



## ASYMPTOMATIC DIFFUSE HEPATIC DISEASE IN A HEALTH CHECKUP PROGRAMME - UTILISING CLINICAL EXAMINATION, LABORATORY PARAMETERS AND SONOELASTOGRAPHY IN A TERTIARY INSTITUTE.

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**(ABSTRACT)** Fatty changes liver and CLD are racing in prevalence globally last decade and became health burden and clinicians should be made aware higher normal blood parameters in asymptomatic patients. Early detection helps management to decrease in morbidity and mortality. The sonoelastography of NAFLD sensitivity is 60%- 90% and specificity 90%. CT & MRI are not significantly superior to Sonography. Asymptomatic patients of 51612 revealed 28025 are hyperechoic liver parenchyma, and a random of 10% of these is 2800 showed 154 CLD. Our aim is to detect fatty changes or chronic liver disease in early stage or both coexisting together by acoustic radiation force impulse, with clinical and laboratory data. The study is done by standard protocol. NAFLD has a potential risk for progressing into NASH later to CLD. Serum biomarkers and imaging and combination of serial algorithms involved in NAFLD to NASH. Liver biopsy sample volume is small 1/50,000 part. It leads to absent variability, speed of disease and dynamic information. Hence ARFI Sonography is a safe alternative. A total of 51612 asymptomatic male: female is 53.3%:46.7%, hypertension 1%, Diabetes 20.1%, BMI.54%, cholesterol 21.4%, LDL24.1%, HDL29.7% AST:16.3%, ALT 16.6%. High percentage of grade 1 fatty liver seen. CLD 4.5% (global range is 4.5% - 9.5%) Hence we conclude that, clinical examination, laboratory values with sonoelastography changes the scenario of fatty, CLD, liver malignancy in early diagnosis by health check up reduces rate of prevalence.

### KEYWORDS :

#### INTRODUCTION:

**CLINICAL LABORATORY AND SONO ARFI PARAMETERS:** Both the fatty changes liver and CLD are racing in prevalence across globally over the last decade. In correlation with Clinical laboratory parameters, Sonography precisely show hyper echoic liver parenchyma in health checkup and asymptomatic individuals. It could detect fatty changes in liver of different grades or could detect early CLD or both conditions may coexist together in the same individual. Fatty liver is common entity with known high prevalence but the Burden of CLD is higher unless clinicians are made aware that normal or near normal blood lab parameters findings may be seen in asymptomatic patients, the earlier indication of asymptomatic patients will allow promising mode with decrease in morbidity and mortality of CLD (1). To find and differentiate is our primary goal since the patient is undergoing checkup in most modern high end tertiary care center in asia. NAFLD is a feature of metabolic syndrome due to visceral obesity, dyslipidemia, insulin resistance diabetes. NAFLD show higher morbidity among causes, and increases liver related death and cardio vascular diseases.(2, 3) The sensitivity of NAFLD of Sonography is 60% - 90%. CT scan and MRI are costly and not significantly superior to sonography. (4,5,6) NAFLD is growing epidemic due to obesity and insulin resistance leading to liver accumulation of triglycerides and free fatty acids. NAFL is basically stasis of fat greater than 5% with no evidence of hepatocyte injury. NASH is characterised by an inflammatory process where by the liver cells become injured. Little is known about NASH oxidative stress, toxic inflammatory process ( cytokinins) liver necrosis ( apoptosis), adipose tissue and gut microbiota.(7)

The clinical examination may reveal signs and symptoms and the laboratory investigations may support either of the conditions but not in all individuals and it may be borderline or reversible parameters. BMI ( basal metabolic rate) is high in many patients with liver disease and can be a predictor in higher grades. This clinical information is extremely useful to clinicians (8) In this situation the role of SONOELASTOGRAPHY a recent high-end modern equipment has significant and unparalleled role which give ARFI TISSUE STIFFNESS ELASTOGRAPHY value. Which proved in many occasions by its higher value in CLD. Where fatty liver in B Mode real time sonography the parenchyma displays fine echotexture of hyper echoic liver parenchyma, with normal portal vein size and flow and absent collaterals which indirectly suggests fatty liver. Adverse presence of Porto systemic collateral including the veins seen in

abdominal wall, a specific sign of severe fibrosis or cirrhosis, splenic palpation secondary to portal hyper tension, ELASTOGRAPHY assesses viscoelastic properties of the two methods of finding include for early pick up is by elastography, shear wave, and blood fibrin test ( fibro meter or Hepascore). CLD remains Asymptomatic in many patients and sometimes only symptomatic when life threatening complications appear (9) In the checkup programme for Asymptomatic individual, B mode ultrasound is used which may or may not differentiate hyper echoic liver parenchyma from CLD and fatty changes in many Individuals. However, both conditions are not acceptable and the CLD is more serious condition and the early diagnosis makes remarkable significance in both and followup and management particularly in CLD. Most DILI ( drug induced liver injury) are reversible, nearly all classes of medicines can cause liver disease with ranges. It should be removed as early as possible (10) Fatty liver is micro and macro vesicular hepatosteatosis due to abnormal retention of lipids within liver cells. Non alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease (AFLD), and metabolic diseases like diabetes, hypertension, obesity, dyslipidemia - are the common causes. Other lesser common causes include abetalipoproteinemia, glycogen storage disorder, WC disease, acute fatty liver, lipodystrophy, nutritional, drugs and toxins.

