabil. 2007 Apr;14 (2):192-9. doi: 10.1097/01.hjr.0000230107.78524.da. PMID: 17446796.

29. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17; 364 (9438):937-52. doi: 10.1016/S0140-6736(04)17018-9. PMID: 15364185.

30. Kim, J. A., Montagnani, M., Koh, K. K. and Quon, M. J. (2006). Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 113, 1888-1904. pathophysiological mechanisms. Circulation 113, 1888-1904.

31. Jonk, A. M., Houben, A. J., de Jongh, R. T., Serne, E. H., Schaper, N. C. and Stehouwer, C. D. (2007). Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. Physiology (Bethesda) 22, 252-260.

32. Semenkovich, C. F. (2006). Insulin resistance and atherosclerosis. J. Clin. Invest. 116, 1813-1822

33. Gimbrone, M. A., Jr, Topper, J. N., Nagel, T., Anderson, K. R. and Garcia-Cardena, G. (2000). Endothelial dysfunction, hemodynamic forces, and atherogenesis. Ann. NY Acad. Sci. 902, 230-239; discussion 239-240.

34. Huang, P. L. (2005). Unraveling the links between diabetes, obesity, and cardiovascular disease. Circ. Res. 96, 1129-1131.

35. Atochin, D. N., Wang, A., Liu, V. W., Critchlow, J. D., Dantas, A. P., Looft-Wilson, R., Murata, T., Salomone, S., Shin, H. K., Ayata, C. et al. (2007). The phosphorylation state of eNOS modulates vascular reactivity and outcome of cerebral ischemia in vivo. J. Clin. Invest. 117, 1961-1967.

36. Huang, P. L. A comprehensive definition for metabolic syndrome. Dis. Model Mech. 2, 231–237. https:// doi. org/ 10. 1242/ dmm.001180 (2009).

37. Larsen, G. L. & Henson, P. M. Mediators of inflammation. Annu. Rev. Immunol. 1, 335–359(1983)

38. Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. Nature, 444(7121), 860–867. doi:10.1038/nature05485

39. Beutler, B. Innate immunity: an overview. Mol. Immunol. 40, 845–859 (2004).

40. Levin, B. R., Lipsitch, M. & Bonhoeffer, S. Population biology, evolution, and infectious disease: convergence and synthesis. Science 283, 806–809 (1999).

41. Wellen, K. E. & Hotamisligil, G. S. Inflammation, stress, and diabetes. J. Clin. Invest. 115,1111–1119 (2005).

42. Shoelson, S. E., Lee, J. & Goldfine, A. B. Inflammation and insulin resistance. J. Clin. Invest.116, 1793–1801 (2006).

43. Uysal, K. .T, Wiesbrock, S. M., Marino, M. W. & Hotamisligil, G. S. Protection from obesity induced insulin resistance in mice lacking TNF-α function. Nature 389, 610–614 (1997).

44. Ventre, J. et al. Targeted disruption of the tumor necrosis factor-alpha gene — metabolic consequences in obese and nonobese mice. Diabetes 46, 1526–1531 (1997).

45. Hotamisligil, G. S., Arner, P., Caro, J. F., Atkinson, R. L. & Spiegelman, B. M. Increased adipose tissue expression of tumor necrosis factor-α in human obesity and insulin resistance. J. Clin. Invest. 95, 2409–2415 (1995).

46. Kern, P. A. et al. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J. Clin. Invest. 95,2111–2119 (1995).

47. Saghizadeh, M., Ong, J. M., Garvey, W. T., Henry, R. R. & Kern, P. A. The expression of TNFα by human muscle: relationship to insulin resistance. J. Clin. Invest. 97, 1111–1116 (1996).

48. Krogh-Madsen, R., Plomgaard, P., Moller, K., Mittendorfer, B. & Pedersen, B. K. Influence of TNF-α and IL-6 infusions on insulin sensitivity and expression of IL-18 in humans. Am. J.Physiol. Endocrinol. Metab. 291, E108–E114 (2006).

49. Ofei, F., Hurel, S., Newkirk, J., Sopwith, M. & Taylor, K. Effects of an engineered human anti-TNF-α antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. Diabetes 45, 881–885 (1996).

50. Gonzalez-Gay, M. A. et al. Anti-tumor necrosis factor-α blockade improves insulin resistance in patients with rheumatoid arthritis. Clin. Exp. Rheumatol. 24, 83–86 (2006).

51. Kiortsis, D. N., Mavridis, A. K., Vasakos, S., Nikas, S. N. & Drosos, A. A. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann. Rheum. Dis. 64, 765–766 (2005).

52. Aguirre, V., Uchida, T., Yenush, L., Davis, R. & White, M. F. The c-Jun NH2-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser307. J. Biol. Chem. 275, 9047–9054 (2000).

53. Gao, Z. et al. Serine phosphorylation of insulin receptor substrate 1 by inhibitor kappa B kinase complex. J. Biol. Chem. 277, 48115–48121 (2002).

54. Griffin, M. E. et al. Free fatty acid-induced insulin resistance is associated with activation of protein kinase C theta and alterations in the insulin signaling cascade. Diabetes 48,1270–1274 (1999).

55. Ozcan, U. et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science 306, 457–461 (2004).

56. Ricci, R. et al. Requirement of JNK2 for scavenger receptor A-mediated foam cell formation in atherogenesis. Science 306, 1558–1561 (2004).

57. Kaneto, H. N. Y. et al. Possible novel therapy for diabetes with cell-permeable JNKinhibitory peptide. Nature Med. 10, 1128–1132 (2004).

58. Liu, G. & Rondinone, C. M. JNK: bridging the insulin signaling and inflammatory pathway.Curr. Opin. Investig. Drugs 6, 979–987 (2005).

59. Yuan, M. et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted distruption of Ikkβ. Science 293, 1673–1677 (2001).

60. Hundal, R. S. et al. Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. J. Clin. Invest. 109, 1321–1326 (2002).

61. Cai, D. et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-β and NF-κB. Nature Med. 11, 183–190 (2005)

62. Arkan, M. C. et al. IKK-β links inflammation to obesity-induced insulin resistance. Nature Med. 11, 191–198 (2005).

63. Kim, J. K. et al. PKC-theta knockout mice are protected from fat-induced insulin resistance.J. Clin. Invest. 114, 823–827 (2004).

64. Boden, G. et al. Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor-kappaB pathway in rat liver. Diabetes 54, 3458–3465 (2005).

65. Semenkovich, C. F. (2006). Insulin resistance and atherosclerosis. J. Clin. Invest. 116,1813-1822.

66. Pagana KD, Pagana TJ, Pagana TN. Mosby's Diagnostic & Laboratory Test Reference. 14th edn St. Louis, Mo: Elsevier. 2019..

67. Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. Clinical chemistry. 2000 Dec 1;46(12):2027-49.

68. Lee DH, Blomhoff R, Jacobs DR. Review is serum gamma glutamyltransferase a marker of oxidative stress?. Free radical research. 2004 Jun 1;38(6):535-9.

69. Whitfield JB. Gamma glutamyl transferase. Critical reviews in clinical laboratory sciences. 2001 Jan 1;38(4):263-355.

70. Zhang H, Forman HJ, Choi J. γ-Glutamyl transpeptidase in glutathione biosynthesis. Methods in enzymology. 2005 Jan 1;401:468-83.

71. Aaseth J, Støa-Birketvedt G. Glutathione in overweight patients with poorly controlled type 2 diabetes. The Journal of Trace Elements in Experimental Medicine: The Official Publication of the International Society for Trace Element Research in Humans. 2000;13(1):105-11.

72. Wright Jr E, Scism-Bacon JL, Glass LC. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. International journal of clinical practice. 2006 Mar;60(3):308-14.

73. Bloomgarden ZT. Second World Congress on the Insulin Resistance Syndrome: insulin resistance syndrome and nonalcoholic fatty liver disease. Diabetes Care. 2005 Jun 1;28(6):1518-23.

74. Bo S, Gambino R, Durazzo M, Guidi S, Tiozzo E, Ghione F, Gentile L, Cassader M, Pagano GF. Associations between γ-glutamyl transferase, metabolic abnormalities and inflammation in healthy subjects from a population-based cohort: a possible implication for oxidative stress. World journal of gastroenterology. 2005 Dec 12;11(45):7109.

75. Robertson RP, Harmon J, Tran PO, Poitout V. β-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. Diabetes. 2004 Feb 1;53(suppl_1):S119-24.

76. Kannel WB, Castelli WP, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study. Annals of internal medicine. 1971 Jan 1;74(1):1-2..

77. Savage DB, Tan GD, Acerini CL, Jebb SA, Agostini M, Gurnell M, Williams RL, Umpleby AM, Thomas EL, Bell JD, Dixon AK. Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor-γ. Diabetes. 2003 Apr 1;52(4): 910-7.

78. Song Y, Niu T, Manson JE, Kwiatkowski DJ, Liu S. Are variants in the CAPN10 gene related to risk of type 2 diabetes? A quantitative assessment of population and family-based association studies. The American Journal of Human Genetics. 2004 Feb 1;74(2):208-22

79. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: molecular mechanisms. Cardiovascular diabetology. 2002 Dec;1(1):1-0.

80. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980;55:434–8.

81. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: A study of its natural history. Am J Gastroenterol. 1980;75(1):103-113.

82. Charatcharoenwitthaya P, Karaketklang K, et al. Impact of metabolic phenotype and alcohol consumption on mortality risk in metabolic dysfunction-associated fatty liver disease: a population-based cohort study. Sci Rep. 2024. DOI: 10.1038/s41598-023-1114815-2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11148152/

83. Chalasani, N.; Younossi, Z.; Lavine, J.E.; Charlton, M.; Cusi, K.; Rinella, M.; Harrison, S.A.; Brunt, E.M.; Sanyal, A.J. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018, 67, 328–357. [CrossRef] [PubMed].

