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SYSTEMIC REVIEW

Systematic Review of Correlation of Sonographic Grading of Fatty Liver with Cholesterol Levels and Liver Enzymes

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ABSTRACT

Aim: To explore data on non alcoholic fatty liver disease. For this systematic review, our major purpose is to compare grading of fatty liver disease diagnosed on ultrasound with cholesterol level and liver enzymes.
Methodology: For this study, total 25 studies were included which follow the Preferred Reporting Items guideline for conducting this systematic review analysis (PRISMA). We search electronic articles from year 2008 to from year 2020 on PUB Med, online Willey library, and ScienceDirect site by using keywords related to sonographic imaging for fatty liver disease.
Results: These case studies shows that increasing grades of fatty liver disease are significantly associated with increasing value of total cholesterol levels and liver enzymes.Comparing the heterogeneity level of studies we observed that AST studies have 85% heterogeneity whereas 77% ALT data and 76% GGT data were similar to each other. On the other hand, we observed complete study 12 studies provide information related to TG, TC, HDL, and LDL respectively.
Conclusion: Our meta-analysis concluded that the severe cases of liver diseases need biopsies and histopathological examination. Though ultrasonography provides a complete liver picture with 84.8% sensitivity and 93.6% specificity which may help in many cases still the majority of the studies failed to observe steatosis, NAS score.
Keywords: Non alcoholic fatty liver disease(NAFLD),ultra sonography,lipid profile ,liver enzymes.

INTRODUCTION

Nonalcoholic fatty liver disease is now a most prevalent issue which needs the attention of global health departments[1]. Statistically, 1.5 billion cases of liver diseases 60% cases are comprised of nonalcoholic fatty liver disease which eventually causes a high mortality rate in different regions of the world[2]. Along with this high prevalence of NAFLD 29% of hepatatis B and 9% cases of hepatitis C were also reported from different geographical regions of the world[2].

It is quite categorized per macrovesicular hepatic steatosis among those individuals who do not consume alcohol. Patients with simple steatosis to nonalcoholic steatohepatitis which enhances the risk of liver cirrhosis are also categorized into NAFLD definition. Obesity and insulin resistance are the general root cause of NAFLD which enhance the morbidity level from 10% to 30% in previous years[3]. At the severe stage of the disease, the patient has chanceries of cirrhosis. In recent years many studies reported that 20% of cases of NAFLD have a probability to transformed into cirrhosis[4]. Many other studies reported that type 2 Diabetes Mellitus patients had a comparitively high chance of NAFLD[5].

Statistics revealed that 60 to 70% of diabetes mellitus patients suffer from NAFLD and 20% of patients had nonalcoholic steatohepatitis (NASH) along with type 2 diabetes8. NASH along with type 2 diabetes increases the chances of cryptogenic cirrhosis up to 80%. Progression of fibrosis was observed in 32 - 37% of NASH cases along with type 2 diabetes[6]. Both NAFLD and NASH enhance the risk of mortality more as compared to cardiovascular disorders in diabetes.

In a recent study of Gupta et al[7], he observed 100 non-alcoholic individuals with type 2 DM through ultrasonography. He reported 48 cases of fatty liver, along with 32 cases of steatohepatitis. From 32 cases 28 patients undergone through urgent biopsies. On the other hand, 87% of cases of type 2 DM along with NAFLD reported in Prashant et al study[8]. In his study, he further observed 37.3% of cases suffer from fibrosis, and 62.6% had exposure to steatohepatitis. In Kalra et al[9] study 56.5% of cases of NAFLD observed along with type 2 DM and his results depict that type 2 diabetic women are more prone to NAFLD as compared to men. Ultrasonography and histopathology are considered as the major source of NAFLD diagnosis. In the past liver, biopsies were considered the gold standard in diagnosing NASH but its limitations including sampling error enhance the questions of biasness[10].

Therefore clinical examination of patients is relayed on abdominal ultrasonography. In many studies sensitivity was observed in between 60%-90% along with 84%-95 specificity which eventually assists in screening liver enzymes of patients[11,12]. Unfortunately Imaging could not provide a line of distinction between steatosis gradings. It also failed to recognize NASH and hepatic fibrosis. This systematic review is specifically designed to analyze the efficacy of the ultrasonography technique for measuring fatty liver disease.

For this systematic review, our major purpose is to compare ultrasonography findings with enzyme profile and cholesterol level of patients.

