Original Research Article

ASSOCIATION OF NON-ALCOHOLIC FATTY LIVER DISEASE WITH SYMPTOMATIC AND ASYMPTOMATIC CHOLELITHIASIS: COHORT FROM SOUTHEAST ASIAN PATIENTS

ABSTRACT

Introduction: With increasing prevalence of metabolic syndrome, sedentary lifestyle, and diabetes mellitus the burden of non-alcoholic fatty liver disease (NAFLD) is also increasing along with its complications including gallstone disease. That is why, this study aims to determine the association between non-alcoholic fatty liver disease with the prevalence of gallstone disease and also, risk factors associated with symptomatic and asymptomatic cholelithiasis.

Methods: A prospective study design was performed and during the data collection phase we have enrolled a total of 218 patients who were diagnosed as a case of NAFLD from Asian Institute of Medical Sciences, Hyderabad between the periods of 19 months from March 2019 to October 2020. Diagnosis of NAFLD was made using liver biopsy and cholelithiasis with ultrasound abdomen. Both males and females with a primary diagnosis of NAFLD were included in this study. Patients were divided into symptomatic and asymptomatic gallstone disease and were further assessed for underlying risk factor associated with symptomatic and asymptomatic gallstone disease. Statistical package for the social sciences version 21 (SPSS) used for the entry of data and final analysis and a p value of <0.05 were considered as statistically significant.

Results: The overall prevalence of gallstone disease in patients with NAFLD was 12.84% (n = 28) among them 19 (67.85%) patients were having symptomatic gallstone disease while 9 patients had asymptomatic gallstones disease (32.14%). Patients having mean age 49.01 years, uncontrolled blood sugar level (209.24 mg/dl), mean alkaline phosphatase 106.22 IU/L, female gender, and having diabetes mellitus were significantly associated with symptomatic gallstones disease (p value <0.05).

Conclusion: In our study, the cohorts have shown bidirectional association between gallstone disease and NAFLD. Also prevalence of symptomatic gallstone disease is quite high and it was strongly associated with increasing age, female gender, raised blood glucose levels, and diabetes mellitus.

KEY WORDS: Gallstone Disease, NAFLD, Pakistan

INTRODUCTION:

With increasing prevalence of metabolic syndrome, sedentary lifestyle, and diabetes mellitus the burden of non-alcoholic fatty liver disease (NAFLD) is also increasing along with its complications (1, 2). The prevalence of NAFLD is greatly increased with a rate of 8.2% per year from 391.2 million in 1990 to 882.1 million in 2017. A recent study conducted by Ge X has shown prevalence of NAFLD in general population ranging from 5% to 30% in Southeast Asia while Shah AS and colleagues in 2018 have observed prevalence of NAFLD in Pakistan was 47% (3).

Antonio Benivenius in 1507 (3) has first ever described the gallstone disease (GD) as abnormal masses of a solid mixture of cholesterol crystals, calcium carbonate, phosphate, bilirubinate, and palmitate, phospholipids, glycoproteins, and mucopolysaccharides. The prevalence of gallstone (GS) in developed countries like united states is ranging from 10% - 20% (4) while in Pakistan the burden is comparatively low (9.03%) (5). Because GS and NAFLD shares common risk factors that is why the chances of having increased prevalence and incidence of GS among patients with NFLAD is highly likely. X li has conducted a study on patients with fatty live disease and found 2.1% of patients having GD younger than 30 years while 15.4% having GD having age more than 70 years (6). Loria P in her study has observed prevalence of GD in NAFLD patients was 10.4% (7) while due to lack of data in Pakistan the actual burden of this disease is not known. Considering the scientific gap present in our area this study aims to determine the burden of gallstone disease in patients having NAFLD.

PATIENTS AND METHODS:

This study was approved by the ethical committee of the Hospital and informed consent was taken from all patients before commencement of the study. A prospective study design was performed and during the data collection phase we have enrolled a total of consecutive 218 patients who were diagnosed as a case of NAFLD from Asian Institute of Medical Sciences, Hyderabad between the periods of 19 months from March 2019 to October 2020.

