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Application of magnetic resonance quantitative technique to calculate liver iron concentration in the diagnosis and efficacy evaluation of transfusion-related iron overload

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► ***Original article***

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ABSTRACT

Background: To explore the diagnosis and evaluation efficacy of liver iron concentration (LIC) based on magnetic resonance quantitative technique in liver iron overload in patients with long-term transfusion. ***Materials and Methods:*** From November 2021 to January 2023, 30 chronic aplastic anemia (CAA) patients with long-term blood transfusion admitted to our hospital were included as the study group. Simultaneously, 20 healthy volunteers with matched gender and age were included in the control group. The serum ferritin (SF), serum iron, total iron binding capacity and transferrin saturation (TSAT) between the two groups was calculated and compared. LIC was evaluated using Liver Magnetic resonance imaging (MRI)-R2* map imaging. The correlation between LIC and SF and TSAT was analyzed, and the diagnosis value of LIC in hepatic iron overload was calculated. Low-risk patients (n=22) diagnosed with iron overload received continuous regular iron removal treatment and the SF, TSAT and LIC were measured after 6 months. ***Results:*** SF, TSAT and LIC were higher in CAA patients relative to the healthy controls (P<0.05). LIC was positively correlated with SF (r=0.74, P<0.001) and TSAT (r=0.67, P<0.001). The sensitivity and specificity of LIC in the diagnosis of hepatic iron overload were 80.00% and 100% based on SF, and 76.0% and 100% based on TSAT, respectively. Additionally, SF, TSAT and LIC were all declined after 6 months of treatment (P<0.05). ***Conclusion:*** The detection of LIC based on MRI-R2* is an effective and non-invasive means for the assessment of liver iron load in patients with long-term transfusion.

INTRODUCTION

Chronic aplastic anemia (CAA) is a refractory leukemia with bone marrow hematopoietic failure induced by multiple causes, and is characterized by hematopoietic stem cell injury and peripheral blood pantocytopenia [1]. The common clinical symptoms of CAA are anemia, bleeding, and infection, with high dependence on long-term blood transfusion [2]. Moreover, the complex pathophysiological mechanism and difficulty in treatment lead to unsatisfactory clinical outcomes in CAA patients [3]. The incidence of CAA in China has been increasing in recent years, resulting in a corresponding increase in clinical blood consumption [4]. Since the life span of imported red blood cells is shorter than that of normal human red blood cells, under the action of mononuclear macrophage system, red blood cells rupture and release a large amount of iron [5]. When the homeostasis regulation level of iron of the body is insufficient to remove excess iron, transfusion-related iron overload will occur [6]. The increase of iron overload in patients can directly lead to the dysfunction of important organs such as heart, liver, and pancreas, increase the risk of infection, and inhibit hematopoietic function of bone marrow and ultimately reduce the quality of life as well as shorten the survival time of CAA patients [7].

Currently, liver biopsy is the gold standard for the detection as well as quantification of liver iron content, but acceptance of patients is low due to its invasiveness and inability to assess the heterogeneity of liver iron overload [8]. At present, serum ferritin (SF) and transferrin saturation (TSAT) are commonly used in clinical evaluation of iron overload [9]. Although this method to measure SF and TAST is simple and feasible, it also has some limitations. Magnetic resonance imaging (MRI) is characterized by safety, noninvasiveness, simple operation and high accuracy [10]. It also can be used to detect and evaluate the distribution and grading of liver iron concentration (LIC) [11].

This study aimed to investigate the value of MRI to calculate LIC in the diagnosis and efficacy evaluation of transfusion-related iron overload, which may provide evidence for the clinical judgment of iron overload in patients with long-term transfusion.

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MATERIALS AND METHODS

General data

From November 2021 to January 2023, 30 CAA patients with long-term blood transfusion admitted to our hospital were selected as the study group. Inclusion criteria: Diagnosed of CAA [12]. Exclusion criteria: (1) Patients with severe heart, brain, liver or kidney disease, psychosis, and tumor. (2) Patients with severe uncontrolled infection, bleeding, and other symptoms. (3) Pregnant or lactating women. (4) Other diseases leading to pancytopenia.

The study group contained 18 males and 12 females, with an average age of 55.43±5.62 years (ranged from 25 to 82 years old). During the same period, 20 healthy volunteers matched in gender and age was selected as control group. All subjects signed the informed consent.

Detection of serum ferritin (SF) and transferrin saturation (TSAT) in patient serum

Fasting venous blood (3 mL) was gathered from the participants in the morning, and serum was collected by centrifugation. Serum iron (SI) together with total iron binding capacity (TIBC) was measured using Ferene method and TSAT=SI/TIBC.