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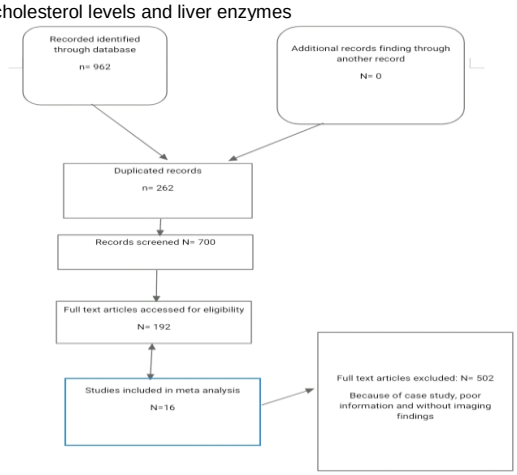
METHODOLOGY

Search Strategy: For this study, we follow the Preferred Reporting Items guideline for conducting this systematic review analysis (PRISMA)[13]. We search electronic articles from year 2008 to 2020 on PUB Med, online Willey library, and ScienceDirect site. We use keywords like Diagnostic Imaging" OR "Diagnostic Radiology" OR "Medical Imaging" OR "primary grading of fatty liver disease" OR " Liver profile Vs sonography" OR "cholesterol levels a good source of liver disease detection", Serum profile and sonography for liver disorder detection", OR "liver imaging guidelines" to search relevant articles. We make assure that all the data have information such as AST, ALT, GGT, LDL and cholesterol levels. With the help of keywords, we analyze the title, abstract aims, and objectives to extract the relevant data.
Inclusion criteria: Articles and case studies with complete demographic information and type of study were included for this research. Information in the form of posters, case studies without imaging, letters to editors, and articles with copied information was excluded from this study.
Exclusion Criteria: Articles which were written in other than English language were not included for this research. On the behalf of keywords we found nine hundred sixty-two articles.
Data analysis: The evaluation of our selected data was further done into two phases first we select the data based on abstract

and title. Secondly, we examine the inner text of articles and include if they were eligible to fill the inclusion criteria of our study. At the initial stage of collecting data, we found nine hundred and sixty-two articles with selected keywords. In the first screening, we excluded 262 duplicate articles and further screen out the rest of 598 articles. Later on, we omitted 502 articles with poor information on mammography and sonographic imaging and 192 articles were further gone through the screening process. At the last stage, we found 25 articles that fulfilled the inclusion criteria and had adequate data on our topic.

We kept demographic information of patients like mean age and range, the sample size in tabular form. We also observed the imaging findings regarding sensitivity and specificity findings of all selected researches.

Fig 1: Inclusion criteria of correlation of sonographic grading of fatty liver with cholesterol levels and liver enzymes



RESULTS

Out of 25 selected studies, we found information relevant to aspartate aminotransferase (AST), alanine transaminase (ALT), and gamma glutamyl transpeptidase (GGT). Comparing the heterogeneity level we observed that AST studies have 85% heterogeneity whereas 77% ALT data and 76% GGT data were similar to each other. On the other hand, we observed complete study 12 studies provide information related to triglyceride TG, TC, High density lipoprotein (HDL), and low density lipoprotein (LDL) respectively. Comparing the data of hetrogenity of TG and TC between selected studies we found heterogeneity for them was 64% and 66% respectively. The pooled data were observed in between -28.7- (-7.28). The pooled analysis was done at 95% CI. On the other hand, the rest two serum profile has 70% and 53% heterogeneity (HDL and LDL respectively). There were no significant changes observed among them. Very few studies observed steatosis, fibrosis, protein density level, and NAS through ultrasonography.

Table 1: Demographic Characteristics of 16 selected studies.

Author	Year	Country	Sample size
Zhu[14]	2008	China	66
Spadaro[15]	2008	Italy	18
Sofi[16]	2010	Italy	6
Kong[17]	2011	China	20
Scorletti[18]	2014	North America	51
Sanyal[19]	2014	North America	64
Janczyk[20]	2015	Poland	30
Boyraz[21]	2015	Turkey	56
Hu[22]	2015	China	26
Dasarathy[23]	2015	USA	18
Qin[24]	2015	China	36
Li[25]	2016	China	39
Oscarrson[26]	2018	Swedan	20
Tobin[27]	2018	USA	81
Parker[28]	2019	Australia	25
Song[29]	2020	China	21
Tutunchi[30]	2020	Iran	95
Abdel et al[31]	2017	Egypt	30
Bakhshimoghaddam[32]	2018	Azarbaijan	90
Cakir et al[33]	2017	Turkey	28
Cuenza[34]	2017	Philippine	100
Umesh[35]	2018	Nepal	109
Lin et al[36]	2011	Taiwan	4360
Musa[37]	2019	Egypt	60
Chen Li	2016	Tainjin	2367

