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Original Article

Quantitative Analysis of Liver Iron Deposition Based on Dual-Energy CT in Thalassemia Patients

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Abstract. ***Background:*** **To explore the feasibility and accuracy of liver iron deposition based on dual-energy CT in thalassemia patients.**
Materials and methods: **105 thalassemia patients were examined with dual-energy CT and MR liver scanning. Dual-energy CT was performed to measure CT values on 80kVp, 140kVp, and virtual iron content (VIC) imaging; ΔH was figured out by the difference in CT values between 80kVp and 140kVp. Using the liver iron concentration (LIC) obtained by FerriScan as a gold standard, the correlation between CT measurements and LIC was evaluated. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance for dual-energy CT in liver iron quantification and stratification.**
Results: **The correlation analysis between CT measurements and LIC showed that 80kVp, 140kVp, VIC, and ΔH all had a high positive correlation with LIC (P<0.001). The correlation analysis among different degree groups of VIC, ΔH, and LIC showed that the normal, moderate, and severe groups of VIC and ΔH had moderate or high positive correlations with that of LIC (P<0.01), but the mild group had no correlation (P>0.05). ROC analysis revealed that the corresponding optimal cutoff value of VIC was -2.8, 6.3,11.9 HU (corresponds to 3.2,7.0,15.0 mg/g dry weight) respectively, while the ΔH were 5.1, 8.4, 17.8HU, respectively. The area under the receiver operating characteristic curves (AUCs) for both VIC and ΔH increased with LIC thresholds.**
Conclusion: **Dual-energy CT can accurately quantify and stratify liver iron deposition, contributing to predicting the status of liver iron deposition in thalassemia patients.**

Keywords: Thalassemia; Liver iron concentration; Dual-Energy computed tomography; Virtual iron content.

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Introduction. Thalassemia is a group of inherited blood disorders characterized by a decrease or absence of one or more globin chains; it is the most common monogenic disease in the world.[1,2] According to the severity of the

disease, thalassemia is classified into mild, moderate, and severe thalassemia. Mild thalassemia usually does not require treatment, but moderate and severe thalassemia require regular blood transfusion and iron chelation therapy.[1] The compensatory enhancement of bone marrow hematopoietic function and intestinal iron absorption in thalassemia patients are significantly increased. Furthermore, blood transfusion further increases the iron deposition in the liver, heart, and endocrine organs, ultimately resulting in organ dysfunction.[3-5]

The liver is the main storage site of iron during iron overload, accounting for about 70% of the total body iron.[5] Studies have shown that hepatic iron overload is an independent factor causing liver damage, which progresses to hepatocyte degeneration, cirrhosis, and hepatocellular cancer.[4-6] Patients with elevated liver iron content (LIC) are at high risk of early death.[1,3] So, treating thalassemia requires a combination with iron chelation therapy.[7] The lower, upper, and intensive LIC thresholds in clinical iron chelation therapy were 3.2, 7.0, and 15.0 mg iron per gram of dry tissue, respectively.[5,8,9] Therefore, the accurate quantitation of liver iron content is significant for evaluating the severity of the disease and formulating the iron chelation therapy plan.[10]

Percutaneous liver biopsy (PLB) is the gold reference standard for determining liver iron concentration.[10] However, it is invasive and has high sampling variability, making it unsuitable for repeated use.[10] Non-invasive methods, such as magnetic resonance imaging (MRI) and dual-energy computed tomography (CT), are available.[8-12] FerriScan (Resonance Health & Resonance Health Analysis Services, Claremont, Australia) is a commercially available MR imaging-based R2 technique that accurately and effectively quantifies LIC. FerriScan was approved by the US Food and Drug Administration.[12-13] However, this technology also has many limiting problems:[15] MRI data of patients need to be sent to FerriScan for off-site post-processing and analysis. Sending patient data to another location requires approval from the relevant center, and the time cost required will prolong the time to obtain LIC results. Additional analysis costs will also increase the cost of LIC monitoring. This has resulted in liver iron quantification using FerriScan technology being limited to a few large medical centers. More importantly, this technology can quantify the upper limit of LIC is 43mg/g dry weight.

With the development of new techniques in CT, dual-energy CT has made great progress in quantifying liver iron content. CT is helpful for quantifying liver iron overload and may solve the problem that MRI cannot measure extremely severe liver iron overload. Dual-energy CT differential method (ΔH method) and the three-material decomposition algorithm (overlay method) are the two main measurement methods in dual-energy CT.[16,17] A previously performed phantom study by Fischer et al. showed that three material decomposition algorithms could specifically reflect the liver iron content and obtained iron-specific algorithm-based virtual iron content (VIC) images with dual-energy analysis.[18] Some previous studies also showed that dual-energy CT could accurately quantify clinically important hepatic iron accumulation.[19] However, according to the commonly used classification system of liver iron accumulation, there are few studies on the classification of liver iron accumulation by dual-energy analysis. Further research and confirmation are needed on quantifying and stratifying liver iron deposition by Dual-energy CT.