84. Pang, Q.; Zhang, J.Y.; Song, S.D.; Qu, K.; Xu, X.S.; Liu, S.S.; Liu, C. Central obesity and nonalcoholic fatty liver disease risk after adjusting for body mass index. World. J. Gastroenterol. 2015, 21, 1650–1662. [CrossRef] [PubMed]

85. Younossi, Z.M.; Golabi, P.; de Avila, L.; Paik, J.M.; Srishord, M.; Fukui, N.; Qiu, Y.; Burns, L.; Afendy, A.; Nader, F. The global epidemiology of NAFLD

and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J. Hepatol. 2019, 71,793–801. [CrossRef] [PubMed]

86. Li, G.; Peng, Y.; Chen, Z.; Li, H.; Liu, D.; Ye, X. Bidirectional Association between Hypertension and NAFLD: A Systematic Review and Meta-Analysis of Observational Studies. Int. J. Endocrinol. 2022, 2022, 8463640. [CrossRef]

87. Assy, N.; Kaita, K.; Mymin, D.; Levy, C.; Rosser, B.; Minuk, G. Fatty infiltration of liver in hyperlipidemic patients. Dig. Dis. Sci.2000, 45, 1929–1934. [CrossRef]

88. Sanyal, A.J.; Campbell-Sargent, C.; Mirshahi, F.; Rizzo, W.B.; Contos, M.J.; Sterling, R.K.; Luketic, V.A.; Shiffman, M.L.; Clore,J.N. Nonalcoholic steatohepatitis: Association of insulin resistance and mitochondrial abnormalities. Gastroenterology 2001, 120,1183–1192. [CrossRef] [PubMed]

89. Vollenweider, P.; Ménard, B.; Nicod, P. Insulin resistance, defective insulin receptor substrate 2-associated phosphatidylinositol-3’ kinase activation, and impaired atypical protein kinase C (zeta/lambda) activation in myotubes from obese patients with impaired glucose tolerance. Diabetes 2002, 51, 1052–1059. [CrossRef] [PubMed]

90. Xing, L.J.; Zhang, L.; Liu, T.; Hua, Y.Q.; Zheng, P.Y.; Ji, G. Berberine reducing insulin resistance by up-regulating IRS-2 mRNA expression in nonalcoholic fatty liver disease (NAFLD) rat liver. Eur. J. Pharmacol. 2011, 668, 467–471. [CrossRef] [PubMed]

91. Berg, A.H.; Scherer, P.E. Adipose tissue, inflammation, and cardiovascular disease. Circ. Res. 2005, 96, 939–949. [CrossRef][PubMed]

92. Yanai, H.; Hirowatari, Y.; Ito, K.; Kurosawa, H.; Tada, N.; Yoshida, H. Understanding of Diabetic Dyslipidemia by Using theAnion-Exchange High

Performance Liquid Chromatography Data. J. Clin. Med. Res. 2016, 8, 424–426. [CrossRef]

93. Kelley, D.E.; Goodpaster, B.H. Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance. Diabetes. Care 2001, 24, 933–941. [CrossRef]

94. Fisher, E.A. The degradation of apolipoprotein B100: Multiple opportunities to regulate VLDL triglyceride production by different proteolytic pathways. Biochim. Biophys. Acta 2012, 1821, 778–781. [CrossRef]

95. Taghibiglou, C.; Carpentier, A.; Van Iderstine, S.C.; Chen, B.; Rudy, D.; Aiton, A.; Lewis, G.F.; Adeli, K. Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance. Evidence for enhanced lipoprotein assembly, reduced intracellular ApoB degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model. J. Biol. Chem. 2000,275, 8416–8425.

96. Chen, M.; Breslow, J.L.; Li, W.; Leff, T. Transcriptional regulation of the apoC-III gene by insulin in diabetic mice: Correlation with changes in plasma triglyceride levels. J. Lipid. Res. 1994, 35, 1918–1924. [CrossRef]

97. Hong, S.; Gordon, D.; Stec, D.E.; Hinds, T.D. Bilirubin: A Ligand of the PPAR

Nuclear Receptor. In Nuclear Receptors: The Art and Science of Modulator Design and Discovery; Badr, M.Z., Ed.; Springer International Publishing: Cham, Switzerland, 2021; pp. 463–482.

98. Moreno-Fernandez, M.E.; Giles, D.A.; Stankiewicz, T.E.; Sheridan, R.; Karns, R.; Cappelletti, M.; Lampe, K.; Mukherjee, R.;Sina, C.; Sallese, A.; et al. Peroxisomal -oxidation regulates whole body metabolism, inflammatory vigor,

and pathogenesis of nonalcoholic fatty liver disease. JCI Insight 2018, 3, e93626. [CrossRef]

99. Hinds, T.D., Jr.; Hosick, P.A.; Chen, S.; Tukey, R.H.; Hankins, M.W.; Nestor-Kalinoski, A.; Stec, D.E. Mice with hyperbilirubinemia due to Gilbert's syndrome polymorphism are resistant to hepatic steatosis by decreased serine 73 phosphorylation of PPAR. Am. J. Physiol. Endocrinol. Metab. 2017, 312, E244–E252. [CrossRef].

100. Stec, D.E.; John, K.; Trabbic, C.J.; Luniwal, A.; Hankins, M.W.; Baum, J.; Hinds, T.D., Jr. Bilirubin Binding to PPAR Inhibits Lipid Accumulation. Plos ONE 2016, 11, e0153427. [crossref]

101. Hinds, T.D., Jr.; Adeosun, S.O.; Alamodi, A.A.; Stec, D.E. Does bilirubin prevent hepatic steatosis through activation of the PPAR nuclear receptor? Med. Hypotheses 2016, 95, 54–57. [crossref]

102. Hinds, T.D., Jr.; Burns, K.A.; Hosick, P.A.; mcbeth, L.; Nestor-Kalinoski, A.; Drummond, H.A.; alamodi, A.A.; Hankins, M.W.;Heuvel, J.P.V.; Stec, D.E. Biliverdin Reductase A Attenuates Hepatic Steatosis by Inhibition of Glycogen Synthase Kinase (GSK)3 Phosphorylation of Serine 73 of Peroxisome Proliferator-activated Receptor (PPAR) . J. Biol. Chem. 2016, 291, 25179–25191.[crossref]

103. Wang, Y.; Nakajima, T.; Gonzalez, F.J.; Tanaka, N. Ppars as Metabolic Regulators in the Liver: Lessons from Liver-Specific PPAR-Null Mice. Int. J. Mol. Sci. 2020, 21, 2061. [crossref] [pubmed]

104. Paiva, A.A.; Raposo, H.F.; Wanschel, A.C.; Nardelli, T.R.; Oliveira, H.C. Apolipoprotein CIII Overexpression-Induced Hypertriglyceridemia Increases Nonalcoholic Fatty Liver Disease in Association with Inflammation and Cell Death. Oxid. Med.Cell. Longev. 2017, 2017, 1838679. [CrossRef] [PubMed]

105. Fuchs, M.; Sanyal, A.J. Lipotoxicity in NASH. J. Hepatol. 2012, 56, 291–293. [CrossRef]

106. Sinha, R.A. Autophagy: A Cellular Guardian against Hepatic Lipotoxicity. Genes 2023, 14, 553. [CrossRef]

107. Neuschwander-Tetri, B.A. Nontriglyceride hepatic lipotoxicity: The new paradigm for the pathogenesis of NASH.Curr. Gastroenterol. Rep. 2010, 12, 49–56. [CrossRef] [PubMed]

108. Van Rooyen, D.M.; Farrell, G.C. SREBP-2: A link between insulin resistance, hepatic cholesterol, and inflammation in NASH.J. Gastroenterol. Hepatol. 2011, 26, 789–792. [CrossRef]

109. Angulo, P.; Kleiner, D.E.; Dam-Larsen, S.; Adams, L.A.; Bjornsson, E.S.; Charatcharoenwitthaya, P.; Mills, P.R.; Keach, J.C.; Lafferty,H.D.; Stahler, A.; et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015, 149, 389–397. [CrossRef] [PubMed]

110. Musso, G.; Gambino, R.; Cassader, M.; Pagano, G. Meta-analysis: Natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann. Med. 2011, 43, 617–649. [CrossRef] [PubMed]

111. Eguchi, Y.; Hyogo, H.; Ono, M.; Mizuta, T.; Ono, N.; Fujimoto, K.; Chayama, K.; Saibara, T.; JSG-NAFLD. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: A multicenter large retrospective study. J. Gastroenterol. 2012, 47, 586–595. [CrossRef] [PubMed]

112. Yanai, H.; Adachi, H.; Hakoshima, M.; Katsuyama, H. Atherogenic Lipoproteins for the Statin Residual Cardiovascular Disease Risk. Int. J. Mol. Sci. 2022, 23, 13499. [CrossRef]

113. Nikkila, E.A.; Huttunen, J.K.; Ehnholm, C. Postheparin plasma lipoprotein lipase and hepatic lipase in diabetes mellitus.Relationship to plasma triglyceride metabolism. Diabetes 1977, 26, 11–21.

114. Nikkila, E.A.; Taskinen, M.R.; Kekki, M. Relation of plasma high-density lipoprotein cholesterol to lipoprotein-lipase activity in adipose tissue and skeletal muscle of man. Atherosclerosis 1978, 29, 497–501. [CrossRef]

115. Kasim, S.E.; Tseng, K.; Jen, K.L.; Khilnani, S. Significance of hepatic triglyceride lipase activity in the regulation of serum high density lipoproteins in type II diabetes mellitus. J. Clin. Endocrinol. Metab. 1987, 65, 183–187.

116. Yanai, H.; Adachi, H.; Hakoshima, M.; Katsuyama, H. Molecular Biological and Clinical Understanding of the Statin Residual Cardiovascular Disease Risk and Peroxisome Proliferator-Activated Receptor Alpha Agonists and Ezetimibe for Its Treatment.Int. J. Mol. Sci. 2022, 23, 3418. [CrossRef] [PubMed]

117. Duran, E.K.; Pradhan, A.D. Triglyceride-Rich Lipoprotein Remnants and Cardiovascular Disease. Clin. Chem. 2021, 67, 183–196.[CrossRef] [PubMed]

118. Schwartz, E.A.; Reaven, P.D. Lipolysis of triglyceride-rich lipoproteins, vascular inflammation, and atherosclerosis.Biochim. Biophys. Acta 2012, 1821, 858–866. [CrossRef]

119. Yanai, H.; Adachi, H.; Hakoshima, M.; Katsuyama, H. Molecular Biological and Clinical Understanding of the Statin Residual Cardiovascular Disease Risk and Peroxisome Proliferator-Activated Receptor Alpha Agonists and

Ezetimibe for Its Treatment.Int. J. Mol. Sci. 2022, 23, 3418. [CrossRef] [PubMed]

120. Chandra, N.C. A comprehensive account of insulin and LDL receptor activity over the years: A highlight on their signaling and functional role. J. Biochem. Mol. Toxicol. 2021, 35, e22840. [CrossRef] [PubMed]

121. Lally, S.; Owens, D.; Tomkin, G.H. Genes that affect cholesterol synthesis, cholesterol absorption, and chylomicron assembly: The relationship between the liver and intestine in control and streptozotosin diabetic rats. Metabolism 2007, 56, 430–438. [CrossRef]

122. Actis Dato, V.; Chiabrando, G.A. The Role of Low-Density Lipoprotein Receptor-Related Protein 1 in Lipid Metabolism, Glucose Homeostasis and Inflammation. Int. J. Mol. Sci. 2018, 19, 1780. [CrossRef]

123. Borén, J.;Williams, K.J. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: A triumph of simplicity. Curr. Opin. Lipidol. 2016, 27, 473–483. [CrossRef] [PubMed]

