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Article

Sex Differences in Patients with MASLD and Their Association with Cardiometabolic Risk Factors: Insights from the Polish Gallstone Surgery Registry

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Abstract

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by the presence of hepatic steatosis and at least one the cardiometabolic risk factors. Differences in the incidence of MASLD between men and women are primarily due to distinct metabolic and cardiovascular profiles. The aim of this observational study was to investigate the prevalence and characteristics of MASLD in men and women. Methods: The study included patients from The Polish Gallstone Surgery Registry diagnosed with MASLD according to current criteria. Results: Among 3419 patients, MASLD was diagnosed in 24.2%. Its prevalence was significantly higher in man (29.8%) than in women (21.9%) ($p<0.0001$), with the highest incidence observed in men aged 70-79 (32.1%) and women aged 70-79 (33.3%). MASLD was associated with overweight in both men (OR 1.60; 95% CI: 1.03–2.48) and women (OR 2.45; 95% CI: 1.80–3.35), as well as with obesity in men (OR 3.44; 95% CI: 2.21–5.34) and women (OR 5.51; 95% CI: 4.10–7.40). Conclusions: In this study, MASLD was diagnosed more frequently in men than in women. The incidence of MASLD increased with age and BMI, with this relationship being more pronounced in women. Therefore, age and excess body weight are key predictors of MASLD, highlighting the need for individualized treatment strategies, regardless of gender.

Keywords: body mass index; metabolic dysfunction-associated steatotic liver disease; obesity; overweight

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as metabolic dysfunction-associated fatty liver disease (MAFLD) and non-alcoholic fatty liver disease (NAFLD), encompasses a broad spectrum of hepatic and extra-hepatic pathophysiological and clinical

manifestations resulting from the liver steatosis [1]. According to the current definition, MASLD is diagnosed after excluding causes of steatosis other than metabolic ones [2,3].

Prevalence of MASLD is continuously rising, making it is the most common liver disease worldwide, affecting approximately 20–30% of adults [4,5]. The risk factors for MASLD are well established with strong association observed with obesity, poor nutrition, dyslipidaemia, and sedentary lifestyle. These factors contribute to lipotoxicity, reactive oxygen species production, dysbiosis of intestinal microbiome, genetic predisposition, and the induction of proinflammatory immune mediators [6].

Consequently, patients with MASLD not only present with a worsened cardiometabolic profile [7,8] but are also at a significantly higher risk of death from cardiovascular disease than from liver diseases complications [9].

The heterogeneity between females and males in the prevalence, risk factors, and mechanisms of MASLD has long been recognized but remains incompletely understood. Regarding sex differences, the prevalence and severity of MASLD are higher in men than in women during the reproductive age. However, after menopause, the condition becomes more frequent in women, suggesting a protective effect of oestrogens [10]. Additionally, oestradiol influences fatty acid synthase expression in hepatic and adipose cells, while saturated fatty acids induce endoplasmic reticulum stress and increase mitochondrial free radical generation, leading to cellular injury and liver steatosis [11].

Moreover, sex and age differences are also observed in the prevalence of diabetes mellitus type 2 (T2DM), visceral adipose tissue accumulation, and components of metabolic syndrome- all major risk factors for MASLD [12,13].

There is a lack of evidence exploring sex-related differences in the epidemiological risk factors for MASLD. Therefore, we aimed to investigate the prevalence of MASLD and its characteristics in men and women.

2. Materials and Methods

2.1. Study Design

The prospective, multicentre, and observational study involved patients from the Polish Gallstone Surgery Registry. Patients who underwent cholecystectomy due to gallstone disease were consecutively enrolled across six surgical hospitals, including four academic centres and two regional hospitals, providing a comprehensive overview of surgical approaches in Poland. The data included patients admitted to one of the participating centres between 2019 and 2022, either for elective or emergency procedures. To ensure an unbiased selection process and create a cohort reflective of real-world conditions, no specific exclusion criteria were applied.

2.2. Patient involvement

Consecutively hospitalised patients who underwent cholecystectomy were included in the study. MASLD was diagnosed based on the current criteria recommended in June 2023 by experts from the following hepatology societies: European Association for the Study of the Liver (EASL), La Asociación Latinoamericana para el Estudio del Hígado (ALEH) and the American Association for the Study of Liver Diseases (AASLD) [10].

