Study on the Equation Between Liver MRI T2* Values and Liver Iron Concentration in Thalassemia Patients

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Research Article

Keywords: Equation, Thalassemia, Iron overload, Liver iron concentration, Accurate calculation

Posted Date: April 14th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1515338/v1

Abstract

Background: The liver iron concentration (LIC_F) provided by FerriScan is already certified. But there are some restrictive factors. Therefore, we explored the relationship curves of LIC_F and MRI liver T2 *, and constructed the equations for both.

Methods: Liver MRI T2* values of 273 thalassemia patients were measured by CMRtools/Thalassemia Tools (CMRtools) and divided into test and verification groups. The T2* values of the test group and LIC_F were used to build the equation, through which the T2* values of the validation group were converted to the liver iron concentration（LIC_e）. The relationship between LIC_e and LIC_F was explored. According to the clinical liver iron concentration grading, LIC_F and LIC_e were grouped to explore the relationship between the them in the validation group.

Results: The equation built by the test group was $LIC_F=37.393T2*^{(-1.22)}$，$R^2=0.971$，$P<0.05$. There was no statistical difference between LIC_e and LIC_F in the validation group（$P>0.05$）, There was significant consistency（$W=0.991, P<0.05$）and significant correlation（$r_s=0.983$，$P<0.05$）between them .There was no statistical difference in the clinical grading between LIC_e and LIC_F in the validation group （$P>0.05$）. There was significant consistency between the clinical grading results（$K=0.943$，$P<0.05$.

Conclusion: Through the equation $LIC_F=37.393T2*^{(-1.22)}$, after measuring the liver T2* value, the liver iron concentration (LIC) equivalent to LIC_F can be accurately calculated.

Introduction

The liver is one of the main iron storage organs, and LIC reflects the total iron load and is an important clinical indicator for clinical monitoring, evaluation and treatment of iron overload [1]. Although the actual liver iron concentration provided by liver biopsy serves as the "gold standard" for clinical indicators, most scholars and medical centers are more inclined to use non-invasive MRI technology to monitor LIC due to the fact that biopsy only provides a small sample size of LIC and has some disadvantages such as invasiveness and poor repeatability [2]. The LIC_F reported by FerriScan (Resonance Health Limited, Burswood, WA, Australia) based on MRI T2/R2 (1000/T2) images has been certified by the US Food and Drug Administration (FDA) and has high reliability [3, 4]. But this technique also has many limitations [5]: this technique requires sending the patient's MRI data to FerriScan for remote post-processing and analysis. Sending patients data to other places requires the approval of relevant institutions, and the time cost prolongs the time to obtain LIC results. Additional analysis costs also raise the cost of monitoring LIC. These lead to a significant reduction in the possibility of using FerriScan technology to regularly monitor patients LIC, especially in areas with poor medical care or underdeveloped economies.

MRI technology based on gradient echo T2* sequence has been identified as a non-invasive standard to quantify tissue iron level [6, 7]. Many centers have been using T2* relaxation method, self-made sequences and corresponding software techniques to measure the T2*, R2* (1000/T2*) values of organs,

so as to obtain the estimated value of organ iron concentration[8]. At present, some studies have explored the relationship between T2*/R2* and LIC, and the corresponding calibration curve equation has been built based on a small sample size [4, 9–13]. Using LIC_F provided by FerriScan as a reference standard, this study aims to build a calibration curve equation between liver T2* values and LIC_F in iron overload patients based on thalassaemia patient data with a large sample size and wide range of LIC, and explore a method to accurately quantify LIC equivalent to the LIC_F by measuring liver T2* values.

Materials And Methods

1.1 Research materials

This is a retrospective study. The clinical data and MRI of 273 thalassemia patients in the First Affiliated Hospital of Guangxi Medical University from January 2011 to December 2015 were collected. The inclusion criteria were: (1) Patients were genetically diagnosed thalassemia and had a regular history of blood transfusion. (2) 9 years old ≤ age ≤ 50 years old. (3)Patients had both the T2* sequence MRI with intact liver 12 echoes and the Ferriscan LIC report in the corresponding period (the required T2 image scan time for FerriScan is the same as the corresponding T2* image scan time, and the difference between the FerriScan LIC reporting time and the corresponding T2* measurement time does not exceed 48 hours). The exclusion criteria were: (1) MRI artifacts were too large to meet the measurement requirements. (2) Patients had other chronic liver diseases or tumor diseases. Among the 273 patients included, there were 152 males and 121 females, aged from 9 to 49 years old, with an average of (21.1 ± 10.53) years old. All patients (or parents/guardians) gave written informed consent to participate in the study.

