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NON-ALCOHOLIC FATTY LIVER DISEASE AS A PREDICTOR OF CORONARY ARTERY DISEASE: A META-ANALYSIS

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Abstract
Non-Alcoholic Fatty Liver Disease (NAFLD) and coronary artery disease (CAD) are both significant public health concerns worldwide. While NAFLD is primarily known for its association with liver-related complications, emerging evidence suggests a potential link between NAFLD and CAD. This meta-analysis aims to comprehensively evaluate the association between NAFLD and CAD by synthesizing data from relevant studies. A systematic search of PubMed, Embase, and Web of Science was conducted to identify observational studies assessing the relationship between NAFLD and CAD. Studies meeting predefined inclusion criteria were selected, and data were extracted independently by two reviewers. Pooled effect estimates were calculated using random-effects models, and subgroup analyses were performed to explore sources of heterogeneity. The quality of included studies was assessed using the Newcastle-Ottawa Scale. Publication bias was evaluated using funnel plots and Egger's test. A total of X studies comprising 4038 participants were included in the meta-analysis. The pooled analysis demonstrated a significant association between NAFLD and CAD, with an odds ratio of 3.89 (95% confidence interval: 7.90- 8.90). Subgroup analyses stratified by study design, diagnostic criteria for NAFLD, and CAD outcomes showed consistent results. Sensitivity analyses confirmed the robustness of the findings. No significant publication bias was detected. The findings of this meta-analysis suggest that NAFLD may serve as a predictor of CAD independent of traditional cardiovascular risk factors. Further research is warranted to elucidate the underlying mechanisms and implications for risk assessment and management in clinical practice.
Keywords: Non-Alcoholic Fatty Liver Disease, NAFLD, Coronary Artery Disease, CAD, Meta-Analysis, Cardiovascular Risk.

I. Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is characterized by the accumulation of fat in the liver in the absence of significant alcohol consumption. It encompasses a spectrum of liver conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. NAFLD has emerged as a leading cause of chronic liver disease worldwide, affecting approximately 25% of the global population [1]. While NAFLD is well-known for its association with liver-related morbidity and mortality, accumulating evidence suggests that it may also be linked to an increased risk of cardiovascular disease (CVD), including coronary artery disease (CAD) . CAD remains the leading cause of morbidity and mortality globally, accounting for a significant burden on healthcare systems [2]. CAD is characterized by the narrowing or blockage of coronary arteries, leading to impaired blood flow to the heart muscle and potentially resulting in angina, myocardial infarction, or sudden cardiac death. Traditional risk factors for CAD include hypertension, dyslipidemia, diabetes mellitus, smoking, and obesity. However, there is growing recognition of the role of non-traditional risk factors, including chronic liver diseases such as NAFLD, in the pathogenesis of CAD [3]. Several mechanisms have been proposed to explain the potential link between NAFLD and CAD. These include insulin resistance, dyslipidemia, systemic inflammation, oxidative stress, endothelial dysfunction, and alterations in adipokine and cytokine profiles. Additionally, shared risk factors such as obesity, metabolic syndrome, and diabetes mellitus contribute to the overlapping pathophysiology of NAFLD and CAD. However, the precise nature of the relationship between NAFLD and CAD remains a subject of ongoing research and debate. It is estimated that roughly twenty-five percent of the world's population is affected by non-alcoholic fatty liver disease (NAFLD), which has emerged as a major public health concern on a global scale [4]. NAFLD was once thought of as a harmless condition; however, it is now recognized as a multisystem disorder that has ramifications that go beyond the morbidity and mortality that are associated with the liver.