Thus, the purpose of our study was to adopt dual-energy CT for evaluating the liver iron content in thalassemia patients and compare it with MRI, explore the quantification and stratification of liver iron deposition based on dual-energy CT, and find a non-invasive and simple method for liver iron quantification.

Materials and Methods.

Number of Patients. This retrospective study was approved by the institutional review board (2022-E364-01). Informed consent was obtained from all patients. One hundred-five thalassemia patients were included from August 2013 to April 2015. Inclusion criteria: patients with a genetic diagnosis of moderate thalassemia or severe thalassemia, transfusion-dependent; age ≥ 5 years; a history of transfusion with at least 10 units of red blood cells (1 unit = 200mL red blood cells) before the examination; have received irregular or regular iron chelation therapy or requiring iron chelation therapy. Exclusion criteria: patients who could not sign informed consent or refused to perform CT or MR examination, had claustrophobia syndrome, or were equipped with pacemakers, ferromagnetic metal implants, or others if were regarded unsafe for MRI examination.

CT Acquisition. All CT examinations were performed using the same 128-slice dual-energy CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). The scan range was from the diaphragm to the lower edge of the liver, including the entire liver. The examination procedure used dual-energy (DE, 80 and 140kVp) with a tin filter to improve the separation of the two energy spectra. The CARE Dose 4D technique was used to adjust tube currents automatically. Other CT parameters were as follows: 64 × 0.6mm and 128 × 0.6mm detector collimation, 150 mAs/rotation, 400 mAs/rotation effective tube currents, 500ms gantry rotation time, 0.6 pitch, 512 × 512 matrix, 1.5 mm slice thickness, 1 mm increment.

CT data analysis. VIC imaging was performed at dual-energy analysis using the three-material decomposition

theory. The two groups of reconstructed images obtained from DECT (DE, 80 and 140kVp) scanning were sent to the post-processing workstation (Single Dual Energy), and the dual energy-virtual plain scanning function was selected (Dual Energy- liver VNC). DECT images were reconstructed using a reconstruction kernel of D30f with a slice thickness of 1.5 mm and a slice spacing of 1 mm. An iron-specific slope value of 1.9 was used in the presetting of the liver VNC algorithm.[19] The CT values of lipid and liver tissues were set as default. The pixel component distribution map of the iron element was extracted by automatic computer calculation and displayed as orange and red superimposed images of different proportions. The VIC images were obtained by setting the ratio of overlay to 100%.

In VIC images regions with uniform density and without intrahepatic blood vessels and bile ducts was regarded as Region of Interests (ROI). Two and three ROIs were randomly selected from the left and right hepatic parenchyma separately, and the size of each was about 3-4cm^2; the average value of the five CT values was VIC value.

MR Image Analysis. All MRI examinations were performed according to the FerriScan's 1.5T MR (Siemens Avanto 1.5T MR, Siemens Healthcare, Forchheim, Germany) scanning standard.[15] Liver iron MR imaging data were uploaded to the FerriScan center, and LIC value was obtained through FerriScan.

Statistical analysis. Statistical analysis was performed using software SPSS 22.0 and MedCalc v15.8. The Kolmogorov-Smirnov test was used to test the normal distribution of the parameters. Spearman or Pearson correlation analysis was used to investigate the relationship between CT measurements and LIC. FerriScan-LIC was set as a standard of reference for determining the liver iron deposition grade. The least significant difference (LSD) test and homogeneity test for variance were used to compare the differences between any grades of VIC and ΔH. Receiver operating characteristic (ROC) analysis was used to judge the thresholds of VIC and ΔH corresponding to each LIC grade. The threshold was derived from the Youden index, which maximized the sum of sensitivity and specificity. The area under the ROC curve (AUC) was calculated for VIC and ΔH. Two paired ROC curves were compared using the z-test. $P<0.05$ was considered a statistically significant difference.

Results

Correlation analysis between CT measurements and LIC in thalassemia patients. Of the 105 patients, the LIC values measured by MR were higher than 43.0 mg Fe/g dry weight in 3 patients, and no specific value was reported. The correlation analysis between CT measurements and LIC in 102 thalassemia patients showed that 80kVp, 140kVp, VIC, and ΔH all had a high positive correlation with LIC ($P<0.01$), VIC and ΔH had a much higher positive correlation with LIC, the correlation coefficients were 0.883 and 0.907 (**Table 1**). The linear regression equations between CT measurements and LIC are shown in **Table 2**. The scatter plots among VIC, ΔH, and LIC are shown in **Figure 1**. The images of a patient with VIC, ΔH and LIC are shown in **Figure 2.**

Correlation analysis among different VIC, ΔH, and LIC degree groups in thalassemia patients. According to the clinical iron chelation therapy, the thresholds of LIC lower limit, upper limit, and more intensive therapy are 3.2, 7.0, and 15.0 mg Fe/g dry weight, respectively.[9] Based on these thresholds and the common grading system, the patients were divided in four groups: normal

Table 1. Relationship between CT measurements and LIC.

