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THE PREVALENCE OF NONALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH ATHEROSCLEROTIC CORONARY ARTERY DISEASE: A PILOT STUDY

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is frequently associated with metabolic and cardiovascular diseases, especially atherosclerotic coronary artery disease (CAD). However, data on the prevalence of NAFLD in patients with atherosclerotic CAD are scarce. **Objective:** To estimate the prevalence of NAFLD in patients with atherosclerotic CAD at a public hospital cardiology outpatient clinic. **Methods:** Cross-sectional study involving 31 patients undergoing coronary artery bypass grafting, percutaneous coronary intervention, or acute myocardial infarction history. The presence of hepatic steatosis was assessed by abdominal ultrasonography and graded as mild, moderate or marked. **Results:** The overall prevalence of NAFLD was 70.97%, 58.06% with mild and 12.9% with moderate steatosis. NAFLD was observed in 66.67% of patients with normal BMI, 85.71% with overweight and 57.14% with grade 1 obesity. Among NAFLD patients, 72% practised less than moderate physical activity and 80% moderate. Of the patients with metabolic syndrome, 81.82% had NAFLD, 54.55% with mild and 27.27% with moderate steatosis. NAFLD was observed in 70% of people with diabetes and 71.43% of nondiabetic patients. **Conclusion:** NAFLD was highly prevalent, but the association with diabetes mellitus did not increase the prevalence, unlike metabolic syndrome and overweight.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) was first described in 1980 in obese individuals with no history of significant alcohol consumption (Ludwig *et al*., 1980). Four decades later, it remains a significant challenge in medical practice, mainly due to its multifaceted characteristic, frequent association with metabolic and cardiovascular diseases, and complex pathophysiology, which culminate in limitations, including the absence of a specific drug for treatment. The frequent association with components of the metabolic syndrome has prompted its description as a hepatic manifestation of this syndrome. Similarly, it is related to comorbidities such as obesity, type 2 diabetes mellitus (DM2), dyslipidemia, and cardiovascular disease (CVD), especially atherosclerotic coronary artery disease (CAD) (Kasper *et al*., 2021; Younossi *et al*., 2015). Like other chronic liver diseases, NAFLD can progress to cirrhosis and hepatocellular carcinoma; however, the most frequent causes of complications are CVD (Targuer *et al*., 2016). NAFLD is defined by the presence of steatosis evidenced by imaging or histology and the absence of secondary causes of intrahepatocyte lipid accumulation, such as significant alcohol consumption, prolonged use of medication with steatogenic potential, or monogenic inherited disorders. It can be categorised histologically into non-alcoholic fatty liver or non-alcoholic steatohepatitis. Both are defined by the presence of ≥5% steatosis, the former without evidence of hepatocellular injury, while in the latter, there is inflammation with hepatocyte injury in the form of ballooning, with or without fibrosis (Chalasani *et al*., 2017). It presents a broad histological spectrum ranging from isolated steatosis, steatohepatitis, advanced fibrosis, and cirrhosis (Ângulo, 2022). Insulin resistance is the key element of its pathophysiology, determining the accumulation of triglycerides in hepatocytes, which triggers oxidative stress, lipid peroxidation, and inflammatory response, which cause injury, cell death, and fibrotic replacement (Savage *et al*., 2007). Most patients with NAFLD are asymptomatic at the time of diagnosis. Increased levels of serum aminotransferases are the most common abnormalities. However, only 2.8% to 5.4% of cases of steatosis without an identifiable cause present this abnormality (Szcepaniak *et al*., 2007). Non-invasive imaging methods, such as ultrasonography, computed tomography, and magnetic resonance imaging, can identify hepatic steatosis. The

