Original Research Paper

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Radio-Diagnosis

QUANTIFICATION OF LIVER IRON IN CHRONIC LIVER DISEASE USING 3 TESLA MRI

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ABSTRACT

Aims And Objectives: 1. To assess the feasibility and evaluate the performance of various 3 Tesla MR imaging techniques in the detection and quantification of hepatic iron in patients with chronic liver disease. 2.To understand the scope of liver diseases with respect to iron deposition and to define a correlation between liver disease and liver iron concentration.

Materials And Methods: Present prospective cross-sectional study was carried out during the period of December 2019 to May 2021 in 31 patients with chronic liver disease who underwent MR imaging using 3T MR scanner (General Electric, Signa Pioneer) with a body coil. Liver signal intensity in three different locations were measured. The L/M ratio (signal intensity ratio/SIR) was calculated by dividing mean liver signal intensity by mean muscle signal intensity. The T2* and R2* method was also carried out from the same sequence.

The Liver Iron Concentration (LIC) was obtained from R2* and SIR using the DICOM Software MRQuantif.

Results: Among the 31 patients studied, 16 of them had serum ferritin ≤464 µg/dL and 15 had Serum Ferritin >464 µg/Dl and 14 of them had TIBC <261 µg/dL and 17 had TIBC ≥261 µg/dL.

A statistically significant (p = <0.001) strong negative correlation was established between Serum Ferritin and T2*and a statistically significant strong positive correlation was established between TIBC and T2*

Considering Liver Iron Concentration, there was a statistically significant strong positive correlation between LIC and Serum Ferritin, and a statistically significant strong negative correlation between TIBC and LIC.

Conclusion: SIR and T2* MR imaging techniques are feasible in determining and quantifying hepatic iron in patients with chronic liver disease. From our study findings we could define a positive correlation between liver disease and liver iron concentration.

KEYWORDS : Liver Iron Quantification, Chronic liver disease, 3 Tesla MRI, Signal intensity ratio.

INTRODUCTION

Liver is one of the main iron storage organs and the first to show iron overload; also, the liver iron concentration has a strong linear relationship with total body iron stores. Hepatic iron therefore can be used as a marker of body iron stores and allows prediction of the risk of complications. Excess accumulation of iron in the liver is toxic and may be a cofactor in the progression of liver damage, cirrhosis, liver failure and hepatocellular carcinoma. Hence detection and quantification of liver iron overload are critical to initiate treatment and prevent complications.

Liver biopsy was the historical reference standard for detection and quantification of liver iron content. However, because of the invasiveness, discomfort, risk, and sampling variability of biopsy, there is an urgent need for accurate, precise, and noninvasive methods to assess liver iron. As there are biologic confounders, blood markers like serum ferritin and transferrin levels should be used with caution to interpret the severity of iron overload. Ultrasonography (US) does not allow detection or quantification of liver iron overload and Conventional single-energy computed tomography (CT) is not sensitive or specific enough for grading overload. Non-invasive Magnetic resonance (MR) imaging is now commonly used for liver iron quantification, including assessment of distribution, detection, grading, and monitoring of treatment response. MRI detects the paramagnetic effects of iron storage in the form of ferritin and hemosiderin, interacting with adjacent hydrogen nuclei, and so indirectly quantifies iron. Several MR imaging techniques have been developed for iron quantification, each with advantages and limitations.

MATERIALS AND METHODS

The study adopted research design of a prospective cross sectional with study period from December 2019 to May 2021.

Inclusion Criteria

Patients with altered echotexture of liver with surface nodularity /irregularity with/without Ascites with/without Splenomegaly on ultrasound evaluation - features suggestive of chronic liver disease.