The diagnostic criteria of MASLD included the presence of liver steatosis with at least one cardiometabolic factors:

- BMI ≥ 25 kg/m²,
- fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) or 2-hour post-load glucose level ≥ 7.8 mmol/L (≥ 140 mg/dL) or HbA1c $\geq 5.7\%$ (39 mmol/L) or diabetes mellitus type 2 (T2DM) or treatment for T2DM,
- blood pressure $\geq 130/85$ mmHg or specific antihypertensive drug treatment,
- plasma triglycerides ≥ 1.7 mmol/L (150 mg/dL) or lipid lowering treatment,

- plasma high-density lipoprotein cholesterol (HDL-C) ≤ 1.0 mmol/L (40 mg/dL) - men and ≤ 1.3 mmol/L (50 mg/dL) - women or lipid lowering treatment.

In the presented study two last factors were collectively referred to as atherogenic dyslipidaemia.

Patients with incomplete diagnostic data for MASLD, particularly those without BMI information, as well as individuals with liver steatosis due to non-metabolic causes, were excluded from the analysis (Figure 1).

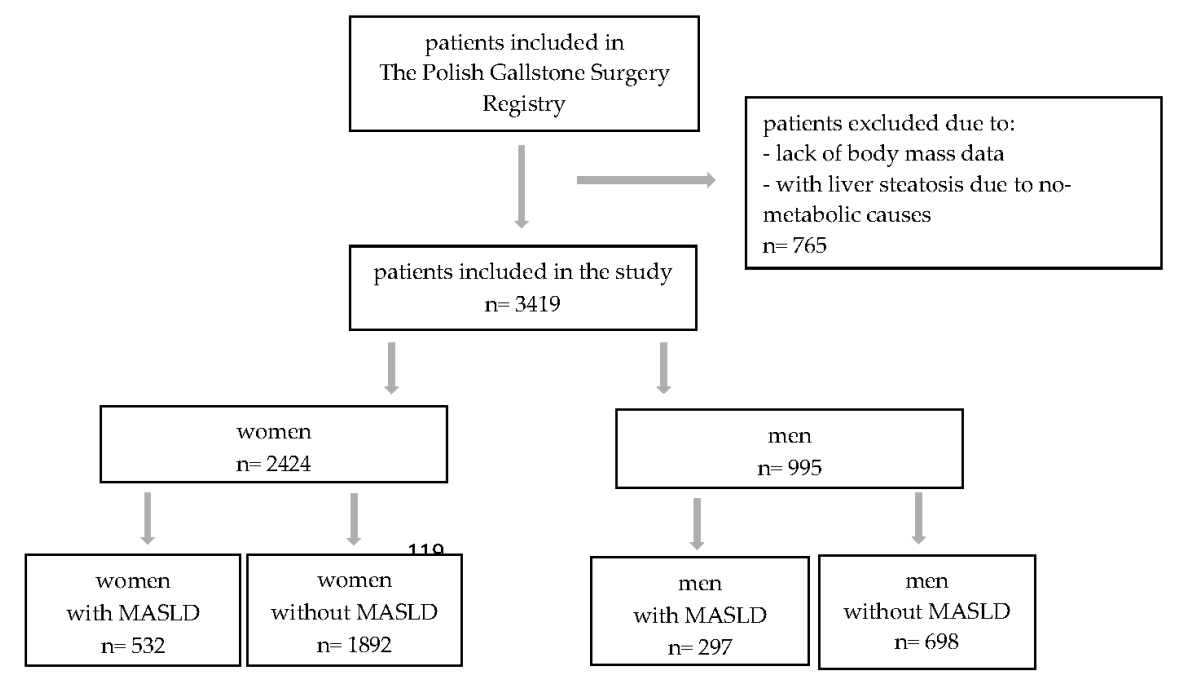


Figure 1. Flow chart of the study. Abbreviation: MASLD, metabolic dysfunction-associated steatotic liver disease.

The study was approved by the Ethics Committee of the Collegium Medicum of The Jan Kochanowski University (104/2022). This work adhered to the ethical guidelines outlined in the Declaration of Helsinki and its subsequent amendments. The requirement for patient informed consent was waived, as this was a retrospective study conducted exclusively using de-identified data.

2.3. Statistical Analyses

Continuous data were described using means and standard deviations, while categorical data were summarized as frequencies and percentages. Groups comparisons were conducted using the chi-square or Fisher exact test for categorical variables and t-test or Mann-Whitney test for continuous variables. Univariable and multivariable analyses were performed using logistic regression models. For these analyses, odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. A two-tailed p-value <0.05 was considered statistically significant. All statistical analyses were conducted using the R software package version 4.0.3.