The fatty changes liver may progress into chronic liver disease, the parenchymal dysfunction and malignancy in the survey of population studies.

The health check-up programme is unique and after complete clinical physical examination, suspicious patients with or without biochemically altered liver enzymes are subjected to ultrasound imaging. Increase in attenuation or hyperechoic with fine echotexture parenchyma are often considered as fatty liver, and in the event if hyper echoic parenchyma is coarse in echotexture or borderline coarse changes, it could be due to early CLD. A ten percent of the total asymptomatic diffuse hyper echoic liver parenchyma patients was randomly subjected to ARFI and if a higher value is obtained is called and marked as CLD changes and if the normal range value is seen it is labelled as fatty changes and they are graded as per intensity as G1,G2, G3,G4,G5 accordingly. Smoking maybe a significant factor with NAFLD than onset in non drinker's Fatty liver adjusted hazard ratio – 1.988, 95% confidence interval 1.057 -3.595; p – 0.034 fatty liver incidence significant in nondrinkers as the number of smokers include (p- 0.001) (11). Hepatic steatosis is in increasing prevalence above 45

percentage (12) The ten percent of patient's selection is only arbitrary and it is taken the best possible means by us with out any inconvenience in the study due to limited available means. The Siemens 2000 highly advanced and latest fully loaded technology which gives perfect accurate value parameters, it's a modern latest expensive equipment which possessed ARFI Sono vascular and other features, it could not accommodate all the very high number of patients per day because of limited number of slots and logistics required in utilising the system for other procedures. Another reason being, non-availability of proper time slots and only a limited number of patients had agreed to undergo the additional test located in another block in the same hospital due to paucity of their time ( since the health check programme promises one day time.) ARFI liver elastography/ stiffness assessed TE and obtained result is good in CFLD cystic fibrosis liver disease and there is significant correlation (p Less than 0.0001) (13). However , the total number asymptomatic 51612 individuals, the diffuse hyperechoic liver parenchyma in number consists is 26,982 (twenty-six thousand nine hundred eighty-two individuals). In this 26982 patients (10%) are randomly selected, and they show a Higher ARFI VALUE including vascular Doppler changes. 157 patients of the total Asymptomatic individuals have values suggesting definite CLD, sorted from hyper echoic parenchyma. Furthermore, according to our study, 5.81 % representation falls into Global prevalence of liver disease from autopsy which ranges from 4.5% to 9.5% among total population. (14,15,16).

Here, the aim of the study is to detect fatty changes or chronic liver disease in early stage in diffuse hyper echoic liver parenchyma seen in routine clinical laboratory and sonography in asymptomatic individuals.

Primary objective is to study the Application of clinical laboratory and breakthrough technology - ACOUSTIC RADIATION FORCE IMPULSE ELASTOGRAPHY in a hyperechoic liver parenchyma to differentiate between FATTY CHANGE OR CLD(chronic liver disease). Secondary objective include the diffuse hyperechoic liver parenchyma with suspicion of CLD, with certainty of clinical and laboratory parameters by utilization of sonoelastography unit value parameters to find fatty changes liver and CLD or both existing in the same asymptomatic patient.

**STUDY SITE:** Apollo Main hospitals, MCLP, Greaves lane, Chennai 600006 India. An Advanced tertiary institute.

**STUDY DURATION:**  
January 2016 to January 2017 (thirteen months)

**INCLUSION CRITERIA:** All adults above 18 yrs. of both genders  
**EXCLUSION CRITERIA:** Patients with existing hepatic disease, marked obesity and poor window is excluded for ultrasound and ARFI contribution on the liver.

**PATIENTS & METHODS:**  
In our retrospective study, clinical physical examination is always first performed before the biochemical parameters for liver enzymes and correlated with ultrasound of liver and the GE PRO – 6 were used and suspicious hyperechoic liver parenchyma are subjected to ARFI LIVER examination. The logic GE PRO -6 sonography units are used in the check-up programme and the very high-end and latest fully loaded ARFI DOPPLER Siemens S 2000 for CLD evaluation purpose is allocated for as per delegated individuals.