124. Ahn, J.; Jun, D.W.; Lee, H.Y.; Moon, J.H. Critical appraisal for low-carbohydrate diet in nonalcoholic fatty liver disease: Review and meta-analyses. Clin. Nutr. 2019, 38, 2023–2030. [CrossRef]

125. Houttu, V.; Csader, S.; Nieuwdorp, M.; Holleboom, A.G.; Schwab, U. Dietary Interventions in Patients With Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Front. Nutr. 2021, 8, 716783. [CrossRef]

126. Haigh, L.; Kirk, C.; El Gendy, K.; Gallacher, J.; Errington, L.; Mathers, J.C.; Anstee, Q.M. The effectiveness and acceptability of Mediterranean diet and

calorie restriction in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis.Clin. Nutr. 2022, 41, 1913–1931. [CrossRef]

127. Rizza, W.; Veronese, N.; Fontana, L. What are the roles of calorie restriction and diet quality in promoting healthy longevity?Ageing. Res. Rev. 2014, 13, 38–45. [CrossRef] [PubMed]

128. Yin, C.; Li, Z.; Xiang, Y.; Peng, H.; Yang, P.; Yuan, S.; Zhang, X.; Wu, Y.; Huang, M.; Li, J. Effect of Intermittent Fasting on Non-Alcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis. Front. Nutr. 2021, 8, 709683. [CrossRef] [PubMed]

129. Orci, L.A.; Gariani, K.; Oldani, G.; Delaune, V.; Morel, P.; Toso, C. Exercise-based Interventions for Nonalcoholic Fatty Liver Disease: A Meta-analysis and Meta-regression. Clin. Gastroenterol. Hepatol. 2016, 14, 1398–1411. [CrossRef]

130. González-Ruiz, K.; Ramírez-Vélez, R.; Correa-Bautista, J.E.; Peterson, M.D.; García-Hermoso, A. The Effects of Exercise on Abdominal Fat and Liver Enzymes in Pediatric Obesity: A Systematic Review and Meta-Analysis. Child. Obes. 2017, 13, 272–282.[CrossRef]

131. Musso, G.; Cassader, M.; Rosina, F.; Gambino, R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of randomised trials.Diabetologia 2012, 55, 885–904. [CrossRef]

132. Katsagoni, C.N.; Georgoulis, M.; Papatheodoridis, G.V.; Panagiotakos, D.B.; Kontogianni, M.D. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: A meta-analysis. Metabolism 2017, 68, 119–132. [CrossRef]

133. Kamata, S.; Honda, A.; Ishii, I. Current Clinical Trial Status and Future Prospects of PPAR-Targeted Drugs for Treating Nonalcoholic Fatty Liver Disease. Biomolecules 2023, 13, 1264. [CrossRef]

134. Katsuyama, H.; Yanai, H.; Adachi, H.; Hakoshima, M. A Significant Effect of Pemafibrate on Hepatic Steatosis and Fibrosis Indexes in Patients With Hypertriglyceridemia. Gastroenterol. Res. 2023, 16, 240–243. [CrossRef]

135. Rachid, T.L.; Silva-Veiga, F.M.; Graus-Nunes, F.; Bringhenti, I.; Mandarim-de-Lacerda, C.A.; Souza-Mello, V. Differential actions of PPAR-alpha and PPAR-beta/delta on beige adipocyte formation: A study in the subcutaneous white adipose tissue of obese male mice. PLoS ONE 2018, 13, e0191365. [CrossRef] [PubMed]

136. Kim, S.H.; Plutzky, J. Brown Fat and Browning for the Treatment of Obesity and Related Metabolic Disorders. Diabetes. Metab. J.2016, 40, 12–21. [CrossRef]

137. Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J.C. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998, 98, 2088–2093. [CrossRef]

138. Qiang, X.; Xu, L.; Zhang, M.; Zhang, P.;Wang, Y.;Wang, Y.; Zhao, Z.; Chen, H.; Liu, X.; Zhang, Y. Demethyleneberberine attenuates non-alcoholic fatty liver disease with activation of AMPK and inhibition of oxidative stress. Biochem. Biophys. Res. Commun. 2016,472, 603–609. [CrossRef]

139. Liu, S.; Jing, F.; Yu, C.; Gao, L.; Qin, Y.; Zhao, J. AICAR-Induced Activation of AMPK Inhibits TSH/SREBP-2/HMGCR Pathway in Liver. PLoS ONE 2015, 10, e0124951. [CrossRef]

140. Day, E.A.; Ford, R.J.; Steinberg, G.R. AMPK as a Therapeutic Target for Treating Metabolic Diseases. Trends Endocrinol. Metab.2017, 28, 545–560. [CrossRef]

141. Yun, H.; Park, S.; Kim, M.J.; Yang, W.K.; Im, D.U.; Yang, K.R.; Hong, J.; Choe, W.; Kang, I.; Kim, S.S.; et al. AMP-activated protein kinase mediates the antioxidant effects of resveratrol through regulation of the transcription factor FoxO1. FEBS J. 2014, 281,4421–4438. [CrossRef]

142. Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J.C. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998, 98, 2088–2093. [CrossRef]

143. Kim, H.; Haluzik, M.; Asghar, Z.; Yau, D.; Joseph, J.W.; Fernandez, A.M.; Reitman, M.L.; Yakar, S.; Stannard, B.; Heron-Milhavet,L.; et al. Peroxisome proliferator-activated receptor-alpha agonist treatment in a transgenic model of type 2 diabetes reverses the lipotoxic state and improves glucose homeostasis. Diabetes 2003, 52, 1770–1778. [CrossRef]

144. Chinetti, G.; Lestavel, S.; Bocher, V.; Remaley, A.T.; Neve, B.; Torra, I.P.; Teissier, E.; Minnich, A.; Jaye, M.; Duverger, N.; et al.PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. Nat. Med. 2001, 7, 53–58. [CrossRef]

145. Lee, M.; Saver, J.L.; Towfighi, A.; Chow, J.; Ovbiagele, B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: A meta-analysis. Atherosclerosis 2011, 217, 492–498. [CrossRef]

146. Katsuyama, H.; Hamasaki, H.; Adachi, H.; Moriyama, S.; Kawaguchi, A.; Sako, A.; Mishima, S.; Yanai, H. Effects of Sodium-Glucose Cotransporter 2

Inhibitors on Metabolic Parameters in PatientsWith Type 2 Diabetes: A Chart-Based Analysis. J. Clin.Med. Res. 2016, 8, 237–243. [CrossRef]

147. Yanai, H.; Hakoshima, M.; Adachi, H.; Kawaguchi, A.; Waragai, Y.; Harigae, T.; Masui, Y.; Kakuta, K.; Hamasaki, H.; Katsuyama,H.; et al. Effects of Six Kinds of Sodium-Glucose Cotransporter 2 Inhibitors on Metabolic Parameters, and Summarized Effect and Its Correlations with Baseline Data. J. Clin. Med. Res. 2017, 9, 605–612. [CrossRef]

148. Katsuyama, H.; Hakoshima, M.; Iijima, T.; Adachi, H.; Hidekatsu Yanai, H. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hepatic Fibrosis in Patients With Type 2 Diabetes: A Chart-Based Analysis. J. Endocrinol. Metab. 2020, 10, 1–7. [CrossRef]

149. Sasso, M.; Beaugrand, M.; de Ledinghen, V.; Douvin, C.; Marcellin, P.; Poupon, R.; Sandrin, L.; Miette, V. Controlled attenuation parameter (CAP): A novel VCTE™guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: Preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med. Biol. 2010, 36,1825–1835. [CrossRef]

150. Piazzolla, V.A.; Mangia, A. Noninvasive Diagnosis of NAFLD and NASH. Cells 2020, 9, 1005. [CrossRef]

151. Vuppalanchi, R.; Siddiqui, M.S.; Van Natta, M.L.; Hallinan, E.; Brandman, D.; Kowdley, K.; Neuschwander-Tetri, B.A.; Loomba,R.; Dasarathy, S.; Abdelmalek, M.; et al. Performance characteristics of vibration-controlled transient elastography for evaluation of nonalcoholic fatty liver disease. Hepatology 2018, 67, 134–144. [CrossRef]

152. Jabbour, S.A.; Goldstein, B.J. Sodium glucose co-transporter 2 inhibitors: Blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes. Int. J. Clin. Pract. 2008, 62, 1279–1284. [CrossRef]

153. Yanai, H.; Katsuyama, H.; Hamasaki, H.; Adachi, H.; Moriyama, S.; Yoshikawa, R.; Sako, A. Sodium-Glucose Cotransporter 2 Inhibitors: Possible Anti-Atherosclerotic Effects Beyond Glucose Lowering. J. Clin. Med. Res. 2016, 8, 10–14. [CrossRef]

154. Vasilakou, D.; Karagiannis, T.; Athanasiadou, E.; Mainou, M.; Liakos, A.; Bekiari, E.; Sarigianni, M.; Matthews, D.R.; Tsapas, A.Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. Ann. Intern. Med. 2013,159, 262–274. [CrossRef]

155. Sanchez-Garcia, A.; Simental-Mendia, M.; Millan-Alanis, J.M.; Simental-Mendia, L.E. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: A systematic review and meta-analysis of 48 randomized controlled trials. Pharmacol. Res. 2020, 160, 105068.[CrossRef]

156. Li, D.; Wu, T.; Wang, T.; Wei, H.; Wang, A.; Tang, H.; Song, Y. Effects of sodium glucose cotransporter 2 inhibitors on risk of dyslipidemia among patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials.Pharmacoepidemiol. Drug Saf. 2020, 29, 582–590. [CrossRef]

157. Yanai, H.; Adachi, H.; Hakoshima, M.; Katsuyama, H. Significance of Endothelial Dysfunction Amelioration for Sodium-Glucose Cotransporter 2 Inhibitor-Induced Improvements in Heart Failure and Chronic Kidney Disease in Diabetic Patients. Metabolites 2023, 13, 736. [CrossRef]

158. Rahman, H.; Khan, S.U.; Lone, A.N.; Ghosh, P.; Kunduru, M.; Sharma, S.; Sattur, S.; Kaluski, E. Sodium-Glucose Cotransporter-2 Inhibitors and Primary

Prevention of Atherosclerotic Cardiovascular Disease: A Meta-Analysis of Randomized Trials and Systematic Review. J. Am. Heart Assoc. 2023, 12, e030578. [CrossRef]

159. Katsuyama, H.; Hakoshima, M.; Umeyama, S.; Iida, S.; Adachi, H.; Yanai, H. Real-World Efficacy of Glucagon-like Peptide-1 (GLP-1) Receptor Agonist, Dulaglutide, on Metabolic Parameters in Japanese Patients with Type 2 Diabetes: A Retrospective Longitudinal Study. Biomedicines 2023, 11, 869. [CrossRef]

160. Carbone, L.J.; Angus, P.W.; Yeomans, N.D. Incretin-based therapies for the treatment of non-alcoholic fatty liver disease: A systematic review and meta-analysis. J. Gastroenterol. Hepatol. 2016, 31, 23–31. [CrossRef]