biopsy is the gold standard for assessing the stage and degree of liver damage. Nevertheless, it is an invasive test and should be used only in cases where the aetiology cannot be defined by other methods or when there is a high risk of steatohepatitis or advanced fibrosis (Sturzeneker *et al*., 2022). There is no specific pharmacological treatment adequately defined for NAFLD; so far, no drug has been approved by the European and North American regulatory agencies for this purpose (Vilar-Gomez *et al*., 2015). In biopsy-proven non-alcoholic steatohepatitis (NASH), pioglitazone and vitamin E can be considered in non-diabetics, and pioglitazone in people with diabetes (Chalasani *et al*., 2017). Treatment is based on changes in lifestyle habits, such as appropriate diet and physical exercises, aiming at body weight and metabolic control, in addition to the treatment of associated diseases, such as obesity, DM2, dyslipidemia, and systemic arterial hypertension (SAH) (Dufour *et al*., 2022). In a prospective cohort study, there was an improvement in NASH in those who achieved at least 5% weight loss, being more significant in individuals who lost 10% or more of body weight (Vilar-Gomez *et al*., 2015). Besides insulin resistance, considered the most important disorder related to the pathophysiology of NAFLD, the renin-angiotensin system plays an important role in this context and its blockade by angiotensin 2 AT1 receptor inhibitors, as well as by angiotensin-converting enzyme inhibition, culminated with histological improvement in an experimental model of NAFLD, suggesting a potential benefit of both classes in patients with NAFLD and NASH (Sturzeneker *et al*., 2011; Struzeneker *et al*., 2019).

NAFLD has been frequently and significantly related in different ways to CVD, independently of classical risk factors and metabolic syndrome. However, its true role in this context remains poorly elucidated (Stahl *et al*., 2019). Common features in the pathophysiology of both point to a significant number of potential links between them (Francque *et al*., 2016). The atherogenic dyslipidemia phenotype, characterised by hypertriglyceridemia, low HDL, and small, dense LDL, was significantly associated with NAFLD, independent of several metabolic risk factors (DeFilippis *et al*., 2013). Endothelial dysfunction, an early manifestation of atherosclerotic disease, has been observed in NAFLD patients (Vilar-Gomez *et al*., 2015). The release of pro-inflammatory cytokines related to the inflammatory process associated with NAFLD may influence the atherogenic process (Francque *et al*., 2016). The significant and independent association of NAFLD and subclinical CVD has been widely described in cross-sectional studies and reinforced in systematic review and meta-analyses (Zhou *et al*., 2018). It has also been related to fatal and nonfatal cardiovascular events. In a meta-analysis that selected prospective and retrospective observational studies, the risk of developing a combined cardiovascular outcome (cardiovascular death and nonfatal cardiovascular event) was 64% higher in individuals with NAFLD (Targher *et al*., 2016).

The worldwide prevalence of NAFLD was previously estimated to be 25.24%; however, it has progressively increased and is currently estimated to be 32.4% (Riazi *et al*., 2022; Younossi *et al*., 2015), with an estimated additional increase of 25% by 2030 (Adams *et al*., 2020). According to the region analysed, there is significant heterogeneity in the prevalence data, with the highest prevalence in the Middle East and South America and the lowest in Africa. This geographical variation reflects known differences in the incidence and severity of the disease among different ethnic groups, with the possibility of the existence of some protective factor in blacks and, conversely, a predisposition in Hispanics (Bambha *et al*., 2012; Younossi *et al*., 2015). A higher prevalence in males and an age-related increase in prevalence have been reported; however, there are a limited number of studies involving individuals older than 70 years of age (Younossi *et al*., 2015). Taking into account the importance of the apparent relationship between NAFLD and atherosclerotic CAD, the scarcity of data in the literature regarding the prevalence of NAFLD in patients with atherosclerotic CAD, as well as the lack of data related to the population of the Southern region of Brazil in this context, the present study was conducted to evaluate this prevalence in the population seen at an outpatient clinic of a public hospital in a city in the state of Paraná, Southern region of Brazil.

OBJECTIVE

To estimate the prevalence of NAFLD in patients with atherosclerotic CAD seen at the cardiology outpatient clinic of the Campos Gerais Regional University Hospital of the State University of Ponta Grossa (HU-UEPG).