Image Type	Mean±SD*	Range（HU）	r (95%CI)	P Value
80kVp	86.28±13.14	58.0-113.5	0.868(0.825-0.907)	<0.001
140kVp	73.93±6.91	55.4-89.4	0.719(0.643-0.795)	<0.001
ΔH	12.34±7.10	0.9-28.9	0.907(0.873-0.938)	<0.001
VIC	6.77±11.74	-13.3-33.5	0.883(0.842-0.915)	<0.001

* SD = standard deviation.

Table 2. Linear regression equations between CT measurements and LIC.

Image Type	Regression quation	R^2	P Value
80kVp	y=0.56x-37.47	0.754	<0.001
140kVp	y=0.88x-54.3	0.517	<0.001
ΔH	y=1.08x-2.68	0.823	<0.001
VIC	y=0.63x+6.32	0.780	<0.001

Notes: x is the CT value of each measurement; y is LIC value; $R^2$is the fit coefficient.

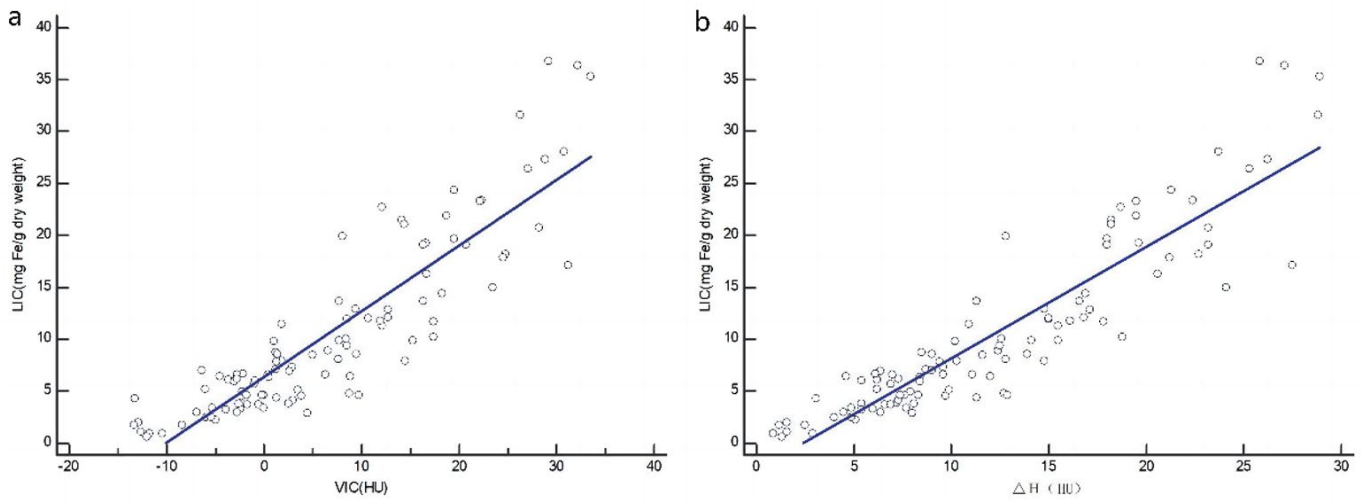

Figure 1. Scatter plots (**a,b**) show correlations among CT measurements (VIC and ΔH) and MR-measured LIC (n = 102). Both showed positive linear correlation with LIC (*P* <0.001).

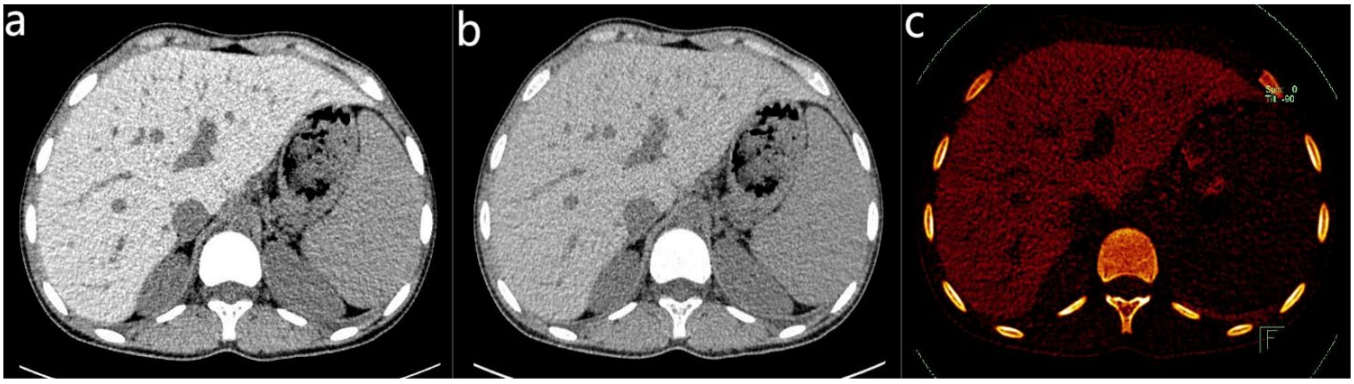

Figure 2. Dual-energy CT images of a β-thalassemia patient whose LIC was 32.5 mg/g dry weight (**a**, dual-energy=80kVp; **b**, dual-energy=140kVp; **c**, virtual iron content=61HU).