Exclusion Criteria

- Haemoglobin >20 gm/dl
- Known cases of hereditary/haemolytic anemias

Patients belonging to the inclusion criteria admitted into various clinical departments of a tertiary care hospital in Mangalore, referred to department of Radiodiagnosis were examined on a 3T MR scanner (General Electric, Signa Pioneer) with a body coil. It was performed by obtaining single gradient echo sequence acquisition with 8-10 TEs in multiples of 1.2ms, alternating in phase and opposed-phase echoes and 20° flip angle, and the time to repetition (TR) is constant at 120 ms. We measured liver signal intensity in three different locations. The ROIs were drawn with 2-3cm^{2}as large as possible, avoiding large vessels or lesions. The first slice was positioned just below the diaphragm through the right lobe of liver, and the next two slices were spaced 8 cms from the first one. To calculate muscle signal intensity, we performed the same procedure by placing two regions of interest on right and left paraspinous muscles, on the same transverse sections as those used to measure liver signal intensity, and avoided inclusion of intermuscular fat. We then calculated the L/M ratio (signal intensity ratio/SIR) by dividing mean liver signal intensity by mean muscle signal intensity. The T2* and R2* method was also carried out from the same sequence.The Liver Iron Concentration (LIC) was obtained from R2* and SIR using the DICOM Software MRQuantif.

Statistical Analysis

The data was entered and tabulated in Microsoft excel sheet. Appropriate descriptive statistical tests were used to describe the data. Sample size (including sample size calculation and justification) n= Z2 (1 – r 2) 2 / □2 + 1 + 6r2 n= [(1.96)2 [1 – (0.937)2] 2 / (0.05)2] + 1 + 6(0.937)2 Methodology Page 89 n= [(3.84 * 0.0148915) / 0.0025] + 6.622 n=22.88 + 6.622 = 29.50 ≈ 30. Using G* Power Software we will get a minimum sample size of 30 with level of significance α = 5 % correlation coefficient r = 0.937

RESULTS

The study was carried out on a total of 31 patients who gave consent and underwent MR imaging. Both SIR technique and the T2* technique in the liver were performed on patients. In SIR technique, the algorithm given by Gandon et al available in the MRQuantif software was used for quantification of LIC.

Majority of the participants were in the age group of 41-50 years (29.0%) (9 nos), followed by those between 31-40 years (25.8%) (8 nos) and 51-60 years (22.6%) (7 nos).16.1% of the participants were between 61-70 Years, and 6.5% of the participants were between 18-30 Years.

Among the 31 patients, 25 were men and 6 were women.

MR LIVER IRON CONCENTRATION

The variable T2* (msec) was not normally distributed (Shapiro-Wilk Test: p = <0.001).

The mean (SD) of T2* (msec) was 10.53 (11.50). The median (IQR) of T2* (msec) was 7.90 (1.95-13.7). The T2* (msec) ranged from 1.2 - 56.4.

The variable Liver Iron Concentration (µmol/g) was normally distributed (Shapiro-Wilk Test: p = 0.090).

The mean (SD) of Liver Iron Concentration (µmol/g) was 102.77 (76.09). The median (IQR) of Liver Iron Concentration (µmol/g) was 102.00 (34.5-156). The Liver Iron Concentration (µmol/g) ranged from 5 – 288.

Majority of the participants (48.4%) belonged to Child Pugh Class C. 32.3% of the participants belonged to Child Pugh Class: A. 19.4% of the participants belonged to Child Pugh Class B.

BIOCHEMICAL LIVER IRON CONCENTRATION

Distribution of Serum ferritin

51.6% of the participants had values ≤464 µg/dL(normal) serum Ferritin, whereas 48.4% of the participants had values >464 µg/dL(elevated)Serum Ferritin.

Distribution of TIBC

45.2% of the participants had altered reduced TIBC values <261 µg/dL, whereas 54.8% of the participants had normal TIBC values of ≥261 µg/dL.

Correlation Between Clinical Child-pugh Scoring, Biochemical Liver Iron Concentration And MRI Liver Iron Quantification:

a) Correlation between clinical Child-Pugh scoring and MRI Liver iron quantification:

- The main component of the study was to compare the clinical Child Pugh scoring from 5 to 15 points and compare with the SIR Gandon method.
- Iron overload is defined as iron that exceeds the upper limit of normal i.e >36Umol/g.
- In Fig 1 graph, we can notice an excellent correlation between these two methods.

