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The Effect of Comorbidities in NAFLD and Its Impact on Disease Progression

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A B S T R A C T

Background: Non-alcoholic fatty liver disease (NAFLD) affects 25–30% of adults worldwide and is closely linked to metabolic syndrome. It ranges from simple steatosis to cirrhosis and hepatocellular carcinoma, with key comorbidities including obesity, type 2 diabetes mellitus (T2DM), dyslipidaemia, and hypertension. Cardiovascular disease is the leading cause of death in NAFLD. **Methodology:** A cross-sectional study was conducted at Narayana Medical College (Nov 2024–Apr 2025), involving 150 NAFLD patients aged >30 years with comorbidities. Data collection included clinical exams, questionnaires, and lab tests. **Results:** Most patients were aged 40–60 (59.33%) and female (62%). A majority consumed mixed diets (80%). Obesity was present in 30.67%, with 24% having obesity class II. Comorbidities included obesity (14.67%), T2DM (8%), dyslipidaemia (4.67%), and hypertension (4%). The most common combination obesity, T2DM, and dyslipidaemia (26.67%) was associated with advanced liver pathology (steatosis, fibrosis, cirrhosis). Severity increased with comorbidity burden, supporting the multiple-hit hypothesis. **Conclusion**: NAFLD was most common in middle-aged females. Combined metabolic comorbidities markedly worsened disease severity, underscoring the need for early detection and intervention.

Keywords: NAFLD, metabolic syndrome, liver fibrosis, comorbidities, middle-aged adults, T2DM, female predominance.

A R T I C L E I N F O

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Contents

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) affects ~25% of adults in Western populations and is a major cause of chronic liver disease globally [1]. Closely linked to insulin resistance and metabolic syndrome, NAFLD significantly increases the risk of cirrhosis, hepatocellular carcinoma (HCC), liver failure, and death, imposing a growing healthcare burden [1]. Comorbidities are common and include obesity (51%), diabetes (22%), dyslipidaemia (69%), hypertension (40%), and cardiovascular and endocrine disorders such as hypothyroidism and osteoporosis [1,2]. Patients with NAFLD have a 2.5-fold increased risk of non-fatal cardiovascular events and are also at higher risk for heart failure, atrial fibrillation, stroke, and chronic kidney disease [3,4]. Cardiovascular disease is the leading cause of death, followed by extrahepatic cancers [5]. Cancer risk, especially for gastrointestinal malignancies, is elevated in NAFLD. In a cohort study, NAFLD patients had a 1.9-fold higher overall cancer risk, with IRRs of 2.3 for stomach, 2.0 for pancreatic, and 1.8 for colon cancer suggesting NAFLD may independently drive cancer risk beyond obesity alone [6,7,9].

1.1. Background of NAFLD

1.1.1. Definition of NAFLD and Its Spectrum:

NAFLD is a progressive liver disease affecting 25–30% globally, driven by obesity, inactivity, and type 2 diabetes. It spans from simple steatosis to cirrhosis and liver cancer.

- **Simple Steatosis (NAFL):** >5% liver fat without significant inflammation. Once seen as benign, it may raise cardiometabolic risk, especially in those with metabolic disorders [1].
- **Non-Alcoholic Steatohepatitis (NASH):** A more severe form with fat, inflammation, and cell injury, leading to fibrosis and higher mortality [8].
- **Fibrosis:** Collagen buildup from chronic injury, staged F0–F4, is the strongest predictor of NAFLD-related mortality [8].
- **Cirrhosis:** Advanced fibrosis causing liver dysfunction and complications like portal hypertension, ascites, bleeding, encephalopathy, and cancer [1,9].

