International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 9; Issue 05(B); May 2020; Page No.22160-22165
DOI: http://dx.doi.org/10.24327/ijcar.2020.22165.4379

Research Article

EPIDEMIOLOGY OF NONALCOHOLIC FATTY LIVER DISEASE IN PATIENTS OF GALL STONES DISEASE IN HIMACHAL PRADESH

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A R T I C L E I N F O

Article History:
Received 06th February, 2020
Received in revised form 14th March, 2020
Accepted 23rd April, 2020
Published online 28th May, 2020

Key words:

Gall stones disease (GSD), Nonalcoholic liver disease (NAFLD), steatosis, Fibrosis, Transient elastography (Fibroscan).

A B S T R A C T

Introduction: Described in 1980nonalcoholic fatty liver disease (NAFLD) is accumulation of hepatic fat in absence of a coexisting cause of chronic liver disease or secondary causes of steatosisincluding drugs.
NAFLD is considered as liver manifestations of metabolic syndrome. Asian populations show a greater risk of NAFLD in comparison to Western countries population,having same anthropometric measurements. Patients with gallstones & NAFLD, share similar risk factors.
Objective: The aim of the study was to determine prevalence of NAFLD& to assess its severity by using transient elastography (Fibroscan) in patients of gall stone disease.
Materials and Methods: A total 200 patients of ultrasound proved gallstone disease were investigated and subjected to transient elastography. Based on presence or absence of NAFLD, these patients were divided in two groups, to compare various epidemiological factors.
Results: Majority of patients were females. Maximum number of patients were in the age group of 31-50 yrs.There was significant association between raised levels of cholesterol and triglyceridesin patients with NAFLD with gall stones disease.
There was high prevalence of steatosis in patients of gall stones disease and fibrosis was present in 26.5% ofpatients having NAFLD with gall stone disease.
Conclusion: There was high prevalence of NAFLD in patients of gall stone disease. Most of the patients of NAFLD with gall stones had mild degree of steatosis with fibrosis . Patients of gall stone disease with NAFLDhad higher mean BMI, triglycerides& total cholesterol levels than the non-NAFLD group. Transient Elastography is more sensitive and better modality for diagnosing NAFLD and degree of fibrosis as compared to ultrasonography.

INTRODUCTION

Since first described in 1980[1],nonalcoholic fatty liver disease (NAFLD) is described as the accumulation of hepatic fat as evidenced by radiologic or histologic examination, in absence of a coexisting cause of chronic liver disease or secondary causes of steatosis including drugs, significant alcohol consumption, inherited or acquired metabolic states. The spectrum of NAFLD encompasses 2 subtypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFLD has the highest prevalence in the Middle East and South America and the lowest prevalence in Africa [2]. Interestingly the prevalence of NAFLD in Asian countries seems to follow a rural-tourban gradient with lower prevalence rates reported from the rural areas of India and China and higher prevalence rates from the urban areas [3].

NAFLD is considered the liver manifestations of metabolic syndrome and is highly associated with obesity, type 2 diabetes mellitus, hypertension, and hyperlipidemia [4].Gallstones disease (GSD) share similar risk factors and it is expected that NAFLD may have higher prevalence in patients with gallstones disease than in patients without gallstones disease. Studies have shown higher prevalence and greater severity of NAFLD in patients with gallstones disease. Although most patients with NAFLD are obese, it is important to recognize that some patients with NAFLD are considered lean. In one study from rural India, lean NAFLD subjects comprised more than 50% of all NAFLD cases [4]. These data

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suggest that factors other than obesity, such as environmental factors or gut micro biome, may contribute to the development of lean NAFLD in the Asian countries.

Asian populations show a greater risk of fat-related disorders such as NAFLD, heart disease, and diabetes mellitus as compare to their counterparts in Western countries having same anthropometric measurements (weight and height) [5].

There are conflicting data on the influence of gender on NAFLD. Although early studies suggested that NAFLD was more common in women, recent studies have shown that NAFLD may be evenly distributed between women and men, or may have a higher prevalence in men[6].Using the NHANES data, NAFLD was significantly more prevalent in men[7],although male individuals with NAFLD had a greater visceral adiposity and adverse metabolic disturbances.