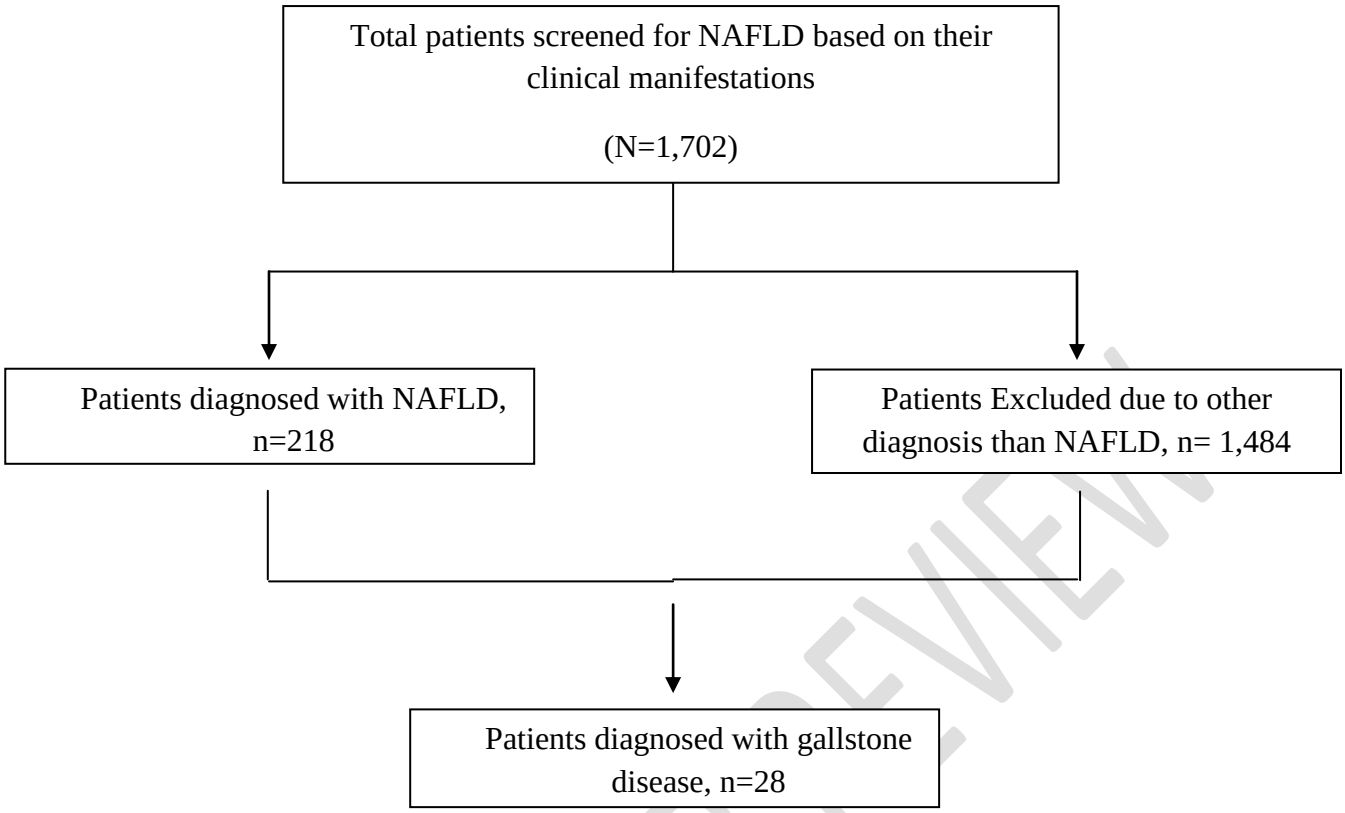

Figure 01: Patients Enrollment Flow Chart

The inclusion criteria for this study was made based on strict supervision of our team and following inclusion criteria was made, age ≥30 and ≤70 years (because most of the patients with NAFLD and cholelithiasis diagnose between this age window), both males and females, and not previously having gallstones disease. Patients with following characteristics were excluded from our study, patients having viral hepatitis, carcinoma of the gallbladder, hepatocellular carcinoma, history of cholecystectomy, pregnant women, and patients with autoimmune hepatitis.

A structured questionnaire was used to collect the baselines and relevant data. Baseline data included age, gender, socioeconomic status, marital status, area of residence, marital status, weight, height, basal metabolic index (BMI), any addiction (alcohol/cigarette). Clinical data include presence of gallstone, random blood sugar, HbA1c, liver function tests, serum total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and serum creatinine.