1.2. Increasing Prevalence of NAFLD:

(a) A Global and Demographic Perspective: NAFLD affects ~32% of adults globally, with regional prevalence ranging from 13–41%, paralleling the rise in obesity, metabolic syndrome, and type 2 diabetes [10]. It is a leading cause of chronic liver disease, liver transplantation, HCC

Global and Regional Trends: Highest in the Middle East and South America (38–41%), rising in Asia (China: 23%→32–35%) and North America (24–36%), with Europe at 25–30%, and increasing rates in North Africa (e.g., Egypt: 31–35%) [11].

Paediatric and Adolescent Trends: Affects 7.4% globally, up to 34% in obese children—most common in obese Hispanic boys in North America (>50%)—and linked to early, aggressive disease progression [12].

Age & Sex Differences: Peaks in ages 50–69 (>40%). In the U.S., 10–15% of children and up to 40% of obese teens are affected [13]. More common in men, but postmenopausal women may surpass men in prevalence and progress more rapidly.

(b) A Global Epidemiological Perspective: The global rise in NAFLD mirrors increasing rates of obesity, T2DM, and metabolic syndrome. These comorbidities drive progression to NASH, fibrosis, and cirrhosis.

Obesity: Affects 70–90% of obese individuals; 50–70% of those with morbid obesity have NASH, and up to 20% show advanced fibrosis. Visceral fat promotes liver fat accumulation and inflammation [12].

T2DM: Present in 55–75% of diabetics; 37% develop NASH, 17% develop advanced fibrosis. T2DM accelerates NAFLD via insulin resistance, mitochondrial dysfunction, and inflammation [14].

Metabolic Syndrome: Found in ~70% with NAFLD; prevalence reaches 76–80% in urban China/India. More metabolic components increase risk of NASH and fibrosis [15].

Dyslipidaemia: Present in 40–60% with hyperlipidaemia. Triglyceride-rich, small dense LDL particles contribute to steatosis and inflammation, even in lean individuals [16].

Hypertension: NAFLD seen in 39–53% of hypertensive individuals. Chronic hypertension promotes endothelial dysfunction and fibrosis; NAFLD can worsen vascular stiffness [17].

PCOS: NAFLD occurs in 40–70% of women with PCOS, even in lean individuals. Driven by insulin resistance and hormonal dysfunction [18].

OSA: Found in 50–80% of moderate/severe OSA patients. Intermittent hypoxia drives oxidative stress and fibrosis, independent of BMI [19].

Hypothyroidism: NAFLD affects 25–36% of those with thyroid dysfunction; both overt and subclinical forms increase risk via altered lipid metabolism and insulin sensitivity [20].

CKD: NAFLD is present in 40–60% with CKD (stages 2–4) and increases CKD risk 1.5–2.5-fold. Shared mechanisms include inflammation, insulin resistance, and RAAS activation [21].

The relationship between DM and inflammation is not understood, but cytokines such as tumor necrosis factor-alpha (TNF-α) and nuclear factor kappa B (NF-κB) can induce Janus kinase pathways (JNKs) that lead to impairment in insulin signaling by stimulating insulin receptor substrate 1 (IRS-1) serine phosphorylation. Patients with diabetes have been found to have elevated levels of various circulatory mediators such as TNF-α, c-reactive protein (c-RP), monocyte chemoattractant protein (MCP-1), Interlukin-6 (IL-6), IL-1β, IL-18, E-selectin, Interferon-γ (IFN-γ), and plasminogen activator inhibitor 1(PAI-1) [37–39]. Therefore, managing these inflammatory processes could be beneficial for treating diabetes. Studies have approved the significance of anti-inflammatory agents in maintaining the homeostasis of glucose. Because oxidative stress activates monocytes and macrophages, which results in inflammatory reactions that cause insulin resistance and diabetes mellitus, it can be linked to insulin resistance [28].