3. Results

3.1. Patient Characteristics

A total of 3,419 participants were analyzed, including 995 men (29.1%) and 2,424 women (70.9%). The **mean age** of the study **population** was 54.8 years (SD: 15.3). Among the participants, 27 (0.8%) were underweight, 849 (24.8%) had a normal body mass, 1,310 (38.3%) were overweight, and 1,233 (36.1%) had obesity. Hypertension was diagnosed in 1,433 patients (41.9%), T2DM or prediabetes in

519 patients (15.2 %), and atherogenic dyslipidemia in 432 patients (12.6%). The baseline characteristics of the study participants according to sex are presented in Table 1.

Table 1. Comparison of patients with and without MASLD by sex.

Clinical characteristics	Women n = 2424			Men n = 995			p MASLD women vs MASLD men
	MASLD n = 532	Non- MASLD n = 1892	p	MASLD n = 297	Non- MASLD n = 698	p	
Age, years, mean (SD)	59.6 (13.0)	52.4 (15.5)	<0.0001	58.5 (13.2)	56.1 (15.6)	0.0150	0.2383
BMI, kg/m ²							
<18.5	1 (0.2)	23 (1.2)	<0.0001	0 (0.0)	3 (0.4)	<0.0001	0.0762
18.5-24.9	61 (11.5)	613 (32.4)		31 (10.4)	144 (20.6)		
25.0-29.9	164 (30.8)	686 (36.3)		116 (39.1)	344 (49.3)		
≥30	306 (57.5)	570 (30.1)		150 (50.5)	207 (29.7)		
BMI, kg/m ² , mean (SD)	31.5 (5.7)	27.7 (5.2)	<0.0001	30.4 (4.8)	28.1 (4.3)	<0.0001	0.0032
Comorbidities							
Hypertension	292 (54.9)	662 (35)	<0.0001	169 (56.9)	310 (44.4)	0.0003	0.5755
T2DM	115 (21.6)	153 (8.1)	<0.0001	60 (20.2)	87 (12.5)	0.0016	0.6323
Prediabetes	29 (5.5)	59 (3.1)	0.0110	7 (2.4)	9 (1.3)	0.2697	0.0361
T2DM or prediabetes	144 (27.1)	212 (11.2)	<0.0001	67 (22.6)	96 (13.8)	0.0006	0.1530
Atherogenic dyslipidemia	255 (47.9)	30 (1.6)	<0.0001	125 (42.1)	22 (3.2)	<0.0001	0.1054
Chronic coronary syndrome	29 (5.5)	88 (4.7)	0.4469	30 (10.1)	57 (8.2)	0.3228	0.0125
Previous myocardial infarction	13 (2.4)	32 (1.7)	0.2561	16 (5.4)	26 (3.7)	0.2328	0.0270
Hypercholesterolemia	80 (15)	135 (7.1)	<0.0001	39 (13.1)	48 (6.9)	0.0014	0.4529
Atrial fibrillation	21 (3.9)	47 (2.5)	0.0710	20 (6.7)	35 (5)	0.2774	0.0760
Thromboembolism Events	7 (1.3)	18 (1)	0.4623	15 (5.1)	25 (3.6)	0.2804	0.0013
Venous thromboembolism	14 (2.6)	31 (1.4)	0.1343	10 (3.4)	20 (2.9)	0.6720	0.5448
Heart failure	12 (2.3)	41 (2.2)	0.9017	14 (4.7)	27 (3.9)	0.5392	0.0515
Acute pancreatitis previous	29 (5.5)	76 (4.0)	0.1511	16 (5.4)	43 (6.2)	0.6365	0.9689
Chronic pancreatitis	3 (0.6)	9 (0.5)	0.7328	2 (0.7)	5 (0.7)	1	1
Malignancy	47 (8.8)	113 (6)	0.0188	16 (5.4)	47 (6.7)	0.4249	0.0725

Data are presented as number (percentage) unless otherwise indicated. Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, diabetes mellitus type 2.

3.2. Prevalence of MASLD in men and women

Among the patients included in the study, MASLD was diagnosed in 829 patients (24.2%). Its prevalence was significantly higher in men (n=297, 29.8%) than in women (n=532, 21.9%) p<0.0001). Lean MASLD was diagnosed in 94 patients (11.3% of those with MASLD), including 63 women (8.9% of women without overweight/obesity) and 31 men (17.2% of men without overweight/obesity), p=0.0012. MASLD in patients with overweight/obesity was diagnosed in 469 women (27.3% of them with overweight/obesity) and in 266 men (32.6% of them with overweight/obesity), p=0.0057.