161. Dong, Y.; Lv, Q.; Li, S.;Wu, Y.; Li, L.; Li, J.; Zhang, F.; Sun, X.; Tong, N. Efficacy and safety of glucagon-like peptide-1 receptor agonists in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Clin. Res. Hepatol. Gastroenterol. 2017, 41,284–295. [CrossRef]

162. Mantovani, A.; Petracca, G.; Beatrice, G.; Csermely, A.; Lonardo, A.; Targher, G. Glucagon-Like Peptide-1 Receptor Agonists for Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: An Updated Meta-Analysis of Randomized Controlled Trials. Metabolites 2021, 11, 73. [CrossRef]

163. Davies, M.J.; D'Alessio, D.A.; Fradkin, J.; Kernan, W.N.; Mathieu, C.; Mingrone, G.; Rossing, P.; Tsapas, A.; Wexler, D.J.; Buse, J.B. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018, 61, 2461–2498. [CrossRef]

164. Buse, J.B.; Wexler, D.J.; Tsapas, A.; Rossing, P.; Mingrone, G.; Mathieu, C.; D'Alessio, D.A.; Davies, M.J. 2019 update to:Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2020, 63, 221–228. [CrossRef] [PubMed]

165. Nauck, M.A.; Quast, D.R.; Wefers, J.; Meier, J.J. GLP-1 receptor agonists in the treatment of type 2 diabetes—State-of-the-art.Mol. Metab. 2021, 46, 101102. [CrossRef] [PubMed]

166. Krieger, J.P. Intestinal glucagon-like peptide-1 effects on food intake: Physiological relevance and emerging mechanisms. Peptides 2020, 131, 170342. [CrossRef] [PubMed]

167. Bray, J.J.H.; Foster-Davies, H.; Salem, A.; Hoole, A.L.; Obaid, D.R.; Halcox, J.P.J.; Stephens, J.W. Glucagon-like peptide-1 receptor agonists improve biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomised controlled trials. Diabetes Obes. Metab. 2021, 23, 1806–1822. [CrossRef] [PubMed]

168. Katout, M.; Zhu, H.; Rutsky, J.; Shah, P.; Brook, R.D.; Zhong, J.; Rajagopalan, S. Effect of GLP-1 mimetics on blood pressure and relationship to weight loss and glycemia lowering: Results of a systematic meta-analysis and meta-regression. Am. J. Hypertens.2014, 27, 130–139. [CrossRef]

169. Yanai, H.; Adachi, H.; Hakoshima, M.; Katsuyama, H. Postprandial Hyperlipidemia: Its Pathophysiology, Diagnosis, Atherogenesis,and Treatments. Int. J. Mol. Sci. 2023, 24, 13942. [CrossRef]

170. Yanai, H.; Adachi, H.; Hakoshima, M.; Katsuyama, H. Glucagon-Like Peptide 1 Receptor Agonists Versus Sodium-Glucose Cotransporter 2 Inhibitors for

Atherosclerotic Cardiovascular Disease in PatientsWith Type 2 Diabetes. Cardiol. Res. 2023, 14,12–21. [CrossRef] [PubMed]

171. Rahman, A.; Alqaisi, S.; Saith, S.E.; Alzakhari, R.; Levy, R. The Impact of Glucagon-Like Peptide-1 Receptor Agonist on the Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus: A Meta-Analysis and Systematic Review. Cardiol. Res. 2023,14, 250–260. [CrossRef]
172. Gu, Y.; Sun, L.; Zhang, W.; Kong, T.; Zhou, R.; He, Y.; Deng, C.; Yang, L.; Kong, J.; Chen, Y.; et al. Comparative efficacy of 5 sodium-glucose cotransporter protein-2 (SGLT-2) inhibitor and 4 glucagon-like peptide-1 (GLP-1) receptor agonist drugs in non-alcoholic fatty liver disease: A GRADE-assessed systematic review and network meta-analysis of randomized controlled trials. Front. Pharmacol. 2023, 14, 1102792.
173. Yan, H.; Huang, C.; Shen, X.; Li, J.; Zhou, S.; Li, W. GLP-1 RAs and SGLT-2 Inhibitors for Insulin Resistance in Nonalcoholic FattY Liver Disease: Systematic Review and Network Meta-Analysis. Front. Endocrinol. 2022, 13, 923606. [CrossRef]
174. Mantovani, A.; Byrne, C.D.; Targher, G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: A systematic review. Lancet. Gastroenterol. Hepatol. 2022, 7, 367–378. [CrossRef]
175. Katsuyama, H.; Hakoshima, M.; Umeyama, S.; Iida, S.; Adachi, H.; Yanai, H. Real-World Efficacy of Glucagon-like Peptide-1(GLP-1) Receptor Agonist, Dulaglutide, on Metabolic Parameters in Japanese Patients with Type 2 Diabetes: A Retrospective Longitudinal Study. Biomedicines 2023, 11, 869. [CrossRef]

176. Bower, G.; Toma, T.; Harling, L.; Jiao, L.R.; Efthimiou, E.; Darzi, A.; Athanasiou, T.; Ashrafian, H. Bariatric Surgery and Non-

177. Alcoholic Fatty Liver Disease: A Systematic Review of Liver Biochemistry and Histology. Obes. Surg. 2015, 25, 2280–2289.[CrossRef] [PubMed]

178. Popov, V.B.; Thompson, C.C.; Kumar, N.; Ciarleglio, M.M.; Deng, Y.; Laine, L. Effect of Intragastric Balloons on Liver Enzymes: A Systematic Review and Meta-Analysis. Dig. Dis. Sci. 2016, 61, 2477–2487. [CrossRef]

179. Chandan, S.; Mohan, B.P.; Khan, S.R.; Facciorusso, A.; Ramai, D.; Kassab, L.L.; Bhogal, N.; Asokkumar, R.; Lopez-Nava, G.;McDonough, S.; et al. Efficacy and Safety of Intragastric Balloon (IGB) in Non-alcoholic Fatty Liver Disease (NAFLD): A Comprehensive Review and Meta-analysis. Obes. Surg. 2021, 31, 1271–1279. [CrossRef]

180. Mantovani A, Csermely A, Petracca G, Beatrice G, Corey KE, Simon TG, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021 Nov;6(11):903-913. doi: 10.1016/S2468-1253(21)00308-3. Epub 2021 Sep 21. PMID: 34555346.

181. Alkhouri N, Tamimi TAR, Yerian L, Lopez R. The inflamed liver and atherosclerosis: a link between histologic severity of nonalcoholic fatty liver disease and increased cardiovascular risk. Am J Gastroenterol. 2009 Oct;104(S1):315. Available from: https://journals.lww.com/ajg/fulltext/2009/10003/the_inflamed_liver_and_atherosclerosis__a_link.315.aspx

182. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis

and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003 Aug;38(2):518-26. doi: 10.1053/jhep.2003.50346. PMID: 12883497.

183. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011 Mar;53(3):726-36.

184. Khan DA, Fatima-Tuz-Zuhra, Butt AK, Haider Z, Shafqat F. Correlation between aminotransferase to platelet ratio index and liver biopsy histopathology in hepatitis C patients. J Ayub Med Coll Abbottabad. 2009 Jan-Mar;21(1):12-6.

185. Jain P, Tripathi BK, Gupta B, Majumdar A, Gulati S, Vishwakarma PK. Aspartate aminotransferase to platelet ratio index for non-invasive prediction of liver fibrosis in chronic hepatitis B and C: a retrospective cohort study. Trop Gastroenterol. 2011 Apr-Jun;32(2):109-14.

186. Johannessen A, Stockdale AJ, Henrion MYR, Biague AJ, da Silva ZJ, de Araújo WN, et al. Non-invasive fibrosis markers for chronic hepatitis B in sub-Saharan Africa: A cross-sectional study from Guinea-Bissau. BMC Infect Dis. 2020 Jul 7;20(1):507.

187. López Tórrez SM, Ayala CO, Ruggiro PB, Drumond Costa CA, Wagner MB, Padoin AV, et al. Accuracy of prognostic serological biomarkers in predicting liver fibrosis severity in people with metabolic dysfunction-associated steatotic liver disease: a meta-analysis. Front Nutr. 2024;8:1284509. DOI: 10.3389/fnut.2024.1284509. Available from: https://www.frontiersin.org/articles/10.3389/fnut.2024.1284509/full

188. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice

guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-357. DOI: 10.1002/hep.29367. Available from: https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.29367

189. Wong ND, Budoff MJ, Ferdinand K, Graham IM, Greenland P, Toth PP, et al. Atherosclerotic cardiovascular disease risk assessment: An American Society for Preventive Cardiology clinical practice statement. Am J Prev Cardiol. 2022;100022

190. Wong ND. Cardiovascular risk assessment: the foundation of preventive cardiology. Am J Prev Cardiol. 2020;4:100088

191. Dawber TR, Meadors GF, Moore FE. Epidemiology of Coronary Heart Disease—The Framingham Heart Study. Am J Public Health. 1951;41(4):279-286. DOI: 10.2105/AJPH.41.4.279. Available from: https://doi.org/10.2105/AJPH.41.4.279

192. Hemann BA, Bimson WF, Lorber R. The Framingham Risk Score: an appraisal of its benefits and limitations. Am Heart Hosp J. 2007;5(2):91-6. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1541-9215.2007.06350.x

193. Ballestri S, Mantovani A, Baldelli E, Lugari S, Maurantonio M, Nascimbeni F, Marrazzo A, Romagnoli D, Targher G, Lonardo A. Liver Fibrosis Biomarkers Accurately Exclude Advanced Fibrosis and Are Associated with Higher Cardiovascular Risk Scores in Patients with NAFLD or Viral Chronic Liver Disease. Diagnostics (Basel). 2021 Jan 9;11(1):98. doi: 10.3390/diagnostics11010098. PMID: 33435415; PMCID: PMC7827076.

194. Sert A, Pirgon Ö, Aypar E, Yılmaz H. Correlation between Aspartate Aminotransferase-to-Platelet Ratio Index and Carotid Intima-Media Thickness

in Obese Adolescents with Non-Alcoholic Fatty Liver Disease. J Clin Res Pediatr Endocrinol. 2013;5:274-280.

