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A Retrospective Study On Liver Function Tests & Urine Protein in Presumptive Non-Alcoholic Fatty Liver Cases Performed in A Local Private Laboratory Service

SAIFUL BAHRI TALIP*[1], MUHAMMAD HAMDI MAHMOOD[1], AZAM HAFIZI AZMI MURAD[1], CHARISMA DEMAI EDMAND[1], VIMAL GENGATHARAN[1] & YVONNE HO KAR KIAT[1]

[1]Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia
*Corresponding author: tsbahri@unimas.my

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) could be diagnosed either by imaging or histology, and laboratory parameters from Renal Function Test (RFT) such as Aspartate-aminotransferase (AST), Alanine-aminotransferase (ALT), Gamma-glutamyltransferase (GGT), as well as Urine Protein (UP). In this study, data were collected from Advanced Pathology Sdn. Bhd. The data was collected from random population in the year of 2020 were used to identify the association between the parameters of AST, ALT, GGT and UP in presumed NAFLD patients, which are being compared by age, and gender. The results show that the level of GGT shows an insignificant association between genders ($p > 0.05$), but shows a statistically significant association between the age group of respondents ($p < 0.05$). In addition, results from AST indicated that the gender of respondents has a significant relationship with AST ($p < 0.05$), but an insignificant correlation between the age groups ($p > 0.05$). The results also showed also that ALT had an insignificant correlation between the gender of respondents ($p > 0.05$), but is significantly correlated with the age of respondents ($p < 0.05$). Lastly, Chi-square test of independence gave a result of p-value = 0.137 ($p > 0.05$), which proved insignificant correlation between the gender of respondents and presence of UP, and p-value = 0.261 ($p > 0.05$), which proved insignificant correlation between age of respondents and presence of UP.

Keywords: Non-alcoholic Fatty Liver Disease, Aspartate-aminotransferase, Alanine-aminotransferase, Gamma-glutamyltransferase, Urine Protein, Liver function test, Renal function test

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is known as the presence of hepatic steatosis (HS), either by imaging or histology, and lack of secondary causes of hepatic fat accumulation such as long period use of steatogenic medication, significant alcohol consumption, or monogenic hereditary disorders (Chalasani et al., 2018). According to Cohen et al (2011), NAFLD is an umbrella term used to describe a wide range of related diseases, due to the disruption of the homeostatic mechanisms that balance the body's synthesis as well as utilization of fat in the liver. Regarding the epidemiology, prevalence of NAFLD in Asia is noted to rise significantly over time which is 28.46% between 2006 and 2011, as well as 33.90% between 2012 and 2017 (Mitra et al., 2020). Within NAFLD, histological subtypes can range from a bland accumulation of triglycerides within the hepatocytes (fatty liver) to non-alcoholic steatohepatitis (NASH) (Parameswaran et al., 2021). In the cases of NAFLD, the clinical presentation of simple steatosis accounts for 80% - 90%; in NASH, it accounts for the remaining 10% - 20% (Hashimoto et al., 2013). Hashimoto et al (2013) also mentioned that simple steatosis is mostly benign and non-progressive, while NASH can severely progress to cirrhosis or even hepatocellular carcinoma (HCC). However, studies with paired liver biopsies also showed that both patients with NAFL and NASH could also have the possibility to develop progressive liver fibrosis (Singh et al., 2015). Schuppan and Afdhal (2008) defined cirrhosis as the *"histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, that leads to portal hypertension and end-stage liver disease"* (p. 838).

Primary hepatic steatosis in NAFLD patients is highly associated with metabolic risk factors which are correlated with metabolic syndrome (MS), such as obesity, insulin resistance, or dyslipidemia (Chalasani et al., 2012).

Higher BMI (overweight/obesity) has been significantly correlated with fatty liver risk, with the overweight population having a risk of 7.59 times and 3.55 times for the obese population getting involved with NAFLD (Fan et al., 2018). A cross-sectional cohort study found that Caucasian children and adolescents with a biopsy-proven diagnosis of NAFLD have shown some alteration in glucose metabolism (Nobili et al., 2019). 124 out of 599 (20.6%) subjects with biopsy-confirmed NAFLD have shown abnormal glucose tolerance, 19.8% (119/599) of them fulfilled the diagnostic criteria of prediabetes; 0.8% (5/599) were found to suffer from diabetes (Nobili et al., 2019). In addition, the peak prevalence of NAFLD was 26.4% and 26.3% between the ages of 30–40 years and 50–60 years, with 37.4% of men and 13.8% of women being diagnosed with NAFLD (Hu et al., 2018). A low percentage of women tends to have NAFLD, possibly due to the putative protective effects of estrogen (Gutierrez-Grobe et al., 2010).