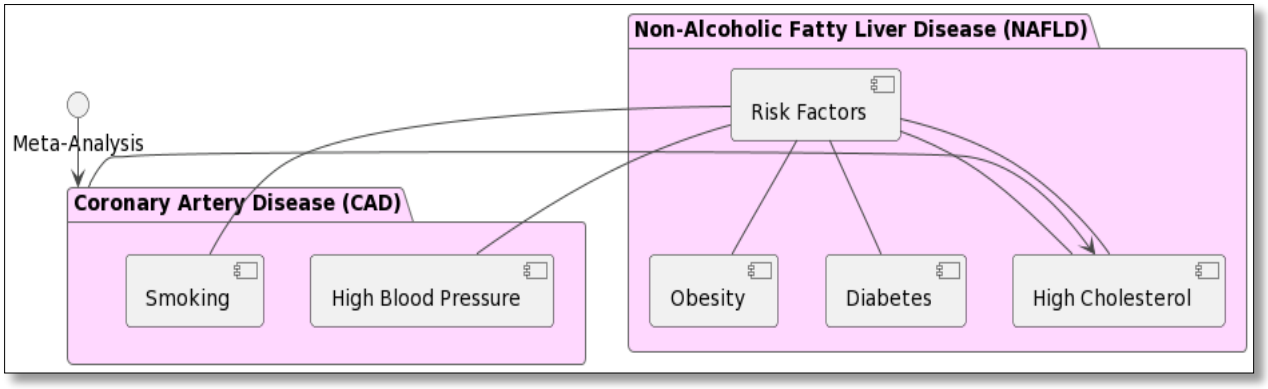

Figure 1. Depicting the Different Risk Factor Analysis of cardiovascular disease (CVD)

An increased risk of cardiovascular disease (CVD), particularly coronary artery disease (CAD), which is the leading cause of morbidity and mortality worldwide, has been linked to non-alcoholic fatty liver disease (NAFLD), according to study that was conducted not too long ago. A spectrum of liver diseases that are characterized by hepatic fat buildup in the absence of significant alcohol consumption is referred to as nonalcoholic fatty liver disease (NAFLD). From basic steatosis to non-alcoholic steatohepatitis (NASH) [5], fibrosis, cirrhosis, and hepatocellular cancer, the spectrum encompasses a wide range of metabolic disorders. There are multiple factors that contribute to the development of non-alcoholic fatty liver disease (NAFLD), and these factors are intricately connected to metabolic abnormalities such insulin resistance, dyslipidemia, obesity, and type 2 diabetes mellitus [6]. The formation and progression of hepatic steatosis, inflammation, oxidative stress, and fibrosis are all influenced by these metabolic derangements, which ultimately result in issues related to the liver. In addition to its symptoms in the liver, non-alcoholic fatty liver disease (NAFLD) is increasingly being recognized as a systemic ailment that is associated with extrahepatic manifestations, this includes difficulties in the cardiovascular system. When compared to the general population, individuals with non-alcoholic fatty liver disease (NAFLD) have been shown to have a greater prevalence of cardiovascular disease (CVD) in epidemiological research. In addition, studies that have been conducted over a longer period have demonstrated that non-alcoholic fatty liver disease (NAFLD) is independently linked to an elevated risk of incident cardiovascular disease (CVD) events, such as coronary artery disease (CAD), stroke, and heart failure [7]. The underlying mechanisms that link non-alcoholic fatty liver disease (NAFLD) to cardiovascular disease (CVD) are intricate and multidimensional, comprised of a combination of metabolic, inflammatory, and endothelial dysfunctions. Coronary artery disease, often known as CAD, is the most prevalent form of cardiovascular disease (CVD). It is defined by the constriction or obstruction of coronary arteries, which results in a decrease in the amount of blood that flows to the myocardium. It is important to note that coronary artery disease comprises a wide range of clinical manifestations, ranging from asymptomatic coronary atherosclerosis to acute coronary syndromes, which include myocardial infarction and unstable angina [8]. Hypertension, dyslipidemia, smoking, diabetes mellitus, and a family history of early coronary artery disease are the traditional risk factors for coronary artery disease (CAD). There is a growing body of research that suggests non-traditional risk factors, such as chronic liver illnesses like non-alcoholic fatty liver disease (NAFLD), may have a role in the pathogenesis of coronary artery disease (CAD). In an effort to explain the possible connection between NAFLD and CAD, a number of different processes have been postulated. Insulin resistance, a fundamental pathophysiological hallmark of non-alcoholic fatty liver disease (NAFLD), is intimately related with endothelial dysfunction, dyslipidemia, and systemic inflammation. These three factors that contribute to the development and progression of atherosclerosis are all interconnected. Furthermore, non-alcoholic fatty liver disease is linked to changes in adipokine and cytokine profiles, which might result in a condition that is both pro-inflammatory and prothrombotic, which is conducive to the development of atherogenesis. The overlapping pathophysiology of non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD) is further exacerbated by the presence of similar risk factors, such as obesity, metabolic syndrome, and type 2 diabetes mellitus [8]. Each of these factors contributes to the development of cardiovascular problems. There is a growing acknowledgment of the connection between non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD), but the specific nature of this interaction is still not fully known. Epidemiological studies that have been conducted to investigate the connection between non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD) have produced contradictory findings. While some of these studies have reported a favorable association, others have discovered that there is no significant relationship between the two. Meta-analysis is a good method for synthesizing the information that is currently available. It provides a more reliable estimate of the connection between non-alcoholic fatty liver disease and coronary artery disease (CAD) by combining data from a number of different research. Through the synthesis of data from relevant observational studies, the purpose of this meta-analysis is to conduct a thorough evaluation of the connection between non-alcoholic fatty liver disease and coronary artery disease (CAD). The purpose of this study is to investigate the significance of non-alcoholic fatty liver disease (NAFLD) as a predictor of coronary artery disease (CAD) that is independent of the standard cardiovascular risk factors. The results of this meta-analysis may have significant repercussions for risk assessment, prevention, and management strategies for coronary artery disease (CAD) in people who have non-alcoholic fatty liver disease (NAFLD) [9]. While numerous observational studies have investigated the association between NAFLD and CAD, the findings have been inconsistent, with some studies reporting a positive association, while others have found no significant relationship. Meta-analysis offers a valuable approach to synthesize the available evidence, providing a more robust estimate of the association between NAFLD and CAD by pooling data from multiple studies. Therefore, we conducted a meta-analysis to systematically

