MRI as an alternative to serum ferritin for diagnosis of iron overload in children in the context of immune response after stem cell transplantation

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ABSTRACT

Multiple blood cell transfusions may cause iron overload or even liver fibrosis, requiring early diagnosis and intervention. SF is the standard for estimating iron levels in the body, but it also increases with inflammation. We hypothesized that T2* magnetic resonance (MR) relaxometry is a more accurate alternative for follow-up in pediatric patients before and after allogenic SCT. Twenty-three children (mean age 10.2 years, 10 female, 13 male) were evaluated prospectively before SCT as well as at least 1 year after SCT with T2* relaxometry on a 1.5 T MR-scanner to estimate liver iron concentrations from the T2* values ("MR-Fe"). The results were compared with SF, while also considering CRP, and correlated with the number of transfusions. Overall, 24.3 transfusions were administered in average, mainly within 100 days of SCT (mean 10.5 units). Both MR-Fe and SF increased after SCT and decreased in the absence of new transfusions 1 year later without chelate therapy. This suggests regeneration of LP and iron loss, although the original states were not reached. Additionally, simultaneous peaks of CRP and SF were observed directly after SCT. MR-Fe did neither reveal these peaks nor was it associated with CRP (P = .39). We postulate that these early CRP and SF peaks after SCT are probably related to inflammatory reactions and not to iron overload. Thus, SF is not reliable for iron overload diagnosis after SCT in every condition. Beside this interaction, SF and MR-Fe revealed similar accuracy. MRI, however, has practical and economical disadvantages in routine estimation of iron.

KEYWORDS

iron overload, liver, MRI, SCT, T2* relaxometry
1 | INTRODUCTION

Children undergoing SCT often require many blood cell transfusions during bone marrow aplasia. This results in iron overload. The iv administration bypasses physiological regulation and leads to an accumulation of ferrous ions in tissues, when physiological transport and storage capacities are exhausted.1 Heart, liver, and neuronal and endocrine organs may be affected with a preference for LP and heart muscle,2–6 suggesting screening of these tissues. In terminal stages, non-reversible liver fibrosis and loss of liver function can be observed.7 Liver biopsy has so far been the only reliable way to assess cellular liver iron concentration (ILC). This invasive method, however, is not always feasible and recommended, especially in young patients after SCT. Nevertheless, assessment is required to diagnose early iron overload and initiate possible interventions, such as chelate therapy. Accurate iron level determination is possible by applying superconducting quantum interference device biospectrometry, but is only available at few locations for research purposes.7 Estimation of accumulated iron is possible with T2* MR relaxometry as the T2*-relaxation time constants show an inverse relationship to LIC.8,9 There is a very good correlation between LIC, calculated from biopsies, and T2*.10,11

Alternatively, estimation of whole-body iron content is more easily performed with SF measurements if the patients are in good medical condition.2,5,12 However, SF is far from being an ideal surrogate parameter of IL as it also increases in various immune responses, such as acute-phase reaction or macrophage activation.2,13 Macrophages themselves can synthesize SF. Inflammation may be observed in the context of SCT due to recruitment of macrophages, especially during GvHD. Many other factors, like malnutrition and malignancy, or different liver and kidney diseases are known to affect SF levels as well.6,9,11,14–17: It would therefore not be very reliable to consider the upper normal range of SF as the limit for iron overload. Thus, an established, higher threshold for clinically significant iron overload has been defined when the SF level exceeds 1000 µg/L in two subsequent determinations. This criterion is used to indicate chelate therapy in patients receiving chronic transfusions, such as in cases of thalassemia.2,5,12

Whereas the specificity of rising SF levels in SCT might be inadequate due to compromised immunity, this limitation has not been described for T2* MR relaxometry. Therefore, we aimed to evaluate its applicability to indicate clinically significant iron overload during follow-up after SCT and compared the results with SF levels in association with CRP levels, which served as surrogate marker of inflammation.

2 | MATERIAL AND METHODS

We identified 58 patients, receiving SCT due to hematological/oncological indications at our institution between 2014 and 2018. The patients were included in this prospective study if they underwent allogenic SCT, if they were younger than 18 years at initial diagnosis, and if they received at least three MR relaxometry examinations. There were 23 patients, meeting the inclusion criteria, who were included in the analyses. Depending on clinical indications, all patients received a different number of red blood cell transfusions prior to and after SCT. There was no patient receiving chelate therapy.

A myeloablative conditioning protocol was performed on every patient prior to the transplantation. They were scheduled for T2* MR relaxometry before SCT and at least at day 100 and day 365 afterward. SF and CRP levels were determined on scheduled visits that occurred more often than the MRI examinations, and these additional values were included to enable a more detailed longitudinal follow-up evaluation, especially early after SCT. CRP values were recorded immediately to identify inflammation (normal value: CRP <7.5 mg/L).