The total participants are asymptomatic 51612 (fifty-one thousand six hundred twelve). In this total Diffuse hyper echoic parenchyma is 28025 (twenty eight thousand twenty five) in this ten percent ARFI evaluation could be done and they constitute 2800 (two thousand eight hundred) and in this 154 cases showed high ARFI value suggesting graded CLD.

This checkup programme consists of initial educating preparation, counselling with all required instructions. It is followed by preliminary history taking, pulse, blood pressure Respiratory rare and BMI ( basal metabolic rate) are recorded by the trained deputed constituent medical team directing the individual for fasting blood and urine & stool collection and fasting sonography, and a structured battery of investigations like x-ray, ECG, echo were included part of review.

**DISCUSSION AND RESULTS:**

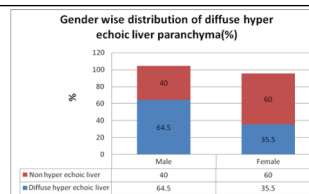
The intention of having a larger series like this above 50,000 asymptomatic individuals were taken for health check-up over a period of thirteen months with meticulously and systematically documented by all established international standards followed in obtaining the best of the parameter information.

When the health checkup programme in asymptomatic individuals are evaluated the largest solid organ liver usually first evaluated and to the surprise we obtained nearly more than 54 percentage showed hyper echoic liver parenchyma which was primarily thought of fatty changes liver but some patients had grainy coarse changes which lead to suspicion of early CLD or both in the asymptomatic patient and an usual interesting observation is fatty changes liver volume is higher normal or mild enlargement due to fat deposition. Among these total hyper echoic liver patients, Ten percentage of patients in random are selected and subjected ARFI elastography which steadily has revolutionising the diagnosis of Diffuse liver disease and also independent of contrast and, it is also interpreted with clinical and laboratory parameters, ARFI elastography helped to understand the molecular mechanisms underlying liver fibrosis (17). Technical related matters confounders of stiffness measurement for assessment of liver fibrosis, future scope of elasticity for monitoring and follow up and to predict complications of CLD, ARFI is an excellent tool particularly in advance and guides the treatment in evaluating the response to therapy (18). Many occasions liver biopsy considered as gold standard even though the risk of complication and even Less percentage death due to bleeding noted. Liver biopsy is though a reference standard for assessing liver fibrosis it is associated with morbidity, subject to sampling, bias, reader variability, and has to some extent poor acceptance (19). In this event non invasive study of portal vein, CD, PD contrast testing, are the methods are able to detect macroscopic changes occurring in liver, spleen and vessels at Porta as progression of disease and ARFI value is higher and correlates with enzymes(20). There are some limitations, non invasive parameters and serum biomarkers helping in staging, of fibrosis such as periportal fibrosis, periportal fibrosis with few bridges or septa, bridging fibrosis, and finally cirrhosis.(21) The NAFLD has potential risk for progressing into non alcoholic state hepatitis NASH which has great risk to develop into CLD. serum biomarkers and imaging and combination of serial algorithms involved in NAFLD to NASH.(22). Before result analyzing and concluding the liver biopsy parametrical analysis done only of a smallest portion of liver tissue which is one in fifty thousand<sup>th</sup> portion parenchyma, then by introducing the sampling variability liver biopsy lacks dynamic information about speed of disease progression. repetitive biopsies has many folds of risk. All and for many reasons liver biopsy is imperfect and these inherent flaws of biopsy can do misinterpretation (23,24,25). With strict and careful analysis done with our data who attended our health check protocol and systematic health checkup revealed larger series analysis of the given data revealed the following findings, The results are classified under various bio parameters and they revealed that High prevalence of fatty changes liver of 28025 with very small number of 154 individuals of very early graded CLD noticed during routine health check-up examination of patients.

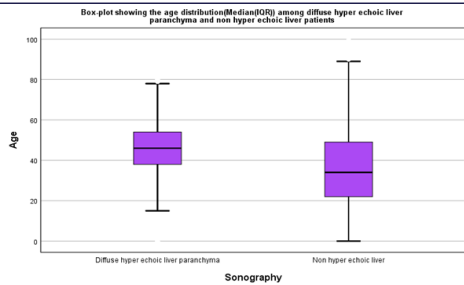
Diffuse hyper echoic liver parenchyma was seen in 27563(53.4%) and 23587(46.6%) were normal in Sonography. Among those with diffuse hyper echoic liver, 17778(64.5%) were male and 9785(35.5%) were female. (Table 1 & Fig 1.). Median age was 46(38-54) years in those with diffuse hyper echoic liver parenchyma and 34(22-49) years in non-hyper echoic patients. (Fig.2).