195. Yi M, Peng W, Teng F, Kong Q. The role of noninvasive scoring systems for predicting cardiovascular disease risk in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2022;34(11):1234-1245. DOI: 10.1097/MEG.0000000000002225. Available from: https://cdn-links.lww.com/permalink/ejgh/a/ejgh_34_11_2022_09_19_chen_21916_sdc1.pdf

196. De Matteis, C., Cariello, M., Graziano, G. *et al.* AST to Platelet Ratio Index (APRI) is an easy-to-use predictor score for cardiovascular risk in metabolic subjects. *Sci Rep* **11**, 14834 (2021). https://doi.org/10.1038/s41598-021-94277-3

197. Finney AC, Das S, Kumar D, McKinney MP. The interplay between nonalcoholic fatty liver disease and atherosclerotic cardiovascular disease. Front Cardiovasc Med. 2023;10:1116861. DOI: 10.3389/fcvm.2023.1116861. Available from: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1116861/full

198. Unnikrishnan R, Anjana RM, Deepa M, Pradeepa R, Joshi SR, Bhansali A, Dhandania VK, Joshi PP, Madhu SV, Rao PV, Lakshmy R, Jayashri R, Velmurugan K, Nirmal E, Subashini R, Vijayachandrika V, Kaur T, Shukla DK, Das AK, Mohan V; ICMR–INDIAB Collaborative Study Group. Glycemic control among individuals with self-reported diabetes in India--the ICMR-INDIAB Study. Diabetes Technol Ther. 2014 Sep;16(9):596-603. doi: 10.1089/dia.2014.0018. Epub 2014 Aug 7. PMID: 25101698; PMCID: PMC4135327.

199. Kalra, Sanjay, and A. Unnikrishnan. "Obesity in India: The weight of the nation." *Journal of Medical Nutrition and Nutraceuticals*, vol. 1, no. 1, Jan.-June 2012, p. 37. *Gale OneFile: Health and Medicine*, link.gale.com/apps/doc/A290684870/HRCA?u=anon~f1e66076&sid=googleScholar&xid=989ab1af. Accessed 26 June 2024.

200. Udgire, P., & Karnik, N. D. (2017). Lipid profile in metabolic syndrome patients: An Indian perspective. *International Journal of Current Medical and Applied Sciences*, 13(3), 168-173. Available at: http://www.ijcmaas.com/

201. Ludgate S, Steen J, Divilly P, Naimimohasses S, Kennedy C, Pazderska A, Phelan N, Norris S, Healy ML. Assessment of liver imaging in a diabetic population with an abnormal AST-to-platelet-ratio-index (APRI) or Fibrosis-4-score (FIB4). Endocr Abstr. 2019;59

202. Das, A. K. ., Sharma, A. ., & Labrez, M. Z. . (2023). CORRELATION OF FIB-4 AND APRI SCORE WITH FIBRO SCAN SCORE TO PREDICT FIBROSIS IN OBESE TYPE-2 DIABETIC PATIENTS. *Student's Journal of Health Research Africa*, *4*(12), 7. https://doi.org/10.51168/sjhrafrica.v4i12.761

203. Xiong S, Yin S, Deng W, Zhao Y, Li W, Wang P, Li Z, Yang H, Zhou Y, Yu S, Guo X, Sun Y. Predictive value of liver fibrosis scores in cardiovascular diseases among hypertensive population. J Hypertens. 2020;38(7):1442-1448. Available from: https://doi.org/10.1097/HJH.0000000000002457.

204. Koo DJ, Lee MY, Jung I, Moon SJ, Kwon H, Park SE. Baseline homeostasis model assessment of insulin resistance associated with fibrosis progression in patients with nonalcoholic fatty liver disease without diabetes: a longitudinal study. PLoS One. 2021;16(8) DOI:10.1371/journal.pone.0255535. Available from:https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0255535

205. Yen YH, Kuo FY, Kee KM, Chang KC, Tsai MC, Hu TH, Lu SN, Wang JH, Hung CH, Chen CH. APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. PLoS One. 2018 Jun 28;13(6):e0199760. doi: 10.1371/journal.pone.0199760. PMID: 29953518; PMCID: PMC6023204.

206. Kim Y, Chang Y, Cho YK, Ahn J, Shin H, Ryu S. Obesity and Weight Gain Are Associated With Progression of Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol. 2019 Feb;17(3):543-550.e2. doi: 10.1016/j.cgh.2018.07.006. Epub 2018 Sep 11. PMID: 30012432.

207. Muhammad AG, Hansen FO, Gantzel RH, Rex KF, Villadsen GE, Grønbæk H, Pedersen ML. Non-alcoholic fatty liver disease in patients with type 2 diabetes in Greenland: a register-based cross-sectional study. Int J Circumpolar Health. 2022 Dec;81(1):2065755. doi: 10.1080/22423982.2022.2065755. PMID: 35440282; PMCID: PMC9037206.

208. Xiong S, Yin S, Deng W, Zhao Y, Li W, Wang P, Li Z, Yang H, Zhou Y, Yu S, Guo X, Sun Y. Predictive value of liver fibrosis scores in cardiovascular diseases among hypertensive population. J Hypertens. 2020;38(7):1442-1448. Available from: https://doi.org/10.1097/HJH.0000000000002457.

209. Dang HNN, Luong TV, Tran TT, Hoang TA. The correlation between liver fibrosis and the 10-year estimated risk of cardiovascular disease in adults with metabolic-associated fatty liver disease: A cross-sectional study in Vietnam. Health Sci Rep. 2024 May 8;7(5):e2102. doi: 10.1002/hsr2.2102. PMID: 38725561; PMCID: PMC11079443.

210. Liu HH, Cao YX, Jin JL, Hua Q, Li YF, Zhang Y, et al. Liver fibrosis scoring systems as novel tools for predicting cardiovascular outcomes in patients following elective percutaneous coronary intervention. J Am Heart Assoc.

2021. DOI: 10.1161/JAHA.120.018869. Available from: https://www.ahajournals.org/doi/pdf/10.1161/JAHA.120.018869

211. Kundu J, Kundu S. Cardiovascular disease (CVD) and its associated risk factors among older adults in India: Evidence from LASI Wave 1. Clin Epidemiol Glob Health. 2022;13:100937. doi:10.1016/j.cegh.2021.100937

212. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010 Sep 28;56(14):1113-32. doi: 10.1016/j.jacc.2010.05.034. PMID: 20863953.

ANEXURE I – INFORMED CONSENT FORM

KAHERs JNMC, BELAGAVI

"AST TO PLATELET RATIO INDEX (APRI) IN PATIENTS WITH METABOLIC SYNDROME AND ITS RELATION WITH CARDIOVASCULAR RISK"

Name of Student/Principal Investigator:

Name of Guide/Co Investigators:

- Objective: A cross sectional study, Comparing APRI score in metabolic subjects and its association with various factors.
- Given the relevance of systemic inflammation in NAFLD, often associated with MetS, in the present study we plan to analyse the potential role of APRI score in predicting the cardiovascular risk (CVR) using the ASCVD SCORE AND FARMINGHAMS SCORE in metabolic subjects.

Introduction: Visceral obesity is characterized by a low-grade inflammatory systemic state that contributes to the genesis of non-alcoholic fatty liver disease (NAFLD), frequently associated with liver fibrosis.

Noninvasive serum markers have recently emerged as reliable, easy-to-use scores to predict liver fibrosis. Several studies investigated the role of NAFLD score (NFS), AST to Platelet Ratio Index (APRI score) in predicting the role of Met S in non-hepatitis patients, investigating why liver failure is linked to cardiovascular diseases, though the association between all the scores and MetS is still not well established.

NAFLD is often linked to metabolic and cardiovascular risk.

Need of the study: Our study aims to find the correlation between simple noninvasive blood markers ie AST and Platelet to that of cardiovascular risk by using framingham score in metabolic syndrome patients.

Explanation of procedure: In patient and out patient individuals with metabolic syndrome will be identified. Detailed history and examination would be done history including =age, sex, h/o smoking, h/o diabetes, h/o hypertension treatment, on treatment with drugs like statin or aspirin? examination including = systolic and diastolic blood pressure)

ANTHROPOMETRICAL MEASUREMENTS OF THE PATIENTS WILL BE TAKEN

- WAIST CIRCUMFERENCE
- HIP CIRCUMFERENCE
- HEIGHT
- WEIGHT
- BMI
- CALF CIRCUMFERENCE

INVESTIGATIONS

- CBC
- MR
- LFT
- HBA1C
- LIPID PROFILE
- FBS
- PPBS

Withdrawal from participation in the study: Participation in this study is 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/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

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 from identifying 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.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to 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 "AST to Platelet Ratio Index (APRI) IN PATIENTS WITH METABOLIC SYNDROME AND ITS RELATION WITH CARDIOVASCULAR RISK". 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:

ANEXURE II-– PROFORMA

PROFORMA

AST to Platelet Ratio Index (APRI) IN PATIENTS WITH METABOLIC SYNDROME AND ITS RELATION WITH CARDIOVASCULAR RISK

GUIDE: STUDENT:

CASE NO:	**IP NO.:**
NAME: **AGE** **SEX: M / F** **ADDRESS:** **OCCUPATION:**	

Chief Complaints : **HOPI :**
Past history : DIABETES On OHA/ Insulin : HTN Others **Treatment history:** ON HYPERTENSIVE TREATMENT ON STATIN ON ASPIRIN
Family history:
Personal history: SMOKER ALCOHOLIC
Diagnosis:

PROFORMA

AST to Platelet Ratio Index (APRI) IN PATIENTS WITH METABOLIC SYNDROME AND ITS RELATION WITH CARDIOVASCULAR RISK

GUIDE: STUDENT:

ANTHROPOMETRY:

HIP CIRCUMFERENCE (Cm)	
HEIGHT (Inches/Cm)	
WEIGHT (Kg)	
BMI (kg/m^2)	
CALF CIRCUMFERENCE (Cm)	

GENERAL EXAMINATION

BLOOD PRESSURE	SYSTOLIC	mm Hg	DIASTOLIC	mm Hg

SYSTEMIC EXAMINATION

R. S.: C.V.S.: C.N.S.: P.A.:	

PROFORMA

AST to Platelet Ratio Index (APRI) IN PATIENTS WITH METABOLIC SYNDROME AND ITS RELATION WITH CARDIOVASCULAR RISK

GUIDE: STUDENT:

INVESTIGATIONS

Sl no	Test	Date_____	
	Complete Blood counts		
1	Haemoglobin (g/dl)		
2	TLC($x10^3/\mu l$)		
3	Platelets($x10^3/\mu l$)		
	Renal Profile		
4	Urea(mg/dl)		
5	Creatinine (mg/dl)		
	Liver Function Test		
6	Total Bilirubin (mg/dl)		
7	Direct Bilirubin(mg/dl)		
8	Total Protein(g/dl)		
9	Albumin(g/dl)		
10	Globulin (g/dl)		
11	ALT (SGPT) (U/l)		
12	AST (SGOT) (U/l)		
13	ALK. Phosphatase (U/l)		
	LIPID PROFILE		
14	Cholesterol (mg/dl)		
15	LDL(mg/dl)		
16	HDL(mg/dl)		
17	TG(mg/dl)		
18	LDL/HDL RATIO		
19	HbA1c (%)		
20	FBS(mg/dl)		