Informed consent was obtained from all patients and parents/legal guardians prior to the evaluation. This study was in accordance with the ethical standards of the institution and within the principle of the Declaration of Helsinki. The local ethical approval was granted (4130-07/14).

2.1 | MR relaxometry

MRI was performed on a 1.5 T clinical whole-body MRI scanner (Magnetom Avanto, Siemens Healthineers). For relaxometry, a T2*-weighted gradient-recalled echo sequence was applied during breath hold (time of repetition—TR 12 ms, echo times—TE 0.81–10.31 ms, flip angle 20°, slice thickness 15 mm, field of view [321 x 380] mm²). T2*-relaxation time constants were extracted from the data within a ROI following appropriate signal processing. These T2* values (ms) were subsequently used to estimate the corresponding LIC based on the approach described by Wood et al (Equation 1)10,11 (“MR-Fe,” expressed in mg of Fe²⁺ per g of dry liver tissue [mg Fe²⁺/g]).

\[
 MR-Fe \left[ \frac{mg Fe^{2+}}{g} \right] = 0.0254 \times \frac{1}{T2^*} + 0.202. \tag{1}
\]

2.2 | SF

Blood samples were analyzed by using a two-step immunoassay (“ARCHITECT,” Abbott Laboratories). Usually, samples were taken twice a week after SCT, although this frequency also depended on the general health condition and related complications during the subsequent follow-up, making hospitalization necessary.

We selected a threshold of SF >1000 µg/L as an indicator for relevant iron overload, which is above the normal range,2 but was intended to increase the specificity in the context of inflammation.

2.3 | IL

The so-called “IL” estimates the maximum iron incorporation, which can result theoretically from blood transfusions. It is calculated from the number of packed red blood cell units, \( N_{pRBC} \), each carrying
TABLE 1  Characteristics of patient cohort at the time of SCT and overview of different diseases

| Patient's characteristics at SCT | Mean value (Min.-Max. value) |
|----------------------------------|------------------------------|
| Age (y)                          | 10.7 (0.5-19.9)              |
| Weight (kg)                      | 32.1 (6.3-66.0)              |
| Height (cm)                      | 135 (63-188)                 |
| BMI in (kg/m²)                   | 17.5 (14.3-22.8)             |

Diagnosis

| Complications after transplantation | Number of patients |
|-------------------------------------|--------------------|
| ALL                                 | 9/23               |
| AML                                 | 6/23               |
| MDS                                 | 3/23               |
| Others a                            | 5/23               |

Complications after transplantation

- Relapse during follow-up: 5/23
- VOD: 2/23
- GvHD: 7/23

aOthers: EWS, HLH, neuroblastoma, JMML, Purtilo syndrome.

Over 200 mg of ferrous ions, and the BW at the time of the measurement (see Equation 2). Small patients weighing <25 kg did not receive an entire unit of red blood cells at once, but between 10 and 20 mL per kg BW. The exact individual amount was taken into account for IL calculation.

\[ IL \left[ \frac{mg Fe^{2+}}{kg} \right] = \frac{N_{SRBC} \times 200 mg Fe^{2+}}{BW[kg]} \]  

(2)

2.4 Statistical analysis

Statistical analyses were performed, and graphical artwork was created in IBM SPSS 25 and Microsoft Excel, respectively. MRI-based findings and SF levels were evaluated at the three different time points (before, 100 days, and 1 year after SCT). These descriptive analyses were complemented with Wilcoxon signed-rank tests to identify significant differences between grouped data ranks. The influence of CRP (>7.5 mg/L vs <7.5 mg/L) on MR-Fe or SF, adjusted for the time of measurement, was analyzed using GEEs to account for correlated data. A gamma distribution and a log link function were assumed. The back-transformed effect estimate is presented as the ratio of means with 95% CI and Wald test-based P-value. This analysis was performed with SAS version 9.4. ROC analysis was used to compare the accuracy of SF and MR-Fe in diagnosing relevant iron overload (we applied a threshold of SF >1000 µg/L, with reference to Ong et al[2]). Spearman’s ρ was used as a measure of their correlation.

The continuous follow-up of blood sample parameters (SF, CRP) and the number of transfusions were analyzed graphically in longitudinal plots for each patient. One typical example case is discussed below.

3 RESULTS

MRI was successfully performed in all 23 patients at the three time points. Patient data are summarized in Table 1. The majority suffered from leukemia, while only a few had other oncological diseases, including EWS or neuroblastoma. The most relevant complications were mainly GvHD or relapses occurring during follow-up (see Table 1). Table 2 contains the mean values of the recorded data. T2* values ranged between 1.53 and 35.4 ms, and were used to estimate MR-Fe (see above) for subsequent analyses.