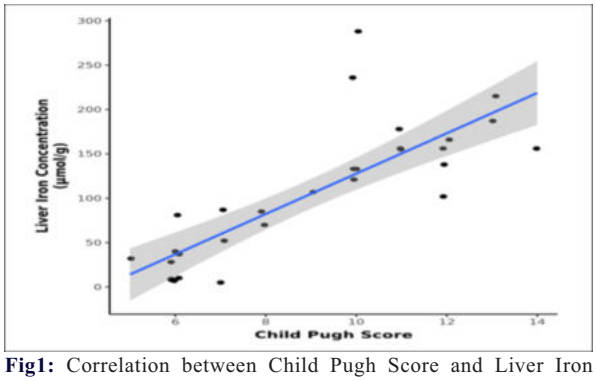
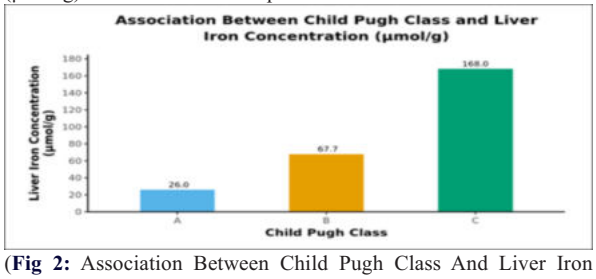


Fig1: Correlation between Child Pugh Score and Liver Iron Concentration (µmol/g) (n = 31)

There was a strong positive correlation between Child Pugh Score and Liver Iron Concentration (µmol/g), and this correlation was statistically significant (rho = 0.84, p = <0.001).

The bar graph (Fig 2) depicts the means of Liver Iron Concentration (µmol/g) in the 3 different Groups



(**Fig 2:** Association Between Child Pugh Class And Liver Iron Concentration(µmol/g))

b) Correlation Between Biochemical Liver Iron Concentration And MRI Liver Iron Quantification:

- Other component of the study was to compare the biochemical liver iron
- Concentrating on serum iron ferritin (normal values of 18-464uG/DL) and TIBC (normal values of 261-462ug/DL) and compare with the SIR Gandon method.
- In Fig 3, we can notice a strong correlation between these two methods.

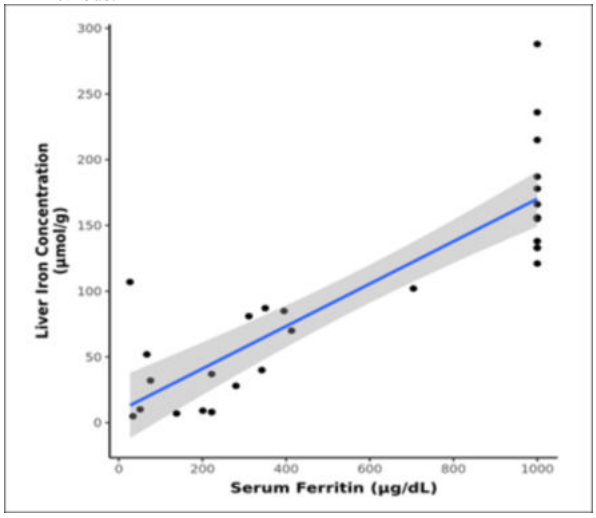


Fig 3: Correlation Between Serum Ferritin (µg/dL) And Liver Iron Concentration (µmol/g) (n = 31)

There was a strong positive correlation between Serum Ferritin (µg/dL) and Liver Iron Concentration (µmol/g), and this correlation was statistically significant (rho = 0.86, p = <0.001).

The Box-and-Whisker plot (Fig 4) depicts the distribution of Liver Iron Concentration (µmol/g) in the 2 groups.

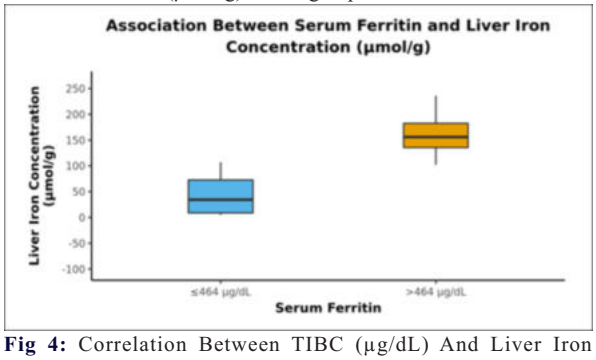


Fig 4: Correlation Between TIBC (µg/dL) And Liver Iron Concentration (µmol/g) (n = 31)