METHODOLOGY

Cross-sectional study, developed from January to October 2022, involving part of the population allocated to the SURF CHD (Survey of Risk Factors in Coronary Heart Disease) study with a history of documented significant atherosclerotic CAD. Patients undergoing coronary artery bypass graft surgery, percutaneous coronary intervention, or a previous acute myocardial infarction history were considered eligible. The study was approved by the research ethics committee of the Universidade Estadual de Ponta Grossa on January 24, 2022 (opinion No. 5.209.153). All patients who met the eligibility criteria underwent an upper abdominal ultrasound to evaluate the presence of hepatic steatosis. The diagnosis of NAFLD was based on the presence of hepatic steatosis evidenced by the method, the absence of significant alcoholic beverage consumption, and prolonged use of steatogenic medications, among other secondary causes of steatosis. The sonographic studies were performed by a radiologist certified by the Brazilian College of Radiology and the Federal Council of Medicine, using a SAMSUNG HS50 device with a 4.0 MHz frequency convex transducer. Standard images in the axial and sagittal planes of the left and right lobes were acquired, totalizing four images per patient. The diagnosis and grading of hepatic steatosis were based on the finding of increased hepatic echogenicity subjectively or in comparison to the right kidney, being stratified into three grades. Grade I (mild): increased hepatic echogenicity with normal visualization of intrahepatic vascular branches and diaphragmatic surface; grade II (moderate): increased hepatic echogenicity with attenuation of the posterior acoustic beam and partial blurring of the intrahepatic vascular branches and diaphragmatic surface; grade III (severe): increased hepatic echogenicity with attenuation of the posterior acoustic beam and complete blurring of the diaphragmatic surface (Dasarathy *et al*., 2009; Yajima *et al*., 1983).

The prevalence was expressed as a percentage, evaluated in general, by gender, age, ethnicity, education, and degree of obesity, according to physical activity, in people with or without metabolic syndrome, diabetics and non-diabetics. For the diagnosis of metabolic syndrome, the criteria defined by the "Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity" were used, requiring the presence of increased abdominal circumference (≥88 cm for women and ≥102 cm for men) as a fundamental condition and at least two more of its componentes: triglycerides ≥150 mg/dL, HDL <40 mg/L for men and <50 mg/dL for women, systolic blood pressure levels ≥130 mmHg and or diastolic blood pressure levels ≥85 mmHg or SAH under treatment, fasting glucose ≥100 mg/dL or diabetes (Alberti *et al*., 2009). Physical activity was considered moderate when performed for 30 minutes three to five times a week and classified as less than moderate, moderate, and more than moderate.

RESULTS

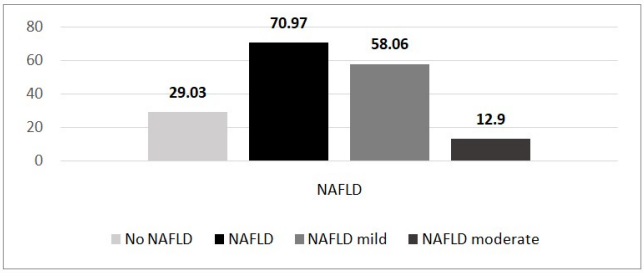
Thirty-one patients were included, characterized in general terms, such as gender, age groups, ethnicity, education, lifestyle habits, obesity, presence of metabolic syndrome, and DM2, as shown in Table I.

Table 1. Characteristics of the study population

		n	%			n	%
Genre	Male	18	58,06%	Ethnicity	White	24	77,42%
	Female	13	41,94%		Black	2	6,45%
Age groups	<65	8	25,8%		Brown	5	16,13%
	65-69	8	25,8%	Schooling	Preschool or elementary	26	83,87%
	70-74	10	32,26%		High	4	12,9%
	75-79	1	3,23%		Higher	1	3,23%
	>=80	4	12,9%	Physical activity	Less than moderate	25	80,65%
Smoking	No	23	74,19%		Moderate	5	16,13%
	Yes	8	25,8%		More than moderate	1	3,23%
Obesity	Normal	9	29,03%	Metabolic syndrome	No	20	64,53%
	Overweight	14	45,16%		Yes	11	35,48%
	Grade 1	7	22,58%	Type 2 diabetes mellitus	No	21	67,74%
	Grade 3	1	3,23%		Yes	10	32,26%
Hypertension	No	2	6,45%				
	Yes	29	93,55%				