3.3. Prevalence of cardiometabolic MASLD diagnostic criteria in men and women according to BMI

Most patients met two diagnostic criteria for MASLD diagnosis. No significant differences were observed in the number of diagnostic criteria between men and women. Table 2 presents the number of diagnostic criteria by sex.

Table 2. Number of factors included in MASLD diagnosis.

Criteria of MASLD diagnosis	All MASLD n=829	Women with MASLD n=532	Men with MASLD n=297	p
1 criterium	162 (19.5)	99 (18.6)	63 (21.2)	0.3648
2 criteria	493 (59.5)	318 (59.8)	175 (58.9)	0.8107
3 criteria	147 (17.7)	98 (18.4)	49 (16.5)	0.4871
4 criteria	27 (3.3)	17 (3.2)	10 (3.4)	0.8939

Data are presented as number (percentage). Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease.

In the normal body mass group, hypertension, T2DM or prediabetes, and atherogenic dyslipidemia were diagnosed more frequently in men than in women (37.7% vs 23.4%; 11.2% vs 5.7%; 14.0% vs 6.7%). In contrast, no significant differences in the incidence of these conditions were observed between male and female patients in the overweight group (Table 3).

Table 3. Prevalence of MASLD and cardiometabolic conditions in various BMI groups among women and men.

	BMI ≤ 24.9 kg/m² n=876			BMI 25-29.9 kg/m² n=1310			BMI ≥ 30 kg/m² n=1233		
	Women n=698	Men n=178	p	Women n=850	Men n=460	p	Women n=876	Men n=357	p
MASLD	62 (8.9)	31 (17.4)	0.001 0	164 (19.3)	116 (25.2)	0.012 6	306 (34.9)	150 (42.0)	0.0194
Hypertension	163 (23.4)	67 (37.6)	0.000 1	353 (41.5)	198 (43.0)	0.596 2	438 (50.0)	214 (59.9)	0.0015
T2DM or prediabetes	40 (5.7)	20 (11.2)	0.009 4	117 (13.8)	57 (12.4)	0.484 5	199 (22.7)	86 (24.1)	0.6040
Atherogenic dyslipidemia	47 (6.7)	25 (14.0)	0.001 5	61 (7.2)	32 (7.0)	0.882 4	177 (20.2)	90 (25.2)	0.0530

Data are presented as number (percentage). Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, diabetes mellitus type 2.

3.4. Comparison of men and women with MASLD

In the present study, women and men with MASLD did not differ significantly in age (59.6 vs 58.5, p=0.2383). The proportion of patients with MASLD and obesity was not statistically higher in women than in men (57.3% vs 50.5%, p=0.0516). However, gender-related differences were observed across obesity classes. Among patients with MASLD and obesity, class I obesity was diagnosed in 180 women (58.8%) and 107 men (71.3%), p=0.0094, class II obesity was diagnosed in 82 women (26.8%) and 27 men (18%), p=0.0385 and class III obesity was observed in 44 women (14.4%) and 16 men (10.7%), p=0.2705.

The clinical characteristics of men and women with MASLD were similar, with no significant differences in the incidence of hypertension, T2DM or prediabetes, atherogenic dyslipidemia, heart failure or atrial fibrillation (Table 1).

3.5. Prevalence of MASLD and stratification by age, BMI, and metabolic disorder

The prevalence of MASLD was not linearly associated with age (Figure 2). In the overall population, the prevalence gradually increased with age, peaking at 32.1% in the 70-79 age group. Interestingly, in men, the prevalence of MASLD rose sharply between the ages of 40-49 and remained stable until age 79, reaching a peak of 33% in the 70-79 age group. In contrast, MASLD prevalence in women gradually increased in the 50-59 age range, peaking at 33.3% between ages 70-79. As expected, the lowest incidence of MASLD in both women and men was observed in the < 30 and ≥ 80 age groups.