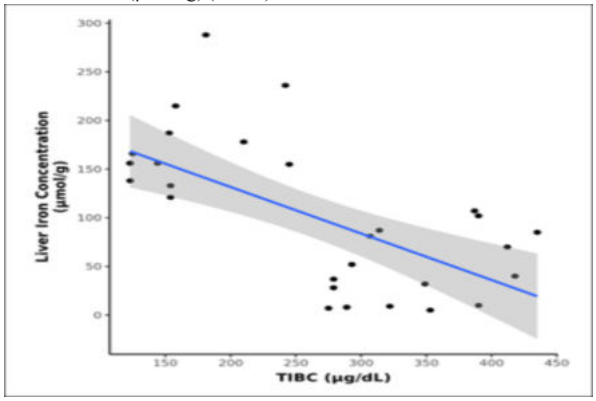


Fig 5: The Correlation Between TIBC (µg/dL) And Liver Iron Concentration (µmol/g).

There was a strong negative correlation between TIBC (µg/dL) and Liver Iron Concentration (µmol/g), and this correlation was statistically significant (rho = -0.64, p = <0.001).

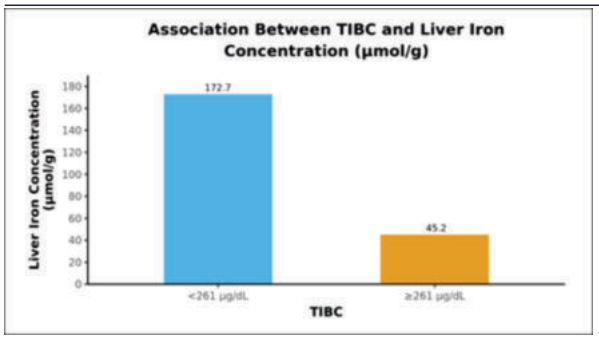


Fig 6: The Means Of Liver Iron Concentration (µmol/g) In The 2 Different Groups

DISCUSSION

Non-invasive MRI is currently widely utilized for liver Fe quantification, including distribution evaluation, detection, grading, and therapy response monitoring. For iron quantification, several MRI approaches have been developed, each with its own set of benefits and drawbacks. The susceptibility effect caused by the accumulation of iron leads to signal loss in the affected tissue, particularly with the T2 weighted sequences, which makes the diagnosis of iron overload possible in a non-invasive way, thereby avoiding repeated biopsies.

This study is to compare a non-invasive approach of iron quantification, such as MRI, with clinical severity score and biochemical markers, resulting in a semi-quantitative and qualitative assessment of iron deposition in liver tissue. Previous researches have used atomic absorptive spectrophotometry, susceptometry, or invasive techniques such as liver biopsy to compare MRI quantification with absolute liver iron levels. These groundbreaking investigations established imaging as the gold standard for and underwent extensive validation and calibration.

Both SIR and T2* methods can be used to quantify liver iron, although SIR method is currently confined to liver iron and fat quantification, but T2* can be utilized in both the liver and the myocardium. The MRQuantIF software, which uses the Gandon method, was explored.

T2 and Biochemical hepatic iron concentration (Serum Ferritin (µg/dl) and TIBC)*

In present study, the correlation between T2* (msec) and variables of biochemical hepatic iron concentration, mainly serum ferritin and TIBC were done.

There was a strong negative correlation between Serum Ferritin and T2*, and this correlation was statistically significant (p = <0.001).

The results obtained were comparable to the study done by Chaosuwannakit N et al[111], in which Serum ferritin levels showed a significant negative correlation with the liver T2* values ($p = 0.01$, $r = 0.318$). Negative correlation between serum ferritin level and T2* was observed by Eghbali *et al*[112] and Fahmy *et al*[113] also.

Considering T2* and TIBC, there was a strong positive correlation between TIBC and T2*, and this correlation was statistically significant (p = <0.001).

Liver Iron Concentration (µmol/g) and Biochemical hepatic iron concentration (Serum Ferritin (µg/dl) and TIBC)

In our study, the correlation of Liver Iron Concentration with Serum Ferritin and TIBC were carried out.