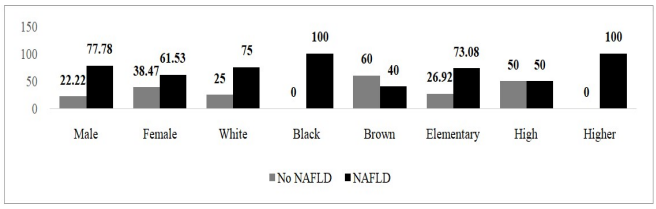
Source: composed by the authors.

The overall prevalence of NAFLD in the study population was 70.97% (22 patients), 58.06% (18 patients) with mild steatosis, 12.9%% (4 patients) with moderate steatosis, none with severe steatosis, and 29.03% had no steatosis (9 patients) (Figure I). The prevalence by gender was 77.78% (14 patients) male and 61.53% (8 patients) female. Regarding ethnicity, eighteen patients were white (75%), two were black (100%), and two were brown (40%). As for education, nineteen had completed elementary school (73.08%), two had completed high school (50%), and one had completed college (100%) (Figure II). NAFLD was not evidenced in two patients <65 years, one aged 65 to 69 years, three aged 70 to 74 years, one aged 75 to 79 years, and two aged 80 years or older. NAFLD was observed in six patients aged <65 years, seven aged 65 to 69 years, seven aged 70 to 74 years, any patients aged 75 to 79 years, and two aged 80 years or older.



Source: composed by the authors. Prevalence expressed as a percentage (%).

Figure 1. Overall prevalence of NAFLD

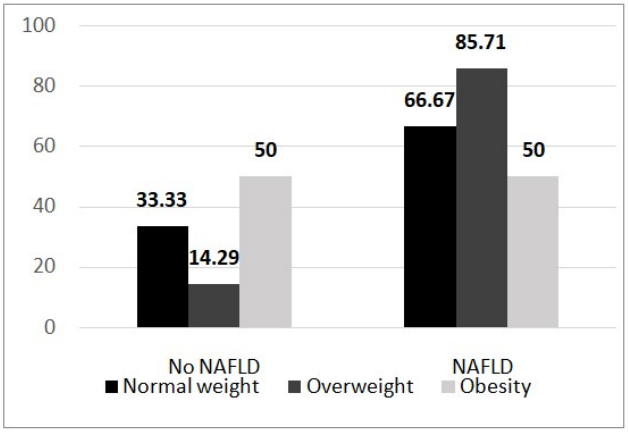


Source: composed by the authors. Prevalence expressed as a percentage (%).

Figure 2. Prevalence of NAFLD by gender, ethnicity and education

NAFLD was observed in six patients (66.67%) with normal BMI, twelve (85.71%) with overweight and four (57.14%) with grade 1 obesity. Three patients (33.33%) with weight within the normal range, two (14.29%) with overweight, three (42.86%) with grade 1 obesity, and one (100%) with grade 3 obesity did not have NAFLD. Among the patients with NAFLD, eighteen (72%) practised less than moderate physical activity and four (80%) moderate. Seven patients (28%) without a diagnosis of NAFLD performed less than moderate physical activity, one (20%) moderate, and one (100%) more than moderate physical activity (Figure III).

Taking into account the presence or absence of metabolic syndrome and DM2, the prevalence of NAFLD was divided into general, absent, mild, moderate, and severe. In the patients with metabolic syndrome, two individuals (18.18%) did not present NAFLD, and nine (81.82%) had the disease, six with mild (54.55%) and three with moderate (27.27%). Among patients without a diagnosis of metabolic syndrome, the prevalence was 65% (thirteen patients), 60% with mild (12 patients) and 5% with moderate (1 patient). In DM2 patients, NAFLD was not observed in three patients (30%) and was observed in seven patients (70%), mild in five (50%) and moderate in two (20%). Of those without DM2, fifteen (71.43%) presented NAFLD, thirteen in mild grade (61.9%) and two in moderate grade (9.52%) (Figure 4).