For the diagnosis of NAFLD we have used proposed guidelines by the American Association for the Study of Liver Diseases (AASLD) in which there must be (1) evidence of hepatic steatosis (HS), either by imaging or histology, and (2) lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long-term use of a steatogenic medication, or monogenic hereditary disorders (3). For the diagnosis of Gallstone Disease (GS) ultrasonography was used in which sonographic evidence of gallstones (one or several echogenic, distally shadowing, possibly movable structures in the gallbladder). Patient with proven abdominal ultrasonoprahic evidence of absence of gallbladder was labeled as cholecystectomy. Basal Metabolic Index was calculated using the formula weight (kg) divided by height (m) squared.

Statistical analysis:

We have used statistical package for the social sciences version 21 (SPSS) for the entry of data and final analysis. Continuous variables such as age and laboratory parameters were recorded as mean and standard deviation and assessed using several non-parametric and parametric tests such as student *t*-test, Pearson's correlation, and two-way ANOVA, where needed. Categorical data presented in the form of numbers and percentages and chi-square test and fisher's exact was used for difference of significance assessment. A p value of ≤ 0.5 was considered as statistically significant.

RESULTS:

A total of 218 patients with NAFLD were finally analyzed and their mean age and SD was 44.87±10.62 years. Among them, majority were females as compared to males, 59.17% (N = 129) and 40.82% (N = 89), respectively. Most of the study subjects (44.49%) had optimal BMI (18.5 – 25 kg/m^2) and diabetic patients were more common as compare to hypertensives, 55.04% vs. 48.62%, respectively. The overall prevalence of gallstone disease in patients with NAFLD was 12.84% (n = 28) among them 19 (67.85%) patients were having symptomatic gallstone disease while 9 patients had asymptomatic gallstones disease (32.14%). Rest of the baseline description shown in table no.1

Association of symptomatic gallstone disease in patients with NAFLD has shown in table no. 1 and 2. Patients having mean age 49.01 years, uncontrolled blood sugar level (209.24 mg/dl),

mean alkaline phosphatase 106.22 IU/L, female gender, and having diabetes mellitus were significantly associated with symptomatic gallstones disease (p value <0.05).

DISCUSSION:

Non-alcoholic fatty liver disease (NAFLD) comprises of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). The burden of this disease is continuously on rise with time and is associated with major burden of hospitalization, impaired quality of life, and even deaths even after the advancement in the treatment. In a previously conducted studies the prevalence of NAFLD ranging from 46% in developed country while 2.7% to 12.2% in developing countries but there is no any proper epidemiological data available from Pakistan hence we have to rely on previously published literatures. The reason behind this could be high consumption of fatty meal/junk food in developed countries as compare to developing. Loria P and colleagues had observed prevalence of gallstones disease in patients with NAFLD and found 19.88% and it was higher in female patients (4). Findings of our study have shown comparatively low prevalence of gallstone disease (12.84%) in patients with NAFLD but it is consistent with higher prevalence observed in females as compared to males. Multiple reasons can define this difference such as low prevalence of gallstones disease in our population could be due to low prevalence of metabolic syndrome which is the most important risk factor causing gallstone disease in patients with NAFLD and prevalence can be as high as 65% (5). Another study conducted by Xu li and colleagues has shown 8.8% prevalence of gallstone disease which is quite lower than ours but it is possibly due to their inclusion criteria in which they have only included younger Chinese patients with NAFLD (6). Higher association of gallstone disease in also observed in patient who had increased age, female gender, and hyperglycemia. This shows liner and common relation of NAFLD and gallstone disease even this can be proved in previous literature (7-10). Ethnic variations may play an important role in the difference between prevalence of gallstone disease in different population and clinical based studies.

Progression and severity of the disease may be associated with the symptoms of gallstone disease as in our study we have observed that prevalence of symptomatic gallstone disease is 67.85%. The mechanism underlying this bidirectional association is incompletely understood. Increase in the insulin resistance, development of metabolic syndrome, and hyperlipidemia could play a

pivot role in the pathogenesis and favoring in the development of symptomatic gallstone disease in patients with NAFLD (1, 11).

Our study has several limitations. First, the sample size of our study was smaller and only included patients from one center. Secondly, we did not know the duration of the NAFLD and gallstone disease which occurred first during the course. Hence, these limitations should be fulfilled in the future prospective studies so the scientific gap could be filled.

CONCLUSION:

In our study, the cohorts have shown bidirectional association between gallstone disease and NAFLD. Also prevalence of symptomatic gallstone disease is quite high and it was strongly associated with increasing age, female gender, raised blood glucose levels, and diabetes mellitus.