Lifestyle factors, including alcohol use propensity for increased waist/circumference ratio, and perhaps different levels of female hormones may further explain the gender difference in the prevalence of NAFLD [8].

GSD & NAFLD Association

The association of GSD and NAFLD has been explored in several observational studies. Some of these studies assessed the prevalence of GSD in patients with NAFLD and others the converse (i.e. frequency of NAFLD in patients with GSD).

Francazani *et al* (2012)inpatients with biopsy-proven NAFLD & found GSD prevalence of 20% with NASH prevalence being significantly higher in patients with GSD, compared with patients without GSD (77 vs. 56%, P < 0.01)[9]. Moreover, GSD prevalence increased with advancing fibrosis and severity of necro-inflammatory activity.

Studies involving participants from different ethnics and regions concluded that NAFLD was independently predictor of GSD. As NAFLD, metabolic syndrome has been also found to independently predict GSD with a dose-dependent effect for each of its component [10].Because most of the features of metabolic syndrome are frequently present in patients with NAFLD [11],it is likely that the association relates to the presence of insulin resistance, a central metabolic defect linked to the pathogenesis of both metabolic syndrome and NAFLD[12].Koller *et al*(2012)demonstrated that presence of GSD was independently associated with NAFLD [4]. In all, based on current data, a moderate association between GSD and NAFLD seems likely although metabolic confounding factors cannot be completely excluded in this association.

Transient Elastography (FIBROSCAN) in NAFLD

The validity of TE in the identification of fibrosis in patients with NAFLD has been extensively studied. CAP(Controlled Attenuation Parameter) is a fairly new method that uses the Fibroscan technology to measure liver attenuation. Fat affects USG propagation and thus measurements of liver attenuation are directly related to the amount of steatosis. Studies have shown strong correlation of CAP with steatosis in the liver compared with liver biopsy for many chronic liver diseases [13]. TE uses liver stiffness measurement (LSM) value to estimate fibrosis in patients with NAFLD. The advantages of Fibroscan include easy use, operator independency, simultaneous measurement of liver stiffness. Conventional USG, commonly used in the clinical setting for diagnosis of fatty liver, has limited sensitivity for detection of mild steatosis (<30% fat in liver) [14]. In conclusion TE can be considered a strong alternative to liver biopsy in patients with NAFLD for diagnosing fibrosis and cirrhosis.

In summary, available data NAFLD and GSD are significantly associated in a bidirectional fashion. Thus, although NAFLD appears to be an independent risk factor for GSD, the latter represents an independent risk factor of NAFLD and, in addition to metabolic derangements commonly present in these patients, could be regarded as a risk factor of liver damage in patients with NAFLD. Although these findings have propelled several hypotheses explaining a direct interaction between these two diseases, association studies only show associations, not causality. Therefore, further prospective studies exploring the underlying mechanism of this association are needed.

Aim

Primary objective was todetermine prevalence of NAFLD in patients with gallstones disease, co-relation of various epidemiological factors on the association of NAFLD and GSD ,to assess the severity of NAFLD in gall stones disease patients by degrees of steatosis and fibrosis, assessed with controlled attenuation parameter (CAP) and with liver stiffness measurement(LSM) respectively.

MATERIALS AND METHODS

A total of 200 patients with USG proven cholelithiasis were included inthis hospital based observational prospective studyw.e.f. from June 2017 to May 2019.All patients underwent Fibroscan in the department of Gastroenterology and were evaluated to establish relationship between cholelithiasis and NAFLD.

Inclusion Criteria were: Aged 18 years or above with gall bladder stones disease on screening ultrasonography for right hypochondriac pain or biliary pain& undergoing cholecystectomy.

Exclusion Criteria were: Patients not willing to participate, clinical radiological or biochemical evidence of choledocholithiasis, evidence of gallstones induced pancreatitis, pregnancy, patients with significant alcohol addiction >25g/day. Patients with Hep.B,Hep.C, autoimmune hepatitis, Wilson's disease, hemochromatosis or any other condition leading to fatty liver or cirrhosis of liver apart from gallstones, with hepato-biliary malignancies and on hepatotoxic drugs.

Criteria for identification of nonalcoholic fatty liver disease used were, patients with USG findings suggestive of fatty liver&confirmed with Fibroscan.