1.2 Mr Scanning Methods

MRI was performed on a 1.5T scanner (MAGNETOM Avanto Fit, Siemens Healthcare, Erlangen, Germany).

T2* data were acquired using a multiecho GRE scanning sequence at the same level above the liver gate at the last breath (Hold breath once and scan for the same level above the hilum). Relevant pulse sequence parameters include: flip angle = 20°, echo time(TE) = 1.29, 2.35, 3.43, 4.6, 5.68, 6.85, 7.93, 9.1, 10.18, 11.35, 12.43, 13.6 ms, repetition time (TR) = 200.00 ms, FOV read = 400 mm, matrix = 256, layer thickness = 10 mm. Scan time was 15s.

The FerriScan acquisition consisted of a free-breathing 2D multislice spin-echo pulse sequence. Relevant pulse sequence parameters include:flip angle = 90°, echo time (TE) = 6, 9, 12, 15, 18 ms, repetition time (TR) = 1000 ms, FOV read = 400 mm, matrix = 256, and 11 slices of 5 mm thickness.

1.3 Data Measurement And Analysis

T2 image data was sent to FerriScan for processing and analysis. The LIC_F used in this study was derived from the final FerriScan report. As mentioned before, the required T2 image scan time for FerriScan is the same as the corresponding T2* image scan time, and the difference between the FerriScan LIC reporting time and the corresponding T2* measurement time does not exceed 48 hours.

The T2* image data were all post-processed by CMRtools(CMRtools/Thalassemia Tools, Cardiovascular Imaging Solutions, London, UK). Measurement process: the anonymous image was imported into the software and, avoiding the intrahepatic blood vessels and bile ducts seen by naked eyes at the same level of the liver, the roughly same ROI were drawn according to the area measured by FerriScan. And the drawn ROI and matching T2* values appeared in the post-processing software. Truncation method [14, 15] was used to discard the interference signal values deviating from the fitting curve, and T2* value was recorded when the determination coefficient value (R^2) ≥ 0.98 (Fig. 1).

1.4 Statistical Methods

Statistical analysis was performed using SPSS 26.0 statistical software package. Using a random number table, 273 cases of T2* data were divided into 191 cases in the test group and 82 cases in the verification group according to the ratio of 7:3. The measured liver T2* values did not conform to the normal distribution by the normality test. By curve fitting (exponential function), the T2* values of the test group and LIC_F were used to build the calibration curve equation.

The T2* value in the verification group was converted to LIC_e by the equation. After inspection, LIC_e and LIC_F did not conform to the normal distribution. Friefmans M test was used to explore the difference between them. If $P > 0.05$, there was no significant difference. Kendall's coefficient was used to explore the consistency between them. If the correlation coefficient $W > 0.75$ and $P < 0.05$, it means there is a high degree of consistency. Spearman rank correlation analysis was used to explore the correlation between the two. If the correlation coefficient $|r_s| > 0.75$ and $P < 0.05$, it means there is a high correlation.

According to the 1.5T MRI grading of liver iron concentration, LIC_e and LIC_F were divided into normal group (0.17-1.8mg/g dry weight), mild group (1.8-7.0mg/g dry weight), moderate group (7.0-14.0mg/g dry weight), severe group (> 14.0 mg/g dry weight). The McNemar test was used to explore the difference of the clinical grading results of LIC_e and LIC_F. If $P > 0.05$, there was no significant difference between them. The Kappa's coefficient was used to explore the consistency of clinical grading results of them. If $K > 0.75$ and $P < 0.05$, it means that there is high consistency between them.

Results

The T2* values and LIC_F results of the test group are shown in Table 1. The T2* values, LIC_F and LIC_e results of the verification group are shown in Table 2. The relationship trend among all data sets is shown in the scatter diagram (Fig. 2).

The curve equation built according to the T2* values and LIC_F of the test group is LIC_F=37.393T2*^(-1.22) (R^2=0.971，P<0.05).

There was no statistical difference between LIC_e and LIC_F in the validation group（Z=-1.269, P>0.05）; There was significant consistency between them （Kendall's W=0.991, P<0.05）; There was significant correlation between them（r_s=0.983，P<0.05）. There was no statistical difference in the clinical grading between LIC_e and LIC_F in the validation group （c^2=3.0，P=0.083>0.05）(Fig. 3) . There was significant consistency between the clinical grading results（Kappa's K=0.943，P<0.05）.