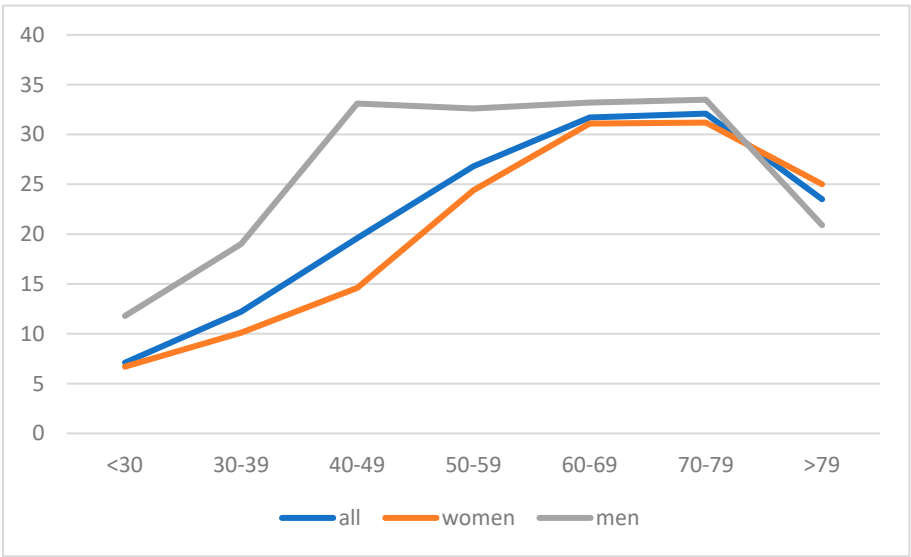


Figure 2. Prevalence of MASLD in different age groups.

The prevalence rates of MASLD in different cardiometabolic groups by sex differed only in patients with overweight and obesity, with a higher incidence in men than in women (32.6% vs 27.2%, $p=0.0057$). In patients with hypertension, with T2DM or prediabetes, and with atherogenic dyslipidemia, the prevalence of MASLD did not differ between women and men. (Table 4).

Table 4. Prevalence of MASLD across different cardiometabolic groups in women and men.

	Overweight or obesity n=2543	Hypertension n=1433	T2DM or prediabetes n=519	Atherogenic dyslipidemia n=432
All	736 (28.9)	461 (32.2)	211 (40.7)	380 (88)
Women	470/1726 (27.2)	292/954 (30.6)	144/356 (40.4)	255/285 (89.5)
Men	266/817 (32.6)	169/479 (35.3)	67/163 (41.1)	125/147 (85)
P value	0.0057	0.0740	0.8879	0.1791

Data are presented as number (percentage). Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, diabetes mellitus type 2.

3.6. Risk factors for MASLD

The relationship between MASLD, age and BMI is presented in Table 5, which shows the incidence of MASLD across BMI groups and various age categories.

Table 5. Binary logistic regression analysis with age and BMI as predictors of MASLD.

		Women			Men		
		Univariable OR	95% CI	p	Univariable OR	95% CI	p
Age, years	< 30	Ref.			Ref.		
	30-39	1.56	0.73-3.31	0.2505	2.40	0.68-8.54	0.1761
	40-49	2.37	1.15-4.89	0.0192	5.08	1.49-17.3	0.0093
	50-59	4.49	2.20-9.14	< 0.0001	4.95	1.45-16.87	0.0105
	60-69	6.28	3.12-12.63	< 0.0001	5.10	1.51-17.20	0.0086
	70-79	6.33	3.10-12.92	< 0.0001	5.17	1.52-17.51	0.0084
	≥ 80	4.72	1.99-11.17	0.0004	2.66	0.66-10.70	0.1691
BMI, kg/m²	< 25	Ref.			Ref.		
	25.0-29.9	2.45	1.80-3.35	< 0.0001	1.6	1.03-2.48	0.0369
	≥ 30	5.51	4.10-7.40	< 0.0001	3.44	2.21-5.34	< 0.0001

Abbreviations: BMI, body mass index; CI: confidence interval; OR: odd ratio; Ref: reference.

Independent of sex, each age group was associated with MASLD incidence, with a higher risk observed in older individuals. However, this observation does not apply to patients over 80 years of age. In both men and women, the highest risk of MASLD was observed in the 70-79 age group. As expected, the risk increased with an increase in BMI. In patients with BMI ≥25 kg/m², the risk is significantly higher in women than in men. Notably, it increased significantly for both men and women when the BMI was ≥30 kg/m² and reached ORs of 5.51 (95% CI 4.10-7.40) for women and 3.44 (95% CI 2.21-5.34) for men.