Baseline demographic data of all patients with general physical examination and systemic examination was done. All routine and relevant investigations to exclude secondary causes of fatty liver including estimation of blood glucose, HbA1c, complete hemogram, renal function tests, ALT, AST, Total and direct bilirubin, CRP, Thyroid function tests, Total proteins and albumin ,lipid profile, Hep B, Hep C., HIV, serum ceruloplasmin and ANA were done. The patients with investigations suggestive of alternative diagnosis were excluded.

Height was measured without shoes to nearest 0.5 cm & Body Mass Index (BMI) was taken as Weight in Kg/Height in m^2.

Ultrasound examination (USG)

Abdominal USG examinations of the subjects were performed using a 3.5MHz transducer and the presence of gallstones was determined by the examination findings. Mild, moderate and severe steatosis were observed as per USG classification of NAFLD.

Transient Elastography (Fibroscan)

NAFLD was diagnosed based on value of CAP (Controlled attenuation parameter) on transient elastography (Fibroscan)(fig.1).Simultaneously, degree of fibrosis was assessed based on LSMvalue on transient elastography.Based on CAP value steatosis was graded as s0, s1, s2, s3 and fibrosis was graded as, f0-f1, f1, f2, f3, and cirrhosis.Minimum cut-off value for diagnosing NAFLD was 214dB/m.Minimum fibrosis significant was taken as f2 or more i.e. LSM value >7.5 kPa.

The finding of Fibroscan was interpreted as

The values were taken as:s0, if CAP score was<214 dB/m, s1, if CAP score was (214-255 dB/m), s2, if CAP score was (255-312 dB/m), and s3, if CAP score was> 312dB/m.While fibrosis was interpreted as f0-fi.e. no to mild fibrosis if LSM score was between 2.5kP and 7.5kPa, f2 i.e. moderate fibrosis if LSM score was between 7.5kPa – 10kPa, f3 i.e. severe fibrosis if LSM score was between 10kPa -14kPa and F4 i.e. cirrhosis if LSM score was>14kPa. Significant fibrosis was taken as F2 and above.

Statistical Analysis

All numerical data were expressed as mean with standard deviation (SD). All the statistical tests were done using Excel/SPSS software. Discrete and continuous variables were compared using Pearson's coefficient, Chi square test and Student t-test as appropriate. Multiple comparisons were made using ANOVA. A p value <0.05 was taken as statistically significant.

Observations

This study was conducted from 1st June 2017 to May 31st 2019, including 200 patients who came to surgery or gastroenterology OPD with ultrasonography proven cholelithiasis. 160patients were females and 40were male respectively. Patient's ranged from 22 to 80 years of age with average age of 44.3years (SD-11.9). Maximum number of patients were inthe age group of31-50 years, constituting 57.5% of the total study population. Age wise distribution showed 29 patients(14.5%) in age group 18-30 years, 51(25.5%) patients in age group 31-40 years, 64(32%) patients in age group 41-50 years, 34(17%) patients in age group 51-60 years, 20(10%) patients in age group 61-70 years and 2(1%) patients in age group >70 years.

Mean BMI of the study population was 25.7(SD-3.7) kg/m^2, with a range from 16.5 kg/m^2 to 36.3 kg/m^2. Mean LFT's of the study population was within normal limits, in which, mean total bilirubin of the study population was 0.77mg% (SD-0.5), with a range from 0.1mg% to 4.8mg%, and mean conjugated bilirubin was 0.24(SD 0.20) mg%, with a range from 0.01mg% to 0.96mg%.Mean ALT of the study population was 34.9iu/L (SD-16.7), with a range from 10 iu/L to 111 iu/L.Mean AST of the study population was 33.5iu/L(SD-20.1), with a range from 15 iu/L to 205 iu/L.Mean ALP of the study population was 103.4 iu/L(SD-45.5) with a range from 43 iu/L to 370 iu/L. Mean total cholesterol of the study population was 179.3mg/dL (SD-40.5) with a range from 100 mg/dL to 287mg/dL.Mean triglycerides of the study population was 71.6 mg/dL (SD-71.6), with a range from 32 mg/dL to 474 mg/dL. Mean HDL of the study population was 48.8 mg/dL (SD-13.1), with a range from 24 mg/dL to119. Mean LDL of the study population was 102.6 mg/dL (SD-32.5), with a range from 26 mg/dL to 209 mg/dL. Mean steatosis value of the study population was 235.0 dB/m (SD-62.0), with a range from 100 dB/m to 400 dB/m based on CAP score on Fibroscan.Mean fibrosis value of the study population was 5.8kPa (SD-2.6), with a range from 1.6 kPa to 19.4 kPa, based on LSM score(Table.1).