We compared IL, MR-Fe, SF, and the ratio between SF and MR-Fe at the three different time points by using box plots (see Figure 1A-D and Table 2). As indicated by the mean values in Table 2, the highest transfusion requirement occurred between SCT (day 0) and day 100 to compensate for the loss of bone marrow function immediately after transplantation; the corresponding IL was strongly increased at day 100 compared with day 0, reflecting cumulative iron intake. Since only few transfusions were administered thereafter, IL remained rather constant (see Table 2 and Figure 1A). Both MR-Fe and SF values decreased at day 365 compared with day 100 (Table 2), suggesting iron elimination with lower LIC after 1 year post-SCT compared with day 100. Repetitive blood sampling, growth, and gastrointestinal loss may be an explanation for this slight trend toward normalization. Menstrual bleeding may also lower iron levels. However, in contrast we found that MR-Fe was even higher for these girls (age >12 years) than for male patients of the same age group in our study population (N = 5 male and N = 4 female patients; mean values of MR-Fe [female]: 9.48 mg Fe²⁺/g and MR-Fe [male]: 6.64 mg Fe²⁺/g). SF values were lower for the female patients (1835 µg/L vs 1967 µg/L). These

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### TABLE 2  Overview of collected data at the three defined time points of measurement

| Parameters                        | Before SCT         | Day 100 after SCT | Day 365 after SCT |
|-----------------------------------|--------------------|------------------|------------------|
| Average of total number of transfused packed red cells (Min.-Max. value) | 11.35 (0-35)       | 21.87 (2-49)     | 24.26 (4-55)     |
| Mean IL (Min.-Max. value) in (mg/kg) | 77.5 (0.0-318.2)  | 156.8 (22.0-490.0) | 161.4 (29.6-430.0) |
| Mean MR-Fe (Min.-Max. value) in (mg Fe²⁺/g) | 4.46 (0.12-12.66) | 6.39 (0.89-16.84) | 5.60 (0.20-13.82) |
| Mean SF (Min.-Max. value) in (µg/L) | 2521 (14-12 268)  | 3986 (335-16 060) | 1622 (46-7780)   |
| Mean CRP (Min.-Max. value) in (mg/L) | 19.4 (2.0-227.0)  | 4.2 (2.0-27.6)   | 6.3 (2.0-55.3)   |

Note: N = 23 patients.
FIGURE 1  (A-D) Non-parametric boxplots of different parameters at the three defined time points before and after SCT. (A) Iron load (IL) in (mg Fe^{2+}/kg); (B) MR-Fe values in (mg Fe^{2+}/g); (C) SF values in (µg/L); (D) SF/MR-Fe ratios in (µg/L)/(mg Fe^{2+}/g); N = 23. Boxplots include the 1st and 3rd quartile as borders of the boxes as well as the median value (thick bar in boxes); the whiskers comprise 1.5 times the interquartile range. Outliers are indicated by circles. IL was increased at day 100 compared with day 0 and stayed stable as only few transfusions were administered between day 100 and day 365 (A); SF values are decreased on day 365 (C)
observations may be confounded by the different IL. The female group received 30.75 transfusions on average and the male control group only 24.6. Only two patients did not receive any transfusions prior to the transplantation. Due to the small number, no statistical conclusions were drawn in this group as regards effects of iron preload on the later response, that is, effects of transfusions on SF or MR-Fe after SCT.

ROC analysis including all patients revealed high accuracy between MR-Fe and SF (see Figure 2), as the AUC was nearly 1, when applying a limit of SF >1000 µg/L for iron overload diagnosis.

We did not find a significant influence \( (P = .39) \) of increased CRP (>7.5 mg/L) on MR-Fe, adjusted for the significant differences between the points of measurement \( (P = .02) \) in GEE. The highest mean values of SF and MR-Fe were observed on day 100 after SCT and the lowest before SCT. The mean value of the SF/MR-Fe ratio was significantly \( (P = .001) \) higher at day 0 compared with 100 days and 1 year later (see Table 1). The observed reduced SF/MR-Fe ratio correlated significantly with lower mean CRP values 100 days after SCT compared with the initial values \( (P = .03; \text{see Table 2 for mean values).} \)

A high, non-parametric correlation was observed between SF and MR-Fe including all 23 patients \( (r = .84; P < .001) \). This correlation was decreased after SCT \( (r = .67; P < .001) \) during the period of high immune responses (up to day 100) and was increased again at day 365 \( (r = .78; P < .001) \).