A diagnostic laboratory is important in finalizing a certain diagnosis whether it is in a private or a public hospital diagnostic laboratory. Prognostication can be done via accurate diagnostic procedures and disease severity staging (Wong et al., 2019). The most common abnormality of laboratory parameters in NAFLD patients are elevated serum levels of transaminases Aspartate-aminotransferase (AST) and Alanine-aminotransferase (ALT) (Dietrich & Hellerbrand, 2014). Anyhow, according to Ulasoglu et al (2019), 107 (20.8%) out of 515 patients with biopsy-proven NAFLD had normal liver enzymes (aminotransferase levels). Therefore, serum Alanine Aminotransferase (ALT), which acts as a significant metabolic indicator, did not possess enough accuracy to confirm the diagnosis of NAFLD (Ma et al., 2020). Thus, more clinical examinations and laboratory diagnostic tests are needed to confirm the diagnosis of NAFLD. Although there are many international studies in the literature on the laboratory tests on NAFLD, there is no report on this condition, particularly in Sarawak. Hence, this research study is conducted to discover and understand the association between the parameters of LFT and RFT (AST, ALT, GGT, and presence of UP) in presumed NAFLD patients, which are being compared by age and gender.

MATERIALS & METHODS

This is a retrospective study of presumptive NAFLD cases performed in a local private laboratory service, Advanced Pathology Sdn. Bhd., Kuching, Sarawak, in 2020, concerning their demographic information such as gender and age. Advanced Pathology Sdn. Bhd. offers laboratory services like blood test, urine test, liver function test, amongst others.

Sample Size Determination

Sample size was calculated using the PS power and Sample Size computer programme of version 3.1.2. A minimum of 88 samples are necessary to obtain 80% confidence level. The margin of error was set as ±5%, and real value is within ±5% of the measured value.

Sampling Technique

The sampling method that was used for this research was stratified random sampling under probability sampling technique. The population of presumed NAFLD patients are divided into age and gender, and from these groups, the frequencies of LFT and urine protein results were drawn. This way, the prevalence of LFT and urine protein results can be analysed based on the age and gender.

Data Collection Method

The data for this investigation was provided by Advanced Pathology Sdn. Bhd. It consists of laboratory test data including liver function tests and urine protein, as well as the patient's demographic information, from January to December 2020. From the data, we only include data with at least two abnormal level of AST, ALT and GGT as a presumed NAFLD cases. As a result, a total of 89 samples was obtained for final analysis after the exclusion. Ethical approval was obtained from Medical Ethics Committee of UNIMAS and permission to make use of laboratory test data to conduct this study was granted by Advanced Pathology Sdn. Bhd.

Data Analysis

Data was entered into the IBM SPSS Statistics version 27.0 software. Independent T test and one-way ANOVA were used to compare the demographic information (age and gender) with AST, ALT, GGT and urine protein level. Meanwhile, chi-square test was used to observe the significant association between the demographic

information with AST, ALT, GGT and urine protein level. The results are presented in the following Tables 1 to 9.

RESULTS

From our findings, out of a total of 89 participants, 38 of them were male. This contributes to 42.7% of the random participants in our sample. In contrast, there were 51 females as our random participants, which make up the remaining 57.3% of the participants. The age findings in this study are spread out as the minimum is 19 years old, while the maximum is 87 years old. The numbers of participants by age group are further detailed in Table 1.

Table 1 Sociodemographic characteristics of respondents (N = 89)

Variables	N	%
Gender		
Male	38	42.7
Female	51	57.3
Age Class		
10-19	1	1.1
20-29	7	7.9
30-39	21	23.6
40-49	20	22.5
50-59	25	28.1
60-69	8	9
70-79	4	4.5
80-89	3	3.4

Gender of respondents and level of GGT

From the analysis, the abnormal levels of GGT are highest among the male gender (84.2%), followed by female gender (80.4%). Chi-square test independence gave a result of p-value = 0.643 (p >0.05), which proved insignificant correlation.

Table 2 Relationship between gender of respondents and level of GGT

Variables	*n*	*Levels of GGT*		*Chi-square p-value*
		Normal (n=16, 18%)	*Abnormal (n=73, 82%)*	
Gender				
Male	38	15.8	84.2	$\varkappa^2 = 0.1995$
Female	51	19.6	80.4	p-value = 0.643

Age of respondents and level of GGT

The analysis below shows that abnormal levels of GGT are highest among the age group of 80-89 years (100.0%), followed by age group 50-59 (96.0%), age group 40-49 (90.0%), age group 60-69 (87.5%), age group 70-79 (75.0%), age group 20-29 (71.4%), age group 30-39 (61.9%), and lastly, age group 10-19 (0.0%). Chi-square test independence gave a result of p-value = 0.025 (p <0.05), which proves that there is a statistically significant association between age of respondents and levels of GGT. This indicated that the eldest respondents tend to have a higher abnormal value of GGT.