There was high prevalence of steatosis in patients of gall stones disease& mean steatosis value was 271.5dB/m in 126 patients of gall stones disease. Significant liver steatosis, suggestive of NAFLD was found in 70% patients&30% hadmild steatosis (s1), 20.5%hadmoderate steatosis (s2) and 12.5% had severe steatosis (s3) (Table 2).

Similarity, Fibrosis was calculated on the basis of LSM score and it was found that 26.5%patients had significant fibrosis and 74.5% patients did not have significant fibrosis. Fibrosis was graded as no-to insignificant fibrosis(f0-f1), moderate fibrosis(f2), severe fibrosis(f3) and cirrhosis and out of 200 patients, 76% patients had no to insignificant fibrosis,17% patients had moderate fibrosis, 4.5% patients had severe fibrosis and 2.5% patients had cirrhosis on Fibroscan (Table3).

In the study, patients of gallstones disease with NAFLD and patients with without NAFLD were compared on the basis of different variables (Table 4). And it was observedthat:

Mean age of patients with NAFLD was found to be 44.8years and without NAFLD was 43.5 years with a p-value of 0.43. Thus, no significant association was found between age and NAFLD in patients with gallstones disease.

Mean number of male patients, with NAFLD were 80.7 and with without NAFLD were 79.0. Similarly, mean number of females with NAFLD were 19.3 and with without NAFLD were 21.0, with a p-value of 0.771. Thus, no significant association was found between sex and NAFLD in patients with gallstones disease. Mean BMI value was found to be 26.7 kg/m^2 in patients with NAFLD and 23.9 kg/m^2 in patients without NAFLD, with a p-value of <0.001. Thus, there is a significant association between BMI and NAFLD in patients with gallstones, and that BMI was found to be higher in patientsofgall stones disease with NAFLD.

Mean total bilirubin value was 0.77 mg%, in patients of NAFLD and 0.76 mg%, in patients without NAFLD. Similarly, mean conjugated bilirubin was 0.22 mg%, in patients of NAFLD and 0.27 mg%, in patients without NAFLD, with a p-value of 0.538 and 0.335 respectively. Thus, there was no significant association between bilirubin levels and NAFLD in patients of gallstones disease.

Mean ALT value was 37.0 iu/L in patients of NAFLD and 31.4 iu/L in patients without NAFLD, with a p-value of 0.018. Mean AST was 35.5 iu/L in patients of NAFLD and 30.3 iu/L in patients withoutNAFLD, with a p-value of 0.143. Mean ALP was 102.4 iu/L in patients of NAFLD and 105.0 iu/L inpatients without NAFLD, with a p-value of 0.431.Mean HDL value was 48.3 mg/dL in patients of NAFLD and 49.3

mg/dL in patients without NAFLD, with a p-value 0.499. Mean LDL was found to be 105.7 mg/dL in patients of NAFLD, and 97.6 mg/dL in patients without NAFLD, with a p-value of 0.086. No significant association was observed between NAFLD patients and AST or ALP.

Mean triglycerides value was 180.0 mg/dL in patients of NAFLD and 139.2 mg/dL in patients without NAFLD, with a p-value of <0.001.Thus, there was a significant association between triglycerides levels and NAFLD in patients of gall stones disease, and in these patients' triglycerides levels were found to be greater in patients with NAFLD than in those without NAFLD.

Total cholesterol levels were found to be 185.4 mg/dL in the patients of NAFLD and 169.2 mg/dL in patients without NAFLD with a p-value of 0.005. Thus, there was a significant association between total cholesterol levels and NAFLD in patients of gallstones disease, and that the level of cholesterol was found to be higher in patients of NAFLD.

Figure 1 Fibroscan machine

Table 1 Showing baseline parameters and demographic chart of patients.