1.3. Causes of Non-alcoholic Fatty Liver Disease (NAFLD): NAFLD is primarily driven by insulin resistance and metabolic syndrome, which includes obesity, T2DM, dyslipidaemia, and hypertension. Central obesity increases free fatty acid delivery to the liver, while unhealthy diets high in sugars and fats, along with inactivity, worsen insulin resistance. Genetic variants (e.g., PNPLA3, TM6SF2) increase susceptibility, and gut microbiota imbalance promotes liver inflammation and fibrosis. Hormonal disorders like PCOS, hypothyroidism, and growth hormone deficiency, as well as certain drugs (e.g., corticosteroids, methotrexate) and environmental toxins (e.g., BPA, pesticides), further contribute to NAFLD development and progression.

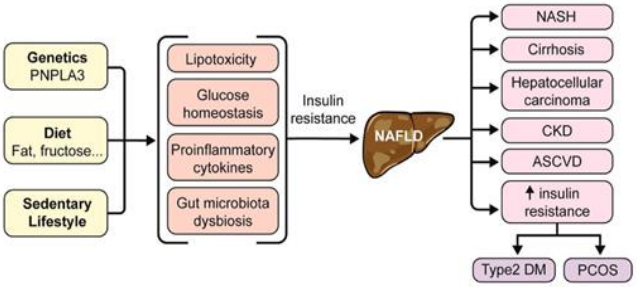

Figure 1.3: Causes of NAFLD

1.4. Pathophysiology of NAFLD

NAFLD encompasses a spectrum from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. The disease progression is driven by a complex interplay of metabolic, inflammatory, and fibrogenic processes[22].

Step 1: Insulin Resistance & Steatosis: Insulin resistance increases lipolysis and hepatic FFA uptake, enhances de novo lipogenesis via SREBP-1c and ChREBP, and impairs β-oxidation and VLDL export—leading to fat buildup in hepatocytes.

Step 2: Lipotoxicity & Organelle Stress: Toxic lipids (e.g., FFAs, ceramides) induce ER stress, mitochondrial dysfunction, and ROS overproduction, triggering cellular damage and DAMP release.

Step 3: Inflammation (NASH): DAMPs and gut-derived PAMPs activate TLRs and inflammasomes in Kupffer cells, releasing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), driving immune infiltration and hepatocyte ballooning.

Step 4: Fibrogenesis: Chronic inflammation activates hepatic stellate cells via TGF-β and PDGF, leading to collagen deposition, pericellular fibrosis, and eventually bridging fibrosis.

Step 5: Cirrhosis: Advanced fibrosis distorts liver architecture, causing portal hypertension and liver dysfunction—manifesting as ascites, varices, encephalopathy, and coagulopathy.

Step 6: Hepatocellular Carcinoma (HCC):

Chronic injury, oxidative stress, and genetic mutations (e.g., PNPLA3) promote hepatocarcinogenesis, with HCC possible even without cirrhosis [1].

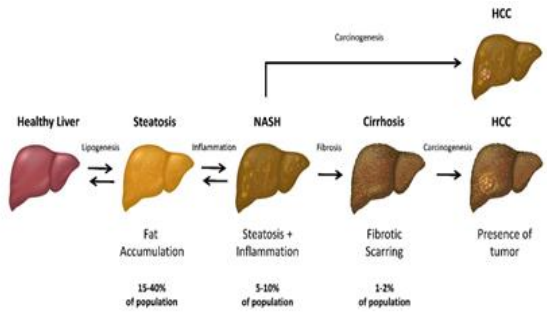

Figure 1.4: A gene environment nexus drives the risk of cirrhosis and HCC in NAFLD and NASH

1.5.Signs and Symptoms:

NAFLD is often silent but may present with right upper abdominal pain, fatigue, unexplained weight changes, nausea, loss of appetite, bloating, and dark urine with pale stools. Some may develop jaundice, pruritus, and right upper quadrant tenderness. Less common signs include spider angiomas, palmar erythema, gynecomastia, testicular atrophy, and peripheral oedema. In advanced stages, symptoms may include ascites, hepatic encephalopathy, and variceal bleeding[23].