Discussion

With the previously mentioned, MRI has been widely regarded as the main method for non-invasive diagnosis of liver iron concentration [7]. FerriScan can generate reports including liver iron concentration, but it cannot be carried out generally due to various restrictive factors, especially for the long-term quantitative monitoring of LIC in patients in economically underdeveloped areas [16]. Relaxation methods and related measurement techniques based on T2*/R2* images have been carried out in many centers. After years of research, many scholars have verified that the T2*/R2* values have obvious linear relationship with LIC and partially constructed the curve equation of the relationship between them [4, 9–13].

This study analyzed the relationship between liver T2* value and LIC in thalassemia patients with a large sample size and a wide range of LIC, and found that the two showed a highly linear exponential function correlation. This is consistent with the trend of T2*-LIC curve equation studied by Garbowski, Jhaveri and etc. [4, 13]

However, the slopes of calibration curves proposed by different studies are different, and for the LIC calculated from the earlier calibration curves, many researchers such as Garbowski[13] proposed further calibration coefficients to calibrate the final LIC. The specific reasons are analyzed as follows: (1) The earlier T2*/R2*-LIC calibration curve equation was based on liver biopsy, such as the research of Henninger, Wood, Hankins, Christoforidis, Garbowski et al. [9–13] LIC provided by liver biopsy has long served as the "gold standard". But in different studies, many factors, such as the materials and methods used during liver biopsy and the heterogeneity of iron in the liver, can lead to differences between studies. (2) The sample size used in some studies is small. A small sample size not only increases sampling error, but also limits the range of LIC used, and the final fitted calibration curve equation is not well suited to quantify a larger range of LIC. The LIC values in 17 patients collected by Henninger [9] and others through liver biopsy ranged from 0.917mg/g to 11.646mg/g. In authors opinion, due to the small range of LIC studied, it is inappropriate to use the corresponding calibration curve to quantify a wider range of LIC. (3) Different models used to measure T2* and R2* will directly lead to differences in the corresponding T2* and R2* values. For example, the offset model used by Wood for R2* measurement is different from the truncation model used by Hankins. The research by Garbowski [13] and others proposed that the R2* values measured by the offset model was high, while the R2* value measured by the truncated model

was low, and the importance of using appropriate measurement models to quantify T2* and R2* values and using the appropriate analytical techniques to construct curve equations in clinical practice were emphasized. (4) The high iron concentration cause low T2* values, correspondingly, a very short minimum echo-times needs to be set for accurate measurement. However, due to the differences in techniques and scan sequences used by different research centers, different minimum echo-times obviously limit the lowest T2* value measured by the center, i.e., the highest LIC value.

The deficiencies of this experiment are as follows: (1) In the setting of ROI, this study tries to keep the delineated T2* image RIO as consistent as possible with the T2 image ROI delineated by FerriScan. However, artificial delineation of ROI is susceptible to a variety of subjective and objective factors, the measurement error is inevitable. (2) The data used in this study are single-center data. Due to the characteristics of endemic sources, the proportion of patients with high iron concentration is relatively large, and the proportion of patients with normal or low iron concentration is relatively small. However, in this study, a larger sample size was used for analysis, and the studied LIC range was wide and the reliability was high. (3) This study is a retrospective analysis based on LIC_F. In other words, the LIC-T2* calibration equation is built under the assumption that the R2-based FerriScan technology is very reliable, and the resulting equation should not be extended to other technologies or organs for actual iron concentration calculations.

In summary, this study constructed a curve equation by exploring the relationship between the liver T2* value of thalassemia patients and the LIC_F provided by FerriScan. After measuring liver T2* values, LIC equivalent to LIC_F can be accurately quantified and to better monitor changes in LIC in patients with iron overload. It is of great reference significance to formulate the corresponding diagnosis and treatment plans in a timely manner and accurately, especially in many areas with limited medical conditions or low economic levels.

Declarations

Ethics approval and informed consent

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University（NO.2022-KY-E-(101)）. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients (or their parents / guardians) signed their written informed consent to participate in the study.

Consent for publication

All authors gave their consent for publication of this manuscript.

Conflict of interest

There are no conflicts of interest to declare.