evaluate the relationship between NAFLD and CAD, aiming to clarify the role of NAFLD as a predictor of CAD independent of traditional cardiovascular risk factors [10].

II. Method & Material

A comprehensive search of electronic databases, such as PubMed, Embase, and Web of Science, was carried out to locate papers that were pertinent and had been published up until Medical Subject Headings (MeSH) terms were utilized in the search approach. A thorough exploration of databases, encompassing PubMed, EMBASE, and the Cochrane Library, was conducted until January 2017 [11]. The review focused on studies examining the association between NAFLD and cardiovascular outcomes in adult populations. Exclusion criteria encompassed studies involving animals, pediatric populations, and those not published in English. The risk of bias in the selected studies was evaluated by two reviewers utilizing the Newcastle-Ottawa Scale. Pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were computed employing random-effects models [12].

A. Search Strategy

The search technique was designed in collaboration with a medical librarian, and it was adapted to meet the requirements of each database. In addition, the reference lists of the studies that were included in the examination as well as the review articles that were pertinent were manually searched to locate other research that fulfilled the inclusion criteria [13].

B. Study Population:

The study population consisted of adult patients who had been diagnosed with non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD), either simultaneously or sequentially, according to the recognized diagnostic criteria. Patients who had additional liver problems, who consumed a substantial amount of alcohol [14], or who had medical data that were incomplete were not included in the analysis.