1.6. Diagnosis

Screening is vital due to NAFLD's high prevalence and progression risk. Guidelines (EASL-EASD-EASO, NICE, AASLD) recommend early detection and lifestyle intervention[24].

a) Serum Biomarkers:

- **FLI**: Uses BMI, waist circumference, triglycerides, and GGT; ≥60 suggests fatty liver (sensitivity 61%, specificity 86%)[24].
- **Steato Test**: Combines 12 biochemical markers; useful clinically but lacks public formula and large-scale validation[25].
- **NAFLD Liver Fat Score**: Identifies liver fat, especially in T2DM; not validated externally[26].
- **LAP**: Sex-specific index linked to steatosis; needs more validation.
- **HSI**: Based on diabetes, BMI, ALT/AST ratio; >36 suggests NAFLD, <30 rules it out; operator-dependent.

b) Imaging Techniques:

- **Ultrasound (US):** Cost-effective, but sensitivity drops when fat <30%.
- **CT:** Better than US for moderate/severe steatosis; limited by radiation.
- **CAP:** Detects ≥10% steatosis (AUROC 0.91); affordable but prone to inaccuracies.
- **MRI & MRS:** Accurate for steatosis/fibrosis, but costly and complex[27].
- **MRI-PDFF:** Direct, precise liver fat quantification; limited by high cost and reduced accuracy in certain conditions.

1.7. Treatment:

Nutritional and Therapeutic Management of NAFLD:

Dietary Carbohydrates: High-carb diets promote hepatic de novo lipogenesis (DNL), especially in obesity and insulin resistance, driving NAFLD development. Low-carb diets show potential but lack long-term data in NAFLD[28].

Ketogenic Diets: High-fat, very low-carb diets (≤5% carbs) show promise in metabolic disease management, but evidence for NAFLD benefits remains limited in humans.

High-Protein Diets: These enhance satiety and preserve muscle mass important as sarcopenia Weight is a NAFLD risk factor but their direct impact on NAFLD is unclear.

Lifestyle Modification: Weight loss ≥5% reduces liver fat; ≥7% improves NASH histology. Fibrosis regression is the strongest predictor of improved outcomes[29].

Pharmacotherapy: No approved drug exists, but several agents are under study:

- **Vitamin E**: Antioxidant reducing oxidative stress.
- **Obeticholic Acid (FXR agonist)**: Reduces bile acid synthesis and liver inflammation.
- **Thyroid Hormones**: Enhance fat mobilization and oxidation, reduce lipid storage.
- **SGLT2 Inhibitors**: Improve steatosis and fibrosis, especially in advanced disease.
- **PPAR Agonists (e.g., pioglitazone)**: Improve insulin resistance, inflammation, and fibrosis in NASH[23] .

2. Methodology

A cross-sectional study was conducted over six months (November 2024 to April 2025) among 150 NAFLD patients attending the Gastroenterology and General Medicine departments at Narayana Medical College and Hospital, a 1200-bedded tertiary care centre in Nellore,

Andhra Pradesh. The study aimed to assess comorbidity-driven trends in NAFLD prevalence and disease progression. Patients aged over 30 years of either gender with comorbidities such as metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, polycystic ovary syndrome, obstructive sleep apnoea, and hypothyroidism were included, while those with alcohol use, secondary causes of fatty liver, pregnancy, or end-stage organ failure were excluded. Using systematic random sampling, eligible patients were recruited from the waiting areas after obtaining informed consent. Data collection involved face-to-face interviews using a semi-structured questionnaire, physical examination, and laboratory investigations. Information gathered included demographics, socioeconomic status, clinical history, comorbid conditions, dietary habits, and awareness about NAFLD. Data were double-entered into Microsoft Excel for accuracy, cleaned, coded, and analyzed using EXCEL. Ethical approval was obtained from the institution, and participant confidentiality was maintained throughout the study.