Table 2: Evaluation of hepatic enzymes parameters in selected studies

Study	Cholesterol	Triglyceride	High-density lipoprotein	Low-density lipoprotein cholesterol	Mean difference
Zhu	-46.4 ± 30.9	-168.4 ± 209.31	5.8 ± 11.2	-3.1 ± 33.23	-34.80 (-107.98, 38.33)
Spadaro	-5 ± 23.3	-37.4 ± 40.14	0.4 ± 9.42		
Sofi	-0.8 ± 25.84	-31.7 ± 77	-2.6 ± 3.91	-6 ± 21.62	-52.10 (-118.36, 14.16)
Kong	-3.5 ± 34.19	-64.1 ± 112.67	-2.8 ± 9.64	16.4 ± 53.63	-99.70 (-180.99, -19.4)
Scorletti	-7 ± 43	-26 ± 106	0 ± 10.53	0.1 ± 0.9	-61 (-95.84, -26.16)
Sanyal	4.4 ± 23.5	-8.3 ± 44.4	1 ± 7.6	2.2 ± 23.6	-15.70 (-32.09, 0.69)
Janczyk	-8.02 ± 42.7	-18.88 ± 47.6	-1.43 ± 7.4	-12.17 ± 35.9	-13.41 (-34.36, 7.54)
Boyraz	-24.8 ± 29.87	-41.7 ± 38.88	9.7 ± 7.64	-3.5 ± 38.21	-8.70 (-23.10, 5.70)
Hu	-7.8 ± 33.32	-80.01 ± 32.09	not mentioned	Not mentioned	-53.40 (-73.02, -33.78)
Dasarathy	4.6 ±49.65	36.3 ± 139.87	0.8 ± 9.35	Not mentioned	91 (-3.41, 185.41)
Qin	-19.1 ± 16.8	-51.4 ± 78.8	1.17 ± 9.4	-7.3 ± 28.6	-54.90 (91.62, -18.82)
Li	-35.1 ± 14.06	-61.6 ± 26.4	1.1 ± 3.3	-15.51 ± 17.71	-44 (-56.95, -31.05)
Oscarrson	not mentioned	Not mentioned	Not mentioned	-5 ± 25.4	-
Tobin	Not mentioned	-34.2 ± 110.41	Not mentioned	Not mentioned	-20.80 (-55.84, 14.24)
Parker	Not mentioned	Not mentioned	Not mentioned	Not mentioned	-
Song	-5.9 ± 24.2	-133 ± 412.7	-0.8 ± 9	-8.89 ± 20.88	-166.40 (-354.67, 21.87)
Tutunchi	219.6 ± 74.2	166.2 ± 59.3	54.2 ± 19.7	151.7 ± 66.1	11 (-3.41, 18.41)
Abdel et al	258.60 ± 31.70	257.80 ± 55.02	48.73 ± 4.83	158.53 ± 23.67	-12.10 (-11.36, 4.16)
Bakhshimoghaddam	195.3 ± 34.7	165.7 ± 60.9	113.8 ± 25.5	113.8 ± 25.5	41 (-3.41, 8.41)
Cakir et al	173.7±26.8	143.1±67.5	43.7±7	101.4±24.5	-17.10 (-20.36, 14.16)
Cuenza et al	205.6 ± 53.1	140.7 ± 65.2	55.4 ±27.5	142.9 ±51.1	119 (-3.41, 85.41)
Umesh et al	4.55 ± 0.86	1.9760 ± 0.779	1.048 ± 0.21	2.637 ± 0.718	18.10 (20.36, 14.16)
Lin et al	205.93 ± 37.86	124.03 ± 115.08	50.84 ± 13.65	135.30 ± 33.49	21 (3.41, 9.41)
Musa	173.3 ± 40.3	124.37 ± 29.4	46.2 ± 7.9	99.5 ± 32.5	3.90 (-20.23, 28.03)
Chen Li	3.99±0.66	1.28±0.88	1.29±0.25	2.14±0.60	-14.10 (-18.36, 12.16)