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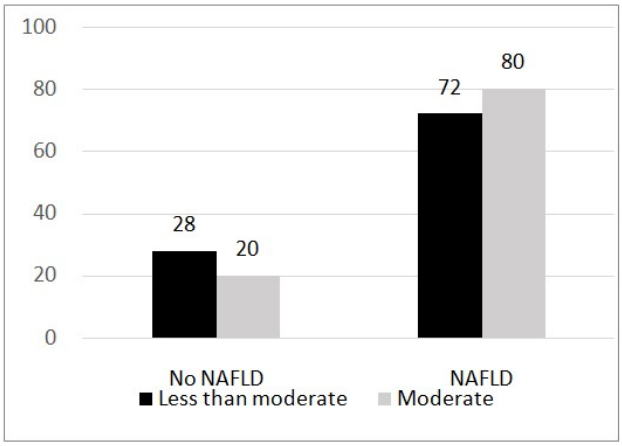
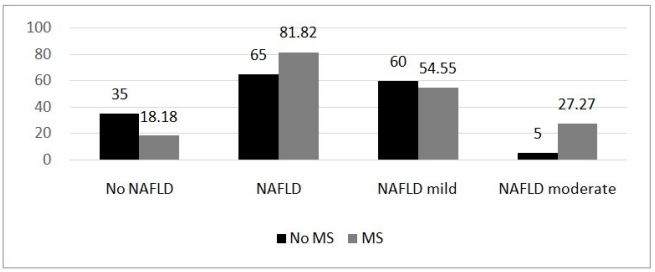


b

Source: composed by the authors. Prevalence expressed as a percentage (%).

Figure 3. Obesity, physical activity and prevalence of NAFLD (a.) Prevalence of NAFLD and body mass index; (b.) Prevalence of NAFLD and physical activity.



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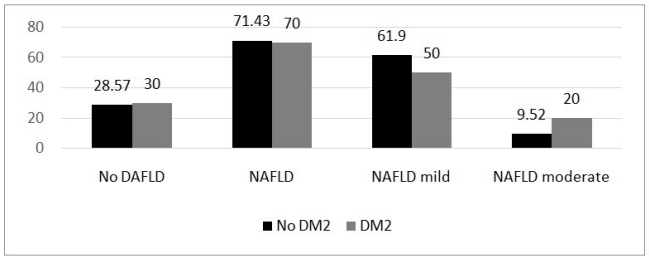

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Source: composed by the authors. Prevalence expressed as a percentage (%).

Figure 4. Prevalence of NAFLD in metabolic syndrome (MS) and DM2. (a.) Prevalence of NAFLD in metabolic syndrome (MS); (b.) Prevalence of NAFLD in type 2 diabetes mellitus (DM2)

DISCUSSION

The frequent and significant association between NAFLD and CVD, especially atherosclerotic CAD, has reinforced the hypothesis that liver disease is at least a risk marker for CVD (Sturzeneker *et al*., 2021). The common features related to the pathophysiology of both indicate a significant number of potential links between them; however, this relationship remains to be elucidated (Francque *et al*, 2016; Stahl *et al*., 2019). In a systematic review that selected 27 observational and cohort studies, NAFLD was associated with increased carotid mediointimal thickness, coronary calcification, endothelial dysfunction and arterial stiffness, demonstrating the significant association of NAFLD with subclinical atherosclerosis, independent of traditional risk factors and metabolic syndrome (Oni *et al*., 2013). In individuals with suspected coronary artery disease undergoing angiotomography of coronary arteries, the presence of increased lipid core and positive remodelling in atheroma plaques, considered vulnerability parameters, was significantly higher in patients with NAFLD regardless of gender, age, alcohol consumption, smoking, BMI, SAH, fasting glucose intolerance, diabetes and dyslipidemia (Akabame *et al*., 2008). In the present study, NAFLD was observed in 22 patients (70.97%), characterizing a high prevalence in this population. A significant but lower prevalence was reported in a subgroup with severe CAD without total occlusion (54.5%) and in 100% of those with total occlusion in a study developed with 800 patients with suspected obstructive CAD. However, those with total occlusion represented 5.5% of the sample (24 patients), and the diagnosis of CAD was established by angiotomography (Saraya *et al*., 2021).