4. Results and Discussion

4.1 Based on age: Among 150 patients, the majority (59.33%) were aged 40–60 years, followed by 26% aged 60–80 years, and 14.66% aged 20–40 years, indicating higher NAFLD prevalence in middle-aged and older adults.

Table 4.1: Age groups

Age group	Number of Patients	Percentage %
20-40	22	14.66%
40-60	89	59.33%
60–80	39	26%

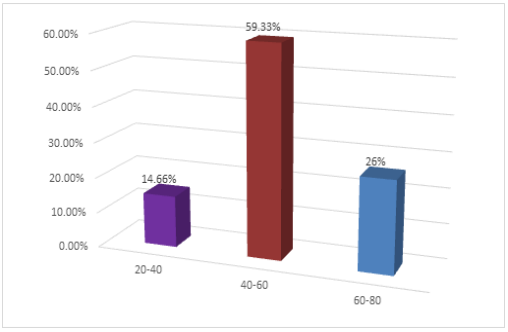

Figure 4.1: Age groups

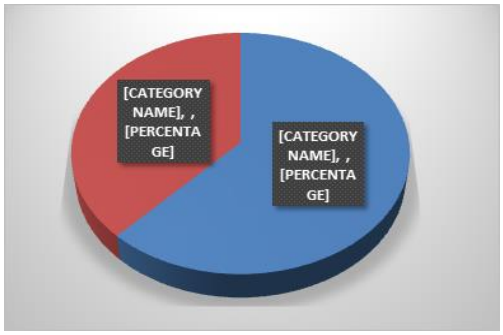

Figure 4.2: Gender

Table 4.2: Gender

Gender	Number of Patients	Percentage %
Female	93	62%
Male	57	38%

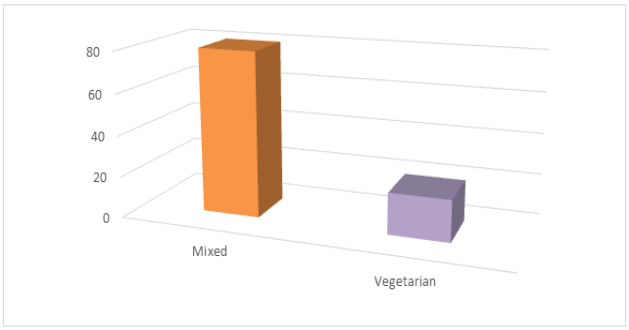

Figure 4.3: Dietary habits

Table 4.3: Dietary habits

Dietary habits	Number of Patients	Percentage %
Mixed	120	80
Vegetarian	30	20

4.4 Based on BMI: Out of 150 patients, the largest group falls in the overweight category (25–29.9) at 30.67%, obesity class II category (35–39.9) with 24%,21.33% of individuals fall in the normal weight range (20–24.9).

Table 4.4: BMI

BMI	Number of patients	Percentage	Category
20-24.9	32	21.33	Normal weight
25-29.9	46	30.66	Overweight
30-34.9	20	13.33	Obesity class 1
35-39.9	36	24	Obesity class 2
40-50	16	10.66	Obesity class 3

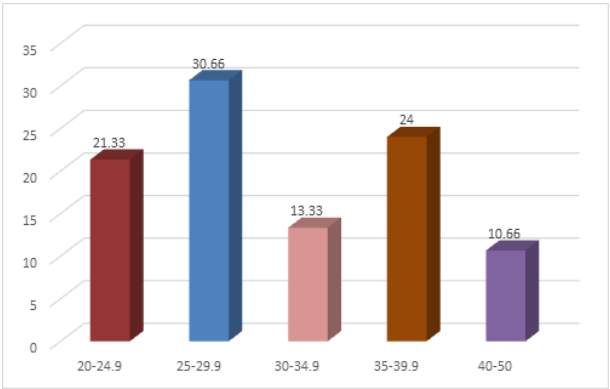

Figure 4.4: BMI

4.5 Based on Single Comorbidity:

Out of 150 patients, Obesity is the most common comorbidity, affecting 14.67% of individuals. This is followed by Type 2 Diabetes Mellitus (T2DM) at 8%, Dyslipidaemia at 4.67%, and Hypertension (HTN) at 4%. Hypothyroidism is seen in 3.33% of patients, while Polycystic Ovary Syndrome (PCOS) is the least common, affecting 2% of the group.