Table 3: Evaluation of serum Lipids Profile of Selected studies

Author	Aspartate aminotransferase	Alanine transaminase	Gamma glutamyl transpeptidase	Mean difference
Zhu	-19.84 ± 34.23	-37.4 ± 43.92	-21.5 ± 33.88	13.92 (1.06, 26.78)
Spadaro	1.1 ± 8.61	-4.2 ± 31	0.9 ± 22.07	-12.90 (-30.19, 4.39)
Sofi	-2.2 ± 3.92	-23.4 ± 7.8	-8.2 ± 25	-7.30 (-21.67, 7.07)
Kong	-2.2 ± 11.68	0.5 ± 19.07	10 ± 26.9	-17.75 (-29.96, -6.21)
Scorletti	-6.5 ± 18.08	-6.5 ± 30.51	Not mentioned	-1.50 (-15.10, 12.10)
Sanyal	-11.2 ± 19	-19.6 ± 34.3	Not mentioned	18.20 (5.19, 31.21)
Janczyk	-6.9 ± 18.8	-25.77 ± 46.7	-9.81± 25.28	-4.03 (-21.99, 13.93)
Boyraz	-10.1 ± 9.85	-13.4 ± 16.67	-1 ± 6.4	-12.40 (-18.56, -6.24)
Hu	-1.6 ± 24.81	-1.7 ± 37.82	Not mentioned	-0.10 (-24.05, 23.85)
Dasarathy	0.1 ± 33.14	-7.1 ± 44.36	-	3.90 (-20.23, 28.03)
Qin	-1.4 ± 7	-6.2 ± 22.1	-3.98 ± 11	-4.40 (-13.58, 4.78)
Li	-7.9 ± 7.82	-10.9 ± 9.18	-	-10.50 (-14.94, -6.06)
Oscarrson	-0.1 ± 6	0.6 ± 14.1	-	6.50 (0.20, 12.80)
Tobin	-1.9 ± 12.9	-5.8 ± 22.73	-10 ± 43.1	6.40 (-3.24, 16.04)
Parker	-2.3 ± 3	-3.6 ± 5.5	-	7.70 (0.32, 15.08)
Song	0.25 ± 7.2	-2.9 ± 15.2	-	-0.20 (-9.99, 9.59)
Tutunchi	27.7 ± 8.6	37.6 ± 16.2	Not mentioned	3.70 (-11.58, 2.78)
Abdul et al	44.05 ± 14.65	81.45 ± 23.32	Not mentioned	2.90 (-10.23, 18.03)
Bakhshimoghaddam	24.6 ± 6.6	34.8 ± 17.2	24.2 ± 9.5	5.40 (-16.58, 4.78)
Cakir et al	45±22.9	56.3±39.8	not mentioned	6.80 (-40.23, 28.03)
Cuenza et al	22.8 ± 6.0	31.03 ±18.83	Not mentioned	4.38 (-9.58, 3.78)
Umesh et al	-	-	-	-
Lin et al	22.33 ± 12.61	28.46 ± 21.18	Not mentioned	2.35 (8.58, 4.78)
Musa	34.1 ± 6.73	39.2 ± 9.3	Not mentioned	7.88 (14.58, 4.78)
Chen Li	Not mentioned	17.05±5.60	Not mentioned	-

Table 4: Ultrasonography screening of selected studies

Author	Mean sensitivity and specificity of ultrasonography	proton-density fat fraction	NAFLD activity score (NAS)	steatosis	fibrosis
Zhu	29 ± 68	-	-	-	-
Spadaro	5 ± 18	_	-	-	-
Scorletti	-	-2 ± 18.86	-	-	-
Sanyal	-	-	-1 ± 1.52	-0.35 ± 0.76	0.01 ± 0.01
Boyraz	21 ± 52	-	-	_	--
Hu	-	-	-	0 ± 0.56	0 ± 0.4
Dasarathy	-	--	-1.7 ± 1.41	0.59 ± 0.74	0.06 ± 0.8
Li	-	-	-	0 ± 0.2	0.1 ± 0.26
Oscarrson	-	0.4 ± 2.72	-	-	-
Tobin	-	-4.4- 6.9	-	-	-