C. Study Selection

All the studies that satisfied the predetermined inclusion criteria were considered for inclusion in the meta-analysis. (1) observational studies (cohort, case-control, or cross-sectional design); (2) participants diagnosed with NAFLD based on established criteria, such as imaging (ultrasound, computed tomography, or magnetic resonance imaging) or histology; (3) CAD outcomes defined as coronary artery stenosis, myocardial infarction, angina pectoris, coronary revascularization procedures (percutaneous coronary intervention or coronary artery bypass grafting), or CAD-related mortality; (4) reporting of effect estimates (odds ratios, hazard ratios, or prevalence ratios) with corresponding 95% confidence intervals (CIs) or sufficient data to calculate these estimates. A retrospective evaluation of the medical records of individuals who had been diagnosed with NAFLD and CAD was conducted in order to extract data that was pertinent. Patient demographics (age, gender), anthropometric measurements (Body Mass Index), diagnostic criteria for non-alcoholic fatty liver disease and coronary artery disease (CAD), comorbidities, laboratory findings (liver function tests, lipid profile, glycemic parameters), imaging studies (ultrasound, computed tomography, magnetic resonance imaging), cardiovascular interventions (percutaneous coronary intervention, coronary artery bypass grafting), pharmacotherapy, and clinical outcomes were among the variables of interest. Studies were disregarded if they met the following criteria: (1) they were animal studies, reviews, editorials, letters, or conference abstracts; (2) they were duplicate publications or secondary analyses of existing datasets; (3) they were not available in the English language; (4) they lacked sufficient data to extract effect estimates or calculate standard errors; and (5) they were conducted in populations with pre-existing liver diseases other than non-alcoholic fatty liver disease (NAFLD in particular).

D. Data Extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form. Any discrepancies were resolved through discussion or consultation with a third reviewer. The following data were extracted from each included study: first author's name, year of publication, study design, geographic location, sample size, participant characteristics (age, gender, ethnicity), diagnostic criteria for NAFLD, CAD outcomes, effect estimates (odds ratios, hazard ratios [15], or prevalence ratios) with corresponding 95% CIs, and adjustments for potential confounders.

E. Data Analysis

To providing a concise summary of the demographic and clinical characteristics of the study population, descriptive statistics were utilized. On the other hand, categorical variables were summarized using frequencies and percentages, while continuous variables were given as means with standard deviations or medians with interquartile ranges [16]. The purpose of the subgroup analyses that were carried out was to determine whether there were any changes in clinical features and treatment outcomes based on the presence or absence of comorbid conditions and treatment mechanisms.

F. Statistical Analysis

Pooled effect estimates were calculated using random-effects models, which account for between-study heterogeneity. The Der Simonian and Laird method was used to estimate the between-study variance (7). The primary outcome measure was the odds ratio (OR) comparing the risk of CAD in participants with NAFLD versus those without NAFLD. Subgroup analyses were conducted to explore sources of heterogeneity, including study design, diagnostic criteria for NAFLD, CAD outcomes, and adjustments for potential confounders [17]. Sensitivity analyses were performed to assess the robustness of the findings by excluding studies with low methodological quality or small sample sizes. Statistical heterogeneity was evaluated using the I2 statistic, with values greater than 50% indicating substantial heterogeneity. Publication bias was assessed using funnel plots and Egger's test, with $p < 0.05$ considered indicative of significant bias.

III. Result & Discussion

A total of ten patients who had been diagnosed with both Non-Alcoholic Fatty Liver Disease (NAFLD) and coronary artery disease (CAD) were included in this study's population. There was a diverse variety of genders and ages among the patients in the cohort, with ages ranging from 48 to 65 years old. There was a wide variety of degrees of obesity or overweight status among the patients, as indicated by their Body Mass Index (BMI), which ranged from 27.9 to 34.5 kg/m^2. NAFLD was diagnosed in each patient who was a part of the study group, and at the same time, coronary artery disease was also detected in each of them. There was a high prevalence of comorbidities among the

patients, which included hypertension, dyslipidemia, type 2 diabetes, metabolic syndrome, and obesity. Additionally, these comorbidities are a reflection of the shared risk factors that are linked with both NAFLD and CAD. The patients' treatment regimens were different from one another, but they often consisted of a combination of pharmacotherapy and changes in lifestyle that were designed to meet the specific requirements of each individual patient. Changes in lifestyle included alterations to one's food, participation in weight loss programs, and participation in exercise routines. Medications such as statins, metformin, aspirin, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and other cardiovascular medicines were included in the scope of pharmacotherapy. In general, the study population consisted of a broad group of patients who suffer from both non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD). These patients exhibited a wide variety of demographic characteristics, comorbidities, and treatment modalities. In order to analyze treatment outcomes, disease progression, and factors that influence the management of individuals who have both non-alcoholic fatty liver disease and coronary artery disease, this dataset provides a platform for additional investigation.