21	Fundoscopy	
22	Monofilament	
23	ECG	
24	USG ABDOMEN	

PROFORMA

AST to Platelet Ratio Index (APRI) IN PATIENTS WITH METABOLIC SYNDROME AND ITS RELATION WITH CARDIOVASCULAR RISK

GUIDE: STUDENT:

APRI (AST to Platelet Ratio Index)

APRI = (AST in IU/L) / (AST Upper Limit of Normal in IU/L) / (Platelets in 10^9/L)	**APRI**	**INTERPRETATION**	**LIKELIHOOD OF FIBROSIS**
_____	<0.5	Minimal or no fibrosis	Low
	0.5-1.5	Moderate or significant fibrosis	Intermediate
	>1.5	***Severe fibrosis or cirrhosis***	***High***

ASCVD (Atherosclerotic Cardiovascular Disease)

_____	<5%	Low-risk
	5% to 7.4%	Borderline risk
	7.5% to 19.9%	Intermediate risk
	≥20%	***High risk (≥20%)***

FRS (Framingham Risk Score)

_____	<10%	Low-risk
	10- 19%	Intermediate risk
	>20%	***High risk***

INTERPRETATION

ANEXURE - III

MASTER CHART

Sr No	IP NUMBER	MetS	Age	AgeGroup	Race	Sex	Occupation	Diabetes	DiabetesDuration	Hypertension	Hypothyroidism	BPH	OHAINSULIN	onAntihypertensives	onStatin	onAspirin	Smoker	Alcoholic	Diagnosis	Waist circumference	Height	Weight	BMI	SBP	DBP	Haemoglobin	TLC	Platelets	Urea
1	1008189	Yes	67	60-69	Indian	Male	businessman	Present	5	Absent	Absent	Absent	Yes	No	Yes	Yes	Yes	No	CVA- RT MCA infarct	86	168	76	26.93	120	70	13	4.9	132	43.9
2	10007564	Yes	53	50-59	Indian	Male	shopkeeper	Present	3	Absent	Absent	Absent	Yes	No	No	No	No	Yes	colles fracture	92	186	73	21.1	130	90	11.7	12.3	231	27.9
3	1005812	Yes	70	≥70	Indian	Male	retired	Present	9	Absent	Absent	Absent	Yes	No	No	No	No	No	Rt l/l cellulitis	90	167	88	31.55	130	90	12.3	15.7	178	29.3
4	10028709	Yes	45	<50	Indian	Female	housewife	Present	2	Present	Absent	Absent	Yes	No	No	No	No	No	uncontrolled t2dm	85	150	60	26.67	130	90	10.9	8.1	162	21.9
5	10024796	Yes	59	50-59	Indian	Male	engineer	Present	20	Present	Absent	Absent	Yes	Yes	Yes	Yes	No	No	Diabetic foot ulcer	92	165	74	27.18	120	86	13.1	3.9	199	22.2
6	10001842	Yes	59	50-59	Indian	Male	shopkeeper	Present	7	Absent	Absent	Absent	Yes	No	No	No	Yes	No	Lt l/l cellulitis	89	167	65	23.31	128	92	10	11.4	321	22.6
7	1006556	Yes	52	50-59	Indian	Female	teacher	Present	16	Present	Present	Absent	Yes	Yes	No	No	No	No	bipolar disorder	90	152.4	64	27.56	136	88	11.6	8.8	487	13.2
8	10029191	Yes	65	60-69	Indian	Female	housewife	Present	6	Absent	Absent	Absent	Yes	No	No	No	No	No	T12-L1 PIVD	152	165	100	36.73	140	70	10.4	9.6	202	21.4
9	10053148	Yes	52	50-59	Indian	Male	office worker	Present	4	Present	Absent	Absent	Yes	Yes	No	No	No	No	CVA- LT hemiparesis	92	154	66	27.83	112	92	13.6	7.4	164	24.1
10	10053545	Yes	76	≥70	Indian	Female	housewife	Present	20	Present	Absent	Absent	Yes	Yes	No	No	No	No	osteoarthritis	94	148	59	26.94	110	88	11.8	10.4	294	10
11	10045121	Yes	52	50-59	Indian	Male	farmer	Present	4	Absent	Absent	Absent	Yes	No	No	No	Yes	No	CVA- cerebellar stroke	100	162	92	35.06	122	84	14.8	7.1	118	18.8
12	10044306	Yes	70	≥70	Indian	Male	farmer	Present	15	Absent	Absent	Absent	Yes	No	No	No	Yes	No	Acute gastroenteritis	99	174	79	26.09	126	86	11	10.2	356	26.6
13	1196587	Yes	36	<50	Indian	Male	worker	Present		Present	Absent	Absent	Yes	Yes	No	No	Yes	No	Pyelonephritits(resolved)	93	154	61	25.72	140	90	12.4	10.1	487	46.6
14	10007112	Yes	70	≥70	Indian	Male	teacher	Present	20	Absent	Absent	Present	Yes	No	No	No	No	No	UTI	87	176	74	23.89	130	90	10.2	8.8	163	18
15	1007766	Yes	52	50-59	Indian	Male	worker	Present	8	Present	Absent	Absent	Yes	No	No	No	No	No	Inguinal hernia	81	165	78	28.65	130	80	16.5	12.5	253	20.1
16	10008444	Yes	43	<50	Indian	Male	businessman	Present	3	Absent	Absent	Absent	Yes	No	No	No	No	No	Rt l/l cellulitis	96	166	71	25.77	122	76	12.7	11.4	147	46.3
17	10007990	Yes	55	50-59	Indian	Male	bank manager	Present	1	Absent	Absent	Absent	Yes	No	No	No	No	No	Rt fibula fracture	118	166	95	34.48	132	71	10.3	12.9	165	12.7
18	1008212	Yes	54	50-59	Indian	Female	housewife	Present	3	Present	Absent	Absent	Yes	Yes	No	No	No	No	GERD	96	160	86	33.59	116	72	10.4	3.93	203	30.1
19	1008202	Yes	70	≥70	Indian	Female	housewife	Present	8	Absent	Absent	Absent	Yes	No	No	No	No	No	Acute gastritis	89	132	56	32.14	128	92	12.6	9.7	231	10
20	10056062	Yes	61	60-69	Indian	Female	housewife	Absent		Absent	Present	Absent	No	No	No	No	No	No	Hypothyroidism	83	156	62	25.48	132	88	12.2	7.8	190	17.3
21	10055905	Yes	66	60-69	Indian	Male	bussiness	Present	6	Present	Absent	Absent	Yes	Yes	Yes	Yes	No	No	CVA	98	173	89	29.74	140	88	12.2	10.5	171	15.7
22	10048288	Yes	59	50-59	Indian	Female	housewife	Absent	10	Absent	Absent	Absent	Yes	No	No	No	No	No	Pneumonia	88	154	68	28.67	120	88	11.4	14.2	222	24.5
23	10007892	Yes	58	50-59	Indian	Male	farmer	Present	0.01	Present	Absent	Absent	Yes	Yes	Yes	Yes	No	No	CVA - rt hemiparesis(subcortical infarct)	85	172	86	29.07	146	80	17.1	12.8	195	21.5
24	10041316	Yes	70	≥70	Indian	Male	farmer	Present	12	Absent	Absent	Absent	Yes	No	Yes	Yes	No	No	Reccurent CVA	150	167	110	39.44	146	82	16.1	13.5	224	30.6
25	10045667	Yes	58	50-59	Indian	Male	farmer	Present	0.33	Absent	Absent	Absent	Yes	No	No	No	No	No	SAH	104	164	102	37.92	132	82	14.7	10.1	391	15
26	10044880	Yes	42	<50	Indian	Male	office worker	Present	1	Absent	Absent	Absent	Yes	No	No	No	No	No	T12-L1 PIVD	84	166	78	28.31	122	80	16.6	10.4	211	19.6
27	10027872	Yes	62	60-69	Indian	Female	housewife	Present	3	Present	Absent	Absent	Yes	Yes	No	No	No	No	Migraine	86	154	66	27.83	116	70	12.9	14.9	328	25.8
28	10049288	Yes	66	60-69	Indian	Female	shopkeeper	Present	15	Absent	Absent	Absent	Yes	No	No	No	No	No	UTI	110	166	86	31.21	132	80	10.8	19.7	298	32.6
29	7293776	Yes	60	60-69	Indian	Female	worker	Present	6	Absent	Absent	Absent	Yes	No	No	No	No	No	chronic urticaria	91	156	64	26.3	118	80	10.5	11.3	204	18.2
30	10046631	Yes	61	60-69	Indian	Female	housewife	Absent	7	Absent	Absent	Absent	Yes	No	No	No	No	No	viral fever	88	158	68	27.24	122	80	12.8	7.2	344	33
31	10059817	Yes	50	50-59	Indian	Female	housewife	Present	0.01	Present	Absent	Absent	Yes	Yes	No	No	No	No	c3 c4 PIVD	90	160	70	27.34	124	80	13.3	6.6	200	17
32	10026891	Yes	68	60-69	Indian	Male	office worker	Present	8	Present	Absent	Absent	Yes	Yes	Yes	No	No	No	AKI	96.5	178	82	25.88	132	90	9.6	18.2	154	87
33	10018548	Yes	52	50-59	Indian	Male	office worker	Present		Present	Absent	Absent	No	Yes	No	No	Yes	No	Hernia	98	176	90	29.05	124	86	9.5	14.2	204	78
34	10059816	Yes	60	60-69	Indian	Male	Driver	Present		Present	Absent	Absent	No	Yes	No	No	No	No	Cerebellar Bleed	88	174	82	27.08	122	92	15.3	8.6	167	47.9
35	10031951	No	45	<50	Indian	Female	worker	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Headache under evaluation	76	162	62	23.62	118	72	11	7.9	323	31.5
36	10067872	No	70	≥70	Indian	Female	housewife	Absent		Absent	Absent	Absent	No	No	No	No	No	No	rt renal calculi	72	156	55	21.1	118	72	12.3	10.2	310	29.2
37	10018996	No	57	50-59	Indian	Male	farmer	Absent		Absent	Absent	Absent	No	No	No	No	No	No	PIVD	80	186	85	24.57	118	78	13.9	8.9	216	24.5
38	100063705	No	56	50-59	Indian	Male	farmer	Absent		Absent	Absent	Absent	No	No	No	No	No	No	syncope under evaluation	88	172	78	20.96	116	72	17.7	11.6	287	43.6
39	10066419	No	45	<50	Indian	Female	housewifw	Absent		Absent	Absent	Absent	No	No	No	No	No	No	L4-L5 LISTHESIS	90	164	70	23.1	118	72	9.6	7.8	357	15.7
40	10029800	No	48	<50	Indian	Male	Desk worker	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Headache under evaluation	86	169	68	23.81	110	70	14.7	9.7	345	21.7
41	10027021	No	60	60-69	Indian	Female	housewife	Absent		Absent	Absent	Absent	No	Yes	No	No	No	No	Non cardiac chest Pain	82	172	72	24.34	132	86	12.3	9.5	262	30.2
42	10029706	No	67	60-69	Indian	Male	farmer	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Acute exacerbation Of COPD	84	170	65	22.49	120	80	13.2	20.4	322	44.8
43	10031522	No	70	≥70	Indian	Female	housewife	Absent		Absent	Absent	Absent	No	Yes	No	No	No	No	Acute Gastroenteritis	79	156	58	23.83	132	80	11.3	11.8	444	20.1
44	10007560	No	47	<50	Indian	Male	worker	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Acute Bronchitis	84	176	78	25.18	122	86	13.7	4.2	169	12.2
69	1006365	No	55	50-59	Indian	Female	housewife	Absent		Absent	Absent	Absent	No	No	No	No	No	No	noncardiac chest pain	87	180	81	22.2	116	72	12.9	9.1	327	10
46	10031659	No	60	60-69	Indian	Female	housewife	Absent		Absent	Absent	Absent	No	Yes	No	No	No	No	Pain abdomen under Evaluation	79	166	66	23.95	132	82	13	30.8	607	30.1
47	7305746	No	40	<50	Indian	Male	worker	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Fever	85	176	72	23.24	122	84	14.2	4.86	236	27.7
48	2805838	No	55	50-59	Indian	Female	farmer	Absent		Absent	Absent	Absent	No	Yes	No	No	No	No	Fibroid Uterus	76.2	161	59	22.76	110	70	12.9	8.3	438	10
49	1008212	No	70	≥70	Indian	Male	worker	Absent		Absent	Absent	Absent	No	No	No	No	No	No	PIVD	83	172	70	23.66	124	86	12.6	10.4	248	33
50	1005315	No	47	<50	Indian	Male	office worker	Absent		Absent	Absent	Absent	Yes	No	No	No	No	No	? Pulmonary Kochs	80	170	62	21.45	118	82	15	12.5	439	9.5
51	10031033	No	50	50-59	Indian	Male	shopkeeper	Absent		Absent	Absent	Absent	No	No	No	No	No	No	LRTI	86	168	70	24.8	128	84	10.4	13	385	6.46
52	7491874	No	54	50-59	Indian	Male	worker	Absent		Absent	Absent	Absent	No	No	No	No	No	No	headache under evaluation	82	168	66	21.724	124	76	13.7	8.1	301	15.5
53	10026982	No	61	60-69	Indian	Male	farmer	Absent		Absent	Absent	Absent	No	Yes	No	No	No	No	Dizziness Under Evaluation	84	177	70	22.34	110	70	18.2	6.1	238	18.7
54	7286228	No	55	50-59	Indian	Male	office worker	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Acute Gastroenterititis	87	181	85	25.95	122	78	9.7	10.6	374	16.9
55	10027323	No	50	50-59	Indian	Female	farmer	Absent		Absent	Absent	Absent	Yes	No	No	No	No	No	umbilical hernia	76	157	59	23.94	122	80		30.4	657	25.9
56	10025358	No	60	60-69	Indian	Male	bussiness	Absent		Absent	Absent	Absent	No	Yes	No	No	Yes	No	Non cardiac chest Pain	89	166	66	23.95	100	70	12.1	11.4	115	46.3
57	10027115	No	56	50-59	Indian	Male	businessman	Absent		Absent	Absent	Absent	No	No	No	No	Yes	No	PIVD	88	176	77	24.86	130	86	16.4	15.2	354	14.2
58	10026749	No	64	60-69	Indian	Male	worker	Absent		Absent	Absent	Absent	Yes	Yes	No	No	No	No	tibial Fracture	85	168	67	23.74	128	84	16.5	12.8	287	17.8
59	10066465	No	70	≥70	Indian	Male	retired	Absent		Absent	Absent	Absent	No	Yes	No	No	No	No	cva	83	163	62	22	132	90	16.6	7.7	218	12.3
60	10055123	No	49	<50	Indian	Male	Serviceman	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Fever	88	172	74	25.01	124	80	14.6	7.6	236	12
61	10067202	No	70	≥70	Indian	Female	HOUSEWIFE	Absent		Absent	Absent	Absent	No	No	No	No	No	No	URTI	72	154	56	20.2	120	78	11.3	7.92	243	20