Table 3 Relationship between age of respondents and level of GGT

Variables	*n*	*Levels of GGT*		*Chi-square p-value*
		Normal (n=16, 18%)	*Abnormal (n=73, 82%)*	
Age				
10-19	1	100	0.0	$\varkappa^2 = 15.212$
20-29	7	28.6	71.4	p-value = 0.025
30-39	21	38.1	61.9	
40-49	20	10.0	90.0	
50-59	25	4.0	96.0	
60-69	8	12.5	87.5	
70-79	4	25.0	75.0	
80-89	3	0.0	100.0	

Gender of respondents and level of AST

From the analysis, the abnormal levels of AST are highest among the female gender (78.4%), followed by male gender (55.3%). Chi-square test independence gave a result of p-value = 0.020 (p <0.05). This indicated that gender of respondents has a significant relationship with level of AST.

Table 4 Relationship between gender of respondents and level of AST

Variables	***n***	***Levels of AST***			***Chi-square p-value***
		Normal (n=28, 31.5%)	***Abnormal (n=61, 68.5%)***		
Gender					
Male	38	44.7	55.3		$\varkappa^2$ = 5.3216
Female	51	21.6	78.4		p-value = 0.020

Age of respondents and level of AST

The analysis below shows that abnormal levels of AST are highest among both age group, which are 80-89 (100.0%), and 10-19 (100.0%) respectively. It is followed by age group 60-69 (87.5%), both age group 70-79, 40-49 (75.0%), age group 30-39 (66.7%), age group 50-59 (60.0%), and lastly, age group 20-29 (42.9%). Chi-square test independence gave a result of p-value = 0.466 (p >0.05), which proved an insignificant correlation between the age of respondents and level of AST.

Table 5 Relationship between age of respondents and level of AST

Variables	***n***	***Levels of AST***			***Chi-square p-value***
		Normal (n=28, 31.5%)	***Abnormal (n=61, 68.5%)***		
Age					
10-19	1	0.0	100.0		$\varkappa^2$ = 6.5167
20-29	7	57.1	42.9		p-value = 0.466
30-39	21	33.3	66.7		
40-49	20	25.0	75.0		
50-59	25	40.0	60.0		
60-69	8	12.5	87.5		
70-79	4	25.0	75.0		
80-89	3	0.0	100.0		

Gender of respondents and level of ALT

From the analysis, the abnormal levels of ALT are highest among the male gender (97.4%), followed by female gender (92.2%). Chi-square test independence gave a result of p-value = 0.291 (p >0.05), which proved an insignificant correlation between gender of respondents and level of ALT.

Table 6 Relationship between gender of respondents and level of ALT

Variables	***n***	***Levels of ALT***			***Chi-square p-value***
		Normal (n=5, 5.6%)	***Abnormal (n=84, 94.4%)***		
Gender					
Male	38	2.6	97.4		$\varkappa^2$ = 1.0523
Female	51	7.8	92.2		p-value = 0.291

Age of respondents and level of ALT

The analysis below shows that abnormal levels of ALT are highest among five age groups, which are 10-19, 20-29, 40-49, 60-69, and 70-79 which are all having 100.0%. It is followed by age group 30-39 (95.2%), age group 50-59 (92.0%), and lastly, age group 80-89 (33.3%). Chi-square test independence gave a result of p-value = 0.001 (p <0.05). This indicated that age of respondents has a significant relationship with level of ALT.

Table 7 Relationship between age of respondents and level of ALT

Variables	*n*	*Levels of ALT*		*Chi-square p-value*
		Normal (n=5, 5.6%)	*Abnormal (n=84, 94.4%)*	
Age				
10-19	1	0.0	100.0	$\varkappa^2 = 19.9958$
20-29	7	0.0	100.0	**p-value = 0.001**
30-39	21	4.8	95.2	
40-49	20	0.0	100.0	
50-59	25	8.0	92.0	
60-69	8	0.0	100.0	
70-79	4	0.0	100.0	
80-89	3	66.7	33.3	

Gender of respondents and presence of UP

From the analysis, there is greater cases regarding the presence of UP in female (90.2%), if compared to male (78.9%). Chi-square test independence gave a result of p-value = 0.137 (p >0.05), which proved insignificant correlation between gender of respondents and presence of UP.