TABLE NO. 01: DEMOGRAPHIC AND CLINICAL PROFILE OF STUDY SUBJECTS

(N = 218)

Variables	N	%
Gender		
Female	129	59.17
Male	89	40.82
Area of Residence		
Urban	138	63.3
Rural	80	36.69
Social Class		
Lower	55	25.22
Middle	131	60.09
Upper	32	14.67
Marital Status		
Single	72	33.02
Married	146	66.97
BMI - kg/m2		
Underweight (<18.5)	9	4.12
Optimal (18.5 - 25)	97	44.49
Overweight (25 - 30)	67	30.73
Obese (>30)	45	20.64
Addiction		
Smoker	92	42.2
Alcohol	31	14.22
Hypertension		
Yes	106	48.62
No	112	51.37
Diabetes Mellitus		
Yes	120	55.04
No	98	44.95
Dyslipidemia		
Yes	66	30.27
No	152	69.72
Gallstone Disease		
Yes	28	12.84
Symptomatic	19	67.85
Asymptomatic	9	32.14

TABLE NO. 02: ASSOCIATION OF CONTINUOUS VARIABLES IN GALLSTONE DISEASE WITH AND WITHOUT SYMPTOMS

(N = 26)

Variables	Gallstones Disease				
	NAFLD Overall (218)	Symptomatic (N = 19)	Asymptomatic (N = 9)	Mean±SD Difference	p value
	Mean±SD	Mean±SD	Mean±SD		
Age – years	44.87±10.62	49.01±0.18	44.21±1.88	4.8±1.7	**0.001***
RBS - mg/dL	198.12±28.34	209.24±18.41	197.60±10.66	11.64±7.75	**0.04***
Total Cholesterol - mg/dL	158±5.10	164.03±3.45	161.39±2.10	2.64±1.35	0.09
Serum Triglycerides - mg/dL	130±3.45	129.60±11.01	129.90±5.05	0.3±5.96	0.21
High-Density Lipoprotein - mg/dL	33.03±0.89	31.72±0.97	32.52±1.61	0.8±0.64	0.71
Low-Density Lipoprotein - mg/dL	101.67±7.08	103.38±5.63	99.92±5.49	3.46±0.14	0.34
Total Bilirubin - mg/dL	1.01±0.34	1.02±0.81	1.11±1.09	0.09±0.28	0.15
Alkaline Phosphatase - IU/L	91.43±6.74	106.22±9.43	90.07±10.27	16.15±0.84	**0.01***
Aspartate Aminotransferase - IU/L	20.14±0.34	21.17±0.39	21.0±80.16	0.09±0.23	0.46
Alanine Aminotransferase - IU/L	28.89±6.83	31.77±5.43	28.73±1.90	3.04±3.53	0.05

TABLE NO. 03: ASSOCIATED RISK FACTORS IN PATIENTS WITH SYMPTOMATIC VS. ASYMPTOMATIC GALLSTONE DISEASE AMONG PATIENTS HAVING NAFLD (N = 26)

Variables	Gallstone Disease		p value
	Symptomatic (N = 19) N (%)	Asymptomatic N = 9) N (%)	
Gender			
Female	12 (63.15)	5 (55.55)	**0.02***
Male	7 (36.84)	4 (44.44)	
Area of Residence			
Urban	13 (68.42)	7 (77.77)	0.06
Rural	6 (31.57)	2 (22.22)	
Social Class			
Lower	6 (31.57)	3 (33.33)	0.71
Middle	11 (57.89)	5 (55.55)	
Upper	2 (10.52)	1 (11.11)	
Marital Status			
Single	4 (21.05)	4 (44.44)	0.72
Married	15 (78.94)	5 (55.55)	
BMI - kg/m2			
Underweight (<18.5)	1 (5.26)	0 (0.0)	0.61
Optimal (18.5 - 25)	6 (31.57)	5 (55.55)	
Overweight (25 - 30)	9 (47..36)	2 (22.22)	
Obese (>30)	3 (15.78)	2 (22.22)	
Addiction			
Smoker	5 (26.31)	3 (33.33)	0.19
Alcohol	2 (10.52)	0 (0.0)	
Hypertension			
Yes	10 (52.63)	3 (33.33)	0.06
No	9 (47..36)	6 (66.66)	
Diabetes Mellitus			
Yes	14 (73.68)	5 (55.55)	**0.03***
No	5 (26.31)	4 (44.44)	
Dyslipidemia			
Yes	8 (42.10)	2 (22.22)	0.12
No	11 (57.89)	9 (77.77)	

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