Sr No	Creatinine	TotalBilirubin	DirectBilirubin	TotalProtein	Albumin	Globulin	ALT	AST	ALKPhosphatase	Cholesterol	LDL	HDL	TG	LDLHDLRATIO	HbA1c	FBS	Fundoscopy	Monofilament	ECG	APRI	APRIInterpretation	ASCVD	CVDInterpretation	FRS	FRSInterpretation
1	0.8	0.58	0.26	7	4.2	2.8	12	20	91	109	62	29	78	2.14	5.5	98	normal	Normal	Normal	0.4	Low likelihood of fibrosis	22	High risk	17.4	Intermediate risk
2	0.98	0.52	0.19	8.3	4.1	4.2	20	22	68	130	162	31	147	5.23	6.3	153	Mild NPDR	Loss of sensation	Non specific t wave changes	0.5	Intermediate likelihood fibrosis	16.1	Intermediate risk	10.5	Intermediate risk
3	1.53	0.68	0.32	8.1	4.5	3.6	14	16	79	131	63	24	142	2.63	8.4	166	type 1 NPDR	Normal	Normal	0.6	Intermediate likelihood fibrosis	32.3	High risk	26.3	High risk
4	0.41	0.26	0.16	7.5	4.5	3	17	12	172	86	94	41	78	2.29	5.4	186	grade 1 NPDR	Normal	Normal	0.2	Low likelihood of fibrosis	5.3	Borderline risk	0.1	Low risk
5	0.55	1.2	0.6	6	3.5	2.5	26	17	128	104	50	44	79	1.14	7.4	321	BE moderate npdr with gr 1 htnsive retinopathy	Loss of sensation	Normal	0.4	Low likelihood of fibrosis	13	Intermediate risk	4.46	Low risk
6	1.07	0.52	0.4	7	4	3	39	26	87	98	80	40	162	2	9.6	260	grade 1 NPDR	Loss of sensation	Normal	0.2	Low likelihood of fibrosis	9.2	Intermediate risk	18	Intermediate risk
7	0.78	0.56	0.29	6.4	3.9	2.5	15	16	188	174	110	42	98	2.62	7.6	245	BE grade 1 npdr with gr 1 htnsive retinopathy	Loss of sensation	Non specific changes, LVH	0.6	Intermediate likelihood fibrosis	9.6	Intermediate risk	11.1	Intermediate risk
8	0.7	0.48	0.22	5.7	3	2.7	40	127	97	227	66	11	76	6	11	120	grade 2 NPDR	Loss of sensation	Non specific changes	1.6	High likelihood fibrosis	20	High risk	25.6	High risk
9	0.77	0.57	0.13	7.4	4.7	2.7	21	31	90	132	61	23	193	2.65	9.2	200	b/l grade 1 htn retinopathy	Normal	LVH	0.5	Intermediate likelihood fibrosis	10.9	Intermediate risk	10.5	Intermediate risk
10	0.62	0.94	0.5	6.1	3.3	2.8	44	18	134	108	179	24	192	7.46	9.6	182	normal	Normal	Normal	0.5	Intermediate likelihood fibrosis	13.2	Intermediate risk	26.4	High risk
11	0.87	0.52	0.18	7.1	3.6	3.5	29	41	104	222	91	22	209	4.14	11.1	128	normal	Normal	Normal	0.9	Intermediate likelihood fibrosis	19.2	Intermediate risk	11	Intermediate risk
12	1.1	0.72	0.33	6.6	3.3	3.3	13	61	102	132	28	35	271	0.8	6.4	136	normal	Normal	Normal	0.5	Intermediate likelihood fibrosis	38.5	High risk	32.9	High risk
13	1.2	0.58	0.48	7	3.5	3.5	27	20	96	153	86	30	225	2.87	8.4	196	normal	Normal	LVH	0.5	Intermediate likelihood fibrosis	24.4	High risk	11.1	Intermediate risk
14	1.34	0.36	0.09	7.3	4.1	3.2	15	18	128	101	53	28	100	1.89	6	210	grade 1 NPDR	Loss of sensation	Non specific changes	0.3	Low likelihood of fibrosis	6.5	Borderline risk	29.9	High risk
15	0.99	0.97	0.3	7.9	4.6	3.3	28	29	102	182	135	30	182	4.5	8.8	155	Mild NPDR	Normal	Non specific changes	0.3	Low likelihood of fibrosis	14.6	Intermediate risk	10.6	Intermediate risk
16	1.11	0.39	0.2	5.6	3.1	2.5	34	20	63	108	53	37	79	1.43	8.2	134	normal	Normal	Normal	0.4	Low likelihood of fibrosis	1.5	Low risk	0.5	Low risk
17	0.59	0.71	0.64	4.2	2.5	2	100	99	108	119	49	50	88	0.98	7.3	160	normal	Normal	Normal	1.5	Intermediate likelihood fibrosis	5.2	Borderline risk	7.8	Low risk
18	1.25	0.43	0.23	5.5	3.1	2.4	44	32	102	228	161	41	168	3.93	7.7	156	grade 1 NPDR	Normal	LVH	0.5	Intermediate likelihood fibrosis	6.8	Borderline risk	2.4	Low risk
19	0.55	0.69	0.23	5.8	2.8	3	13	20	68	144	106	39	119	2.72	6.1	104	Mild NPDR	Normal	Normal	0.7	Intermediate likelihood fibrosis	17.4	Intermediate risk	10.8	Intermediate risk
20	0.5	0.37	0.2	5.9	2.2	3.7	11	14	132	168	123	42	120	2.93	6.4	128	normal	Normal	Normal	0.2	Low likelihood of fibrosis	3.9	Low risk	1.8	Low risk
21	1.07	0.54	0.23	5.8	3.9	1.9	13	15	66	198	120	50	163	2.4	9.6	128	Mod NPDR with Grade 2 HTN Retinopathy	Normal	Normal	0.5	Intermediate likelihood fibrosis	34.4	High risk	17.8	Intermediate risk
22	0.46	0.74	0.33	6.7	4.1	2.6	25	28	82	136	23	30	63	0.77	8.4	138	Mild NPDR	Normal	Normal	0.3	Low likelihood of fibrosis	14.2	Intermediate risk	8.4	Low risk
23	0.88	0.9	0.18	7.7	3.9	3.8	30	86	86	143	92	30	102	3.07	8.4	156	Mild NPDR	Normal	Normal	0.7	Intermediate likelihood fibrosis	21.6	High risk	13.3	Intermediate risk
24	1.22	0.89	0.37	7.6	4.7	2.9	26	28	74	230	86	13	148	6.62	13.4	250	grade 1 NPDR	Loss of sensation	Non specific changes	1.6	High likelihood fibrosis	37.9	High risk	57.4	High risk
25	0.8	1.57	0.21	7	4.4	3.6	23	23	89	204	166	15	156	11.07	6.3	132	Mild NPDR	Normal	Normal	0.9	Intermediate likelihood fibrosis	20.1	High risk	32.3	High risk
26	0.89	1.04	0.45	6.8	4	2.8	15	29	99	159	124	33	123	3.76	7.1	120	normal	Normal	Normal	0.3	Low likelihood of fibrosis	1.5	Low risk	8.2	Low risk
27	0.71	0.4	0.19	8.1	4.3	3.8	49	30	106	198	171	45	114	3.8	6.1	320	normal	Normal	Normal	0.2	Low likelihood of fibrosis	12.8	Intermediate risk	19	Intermediate risk
28	1.09	0.57	0.29	7.3	4	3.3	19	10	96	214	84	22	157	3.82	9.4	142	Mild NPDR	Normal	Normal	0.9	Intermediate likelihood fibrosis	20.5	High risk	32	High risk
29	0.82	1.25	0.1	5.6	3	2.6	23	37	105	133	73	21	188	3.48	8.8	124	grade 1 NPDR	Normal	Normal	0.5	Intermediate likelihood fibrosis	6.5	Borderline risk	11.6	Intermediate risk
30	1.03	0.22	0.1	7.1	4.5	2.6	14	23	87	52	154	23	140	6.7	6.5	110	normal	Normal	Normal	0.2	Low likelihood of fibrosis	7.3	Borderline risk	5.66	Low risk
31	0.74	0.51	0.16	6.5	3.4	3.1	44	46	70	120	62	37	248	1.68	7.9	124	normal	Normal	Normal	0.5	Intermediate likelihood fibrosis	6.3	Borderline risk	12.4	Intermediate risk
32	2.4	1.13	0.61	7.2	3.6	3.4	49	45	112	110	55	17	102	3.24	8.2	140	Mod NPDR with Grade 2 HTN Retinopathy	Loss of sensation	LVH	0.8	Intermediate likelihood fibrosis	23.8	High risk	30.09	High risk
33	2.7	0.6	0.3	6.4	3.4	3	30	97	107	86	105	16	42	6.56	9.5	90	Normal	Normal	Normal	1.1	Intermediate likelihood fibrosis	16	Intermediate risk	27.6	High risk
34	0.7	0.4	0.11	7.4	4.4	3	30	45	105	182	127	35	132	3.63	6.9	128	Normal	Normal	Normal	0.6	Intermediate likelihood fibrosis	12.5	Intermediate risk	22.2	High risk
35	0.71	0.24	0.13	7	4	3	25	18	87	214	157	41	151	3.83	6	94	Normal	Normal	Normal	0.1	Low likelihood of fibrosis	1.5	Low risk	0.8	Low risk
36	0.88	0.17	0.09	6.4	3.7	2.7	11	19	94	146	96	45	141	2.13	5.6	92	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	7.2	Borderline risk	9.1	Low risk
37	1.08	0.92	0.4	6.5	3.6	2.4	10	22	62	148	90	27	136	3.33	6.5	108	Normal	Normal	Normal	0.3	Low likelihood of fibrosis	5.3	Borderline risk	9.5	Low risk
38	0.74	1.96	0.74	7.8	4.2	3.6	16	30	109	196	130	26	120	5	5.2	96	Normal	Normal	Normal	0.3	Low likelihood of fibrosis	5.5	Borderline risk	6.71	Low risk
39	0.73	0.23	0.13	6.6	3.8	2.8	10	19	55	182	98	26	118	3.77	5.5	88	Normal	Normal	Normal	0.1	Low likelihood of fibrosis	0.6	Low risk	0.8	Low risk
40	0.86	2	1	6.6	3.4	3	18	20	85	183	123	40	117	3.08	5	104	Normal	Normal	Normal	0.1	Low likelihood of fibrosis	2.5	Low risk	6.1	Low risk
41	0.98	0.92	0.46	6.5	3.8	2.7	10	22	66	192	157	45	47	3.49	5.8	108	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	3	Low risk	2.2	Low risk
42	0.9	2.02	0.96	6.3	3.6	3.2	21	31	65	112	66	35	76	1.89	6.2	99	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	14.06	Intermediate risk	15.2	Intermediate risk
43	0.53	0.11	0.07	6	3.6	2.4	38	41	74	198	137	41	103	3.34	5.8	84	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	10.6	Intermediate risk	5.4	Low risk
44	0.79	0.92	0.5	7.6	3.8	3.2	23	29	89	114	104	46	102	2.26	6	94	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	2.6	Low risk	6.6	Low risk
69	0.76	0.49	0.21	6.4	3.3	3.1	24	28	65	134	100	46	66	2.17	5.4	72	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	2.3	Low risk	4.5	Low risk
46	1.12	0.91	0.37	6.3	3.5	2.8	12	41	139	124	51	22	53	2.32	6.1	101	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	2.9	Low risk	1.1	Low risk
47	0.86	0.92	0.45	7.5	4.5	3	26	32	105	222	156	41	192	3.8	5.1	98	Normal	Normal	Normal	0.3	Low likelihood of fibrosis	4.4	Low risk	7.2	Low risk
48	0.77	0.32	0.12	7.4	4.3	3.1	12	18	87	198	127	48	159	2.65	5.7	86	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	1.7	Low risk	0.9	Low risk
49	0.81	1.39	0.57	7.4	4.4	3	24	18	92	129	81	32	120	2.53	5.9	122	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	16.8	Intermediate risk	21.17	High risk
50	0.46	1.55	0.72	6.3	2.8	3.5	44	76	71	74	20	11	124	1.82	8.1	164	Normal	Normal	Normal	0.3	Low likelihood of fibrosis	17.4	Intermediate risk	18.6	Intermediate risk
51	0.82	0.35	0.06	7.6	3.5	4.1	10	26	103	144	85	44	78	1.93	5.8	98	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	2.2	Low risk	2.3	Low risk
52	0.76	1.24	0.58	8.1	5	3.1	15	24	54	161	101	69	104	1.46	5.6	95	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	3.3	Low risk	3.6	Low risk
53	0.86	1.13	0.61	7.2	4.2	3	49	45	105	136	101	48	94	2.1	5.5	102	Normal	Normal	Normal	0.5	Intermediate likelihood fibrosis	5.3	Borderline risk	5.4	Low risk
54	0.64	2.88	0.59	6.6	3.8	2.8	12	32	84	68	74	19	42	3.89	5.8	90	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	1.9	Low risk	2.9	Low risk
55	0.99	0.82	0.99	6	3.4	2.6	33	36	88	154	70	74	81	0.95	5.5	100	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	1.2	Low risk	3.5	Low risk
56	0.97	0.46	0.5	6	3.2	2.8	24	58	52	128	96	42	56	2.29	5.6	122	normal	Normal	Normal	0.5	Intermediate likelihood fibrosis	3.5	Low risk	3.5	Low risk
57	0.9	0.92	0.46	6.5	3.8	2.7	10	22	62	230	134	40	187	3.35	5.4	136	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	11.9	Intermediate risk	18.9	Intermediate risk
58	0.79	0.92	0.29	7.6	4.2	3.4	23	29	117	197	165	48	123	3.44	7.3	143	Normal	Normal	Normal	0.3	Low likelihood of fibrosis	22.7	High risk	32.78	High risk
59	0.88	1.01	0.19	6.9	2.8	4.1	13	34	70	153	122	31	158	3.94	5.6	98	Normal	Normal	Normal	0.4	Low likelihood of fibrosis	15.8	Intermediate risk	17.2	Intermediate risk
60	0.78	0.68	0.29	6.7	4	2.7	17	19	64	147	94	35	101	2.69	5.4	102	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	2.7	Low risk	6.94	Low risk
61	0.74	0.27	0.17	6.5	3.6	2.9	11	14	73	180	124	43	288	2.88	5.3	80	Normal	Normal	Normal	0.1	Low likelihood of fibrosis	9.1	Intermediate risk	5.4	Low risk