Table 3. Correlation among different degree groups of VIC, ΔH and LIC.

Grade	VIC		ΔH	
	r (95%CI)	P Value	r (95%CI)	P Value
normal	0.745(0.591-0.911)	0.004	0.812(0.666-0.927)	0.001
mild	0.078(-0.215-0.356)	0.656	0.178 (-0.112-0.471)	0.307
moderate	0.664(0.375-0.851)	<0.001	0.703(0.445-0.871)	<0.001
severe	0.584(0.274-0.805)	0.003	0.622(0.326-0.848)	0.001

Table 4. Comparison between any two grade of VIC and ΔH.

Grade	VIC	ΔH
	P Value	P Value
normal and mild	<0.001	<0.001
normal and moderate	<0.001	<0.001
normal and severe	<0.001	<0.001
mild and moderate	<0.001	<0.001
mild and severe	<0.001	<0.001
moderate and severe	<0.001	<0.001

(n=13), mild (n=35), moderate (n=30) and severe (n=24) iron overload groups. The correlation analysis among different degree groups of VIC, ΔH, and LIC showed that the normal, moderate, and severe groups of VIC and ΔH had moderate or high positive correlations with that of LIC (*P*<0.01), but the mild group had no correlation (*P*>0.05) (**Table 3**). After LSD test and homogeneity test for variance in the four groups of VIC and ΔH, results showed that the differences between any two groups had statistical significance (*P*<0.01) (**Table 4**).

Diagnostic performance of grading based on LIC levels in thalassemia patients. The LIC obtained from FerriScan was set as a reference standard for determining the liver iron deposition grading. For discriminating clinically significant LIC thresholds (3.2, 7.0, 15.0 mg Fe/g dry weight), ROC analysis revealed that the

Table 5. Comparison of LIC grading performance between methods of VIC and ΔH using FerriScan-LIC as a reference (n=102).

LIC threshold (mg Fe/g dry weight)	VIC				ΔH				z statistic	P Value
	Optimal criterion (HU)	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)	Optimal criterion (HU)	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)		
3.2	-2.8	88.76 (80.30-94.50)	92.31 (64.00-99.80)	0.944 (0.880-0.980)	5.1	96.63 (90.50-99.30)	84.62 (54.60-98.10)	0.965 (0.909-0.992)	1.304	0.192
7	6.3	83.33 (70.70-92.10)	93.75 (82.80-98.70)	0.956 (0.897-0.987)	8.4	100 (93.4-100.00)	81.25 (67.40-91.10)	0.972 (0.919-0.995)	1.937	0.053
15	11.9	95.83 (78.90-99.90)	87.18 (77.70-93.70)	0.967 (0.911-0.992)	17.8	95.83 (78.90-99.90)	97.44 (91.00-99.70)	0.979 (0.930-0.997)	1.501	0.133

corresponding optimal cutoff value of VIC were -2.8, 6.3, 11.9 HU, respectively, while the ΔH were 5.1, 8.4, 17.8HU, respectively (**Table 5**).

The AUC values of VIC and ΔH both increased with the increase of LIC thresholds. The AUC values were all above 0.940. It suggested that VIC and ΔH have high diagnostic performance for liver iron deposition grading.

At thresholds of 3.2 and 7.0 mg Fe/g dry weight, VIC showed sensitivities of 88.76% and 83.33%, respectively, which were relatively lower than those of ΔH (96.63% and 100%). However, the specificities of VIC (92.31% and 93.75%) were higher than those of ΔH (84.62% and 81.25%). At the threshold of 15 mg Fe/g dry weight, VIC and ΔH both showed sensitivities of 95.83%, and the specificity of ΔH (97.44%) was higher than that of VIC (87.18%). The comparative analysis between the AUCs of VIC and ΔH showed no significant difference in all thresholds. These results indicated that VIC and ΔH have the same diagnostic performance for the clinical significance of liver iron deposition grading. Both can accurately quantify and grade liver iron concentration.