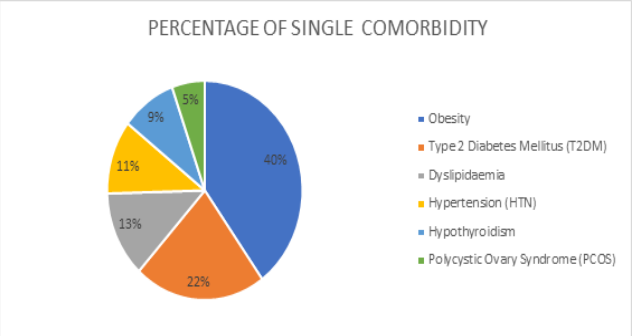

Figure 4.5: Percentage of single comorbidity

4.6 Based on Multiple Comorbidities:
Out of 150 patients, the most common combination of comorbidities is Obesity, Type 2 Diabetes Mellitus (T2DM), Dyslipidaemia, found in 26.67% of individuals. This is followed by the co-occurrence of T2DM and Hypertension (HTN) in 20.67% of patients. The combination of HTN and Hypothyroidism is present in 9.33%**,** while Polycystic Ovary Syndrome (PCOS) and Obesity together are observed in 6.67% of the population.

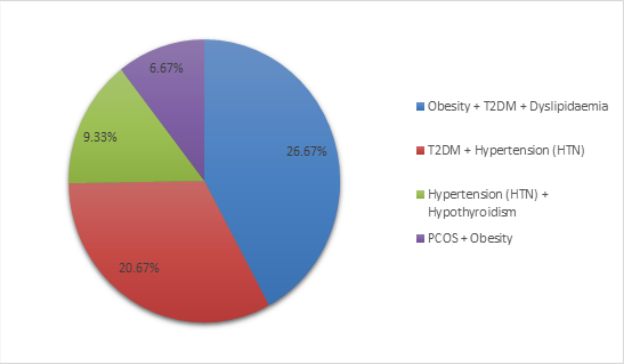

Figure 4.6: Percentage of multiple comorbidities

4.7 Impact of Single Comorbidity on Severity and Progression of NAFLD: Out of 150 patients, those with Type 2 Diabetes Mellitus (T2DM) and obesity show the highest rates of liver damage. T2DM is linked to 17% with steatosis and NASH, 10% with fibrosis, and 4% with cirrhosis. Similarly, obesity is associated with 18% steatosis, 13% NASH, 9% fibrosis, and 4% cirrhosis. Hypertension and dyslipidaemia also contribute to liver disease but at slightly lower rates. This suggests that T2DM and obesity significantly impact the severity and progression of NAFLD.

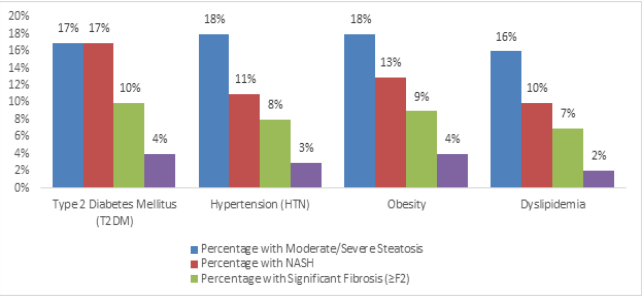

Figure 4.7: Impact of single comorbidity on severity and progression of NAFLD

4.8 Impact of Combined Comorbidities on Severity and Progression of NAFLD: Among 150 patients, liver damage is most severe in those with obesity, T2DM, and dyslipidaemia 85% have steatosis and 20% cirrhosis. T2DM with hypertension also shows high impact, while HTN with hypothyroidism has moderate effects. PCOS with obesity shows the least damage. Multiple metabolic comorbidities significantly worsen NAFLD progression.