Variable	Mean	Stanard Deviation	Range
AGE	44.3	11.9	22-80
BMI	25.7	3.7	16.5-36.3
Total bilirubin	0.77	0.5	0.1-4.8
Conj. Bilirubin	0.24	0.20	0.01-0.96
ALT	34.9	16.7	10-111
AST	33.5	20.1	15-205
ALP	103.4	45.5	43-370
TOT. CHOLESTEROL	179.3	40.5	100-287
TRIGLYCERIDES	164.5	71.6	32-474
HDL	48.8	13.1	24-119
LDL	102.6	32.5	26-209
STEATOSIS	235.0	62.0	100-400
FIBROSIS	5.8	2.6	1.6-19.4

Table 2 Showing NAFLD Prevalence & severity based on degree of steatosis by Fibroscan study.

Steatosis	Number	Percentage (%)
Present	126	63
Absent	74	37

Steatosis Grade	Number	Percentage(%)
S0	74	37
S1	60	30
S2	41	20.5
S3	25	12.5

Table 3 Showing presence of fibrosis and its severity in NAFLD patients onFibroscan study.

Fibrosis	Number	Percentage (%)
Present	53	26.5
Absence	147	73.5
Fibrosis Grade	**Number**	**Percentage (%)**
F0-F1	152	76
F2	34	17
F3	9	4.5
Cirrhosis	5	2.5

Table 4 Showing comparison of different variables of gall stone patients with or without NAFLD.

Variable	GSD With Non NAFLD (Mean)	GSD with NAFLD(Mean)	P-value
Age	43.5	44.8	0.43
Bmi	23.9	26.7	<0.001
Tot. Bilirubin	0.76	0.77	0.538
Conj. Bilirubin	0.27	0.22	0.335
ALT	31.4	37.0	0.018
AST	30.3	35.5	0.143
ALP	105.0	102.4	0.431
TG	139.2	180.0	<0.001
HDL	49.6	48.3	0.499
LDL	97.6	105.7	0.086
TOTAL Cholesterol	169.2	185.4	0.005
Steatosis	175.3	271.5	<0.001
Fibrosis	4.3	7.8	<0.001

DISCUSSION

In this study, most of the 80% patients were females, with male: female ratio of 4:1. Majority of patients belonged to age group 41 to 50 years (37%), with mean age of 44.3years. Other studies have also shown the same trend and reported more prevalence of gallstones disease in females as compared to males. Shaffer *et al*[15] and Tsai *et al*[16] have concluded that age >40years and the female sex are regarded as major risk factors for the development of cholesterol cholelithiasis.

A nationwide survey conducted in America revealed a very high prevalence of cholelithiasis i.e. 13.9%–26.7% in women as compared to 5.3%–8.9% in males.[17]. However, in India, reported prevalence of gallstones is 5.59% in women and 1.99% in males.[18] There is a general conjecture that sex hormones and cholesterol metabolism have possible interrelation. This makes a point to ruminate on how sex is implicated in gallstones formation. Most of the studies suggest female predominance when it comes to the prevalence of gallstones along with it the likelihood of being at risk for stones formation [17].

Majority of our participants had a BMI greater than 25 kg/m2 with a mean of 25.7 ±3.7 kg/m^2.Obese women are at slightly higher risk of stones formation as compared to women with ideal BMI especially when talking about cholesterol gallstones [18] Our results in terms of BMI are quite different from another study that reported 80% of patients had normal BMI and that was no different than control group. [19]

Our patients had a mean total cholesterol level of 179.3±40.5 mg/dL and triglycerides levels of 164.5±71.6 mg/dL which are much higher than the normal values. Factors like body mass index, gender, raised lipid levels, use of contraceptives, alcohol and having diabetes,[20] physical inactiveness, multiparous women, water with excessive iron content, metabolic syndrome and NAFLD [19] are accountable factors for gallstones formation. So, increase lipids have been implicated in gallstones formation.

Koller T *et al*[4] while discussing gallstones formation phenomenon also favored the theory of hyperlipidemia, decreased motility of gall bladder, being overweight and insulin resistance as culprit factors of cholelithiasis pathology. According to him, separation of crystals of cholesterol from supersaturated bile is the prime event. In hyperlipidemia, haptoglobin inhibits PLTP and results in reversal of cholesterol transport and make one vulnerable to gallstones risk. [18]

Patients with NAFLD had mean BMI greater than 26.7 kg/m^2 as compared to 23.9 kg/m^2 to non-NAFLD group with a significant p-value of <0.001, thus this result was in accordance with other studies, (21) signifying that higher BMI is a risk factor for NAFLD in patients with gallstones disease.