Discussion. An accurate assessment of the degree of hepatic iron deposition is essential for the quantitative classification of hepatic iron deposition and the determination of the need for iron chelation therapy.[1,8,11,] MR is a mature non-invasive detection technology, and Ferriscan-LIC is also an internationally recognized gold standard.[13-15] However, when LIC>43mg/g dry weight, MRI cannot quantify the LIC.[20,21] In recent years, various dual-energy CT techniques have been gradually improved and applied in clinical practice. Dual-energy CT differential method (ΔH method) and the three-material decomposition algorithm (overlay method) are two primary methods of determining liver iron content. ΔH is the difference between two CT values at high and low voltages in the region of interest, which reflects the mixed information of multiple substances, including all information about liver parenchyma, fat, iron, etc.[22] This method was first used in 1982 by Goldberg et al. who carried out a study on an animal model with hemochromatosis using 120kVp and 80kVp, whose results showed that the liver iron concentration predicted by CT was highly correlated with the actual one.[23] Hereafter, the dual-energy CT measurement method has gradually attracted people's attention as a new non-invasive method. Three-material decomposition algorithm was used for calculating iron content by using iron-specific slope value and estimating iron concentration through formula conversion. An in vitro study by Fischer et al. confirmed that the interference of hepatic tissue and intrahepatic fat could be eliminated by applying a three-material decomposition algorithm, specifically reflecting liver iron content.[18] This study showed that VIC and ΔH had a significant positive correlation with LIC which is similar with the findings of Joe and colleagues.[19] In 2012 Joe et al performed a quantitative study of hepatic iron on liver transplant recipients and liver donors by using dual-energy CT, the results indicated that ΔH was positively correlated with hepatic iron deposition.[19] However, its correlation coefficient was lower than that of our study (0.430 Vs. 0.907). The reason could be that the clinical subjects of the two studies were different. The subjects of our study were mainly transfusion-dependent β-thalassemia major patients (with irregular iron chelation treatment) with liver iron overload caused by ineffective hematopoiesis and long-term blood transfusion. In the study of Joe the patients were liver transplant recipients and liver donors, in these patients liver iron concentration was normal to mild , instead the range of liver iron concentration in our study was greater (from normal to severe).[19] ΔH probably reflects the mixed information of multiple substances and the interference of fat may not be completely eliminated. The above liver transplantation study indicated that ΔH had a weak but statistically significant negative correlation with fat deposition degree. Probably, because of the disease characteristics of the cases in our study, the amount of fat deposition in the liver is lower than in the context of liver transplantation. Therefore there may be less interference of fat on ΔH and the correlation coefficient of ΔH method was higher than that of the above study. The VIC image is based on the three-material decomposition algorithm, and the iron ratio slope value is used. In Fischer experiment, an experiment on the interference of fat factor on quantitative hepatic iron was designed.[18] Fat deposition in the liver of subjects was not analyzed in our study, while the same iron-specific slope value as the above experiment was used, so it could be ensured to

eliminate the effect of fat on liver iron quantification. In a recent study of LUO et al,[24] dual-energy CT and MR relaxation techniques were used on patients with suspected liver iron overload, the results indicated that VIC and ΔH had highly positive linear correlation with LIC.[24] Its correlation coefficient was compared with the result of our study, indicating that VIC and ΔH could be used for quantitative liver iron deposition, however, the effect of fat on liver iron quantification, especially the respective quantification of combined deposition of iron and fat, is worthy of further clinical study and discussion.

For CT quantitative analysis of liver iron content, quantification and grading also shall be carried out accordance with clinical liver iron grading diagnosis system. The results related to VIC, ΔH and LIC of liver iron deposition grading in our study showed that VIC and ΔH were positively correlated with LIC of normal, moderate and severe group, and were not correlated with that of mild group, while VIC and ΔH of different degrees groups had statistically significant between-group difference, indicating that the degree of hepatic iron on CT could be graded according to LIC thresholds. However, VIC and ΔH were not correlated with LIC of mild group, which could be due to the difference in examination technology. Iron deposition in the liver during MRI scanning results in inhomogeneities of the magnetic field, which accelerate signal dephasing in MRI sequences, thereby increasing the R2 value.[25] This indicates that MR-related techniques are more sensitive in quantifying non-heavy iron overload. While the detection of iron by dual-energy CT is realized depending on X-ray attenuation absorption of substance, the degree of X-ray attenuation is closely related to substance content. In mild liver iron deposition, the attenuation of hepatic CT value is not changed obviously, which result in decreased sensibility of dual-energy CT. When the liver iron content is further increased, the sensibility of dual-energy CT is also improved further.[24] Therefore, CT measurements is less correlated with LIC in mild group. In addition, 7.0 mg Fe/g of liver iron concentration is a clinically significant threshold and also the target value for monitoring the efficacy of iron chelation therapy.[12,28] In our study, VIC and ΔH were above this threshold and had a high positive correlation with LIC. Therefore, quantifying and grading liver iron concentration by dual-energy CT have a certain clinical application value. However, the application of dual-energy CT in quantitative analysis of mild liver iron deposition needs further study. In fact, the assessment and follow-up of iron are done with MRI, such as T2* technology.[12,28] However, using the MRI T2* technique is greatly limited in quantifying the LIC in patients with heavy hepatic iron overload, especially with the use of the 3T MRI.[29] Dual-energy CT could be a second line examination in patients that are unable to undergo MRI, especially in heavy hepatic iron overload and older patients when radiation dose is less an issue.