The high prevalence was also reported in another study involving 170 individuals with documented CAD, characterized by stenosis of one of the main coronary arteries or its branches, and the prevalence of NAFLD was estimated at 47%. Similarly to the present study, the diagnosis of NAFLD was made by ultrasonography; however, patients undergoing coronary artery bypass grafting (Baharvand-Ahmadi *et al*., 2016), representing 45.16% of our sample, were excluded. A lower prevalence (39.1%) was observed in a study that classified as severe the three-vessel CAD regardless of the degree of obstruction or at least one vessel with 70% lesion. However, this study was conducted in a region with specific ethnicity and used its own criteria for CAD severity (Hashemi *et al*., 2016). Regarding the prevalence according to the severity of NAFLD, eighteen patients with mild steatosis (58.06%) and four patients with moderate steatosis (12.9%) were observed. We observed the predominance of mild steatosis and absence of severe steatosis in the current study population, a finding similar to that evidenced in a previously mentioned study, with 63 and 17 patients with mild (37.06%) and moderate (10%) (Baharvand-Ahmadi *et al*., 2016). There is a significant heterogeneity of data regarding the prevalence of NAFLD, varying according to region, gender, and ethnicity, with a tendency to a higher prevalence in individuals with advancing age, males, and Hispanics (Bambha *et al*., 2012; Younossi *et al*., 2015). In the present study, the prevalence followed this trend regarding gender, with fourteen males (77.78%) and only eight females (61.53%). Most of the sample studied was of white ethnicity (24 patients), with a prevalence of NAFLD of 75% (eighteen patients), two black and two brown individuals, with the prevalence of 100% and 40%, respectively in both ethnicities. However, the percentage of black and brown people in the sample was low, 6.45% and 16.13%, respectively, compromising the interpretation of these results. The mean age of the sample was 66.93 years, the youngest being 45 years, which corroborates a higher prevalence of NAFLD.

In our study, the prevalence of NAFLD in people with diabetes was 70% (7 patients), higher than that estimated in a regional study conducted in the United States of America (50%). However, besides possible ethnic differences, the individuals evaluated in the cited study were not exclusively carriers of significant atherosclerotic CAD (Portillo-Sanchez ***et al***., 2015). In our sample, the prevalence of NAFLD in patients with metabolic syndrome was 81.82% (9 patients) and 65% (13 patients) in non-carriers. In overweight or obese individuals, the prevalence was 85.71% (12 patients) and 50% (4 patients), respectively. In a study evaluating obese patients in grade 3 who underwent bariatric surgery, the prevalence of NAFLD was estimated at >95% (Subichin ***et al***., 2015). However, in the present study, the majority of the sample was not obese but overweight. The main limitation of this study is the small population sample, which may have directly influenced all the results. The high prevalence of NAFLD evidenced in the population analyzed may have been overestimated. On the other hand, the diagnosis of NAFLD was made by ultrasound, whose sensitivity is low to detect mild steatosis, especially in obese patients (Petzold, 2022). The allocated patients were already under treatment; therefore, they had received guidance regarding lifestyle habits and specific pharmacological therapy for DM2, dyslipidemia, and cardiovascular diseases in general, which may have also influenced the prevalence data. This is a pilot study, which will be continued and other studies are needed to sediment these findings and add information in this extremely important context, which is the association of atherosclerotic CAD and NAFLD.

CONCLUSION

In this sample of patients, NAFLD was highly prevalent, and the association of DM2 did not increase this prevalence. BMI consistent with overweight and the presence of metabolic syndrome increased this prevalence, although the significance of these data cannot be assessed due to the small number of patients.

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