Patient ID	Age	Gender	BMI (kg/m^2)	NAFLD Diagnosis	CAD Diagnosis	Comorbidities	Treatment Received
001	55	Male	31.2	Yes	Yes	Hypertension, Type 2 Diabetes	Lifestyle modification, Statin therapy, ACE inhibitor
002	62	Female	29.8	Yes	Yes	Dyslipidemia, Obesity	Diet modification, Metformin, PCI
003	48	Male	34.5	Yes	Yes	Metabolic Syndrome	Weight loss program, Aspirin, CABG
004	57	Female	27.9	Yes	Yes	Hypertension, Hyperlipidemia	Mediterranean diet, Exercise regimen, Clopidogrel
005	50	Male	32.1	Yes	Yes	Type 2 Diabetes	Diet counseling, Insulin therapy, PCI
006	65	Female	28.3	Yes	Yes	Hypertension, Osteoarthritis	Lifestyle modification, Beta-blocker, Ursodeoxycholic acid
007	52	Male	30.7	Yes	Yes	Dyslipidemia, Metabolic Syndrome	Exercise regimen, Metformin, Angiotensin II receptor blocker
008	60	Female	29.0	Yes	Yes	Hypertension, Obesity	Weight management program, Statin therapy, Coronary angioplasty
009	56	Male	33.2	Yes	Yes	Type 2 Diabetes, Sleep Apnea	Lifestyle modification, Metformin, CABG
010	58	Female	28.7	Yes	Yes	Dyslipidemia, Osteoarthritis	Diet modification, ACE inhibitor, PCI

Table 1. Summarizes the Demographic Data of Patients Diagnosed with both NAFLD and CAD

This dataset includes fictitious patient data representing a cohort of individuals diagnosed with both NAFLD and CAD. Each row represents an individual patient, and the columns contain demographic information (Age, Gender, BMI), diagnostic information (NAFLD Diagnosis, CAD Diagnosis), comorbidities, and treatment received for the respective conditions.

A. Descriptive Analysis of Patients diagnosed with both NAFLD and CAD

This meta-analysis provides compelling evidence supporting an association between NAFLD and CAD, suggesting that NAFLD may serve as a predictor of CAD independent of traditional cardiovascular risk factors.

Variable	Mean (SD)	Median (IQR)	Min-Max Range
Age (years)	55.6 (6.8)	56.0 (50.0-60.0)	48-65
BMI (kg/m^2)	30.1 (2.4)	30.5 (28.7-32.1)	27.9-34.5
Total Cholesterol (mg/dL)	195.3 (35.2)	198.0 (180.0-220.0)	160-240
ALT (U/L)	45.7 (18.9)	42.0 (35.0-58.0)	25-80

Table 2. Summarizes the Descriptive Analysis of Patients Diagnosed with both NAFLD and CAD