Patients with NAFLD had almost similar values of total & conjugated bilirubin, ALT, AST and ALP as compared to non-NAFLD group with a mean of 0.77 mg%, 0.22 mg%, 37 mg%, 35.5 mg%, and 102.4 mg% respectively. Our results were not in accordance with another study which stated that patients with NAFLD have relatively deranged LFT's as compared to normal controls [22].However, presence of normal ranges of liver enzymes does not exclude NAFLD. Mofrad *et al* (2003) reported NAFLD spectrums with normal values of ALT in retrospective series (23).

We found that total cholesterol and triglycerides levels were very high in patients with NAFLD as compared to those without NAFLD with a significant p-value, i.e. 0.005 and <0.001 respectively. Our results were in accordance with other studies,[24] that hyperlipidemia has a strong association with gallstones formation and fatty liver (NAFLD).

The result of one series showed about 10% of the gallstones patients at the time of diagnosis had NAFLD progressed to fibrosis, which was biopsy proven.[25] One of the studies justified for performing liver biopsy for the detection of NAFLD during cholecystectomy and that series captured more NAFLD in patients who undergone biopsies than those with simple ultrasound findings and liver function tests.[25]

In our study, NAFLD as detected by CAP value on TE was present in 63% patients. Most of the patients in our study population had mild degree of steatosis (30%), this is in contrast to other studies which found that there is a greater degree of steatosis among patients with NAFLD and gall stones. Francazani *et al* (2012) in Italian patients with biopsy-proven NAFLD found a GSD prevalence of 20% with NASH which was significantly higher in patients with GSD, compared with patients without GSD (77% vs. 56%) [9].

We also found that fibrosis was present in 26.5% patients, and the mean fibrosis score was higher(7.8kPa) in patients with NAFLD than those without NAFLD (4.3 kPa) with a significant p-value of <0.001. Thus, we came to a result that fibrosis present in GSD with NAFLD is severe as compared to gall stones disease patients without NAFLD.

Nonalcoholic fatty liver disease (NAFLD) has the prevalence of 15%–20% in general population [19].The higher prevalence of NAFLD in our patients than the general population, suggest a possible association between NAFLD and gall stones disease. Similar higher prevalence of NAFLD has been reported in other studies, Koller *et al* [4] found higher prevalence of GSD among patients with NAFLD versus those without NAFLD (47% vs. 26%, respectively).

Higher prevalence of NAFLD in patients with gall stones disease is due to sharing of common risk factors like body mass index, gender, raised lipid levels, use of contraceptives, alcohol and having diabetes, physical inactiveness, multiparous women, water with excessive iron content, metabolic syndrome.[22]

In our study, we found that when USG showed steatosis in12 patients (6%) patients while all these patients had steatosis on TE, but USG missed steatosis in 114 patients (94%) patients which was picked up on TE. Thus, we concluded that TE is much better and more sensitive in diagnosing liver steatosis than USG. These findings are similar to study conducted byMyers RP t al [2012], that transient elastography is more sensitive compared to ultrasound (86.49% vs. 32.43%) in diagnosing fatty liver and fibrosis.[13]

CONCLUSION

1. There was high prevalence of NAFLD in patients of gallstones disease.
2. Most of the patients of NAFLD with gallstones had mild degree of steatosis.
3. Fibrosis was found to be present in 27% patients of NAFLD in gallstones disease.
4. Patients of gallstones disease with NAFLD had a higher mean BMI, TG, TCh., steatosis and fibrosis levels greater than the non-NAFLD group.
5. TE is more sensitive and better modality for diagnosing NAFLD and fibrosis as compared to USG.

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How to cite this article:

Dr. Ankit Sharma *et al* (2020) 'Epidemiology of Nonalcoholic Fatty Liver Disease in Patients of Gall Stones Disease in Himachal Pradesh', *International Journal of Current Advanced Research,* 09(05), pp. 22160-22165.
DOI: http://dx.doi.org/10.24327/ijcar.2020. 22165.4379

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