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Peng Peng contributed to the study conception and design. Material preparation and data collection were performed by Feng-ming Xu Ji-xing Yi, Chao-tian Luo, Fei Peng, Yu-zhao Peng and Peng Peng. Data analysis were performed by Feng-ming Xu and Ji-xing Yi. The first draft of the manuscript was written by Feng-ming Xu, Bu-min Liang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated during and/or analysed during the current study are not publicly available due the FerriScan iron concentration data has cost a large cost, but are available from the corresponding author on reasonable request.

Funding

This work was supported by grants from the Natural Science Foundation of China (81760305), Natural Science Foundation of China (81641066) and Innovation Project of Guangxi Graduate Education (YCSW2021135).

Acknowledgments

We sincerely thank all the participants of our study. We also thank the Department of Radiology and the Department of Blood in the First Affiliated Hospital of Guangxi Medical University for their generous support. We thank Yi-ling Wang for her guidance in the preparation of the manuscript.

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Tables

Table 1 The liver T2*‐ms‐values and LIC_F (mg/g dry weight) values of 191 thalassemia patients in the test group

name	*n*	*range*	*25%*	*75%*	*M*
*T2**	*191*	*0.86‐28.92*	*1.19*	4.25	2.00
LIC_F	*191*	*0.60‐43.00*	*5.70*	29.50	14.90

Table 2 The liver T2*‐ms‐values, LIC_F values and LIC_e (mg/g dry weight) values of 82 thalassemia patients in the validation group

name	*n*	*range*	*25%*	*75%*	*M*
*T2**	*82*	*0.90–25.44*	*1.0875*	4.4375	1.85
LIC_F	*82*	*0.90–43.00*	*6.0250*	35.9250	14.60
LIC_e	*82*	*0.72–42.52*	*6.0800*	33.7550	17.60