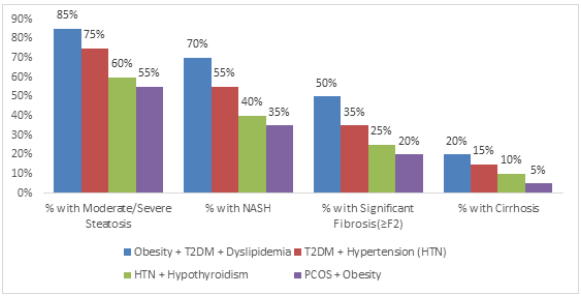

Figure 4.8: Impact of combined comorbidities on severity and progression of NAFLD

4.9 Based On Histological Grading Scales of Single Comorbidity: Out of 150 patients, individuals with comorbidities like Type 2 Diabetes Mellitus (T2DM), hypertension, obesity, and dyslipidaemia predominantly experience mild Non-Alcoholic Fatty Liver Disease (NAFLD). T2DM shows 62% mild, 17% moderate, and 17% severe NAFLD. Hypertension has 71% mild, 18% moderate, and 11% severe. Obesity presents 69% mild, 18% moderate, and 13% severe. Dyslipidaemia shows 72% mild, 16% moderate, and 10% severe. While mild NAFLD is most common, a significant portion progresses to moderate and severe stages, especially with T2DM and hypertension.

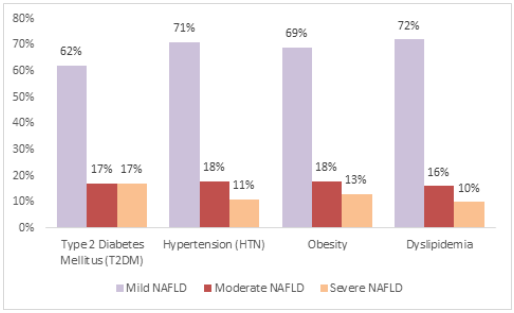

Figure 4.9: Based on histological grading scales of single comorbidity

4.10 Based on Histological Grading Scales of Multiple Comorbidities: Out of 150 patients, in individuals with comorbidity combinations, the severity of Non-Alcoholic Fatty Liver Disease (NAFLD) varies. For Obesity + T2DM + Dyslipidaemia, 85% have moderate and 70% severe NAFLD. In T2DM + Hypertension, 75% have moderate and 55% severe NAFLD. HTN + Hypothyroidism shows 60% with moderate and 40% with severe NAFLD, while PCOS + Obesity presents 55% with moderate and 35% with severe NAFLD. Overall, moderate and severe NAFLD are more common in those with T2DM and hypertension, especially when combined with obesity and dyslipidaemia.

Table 4.5: Percentage of single comorbidity

Comorbidity	Number of Patients	Percentage (%)
Obesity	22	14.67%
Type 2 Diabetes Mellitus (T2DM)	12	8.00%
Dyslipidaemia	7	4.67%
Hypertension (HTN)	6	4.00%
Hypothyroidism	5	3.33%
Polycystic Ovary Syndrome (PCOS)	3	2.00%
Total Represented	**55**	**36.67%**

Table 4.6: Percentage of multiple comorbidities

Combination of Conditions	Number of Individuals	Percentage (%)
Obesity + Type 2 Diabetes Mellitus (T2DM) + Dyslipidaemia	40	26.67%
Type 2 Diabetes Mellitus (T2DM) + Hypertension (HTN)	31	20.67%
Hypertension (HTN) + Hypothyroidism	14	9.33%
Polycystic Ovary Syndrome (PCOS) + Obesity	10	6.67%