The classification criteria for SF and TSAT assessment of iron overload were as follows: SF<400 μg/L was normal, 400-2500 μg/L was mild/moderate, and SF >2500 μg/L was severe. TSAT was considered normal at 20%-45% in men and at 20%-50% in women, mild/moderate at 45%-70% in men and at 50%-70%women, and considered to be severe at >70%.

Calculation of LIC

The GE signa HDxt 1.5 T MR Scanner (GE Healthcare, Milwaukee, WI, USA) with a 16-channel body coil was used to acquire $R2^*$ imaging of the liver. Subject lied on his back and entered the instrument foot first. R2* scanning adopted gradient echo sequence, deep inspiration and end breath-holding scanning, and the scanning range was 5 levels above and below the maximum cross-section of the liver. Parameter setting: repetition time (TR)=200 ms, echo times (TE)=1.1 ms, 2.0 ms, 2.9 ms, 3.8 ms, 4.7 ms, 5.6 ms, 6.5 ms, 7.4 ms, flip angle (FA)=20°, layer spacing at 1 mm, layer thickness at 10 mm, field of view (FOV) at 400 mm × 400 mm and the matrix at 192 × 192. Two physicians with experience in abdominal MRI diagnosis for more than 5 years were responsible for image processing using R2Star software of Functool package on GE AW4.4 workstation (Advantage Windows; GE Healthcare, USA). Four regions of interest were selected at each level of the liver, paying attention to avoiding the large blood vessels, bile ducts and liver margins, and the mean $R2^*$ value represented the $R2^*$ value of patients. LIC calculation formula was LIC=0.025 4×1000/$R2^*$+0.202. The classification criteria for LIC assessment of iron overload were as follows: LIC less than 3.2 mg/(g·dw) was normal, LIC at 3.2-15 mg/(g·dw) was mild or moderate, and LIC over 15 mg/(g·dw) was severe.

Statistical analysis

SPSS 17.0 software (IBM Corporation, Chicago, IL, USA) was adopted for data analysis. Measurement data were expressed as the mean ± standard deviation, and data comparison was subject to t-test. Spearman analysis was implemented for correlation analysis. P<0.05 was statistically significant. The diagnostic efficacy of LIC for liver iron overload was calculated, with sensitivity = true positive value/(true positive value + false negative value), specificity = true negative value /(true negative value + false positive value).

RESULTS

Comparison of serum levels of SF and TSAT in both groups

Higher serum levels of SF and TSAT were determined in the study group relative to the control (P<0.05, figure 1).

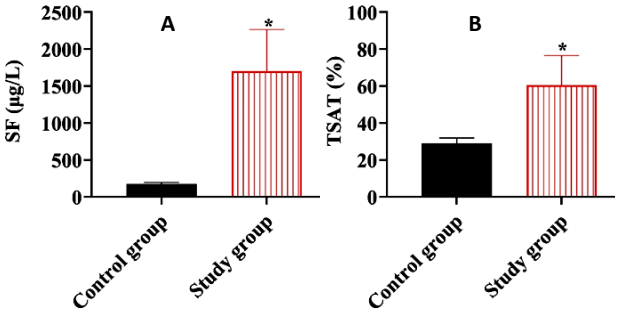


Figure 1. SF and TSAT levels in the serum of patients in the control and study groups. **(A)** Level of SF in patients in the two groups. **(B)** TSAT levels in the serum of patients in the two groups. SF, serum ferritin; TSAT, transferrin saturation. *P<0.05.

Comparison of LIC in both groups

MRI-$R2^*$ sequence scanning indicated that the liver signal of 22 CAA patients was decreased with the extension of TE, with $R2^*$ value decreased, and $R2^*$ value increased relative to the control, suggesting the presence of iron overload in patient liver. The liver signal of the other 8 patients in the study group and the control group decreased slightly with the extension of TE, indicating no iron deposition in the liver. The MRI R2* images of a healthy volunteer in the control and a CAA patient in the study group were shown in figure 2. The LIC value was revealed to be higher in the study group in comparison with the control group (P<0.05, figure 3).

Correlation between LIC and SF and TSAT

As displayed in figure 4, LIC was positively

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correlated with both SF (r=0.74, P<0.001) and TSAT (r=0.67, P<0.001).