In paired ROC analysis, both VIC and ΔH have high diagnostic performance for liver iron deposition grading, the diagnostic performance of which increased with the increase of LIC thresholds. However, the specificity of VIC in mild and moderate groups is higher than that of ΔH, and the specificity of ΔH is higher than that of VIC in the severe group. The cause may be that in mild and moderate iron deposition, the interference of the fat factor is eliminated by VIC, and ΔH may be affected by the intrahepatic fat. In the case of mild iron deposition, the CT value of VIC is negative, which may be related to the iron-specific slope value. This slope is based on a phantom study and could not be optimal for the clinical study of patients. Similarly, the clinical study of iodine quantitation also reports some negative values.[30] Besides, the emergence of negative CT value could also be affected by imaging motion or hardening artifact, which results in a decrease in the sensitivity of VIC. In the case of severe iron deposition, hepatic iron is relatively high, the attenuation of CT value is changed, the sensitivity of VIC is improved, and the specificity is decreased. In severe iron deposition, the difference in CT values of fat and hepatic tissues at two voltages is negligible, which makes the specificity of ΔH much higher. In our study, there is no statistically significant difference between AUC values of VIC and ΔH in all ranges of LIC ($P>0.05$), indicating that the diagnostic performance of VIC and ΔH is not different for clinically significant liver iron deposition grading, both can achieve precise quantification and grading of liver iron concentration. The interference of the fat factor is eliminated by VIC, which is more likely to be the new indicator for the efficacy assessment of iron chelation therapy.

There are some limitations in our study. First, FerriScan-LIC rather than LIC obtained through liver biopsy is selected as the reference. The T2* technique can also be used to evaluate liver iron overload.[31] The technique is easy to perform and does not require off-site evaluation since many softwares allow the evaluation of T2* of the organs of the upper abdomen and the heart. However, since few of the patients in this study were willing to perform multiple radiology examinations simultaneously, none had an MRI T2* scan. The direct correlation between VIC and LIC obtained from DE CT and MRI T2* could be evaluated in a future study. Second, although clinically potential liver iron deposition cases were included, according to deposition grading thresholds, their sample size was relatively small; therefore, measurement errors may exist.

Conclusions. VIC and ΔH have a significant positive correlation with FerriScan-LIC. In addition, accurate quantification and grading of liver iron deposition by dual-energy CT with reference to LIC threshold is good for dynamic and non-invasive observation of liver iron

deposition in thalassemia patients, and provides a diagnostic basis for evaluation of the efficacy of iron chelation therapy. However, further clinical studies with larger sample size are needed to confirm the value of dual-energy CT to quantitative liver iron.

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Author Contributions. Material preparation and data collection were performed by Fengming Xu, Cheng Tang, Yiling Huang, Linlin Liang, Fuling Huang and Gaohui Yang. Data analysis were performed by Fengming Xu, Cheng Tang and Yiling Huang. The first draft of the manuscript was written by Fengming Xu, Cheng Tang and Peng Peng and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Peng Peng contributed to the study conception and design.

Data Availability. The dataset used in support of the findings of this study are available from the corresponding author at email address upon request.

Ethics Approval. This study was performed in line with the principles of the Declaration of Helsinki. And the study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (No.2022-E364-01).

Conflict of Interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References:

1. Kattamis A, Kwiatkowski JL, Aydinok Y. Thalassaemia. Lancet. 2022 Jun 18;399(10343):2310-2324. https://doi.org/10.1016/S0140-6736(22)00536-0 PMid:35691301
2. De Sanctis V., Kattamis C., Canatan D., Soliman A. T., Elsedfy H., Karimi M., Daar S., Wali Y., YassinM., Soliman N., Sobti P., Al Jaouni S., El Kholy M., Fiscina B., Angastiniotis M. β-thalassemia distribution in the old world: an ancient disease seen from a historical standpoint. Mediterr J Hematol Infect Dis 2017, 9(1): e2017018 https://doi.org/10.4084/mjhid.2017.018 PMid:28293406 PMCid:PMC5333734
3. Wood J. C. (2008). Cardiac iron across different transfusion-dependent diseases. Blood reviews, 22 Suppl 2(Suppl 2), S14-S21. https://doi.org/10.1016/S0268-960X(08)70004-3
4. Al-Khabori, M., Daar, S., Al-Busafi, S. A., Al-Dhuhli, H., Alumairi, A. A., Hassan, M., Al-Rahbi, S., & Al-Ajmi, U. (2019). Non-invasive assessment and risk factors of liver fibrosis in patients with thalassemia major using shear wave elastography. Hematology (Amsterdam, Netherlands), 24(1), 183-188. https://doi.org/10.1080/10245332.2018.1540518 PMid:30453843
5. Kanbour I., Chandra P., Soliman A., De Sanctis V., Nashwan A., Abusamaan S., Moustafa A.,Yassin M.A..Severe liver iron concentrations (lic) in 24 patients with β-thalassemia major: correlations with serum ferritin, liver enzymes, and endocrine complications. Mediterr J Hematol Infect Dis 2018, 10(1): e201806 https://doi.org/10.4084/mjhid.2018.062 PMid:30416694 PMCid:PMC6223579
6. De Sanctis V., Soliman A.T., Daar S., Alansary N., Kattamis A., Skafida M., Galati M.C., Christou S., Campisi S., Messina G., Yassin M.A., Canatan D., Di Maio S., Al Jaouni S., Raiola G., Karimi M., Kaleva V., Kakkar S., Mariannis D., Kattamis C.A concise review on the frequency, major risk factors and surveillance of hepatocellular carcinoma (HCC) in β-thalassemias: past, present and future perspectives and the ICET-A experience. Mediterr J Hematol Infect Dis 2020, 12(1): e2020006 https://doi.org/10.4084/mjhid.2020.006 PMid:31934316 PMCid:PMC6951357
7. Olivieri, N. F., & Brittenham, G. M. (1997). Iron-chelating therapy and the treatment of thalassemia. Blood, 89(3), 739-761 https://doi.org/10.1182/blood.V89.3.739 PMid:9028304
8. Werner, S., Krauss, B., Haberland, U., Bongers, M., Starke, U., Bakchoul, T., Enkel, S., Nikolaou, K., & Horger, M. (2019). Dual-energy CT for liver iron quantification in patients with haematological disorders. European radiology, 29(6), 2868-2877. https://doi.org/10.1007/s00330-018-5785-4 PMid:30406312
9. Imajo, K., Kessoku, T., Honda, Y., Hasegawa, S., Tomeno, W., Ogawa, Y., Motosugi, U., Saigusa, Y., Yoneda, M., Kirikoshi, H., Yamanaka, S., Utsunomiya, D., Saito, S., & Nakajima, A. (2022). MRI-Based Quantitative R2* Mapping at 3 Tesla Reflects Hepatic Iron Overload and Pathogenesis in Nonalcoholic Fatty Liver Disease Patients. Journal of magnetic resonance imaging : JMRI, 55(1), 111-125. https://doi.org/10.1002/jmri.27810 PMid:34184822
10. Rose C, Vandevenne P, Bourgeois E, Cambier N, Ernst O. Liver iron content assessment by routine and simple magnetic resonance imaging procedure in highly transfused patients. Eur J Haematol. 2006 Aug;77(2):145-9. https://doi.org/10.1111/j.0902-4441.2006.t01-1-EJH2571.x PMid:16608501
11. Henninger, B., Alustiza, J., Garbowski, M., & Gandon, Y. (2020). Practical guide to quantification of hepatic iron with MRI. European radiology, 30(1), 383-393. https://doi.org/10.1007/s00330-019-06380-9 PMid:31392478 PMCid:PMC6890593
12. Khadivi Heris, H., Nejati, B., Rezazadeh, K., Sate, H., Dolatkhah, R., Ghoreishi, Z., & Esfahani, A. (2021). Evaluation of iron overload by cardiac and liver T2* in β-thalassemia: Correlation with serum ferritin, heart function and liver enzymes. Journal of cardiovascular and thoracic research, 13(1), 54-60. https://doi.org/10.34172/jcvtr.2021.18 PMid:33815703 PMCid:PMC8007896
13. Jhaveri, K. S., Kannengiesser, S., Ward, R., Kuo, K., & Sussman, M. S. (2019). Prospective Evaluation of an R2* Method for Assessing Liver Iron Concentration (LIC) Against FerriScan: Derivation of the Calibration Curve and Characterization of the Nature and Source of Uncertainty in the Relationship. Journal of magnetic resonance imaging : JMRI, 49(5), 1467-1474. https://doi.org/10.1002/jmri.26313 PMid:30291649
14. Xu F., Yi J., Liang B., Tang C., Feng Q., Peng P. Comparative study on the measurement of liver LICdw between Ferriscan and T2* based LICdw obtained by different software's. Mediterr J Hematol Infect Dis 2022,14(1): e2022072. https://doi.org/10.4084/MJHID.2022.072