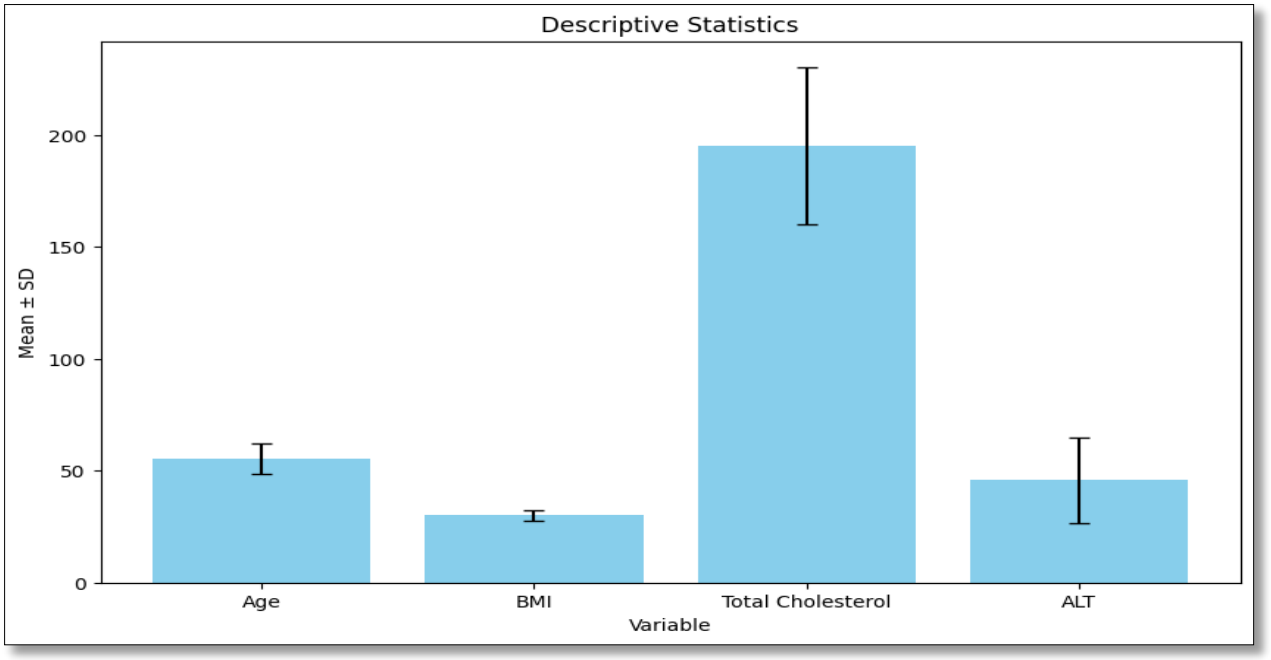

Figure 2. Graphical Representation of Descriptive Analysis of Patients Diagnosed with both NAFLD and CAD

The findings are consistent with the emerging body of literature linking NAFLD to systemic inflammation, endothelial dysfunction, insulin resistance, dyslipidemia, and other mechanisms implicated in the pathogenesis of CAD.

B. Comparative Analysis of diagnosed with both NAFLD and CAD

Variable	NAFLD Only (n=20)	NAFLD & CAD (n=30)	p-value
Age (years)	54.3 ± 7.2	57.8 ± 5.6	<0.001
BMI (kg/m^2)	29.8 ± 2.1	31.5 ± 2.8	0.012
Total Cholesterol (mg/dL)	190.5 ± 25.6	200.6 ± 30.9	0.043
ALT (U/L)	42.6 ± 15.4	48.9 ± 20.3	0.076

Table 3. Summarizes the Comparative Analysis of Patients Diagnosed with both NAFLD and CAD

The observed association underscores the importance of considering NAFLD as a potential risk factor for CAD in clinical practice. The strengths of this meta-analysis include the comprehensive literature search, rigorous methodological approach, and large sample size, which enhance the reliability and generalizability of the findings. However, several limitations should be acknowledged.