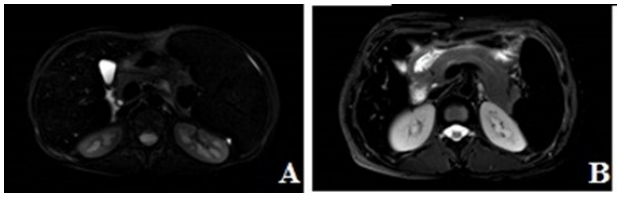


Figure 2. MRI R2* images of one healthy volunteer in the control group (**A,** LIC: 1.248-1.748) and a CAA patient in the study group (**B,** 8.2381-10.40).

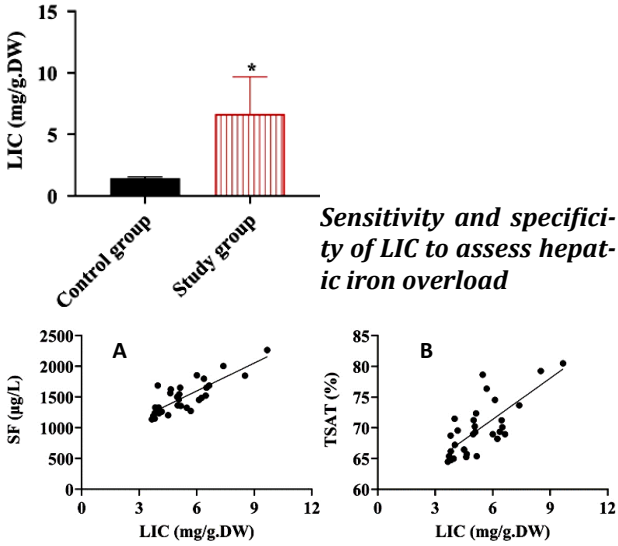


Figure 4. Correlation between the levels of LIC with SF or TSAT in patient serum. **(A)** The correlation between LIC and SF levels in patient serum. **(B)** The correlation between LIC and TSAT levels in patient serum. LIC, liver iron concentration; SF, serum ferritin; TSAT, transferrin saturation.

The sensitivity and specificity of LIC in the diagnosis of hepatic iron overload were 80.00% and 100% based on SF (table 1) and 76.0% and 100% based on TSAT, respectively (table 2).

Table 1. Sensitivity and specificity of LIC to assess hepatic iron overload based on SF.

LIC	SF		Total
	Hepatic iron overload	Non-hepatic iron overload	
Positive	20 (true positive)	0 (false positive)	20
Negative	5 (false negative)	5 (true negative)	10
Total	25	5	30

LIC, liver iron concentration; SF, serum ferritin.

Table 2. Sensitivity and specificity of LIC to assess hepatic iron overload based on TSAT

LIC	TSAT		Total
	Hepatic iron overload	Non-hepatic iron overload	
Positive	19 (true positive)	0 (false positive)	19
Negative	6 (false negative)	5 (true negative)	11
Total	25	5	30

LIC, liver iron concentration; TSAT, transferrin saturation.

Comparison before and after iron removal treatment

Twenty-two low-risk patients diagnosed with iron overload received continuous regular iron removal treatment of desferramine mesylate with 20~60 $mg \cdot kg^{-1} \cdot d^{-1}$, subcutaneous pumping for 12 h, 14 d as a course of treatment, with 1 week interval for each course, and reviewed after 6 months. The changes of SF, TSAT and LIC before and after treatment were compared. As displayed in Figure 5, SF, TSAT and LIC were all declined after 6 months of treatment (P<0.05).

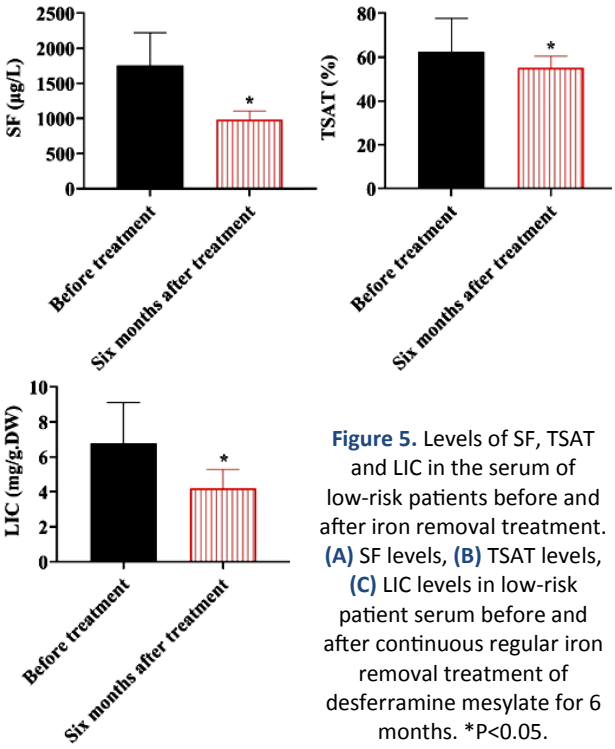


Figure 5. Levels of SF, TSAT and LIC in the serum of low-risk patients before and after iron removal treatment. **(A)** SF levels, **(B)** TSAT levels, **(C)** LIC levels in low-risk patient serum before and after continuous regular iron removal treatment of desferramine mesylate for 6 months. *P<0.05.