There was a strong positive correlation between Liver Iron Concentration and Serum Ferritin, and this correlation was statistically significant (p = <0.001).

In the present study, among the 31 patients studied, 14 of them had TIBC <261 µg/dL and 17 had TIBC ≥261 µg/dL.

There was a strong negative correlation between TIBC and Liver Iron Concentration, and this correlation was statistically significant (p = <0.001).

The results obtained were comparable to study by Paisant et al[92], where the linear correlation between biochemical hepatic iron concentration and MR-hepatic iron concentration was excellent with a correlation coefficient = 0.96, p<0.0001.

Biochemical Hepatic Iron Concentration And Child Pugh Score

In the present study, among the 31 patients studied, 16 of them had serum ferritin ≤464 µg/dL and 15 had Serum Ferritin >464 µg/dL.

Association between serum ferritin and Child Pugh Class were studied and results showed that in the group of patients with serum ferritin ≤464 µg/dL, 10 were in class A and 6 were in class B. In the group of patients with serum ferritin >464 µg/dL, all 15 were in class C.

There was a strong positive correlation between Child Pugh Score and Serum Ferritin, and this correlation was statistically significant (p = <0.001).

In the group of patients with TIBC <261 µg/dL, 14 were in class C and in the group with TIBC ≥261 µg/dL, 10 were included in class A, 6 were included in class B and 1 were in class C.

There was a strong negative correlation between TIBC and Child Pugh Score, and this correlation was statistically significant (p = <0.001).

T2 and Child Pugh score*

There was a strong negative correlation between Child Pugh Score and T2* (msec), and this correlation was statistically significant (rho = -0.82, p = <0.001).

Liver Iron Concentration (µmol/g) and Child Pugh score

There was a strong positive correlation between Liver Iron Concentration (µmol/g) and Child Pugh Score, and this correlation was statistically significant (rho = 0.84, p = <0.001).

Splenic Iron Overload

One additional motive of the study was to determine the R2* of spleen, splenic iron concentration, evaluate if pathological or not, and if feasible, to determine the threshold for the clinicians.

However, in our study, majority of the participants (77.4%) showed nil splenic iron overload, whereas 22.6% of the participants showed slight splenic overload. There was no proportionate increase in splenic iron content in participants with respect to either severity of chronic liver disease using Child Pugh score clinically or biochemical severity of iron overload using serum ferritin and TIBC as markers. So, we were not able to analyze its reproducibility with respect to splenic iron overload parameter.

Alfred et al earlier reported iron content in thalassemic patients utilizing T2* methods, but the technique's reproducibility and validity were not tested. According to a study by St. Pierre et al, the traditional approach of determining iron overload using the T2* methodology is not reliable and has to be validated. Also, a reference medium is required to validate the T2* technique's robustness. As a result, the commercially available Ferriscan software that uses T2* data as an input was created. Calculating with this commercial software is expensive, and a full report of the iron content is acquired after processing the data with supercomputers. The Ferriscan programme may be more reliable since it measures iron content pixel by pixel across the entire liver, whereas the MRQuantif measures iron concentration in three uniform areas throughout the liver. In this respect, it's worth noting that the open source MRQuantIF programme, which is based on the SIR approach, processes muscle as a reference medium and background noise as a constant. Due to the lack of availability of the Ferriscan programme for quantification, we were unable to do a comparison.

CONCLUSION

Being an opensource software, the MRQuantIF can be used clinically for cost-effective and repeated estimation of iron content in the liver for chronic liver disease patients.

Both SIR and T2* methods can be used to quantify liver iron, although SIR method is currently confined to liver iron and fat quantification, but T2* can be utilized in both the liver and the myocardium.

Key component of the study was to compare the biochemical liver iron concentration using serum iron ferritin (normal values of 18-464uG/DL) and TIBC (normal values of 261-462ug/DL) and compare

with the SIR Gandon method. There was a strong correlation between these two methods.

Another key component of the study was to compare the clinical Child Pugh scoring from 5 to 15 points and compare with the SIR Gandon method. There was an excellent correlation between these two methods. With the above findings, we could define a positive correlation between liver disease and liver iron concentration.

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