**Table 1: Sonography Distribution Gender Wise**

Sonography Finding	Male	Female
Diffuse hyper echoic liver parenchyma fatty changes liver and CLD ( chronic liver disease)	64.5	35.5
Non hyper echoic liver	40	60



**Figure 1: Gender wise distribution of diffuse hyper echoic liver parenchyma (%)**



**Figure 2: Age distribution among diffuse hyper echoic liver and non hyper echoic liver pa-tients**

**Table 2: Liver Severity Gender Wise Distribution**

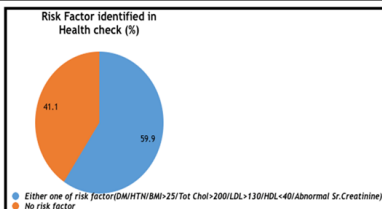
Liver severity	Male	Female
Non hyper echoic liver	34.3	58.7
Diffuse hyper echoic Liver with CLD Grade 1	52.1	34.2
Diffuse hyper echoic liver with CLD Grade 2	12.8	6.7
Diffuse hyper echoic liver with CLD Grade 3	0.8	0.4

Positive diffuse hyper echoic liver findings with graded CLD categorised by severity. Pa-tients graded as diffuse hyper echoic liver with CLD grade 1 among males were 52.1% and 34.2% among females respectively. Diffuse hyper echoic liver with CLD grade 2 among males were 12.8% and 6.7% among females. Diffuse hyper echoic liver with CLD grade 3 among males were 0.8% and 0.4% among females respectively. (Table 2).

Positive Diffuse hyper echoic liver findings in patients with comorbidities such as Hyperten-sion: 540 individuals (1%), Diabetes mellitus: 10375 (20.1%), Lipids- Cholesterol: 4163(21.4%) LDL: 12426(24.1%) HDL: 15307 (29.7%), BMI: 25408(54%)

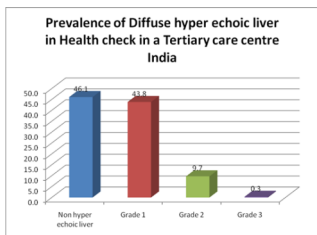
**Table 3: Risk Factors Identified In The Health Check**

Risk factor	%
Either one of risk factor(DM/HTN/BMI>25/Tot Cholesterol>200/LDL>130/HDL<40/Abnormal Sr.creatinine)	59.9
No risk factor	41.1



**Figure 3: Risk factor identified in health check (%)**

Among those patients who found diffuse hyper echoic liver in Sonography, 59.9% of them had either one of risk factor (Table 3 & Fig 3). Laboratory parameters of Liver enzymes: AST in 40479 available patients showed 8401(16.3%) elevated values. ALT in 433356 available patients showed 8586(16.6%), Age, Gender, Alcohol and non-alcoholics are also analysed. A total of 51612 asymptomatic individuals had undergone routine medical check-up revealed- gender ratio Male: 27508(53.3%) Female: 24104(46.7%). Hypertension: 540 individuals (1%), Diabetes mellitus: 10375 (20.1%), BMI: 25408(54%) Lipids- Cholesterol: 4163(21.4%) LDL: 12426(24.1%) HDL: 15307 (29.7%). According to centre for disease control and prevention hepatitis B is 240 million, 160 million of hepatitis C (26). Sonography findings show 43.8% grade 1, 9.9% grade 2 and 0.6% grade 3 diffuse hyper echoic liver respectively. (Figure 4).



**Figure 4: Prevalence of diffuse hyper echoic liver in health check in a tertiary care center In-dia.**

**LIMITATION:** ARFI ELASTOGRAPHY, finds fibrosis but not cause, and in question, the correlation with conventional images, laboratory findings, clinical features and possibly biopsy under image guidance may be needed for corroborated establishment of the disease process and management. (26)

**Our study has minor limitations:**

like High end ARFI imaging Equipment resource, more number of skilled experienced personal, Patient body habits and patient willing to co operate for study.

**CONCLUSION AND RECOMMENDATION:**

Clinical examination bio and laboratory and sonoelastography investigations revealed that there is an increase in the high incidence of fatty changes liver and even though smaller number but rapidly growing CLD also found out in asymptomatic healthy adults. The role of invasive biopsy even though is a measure of gold standard and the most advanced ARFI of liver parenchyma with other corroborative clinical and other evidences gradually and significantly re-duc-ing the need for liver biopsy for early detection and management. Recommendations include: More advancements in ARFI ELASTOGRAPHY to reduce averaging, Increase measuring depth above 8 cm, New incorporator in the same equipment to find fat content in grading. Skill development to operator. AI for the collected clinical, laboratory and ARFI sonography for quicker segregation from normal.

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