DISCUSSION

Iron overload is the most common complication of CAA, which has attracted increasing attention in recent years [13]. Studies have demonstrated that iron overload not only reduces the physiological function of organs, but also changes the structure of organs [14]. In addition, excessive iron can also reduce the immune function of natural killer cells and macrophages, causing extensive damage to related tissues and organs [15]. Therefore, it is particularly important to correctly evaluate iron deposition in CAA patients to guide the treatment of iron removal.

Currently, the commonly used indexes to evaluate iron overload in clinic are SF and TSAT [16]. Long-term transfusion with a large amount of hemoglobin input can lead to a significant increase of SF and TSAT [17, 18]. SF is easy to detect with low cost. It is often associated with systemic iron storage and can be used to indirectly measure the iron overload in the liver [19]. However, SF is susceptible to various factors, such as malignant tumor, liver disease, ascorbic acid deficiency, and inflammatory reaction, and studies have shown that the rate of increased SF after transfusion also depends on the transfusion rate

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and disease characteristics [20, 21]. TSAT is a serological marker widely used to evaluate iron balance in vivo, and its elevation is associated with methemoglobinemia [22]. However, TSAT is not a quantitative indicator of iron storage in the body or an accurate indicator of iron content in tissues [23]. Liver biopsy is a quantitative, direct assessment of iron content in the liver. It is highly specific and sensitive, but complications occur in about 0.5% of patients undergoing liver biopsy [24]. Additionally, high sampling variability due to different biopsy specimen size or uneven distribution of iron in the liver may lead to differences in biopsy results [25]. Therefore, a real-time, simple and noninvasive method is urgently needed to evaluate iron content in the liver.

With the rapid development of MRI technology, its role in liver iron overload evaluation is increasingly valued [26]. MRI is extensively used to detect the distribution and grading of iron content in the liver and monitor the effect of iron removal therapy [27]. The principle of T_2/R_2 technique for detecting iron content in liver is that iron deposited in liver has paramagnetic effect, which can cause uneven local magnetic field, thus reducing T_2 value of liver parenchyma and increasing R_2 value [28]. Compared with T_2, T_2^* map sequence based on MR Multi-echo technique can better reflect the signal inhomogeneity in tissues, with advantages such as shorter scanning time and smaller artifacts [29]. Wood *et al*. have converted the R2* value into LIC value and found that it the same as the liver iron content unit obtained by puncture, which could be directly compared [30]. Some scholars advocate the quantification of liver iron content using MRI-LIC and suggest it as the standard for LIC evaluation in most patients [31].

In our study, we used serum SF and TSAT as diagnostic criteria to evaluate the value of LIC test based on MRI-R2* for the evaluation of liver iron overload in long-term transfusion patients. The results revealed that the R2* based LIC was higher in the CAA patients, indicating the presence of liver iron overload, which was consistent the results of SF and TSAT. Furthermore, the positive correlation between LIC and serum SF or TSAT was demonstrated. Besides, the sensitivity and specificity of LIC in the diagnosis of hepatic iron overload were 80.00% and 100% based on SF and 76.0% and 100% based on TSAT, respectively. In addition, the comparison of the results before and after regular deironing treatment in CAA patients with iron overload showed that iron removal treatment effectively reduced the SF and LIC levels in CAA patients.

CONCLUSION

The detection of LIC based on MRI-R2*, with high sensitivity and specificity, is an effective and non-invasive method to asses liver iron load in patients with long-term transfusion. The accurate assessment and monitoring of hepatic iron overload has a significant impact on the prognosis and life quality of long-term transfusion patients. As an ideal way to evaluate the liver iron content, the R2* based LIC test has a good consistency with the clinical iron overload index, which can be used to guide individualized iron removal therapy.

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***Conflicts of interests*:** The authors declare no conflicts of interest in this study.

***Ethical consideration*:** This study was approved by the Ethics Committee of The First People's Hospital of Lanzhou City (approval number: LZLL(01)2020).

***Author contribution*:** Y.N. and X.Z. conceived and designed the study. Y. X. and S. Z. collected and analyzed clinical data. Y. N. wrote the draft manuscript. All authors reviewed and approved the final version of manuscript.

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