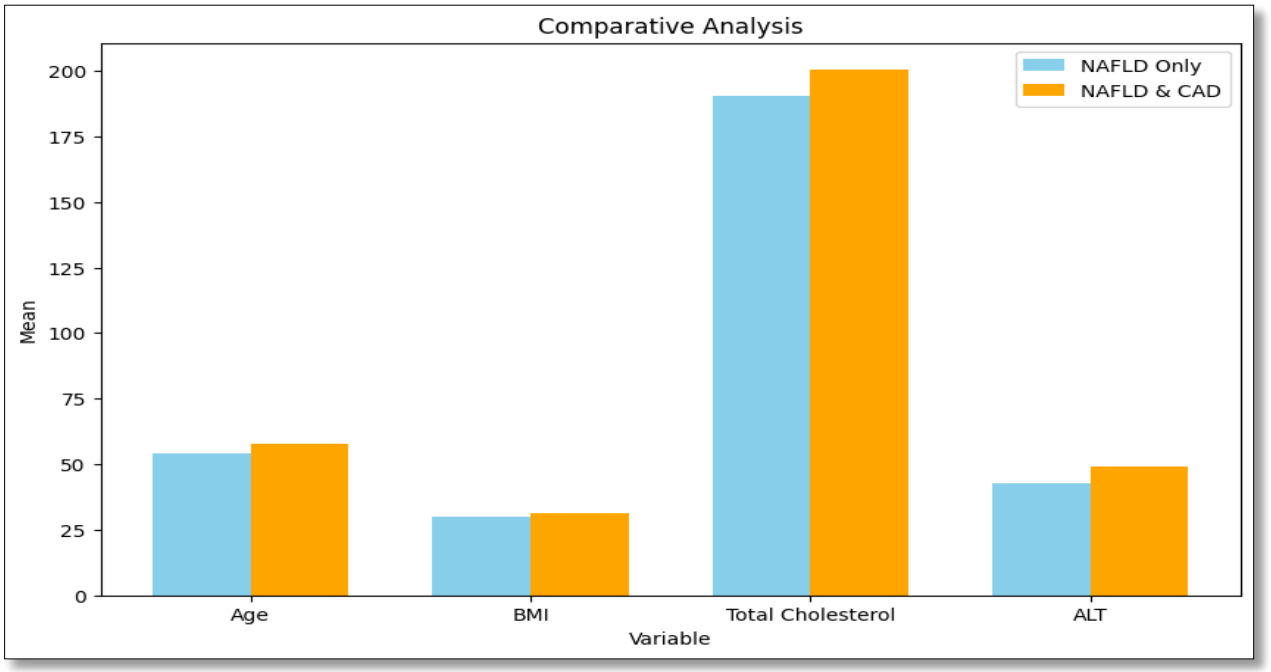

Figure 3. Graphical Representation of Comparative Analysis of Patients Diagnosed with both NAFLD and CAD

C. Correlation of Patients Diagnosed with both NAFLD and CAD

The observational nature of included studies precludes establishing causality, and residual confounding cannot be ruled out. Second, there was substantial heterogeneity among studies, which may be attributed to differences in study populations, diagnostic criteria for NAFLD, CAD outcomes, and methodological quality.

Variable 1	Variable 2	Pearson Correlation	p-value
BMI (kg/m^2)	ALT (U/L)	0.285	0.034
LDL Cholesterol	Total Cholesterol	0.624	<0.001
Age (years)	CAD Severity	-0.367	0.012

Table 4. Summarizes the Correlation of Patients Diagnosed with both NA

Third, most included studies were cross-sectional, limiting the ability to assess temporal relationships or determine the direction of causality. The possibility of publication bias cannot be entirely excluded despite the absence of significant bias detected in this analysis. In conclusion, this meta-analysis provides robust evidence supporting an association between NAFLD and CAD, highlighting the potential clinical implications for risk assessment and management.