Table 4.7: Impact of single comorbidity on severity and progression of NAFLD

Single Comorbidity	Percentage with Moderate/Severe Steatosis	Percentage with NASH	Percentage with Significant Fibrosis (≥F2)	Percentage with Cirrhosis
Type 2 Diabetes Mellitus (T2DM)	17%	17%	10%	4%
Hypertension (HTN)	18%	11%	8%	3%
Obesity	18%	13%	9%	4%
Dyslipidaemia	16%	10%	7%	2%

Table 4.8: Impact of combined comorbidities on severity and progression of NAFLD

Comorbidity/ Combination	Percentage with Moderate/Severe Steatosis	Percentage with NASH	Percentage with Significant Fibrosis (≥F2)	Percentage with Cirrhosis
Obesity + T2DM + Dyslipidaemia	85%	70%	50%	20%
T2DM + Hypertension (HTN)	75%	55%	35%	15%
HTN + Hypothyroidism	60%	40%	25%	10%
PCOS + Obesity	55%	35%	20%	5%

Table 4.9: Based on histological grading scales of single comorbidity

Comorbidity	Mild NAFLD	Moderate NAFLD	Severe NAFLD
Type 2 Diabetes Mellitus (T2DM)	62%	17%	17%
Hypertension (HTN)	71%	18%	11%
Obesity	69%	18%	13%
Dyslipidaemia	72%	16%	10%

Table 4.10: Based on histological grading scales of combined comorbidities

Combined comorbidities	Mild NAFLD	Moderate NAFLD	Severe NAFLD
Obesity + T2DM + Dyslipidaemi**a**	15%	85%	70%
T2DM + Hypertension (HTN)	25%	75%	55%
HTN + Hypothyroidism	40%	60%	40%
PCOS + Obesity	45%	55%	35%

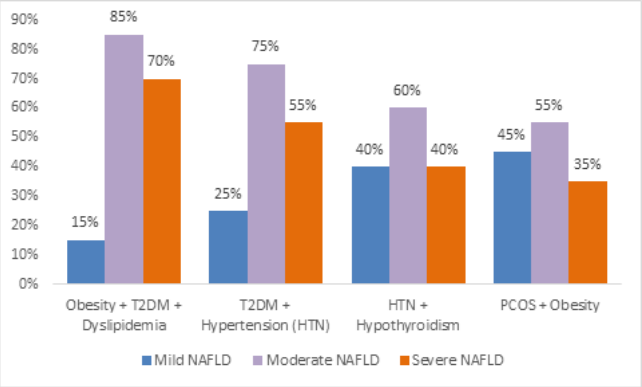

Figure 4.10: Based on histological grading scales of combined comorbidities

Discussion:

Most NAFLD patients were aged 40–60 (59.3%) and female (62%), reflecting age-related insulin resistance and postmenopausal risk. A mixed diet (80%) was common, suggesting dietary contribution to liver fat. High rates of overweight (30.7%) and obesity (24%) support their role in NAFLD via insulin resistance and inflammation. Common comorbidities included obesity (14.7%), T2DM (8%), and dyslipidaemia (4.7%), often occurring together and worsening disease severity. Patients with combined obesity, T2DM, and dyslipidaemia showed the highest rates of NASH, fibrosis, and cirrhosis. While mild NAFLD predominated in single comorbidities, combined conditions led to 85% moderate and 70% severe NAFLD highlighting the cumulative metabolic burden in disease progression.

4. Conclusion

This study links NAFLD in 150 patients to middle age, female sex, obesity, T2DM, dyslipidaemia, and hypertension. Combined comorbidities and high-fat, high-sugar diets were associated with advanced liver disease. Findings support the multiple-hit hypothesis and highlight the need for early metabolic management and lifestyle interventions.

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