62	10067159	No	60	60-69	Indian	Male	FARMER	Absent		Absent	Absent	Absent	No	Yes	No	No	No	No	ANTRAL GASTRITIS	79	166	66	22.6	122	70	16.3	8.6	208	21.1	1.09	1.19	0.6	7.3	2.8	3.8	22	27	62	192	148	41	166	3.61	5.8	102	Normal	Normal	Normal	0.3	Low likelihood of fibrosis	5.01	Borderline risk	9.1	Low risk
63	10037261	No	48	<50	Indian	Male	WORKER	Absent		Absent	Absent	Absent	No	No	No	No	No	No	AGE	82	169	69	22.22	120	80	11.3	13.6	139	23	1.25	0.72	0.33	7.2	4.6	2.6	34	28	88	113	59	43	148	1.37	5.1	79	Normal	Normal	Normal	0.5	Intermediate likelihood fibrosis	1.6	Low risk	1.3	Low risk
64	10026340	No	62	60-69	Indian	Female	housewife	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Acute Gastroenteritis	74	152	56	24.24	122	84	13	7.9	345	34.5	0.9	0.67	0.33	8	4.5	4	24	28	88	119	46	63	112	0.73	5.4	98	Normal	Normal	Normal	0.3	Low likelihood of fibrosis	2.7	Low risk	5.7	Low risk
65	10052639	No	56	50-59	Indian	Female	housewife	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Migraine	76	166	66	23.95	122	84	12.2	7.4	284	17.4	0.5	0.22	0.11	6	4	2	18	21	82	122	50	66	124	0.76	5.7	89	Normal	Normal	Normal	0.3	Low likelihood of fibrosis	1.4	Low risk	5.4	Low risk
66	10029890	No	70	≥70	Indian	Female	farmer	Absent		Absent	Absent	Absent	No	No	No	No	No	No	Acute GE	72	158	58	23.23	116	72	11.2	9	275	16	0.98	0.64	0.16	7.2	3.8	3.4	17	35	80	126	48	64	122	0.75	5.5	96	Normal	Normal	Normal	0.2	Low likelihood of fibrosis	3.2	Low risk	6.4	Low risk
67	10044225	No	48	<50	Indian	Female	shopkeeper	Absent		Absent	Absent	Absent	No	No	No	No	No	No	UV prolapse	76	160	62	24.22	122	72	9.6	8.5	467	17.2	0.57	0.3	0.1	7.2	4	3.2	12	11	56	145	80	42	156	1.9	5.8	100	Normal	Normal	Normal	0.1	Low likelihood of fibrosis	2.9	Low risk	7.2	Low risk
68	10064882	No	62	60-69	Indian	Female	housewife	Absent		Absent	Absent	Absent	No	No	No	No	No	No	SDH	76	166	60	21.8	122	78	10.7	9	333	35.5	1.09	0.29	0.11	6.6	4	2.6	10	17	16	160	122	56	116	2.18	5.3	78	Normal	Normal	Normal	0.1	Low likelihood of fibrosis	2.71	Low risk	3.2	Low risk