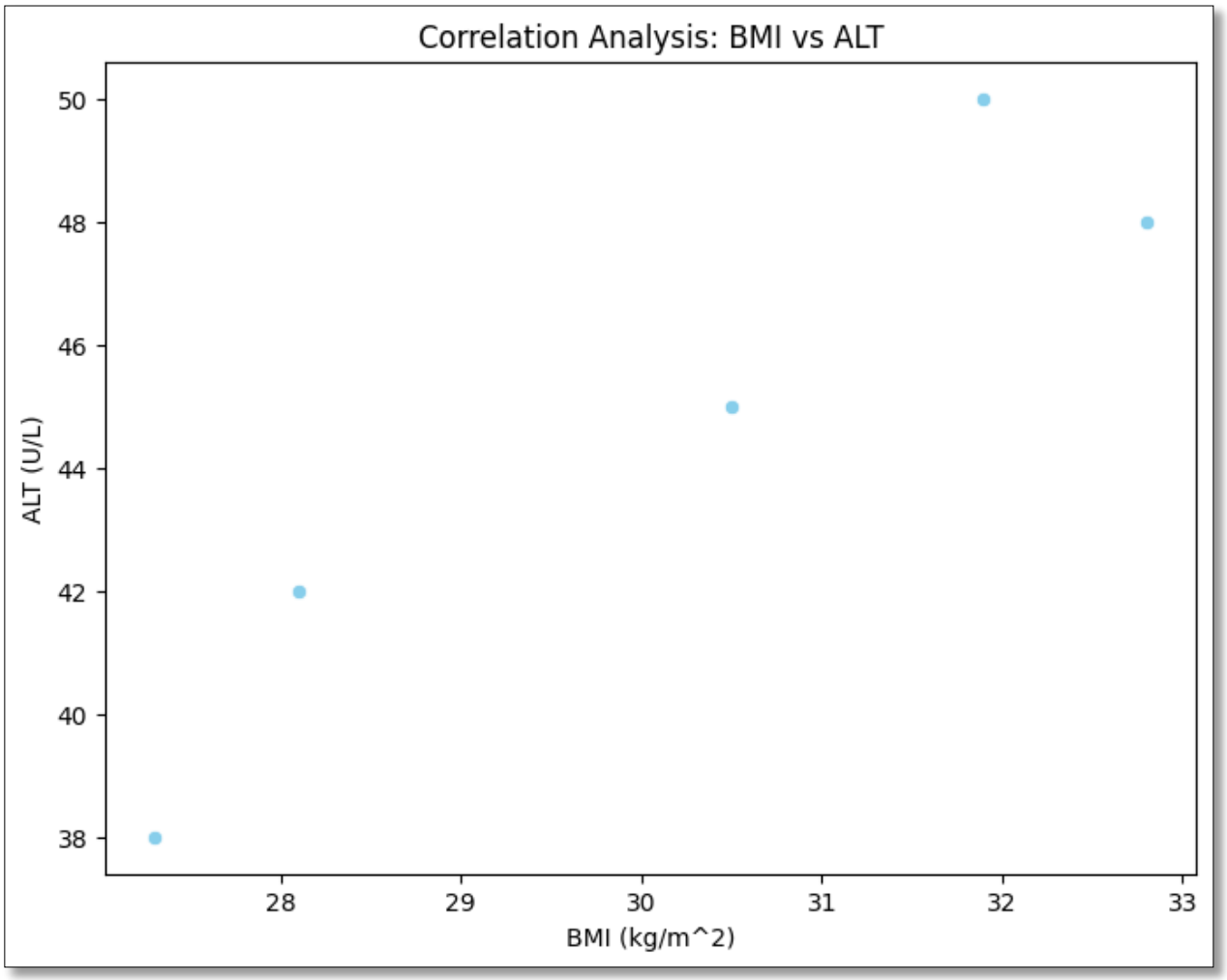

Figure 4. Graphical Representation of Correlation of Patients Diagnosed with both NA

Future research should focus on elucidating the underlying mechanisms linking NAFLD to CAD, exploring the impact of NAFLD treatment on cardiovascular outcomes, and identifying high-risk subgroups for targeted interventions. Incorporating NAFLD screening and management strategies into cardiovascular risk assessment algorithms may help mitigate the burden of CAD in individuals with NAFLD.

IV. Conclusion

Non-Alcoholic Fatty Liver Disease (NAFLD) is emerging as a predictor of coronary artery disease (CAD), independent of traditional cardiovascular risk factors. This meta-analysis provides compelling evidence supporting the association between NAFLD and CAD, underscoring the importance of considering NAFLD in cardiovascular risk assessment and management. Further research is warranted to elucidate the underlying mechanisms and implications for clinical practice. The prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) escalates alongside cardiometabolic conditions. Key pathophysiological mechanisms within NAFLD, including insulin resistance, dysfunction of adipose tissue, atherogenic dyslipidemia, oxidative stress, inflammation, and endothelial dysfunction, contribute significantly to the development of atherosclerotic cardiovascular disease (CVD). Additionally,

individuals with NAFLD exhibit an elevated risk of coronary heart disease (CHD), which remains significant even after adjusting for other conventional cardiovascular risk factors. Numerous studies in the literature have linked NAFLD with both subclinical and clinical manifestations of CHD, whether in acute or chronic settings. Moreover, NAFLD patients experiencing acute coronary syndromes tend to experience poorer outcomes compared to those without NAFLD.

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