Fig 2: Forest Plot Hepatic parameters

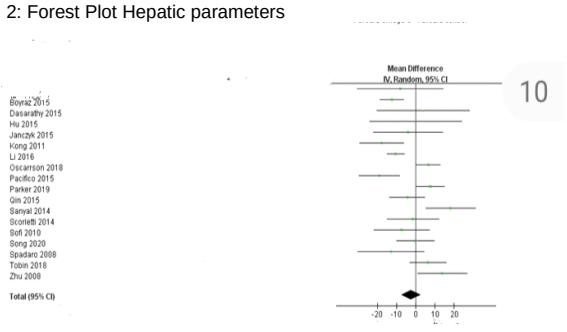
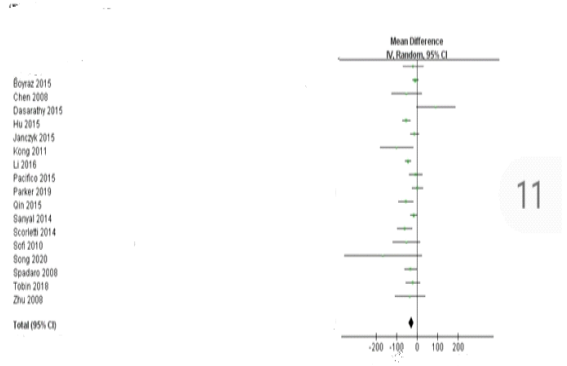


Fig 3: Forest plot of serum lipids profile



DISCUSSION

This is an updated systematic review and meta-analysis based on the evidence of fatty liver disease taken from the year 2013 to the year 2020. Only one study of Tobin was taken from 2008 to check the mean difference among steotosis rate, triglyceride, and lipoprotein cholesterol. We include aspartate aminotransferase, alanine transaminase, and gamma-glutamyl transpeptidase in the category of hepatic enzymes. We only take random control trials to reduce the issue of heterogeneity and biases. From the selected studies we observed the variations in the serum lipids profile of patients occur in the recent decade.

Clinical evidence including histology and imaging is the main diagnosis technique for analyzing fatty liver disease[39]. Though the many upgrades occur in ultrasonography still histological evidence needed to check the level of fatty liver disease especially grading of the liver disease needs histological analysis[40]. Based on the evidence we concluded that very few events are notified through ultrasonography which may alter the patient's conditions if not diagnosed properly.

Ultrasonographic evaluation is the key process of diagnosing liver disease and is widely used worldwide with good Specificity (93.6%) and sensitivity (84.8%) respectively[41,42]. It also helps to detect hyperechogenicity inside the liver parenchymal tissues, helps in blurring vascular margins, and assists in acquiring high contrast liver imaging[43, 44]. This remarkable achievement of ultrasonography still has certain limitations including poor diagnosis of trivial hepatic steatosis[45]. Imaging could not provide a line of distinction between steatosis gradings. It also failed to recognize NASH and hepatic fibrosis[46, 47].

Comparing the data with the 2008 study of Chen[48] we demonstrated that ultrasonography has high potential in the detection of fatty liver disease in past. As a result, histological analysis and liver biopsies play a key role in examining patient conditions. Unfortunately, liver biopsies have a limited potential to obtain specimens which raised questions on their accuracy because of errors that emerged out during sampling[49]. Discussing our meta-analysis we did not find any significant differences between NASH, fibrosis, and steatosis gradings. Analyzing the time duration of selected studies we observed that majority of studies were based on long-term follow-up (maximum duration was noted as 18 months). The reason is steatosis and fibrosis take a long time duration to achieve an improved level. In five studies researchers observed Hepatic steatosis improvements through imaging but those studies were poor in defining liver enzymes and lipid profile. Total four studies had good quality data on liver enzymes, lipid profile, and BMI. Two selected studies of Boyraz and Spadaro used blind operator procedure during imaging still the chances of biasness in performance were quite high as compared to other studies. After 3 months different treatments reflect improvements in TC, TG, HDL, and BMI. Contrary to within three months these authors did not find any significant improvements in AST, ALT, GGT, LDL, HOMA-IR, or FBS. However, we did not find any statistically significant differences among the serum lipids profile of patients.

However, we try to find relevant and specific information still this meta-analysis has many limitations. In many selected studies, there were only male populations with all sample sizes. These authors only selected children and adolescents so the imaging efficacy cannot be measured in the old age group.

CONCLUSION

Our meta-analysis concluded that the severe cases of liver diseases need biopsies and histopathological examination. Though ultrasonography provides a complete liver picture with 84.8% sensitivity and 93.6% specificity which may help in many cases still the majority of the studies failed to observe steatosis, NAS score, protein density level, and fibrosis through ultrasonography only. There is a need to evaluate the ways through which we find complete liver examination with the least drawbacks.

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