PMid:36425151 PMCid:PMC9652007
15. Padeniya, P., Siriwardana, S., Ediriweera, D., Samarasinghe, N., Silva, S., Silva, I., Ahamed, N., Niriella, M., & Premawardhena, A. (2020). Comparison of liver MRI R2(FerriScan®) VS liver MRI T2* as a measure of body iron load in a cohort of beta thalassaemia major patients. Orphanet journal of rare diseases, 15(1), 26. https://doi.org/10.1186/s13023-020-1301-4 PMid:31969179 PMCid:PMC6977251
16. Abadia, A. F., Grant, K. L., Carey, K. E., Bolch, W. E., & Morin, R. L. (2017). Spatial Distribution of Iron Within the Normal Human Liver Using Dual-Source Dual-Energy CT Imaging. Investigative radiology, 52(11), 693-700. https://doi.org/10.1097/RLI.0000000000000393 PMid:28562414
17. Luo, X. F., Xie, X. Q., Cheng, S., Yang, Y., Yan, J., Zhang, H., Chai, W. M., Schmidt, B., & Yan, F. H. (2015). Dual-Energy CT for Patients Suspected of Having Liver Iron Overload: Can Virtual Iron Content Imaging Accurately Quantify Liver Iron Content?. Radiology, 277(1), 95-103. https://doi.org/10.1148/radiol.2015141856 PMid:25880263
18. Fischer, M. A., Reiner, C. S., Raptis, D., Donati, O., Goetti, R., Clavien, P. A., & Alkadhi, H. (2011). Quantification of liver iron content with CT-added value of dual-energy. European radiology, 21(8), 1727-1732. https://doi.org/10.1007/s00330-011-2119-1 PMid:21472472
19. Joe, E., Kim, S. H., Lee, K. B., Jang, J. J., Lee, J. Y., Lee, J. M., Han, J. K., & Choi, B. I. (2012). Feasibility and accuracy of dual-source dual-energy CT for non-invasive determination of hepatic iron accumulation. Radiology, 262(1), 126-135. https://doi.org/10.1148/radiol.11110060 PMid:22106352
20. St Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, Pootrakul P, Robins E, Lindeman R. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood. 2005;105(2):855-861. https://doi.org/10.1182/blood-2004-01-0177 PMid:15256427
21. St Pierre, T. G., El-Beshlawy, A., Elalfy, M., Al Jefri, A., Al Zir, K., Daar, S., Habr, D., Kriemler-Krahn, U., & Taher, A. (2014). Multicenter validation of spin-density projection-assisted R2-MRI for the non-invasive measurement of liver iron concentration. Magnetic resonance in medicine, 71(6), 2215-2223. https://doi.org/10.1002/mrm.24854 PMid:23821350 PMCid:PMC4238736
22. Pickhardt, P. J., Graffy, P. M., Reeder, S. B., Hernando, D., & Li, K. (2018). Quantification of Liver Fat Content With Unenhanced MDCT: Phantom and Clinical Correlation With MRI Proton Density Fat Fraction. AJR. American journal of roentgenology, 211(3), W151-W157. https://doi.org/10.2214/AJR.17.19391 PMid:30016142 PMCid:PMC6615548
23. Goldberg, H. I., Cann, C. E., Moss, A. A., Ohto, M., Brito, A., & Federle, M. (1982). Non-invasive quantitation of liver iron in dogs with hemochromatosis using dual-energy CT scanning. Investigative radiology, 17(4), 375-380. https://doi.org/10.1097/00004424-198207000-00013 PMid:7129818
24. Luo, X. F., Xie, X. Q., Cheng, S., Yang, Y., Yan, J., Zhang, H., Chai, W. M., Schmidt, B., & Yan, F. H. (2015). Dual-Energy CT for Patients Suspected of Having Liver Iron Overload: Can Virtual Iron Content Imaging Accurately Quantify Liver Iron Content?. Radiology, 277(1), 95-103. https://doi.org/10.1148/radiol.2015141856 PMid:25880263
25. Ghugre, N. R., & Wood, J. C. (2011). Relaxivity-iron calibration in hepatic iron overload: probing underlying biophysical mechanisms using a Monte Carlo model. Magnetic resonance in medicine, 65(3), 837-847. https://doi.org/10.1002/mrm.22657 PMid:21337413 PMCid:PMC3065944
26. Hoffbrand, A. V., Taher, A., & Cappellini, M. D. (2012). How I treat transfusional iron overload. Blood, 120(18), 3657-3669. https://doi.org/10.1182/blood-2012-05-370098 PMid:22919029
27. Belmont, A., & Kwiatkowski, J. L. (2017). Deferiprone for the treatment of transfusional iron overload in thalassemia. Expert review of hematology, 10(6), 493-503. https://doi.org/10.1080/17474086.2017.1318052 PMid:28448199
28. Doyle, E., Ghugre, N., Coates, T. D., & Wood, J. C. (2020). Fixing the MRI R2-iron calibration in liver. American journal of hematology, 95(5), E120-E122. https://doi.org/10.1002/ajh.25754 PMid:32048331
29. d'Assignies, G., Paisant, A., Bardou-Jacquet, E., Boulic, A., Bannier, E., Lainé, F., Ropert, M., Morcet, J., Saint-Jalmes, H., & Gandon, Y. (2018). Non-invasive measurement of liver iron concentration using 3-Tesla magnetic resonance imaging: validation against biopsy. European radiology, 28(5), 2022-2030. https://doi.org/10.1007/s00330-017-5106-3 PMid:29178028
30. Toepker, M., Moritz, T., Krauss, B., Weber, M., Euller, G., Mang, T., Wolf, F., Herold, C. J., & Ringl, H. (2012). Virtual non-contrast in second-generation, dual-energy computed tomography: reliability of attenuation values. European journal of radiology, 81(3), e398-e405. https://doi.org/10.1016/j.ejrad.2011.12.011 PMid:22236702
31. Wood, J. C., Zhang, P., Rienhoff, H., Abi-Saab, W., & Neufeld, E. J. (2015). Liver MRI is more precise than liver biopsy for assessing total body iron balance: a comparison of MRI relaxometry with simulated liver biopsy results. Magnetic resonance imaging, 33(6), 761-767. https://doi.org/10.1016/j.mri.2015.02.016 PMid:25708262