Table 8 Relationship between gender of respondents and presence of UP

Variables	*n*	*Presence of UP*		*Chi-square p-value*
		Presence (n=13, 14.6%)	*Absence (n=76, 85.4%)*	
Gender				
Male	38	21.1	78.9	$\varkappa^2 = 2.1168$
Female	51	9.8	90.2	**p-value = 0.137**

Age of respondents and presence of UP

The analysis below shows that cases of presence of UP are highest among age group 80-89 (66.7%). It is followed by age group 70-79 (25.0%), age group 50-59 (16.0%), age group 40-49 (15.0%), age group 20-29 (14.3%), age group 30-39 (9.5%), and lastly, both age group 10-19 and 60.69 with 0.0%. Chi-square test independence gave a result of p-value = 0.261 (p >0.05), which proved insignificant correlation between the age of respondents and presence of UP.

Table 9 Relationship between age of respondents and presence of UP

Variables	*n*	*Presence of UP*		*Chi-square p-value*
		Presence (n=13, 14.6%)	*Absence (n=76, 85.4%)*	
Age				
10-19	1	0.0	100.0	$\varkappa^2 = 9.7117$
20-29	7	14.3	85.7	**p-value = 0.261**
30-39	21	9.5	90.5	
40-49	20	15.0	85.0	
50-59	25	16.0	84.0	
60-69	8	0.0	100.0	
70-79	4	25.0	75.0	
80-89	3	66.7	33.3	

DISCUSSION

General findings of LFT in NAFLD

In patients with suspected NAFLD, we discovered that the levels of GGT, AST, and ALT are elevated. A substantial positive link between the LFT and NAFLD has been found by analysis of patient data from our research that were suspected to have NAFLD. Greater than 50% of those with NAFLD will have high GGT (Giannini et al., 2005). The fact that 82% of the patients, or more than half have high GGT lends substantial support to this hypothesis of our findings.

Mechanism of LFT enzymes elevation in NAFLD

Hepatic steatosis is caused by insulin resistance and fat build-up in the liver cells, which is subsequently followed by inflammation caused by pro-inflammatory cytokines and reactive oxygen species generated by dysfunctional mitochondria (Paschos and Paletas, 2009; Cobbina and Akhlaghi, 2017). These will cause significant hepatocyte destruction, releasing AST and ALT from their cytoplasm and significantly increasing blood ALT and AST levels (Giannini et al., 2005). Hepatocyte death in NAFLD patients will result in mitochondrial malfunction and caspase activation, hence an increase in GGT is linked to hepatocyte apoptosis (Tahan et al., 2008).

Association of gender and metabolic syndrome in NAFLD

From this study, we have found that gender is a risk factor for NAFLD. More than half of the patients or 57.3% are females with presumed NAFLD. Metabolic syndromes among females are attributed to the rise in the prevalence of NAFLD among women (Arshad et al., 2019; Lin et al., 2021). According to Ruhl and Everhart (2003), women may be more susceptible to NAFLD. NAFLD is caused by metabolic syndrome, which also causes an increase in visceral adipose tissue and hepatotoxic fatty acid accumulation (Ruhl and Everhart, 2003).

Urine protein in NAFLD

13 patients, or 14.6% of the patients with presumed NAFLD have urinary protein. According to Sun et al. (2018), people with fatty liver may have lower estimated glomerular filtration rate (eGFR) and higher urine albumin. Research done on Chinese and American populations concluded that patients with NAFLD have proteinuria at higher rates and with greater significance than those without NAFLD (Zhang et al., 2020).

Sources of errors

Due to the retrospective nature of the research and the use of secondary data, some details on the clinical status, complaints, and past medical history of the patients may be missed. First, the data do not take into account the patients' history of drinking or smoking. It has been discovered that drinking alcohol and smoking together raise AST and GGT levels (Mehlig et al, 2021). Second, no diagnostic tests have been done on the patients to confirm the NAFLD diagnosis. Due to the nature of the study methodology, there is insufficient information and confirmatory diagnostic tests, which could decrease the precision of the study.

CONCLUSION

The outcomes of this study show that the abnormal level of GGT for presumed NAFLD cases is 82%, followed by AST (68.5%), ALT (94.4%), and the presence of UP (14.6%). There are more than half of the patients or 57.8% are females while 42.2% are males based on our presumed NAFLD cases. However, further diagnostic laboratory is important in finalizing a certain diagnosis. According to the research findings, for GGT, there was an insignificant association between gender, but there is a statistically significant association between the age group of respondents. In addition, regarding AST, results indicated that the gender of respondents has a significant relationship with the level of AST, however insignificant correlation between the age groups. ALT has been found to have an insignificant correlation between gender of respondents but is significantly correlated with the age of respondents. NAFLD is a rapidly growing cause of chronic liver disease, mirroring the rising incidence of obesity and metabolic syndrome. Thus, a health screening program should be done every year, to avoid the progression of NAFLD to the most severe stage.

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