4. Discussion

The prevalence of MASLD appears to differ between men and women depending on age and the presence of comorbidities. The major findings of this study are as follows. First, our country-specific registry data revealed that the incidence of MASLD is higher in men than in women. Second, the incidence of MASLD increases with age and in both sexes, reaching a peak between 70 and 79 years. Third, the higher the body weight, the greater the risk of developing MASLD, with this relationship being particularly pronounced in women.

Our findings indicate that MASLD poses a significant burden on the population undergoing cholecystectomy, with an overall prevalence of 24.2%. Although the study population consists of patients with gallstone disease, the incidence of MASLD is similar to that in the general population. Notably, we observed a sex-specific difference in MASLD prevalence, with men having a higher prevalence (29.8%) than women (21.9%), suggesting that men are more susceptible to MASLD than women. The higher prevalence of MASLD in men may increase their vulnerability to chronic diseases such as hypertension, cardiovascular disease, T2DM, and stroke.

Crudele et al. [14] reported that MASLD was diagnosed in 59% of patients with metabolic syndrome, with a higher incidence in men. A Spanish study found the overall prevalence of NAFLD to be 19.1%, with rates of 27.9% in men and 6.8% in women, increasing across age groups [15]. Data from the National Health and Nutrition Examination Survey III (NHANES III) also indicated that MASLD is more common in men than in women. Similarly, Chang et al. [17] demonstrated a clear male predominance in MAFLD prevalence, with a higher rate in men (45.7%) than in women (23.9%). It is important to note that MAFLD is more frequently observed in Asian populations [18,19]. However, another study reported a higher prevalence in women (31.7%) compared to men (25.5%), which may be attributed to a smaller sample size and, more significantly, differences in the age

distribution of the study population [20]. That study included patients with a mean age of 67 years, whereas the mean age in our study was 55.

The inclusion of a higher proportion of postmenopausal women may have influenced the results, as estrogen has been shown to have a protective effect against MASLD [21–23]. Studies on sex differences in MASLD show that it is more prevalent in men than in women of reproductive age. However, after menopause, this difference diminishes, exposing older women to higher rates of MASLD. The results of the Polish Gallstone Surgery Registry showed that the incidence of MASLD increased with age, with the highest percentage of patients observed in the 70–79 age group for both women and men. Chang et al. [17] reported the highest prevalence of MAFLD in the 50–59 age group, suggesting that MAFLD is more common in middle-aged individuals. A high proportion of MASLD diagnoses in men was observed between 40 and 49 years, whereas in women it was most common between 50 and 59 years. This difference may be influenced by hormonal changes in women, making them more susceptible to MASLD at an older age. Conversely, younger men have a higher incidence of metabolic and cardiovascular diseases, which may predispose them to develop MASLD at an earlier age than women.

Interestingly, in the present study, the incidence of MASLD did not differ between men and women in the subgroups of patients with hypertension, T2DM/prediabetes, or atherogenic dyslipidemia. Numerous epidemiological studies have shown that overweight and obesity are significant, independent, and modifiable risk factors for MASLD, as evidenced by the parallel rise in obesity rates and MASLD prevalence [7,24]. Chen et al. [18] also identified a strong, nearly linear relationship between MASLD incidence and increased BMI. Regardless of other metabolic abnormalities, patients with obesity face a higher risk of developing MASLD.

However, our subgroup analysis of age and BMI revealed distinct sex differences, showing that women are more prone to MASLD than men at any given BMI. Chen et al. [18] reported similar findings. Furthermore, our data demonstrated a significant link between MASLD, BMI, and age, with higher BMI and older age strongly associated with greater prevalence. These findings suggest that both elevated BMI and advancing age may be key factors in the onset and progression of MASLD.

5. Limitations

This study has inherent limitations. The primary limitation is the specific population analyzed - patients who underwent cholecystectomy for gallstone disease. Consequently, these findings may not be generalizable to a broader group, even though the incidence of MASLD observed in this study aligns with that of the general population. Additionally, it is important to note that the study cohort consists predominantly of women, which could have influenced the results.

6. Conclusions

Our results suggest a high prevalence of MASLD and other metabolic conditions, particularly obesity, in patients undergoing cholecystectomies. In both men and women, the prevalence of MASLD increased with age and BMI. Prioritizing the prevention and management of metabolic disorders, especially obesity, is crucial for the effective treatment of MASLD. These findings underscore the importance of developing personalized interventions to prevent and manage MASLD in both women and men.

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Informed Consent Statement: The requirement for patient informed consent was waived.

Conflicts of Interest: The authors declare no conflict of interest.

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