Figures

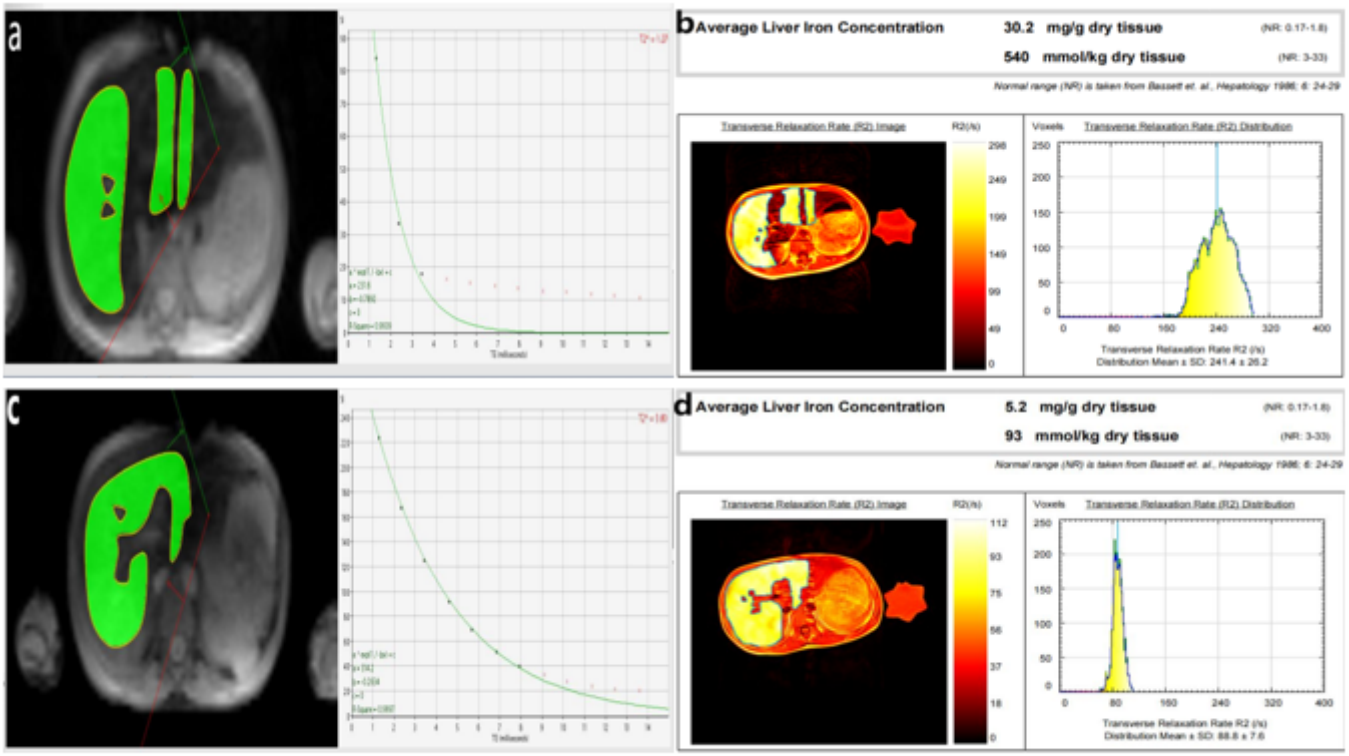

Figure 1

Male, 14 years old, patient with iron overload thalassemia in the severe liver group; CMRtools showed that the mean value of T2* is 1.27ms, R^2 is 0.9939, and LIC grade is severe (a); LIC_F was 30.2mg/g dry weight (b). Female, 9 years old, patient with iron overload thalassemia in the mild liver group; CMRtools showed that the mean value of T2* is 3.80ms, R^2 is 0.9997, and LIC grade is mild (c);LIC_F was 5.2mg/g dry weight (d).

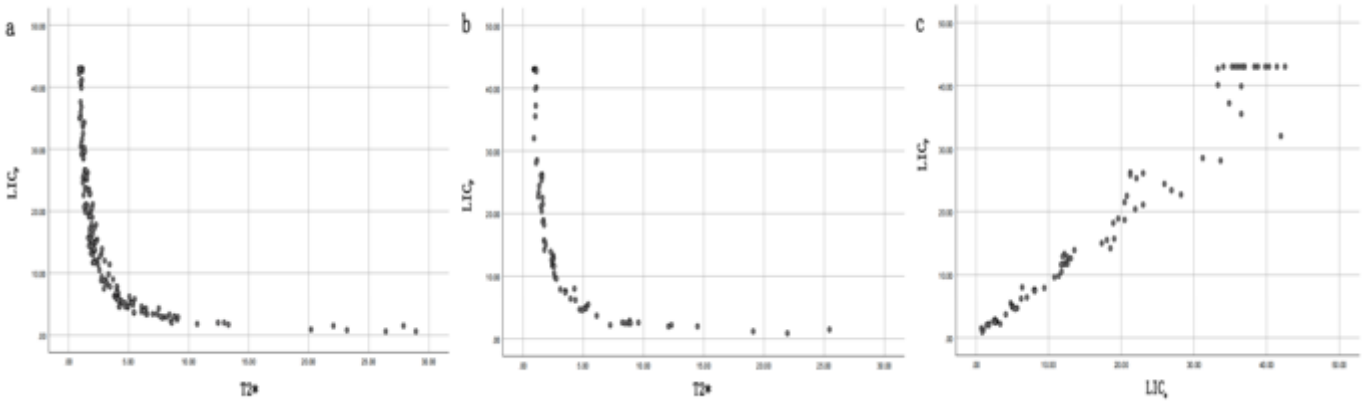

Figure 2

Scatter plot of the relationship between LIC_F and T2* values in the test group (a); Scatter plot of the relationship between LIC_F and T2* values in the validation group (b); Scatter plot of the relationship between LIC_F and LIC_e in the validation group (c).

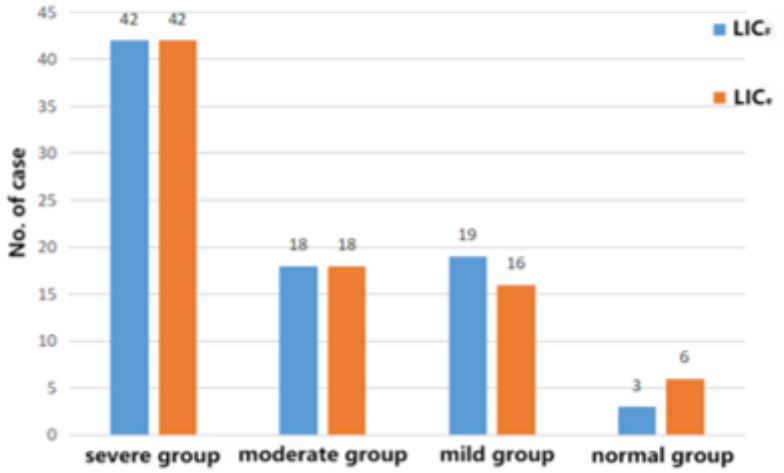

Figure 3

The distribution of clinical grade composition ratio of hepatic iron concentration in 82 thalassemia patients by LIC_e and LIC_F in the validation group .