All available SF and CRP values were compared longitudinally for each patient individually to evaluate immune responses to SCT in more detail than at just the three time points described above. One typical plot for an 18-year-old female patient, additionally including the further available MR-Fe values and the number of transfusions, is exemplarily shown in Figure 3. This patient was transplanted twice due to a relapse after 50 months, causing a typical response each time: Directly after SCT (10-14 days), CRP levels increased to the highest registered peaks, followed by high rises of SF. Both peaks decreased after some weeks; CRP normalized quickly, whereas SF values remained elevated. The immune responses (increased CRP levels) were highest within the first 30 days after transplantation. The highest number of transfusions was also administered during the aplasia period immediately after SCT and rising MR-Fe values followed, indicating high iron uptake.

Both MR-Fe and SF values slightly decreased later (notably after first SCT) as there was no need of numerous transfusions. Unfortunately, there were no additional MRI examinations after the second SCT, preventing an interpretation of the MR values' trend beyond that time point.

4 DISCUSSION

Iron storage in LP appears to be partly reversible, as LIC by MR-Fe and SF mean values decreased 1 year after SCT (Table 2). Both values were lower 1 year after SCT than at day 100, although chelate therapy was not administered in all patients. The individual follow-up plots (Figure 3) are showing no association of CRP peaks and rising MR-Fe. Further, the GEE analysis proves that there is no significant association of MR-Fe with elevated CRP for every time point. So, inflammation is not explaining these observations. The probable causes are iron loss or regeneration of LP and the well-described downregulation of iron transporting proteins.\(^5,18,19\) Restitution of LP stands for LP (Equation 3).

\[
\text{eLIC} = \frac{\text{IL}}{10.6} \text{in [mg Fe}^{2+}/\text{g of dry LP].} \tag{3}
\]

According to different studies, eLIC \( >7 \text{ mg Fe}^{2+}/\text{g} \) is considered as highly elevated.\(^5,18,23\) Thus, 17 of 23 patients in our study revealed iron overload at least at one measurement during follow-up and the IL mean was consequently above this threshold at all 3 time points (see Table 3, center row). Estimated iron levels from MR relaxometry
"MR-Fe," Table 3, bottom row) by Wood11 were much smaller than the estimated eLIC calculated from the number of administered transfusions by following Angelucci et al.23 A direct correlation between the administered amount of iron and eLIC was not possible, as the incorporation and the distribution were not identical between the different patients and not even between their organs as well.3,4 The BW further influences the reliability of IL, as it might either increase (growth) or decrease (resulting from disease or treatment) during the surveillance period. Our observation nevertheless shows that there are substantial amounts of iron incorporated even within 1 year after SCT. Interventions like chelate therapy may be initiated to protect the patients from late complications (ie, cardiac dysfunction or endocrinopathies, which may lead to growth disturbances or incomplete puberty).5,24,25 Although it is not a standard for pediatric patients after SCT lately, but as most of our patients (17/23) revealed iron overload according to Angelucci et al23 (eLIC >7 mg/g Fe²⁺), it is worth considering the indication for chelate therapy individually. However, an initiation must be carefully considered, taking into account the long-term administration and the chelate's side effects,24,25 and simple SF determination does not seem to be accurate enough.

Our study clearly shows that immune responses are influencing SF values whereas MR-Fe values are not affected to that extent. The individual follow-up evaluation plots of CRP and SF revealed simultaneous peaks of both markers during the period of SCT. Increases in SF attributed to iron intake would not be expected to normalize so quickly because iron overload is understood as an irreversible process.18,23 Transient immune responses, leading to macrophage activation, are more likely to cause these spikes.2,13,26 GvHD was observed in seven patients with three of

**FIGURE 3** Exemplary follow-up evaluation for one patient who was transplanted twice (at 0 and 50 mo): Two peaks of CRP (light broken line) and ferritin (bold dark line) can be observed directly after both transplantations in the lower chart; the peaks are not corresponding to the number of transfusions (dark gray rhomboids and pointed line in the upper chart). MR relaxometry ("MR-Fe," estimated by Wood et al11; light bold line in the upper chart) increased related to many transfusions after the transplantations, but decreased in the interim.

**TABLE 3** Mean values of the IL, estimated liver iron concentration (eLIC) from total number of transfusion (2nd line, by Angelucci et al—see Equation 3), and MR-Fe (bottom row, T₂* conversion by Wood et al, Equation 1)

| Day after SCT | 0  | 100 | 365 |
|--------------|----|-----|-----|
| IL           | 77.5 mg Fe⁺⁺⁺/kg (BW) | 156.8 mg Fe⁺⁺⁺/kg (BW) | 161.4 mg Fe⁺⁺⁺/kg (BW) |
| eLIC by Angelucci et al | 7.48 mg Fe⁺⁺⁺/g | 14.79 mg Fe⁺⁺⁺/g | 15.23 mg Fe⁺⁺⁺/g |
| MR-Fe by Wood et al | 4.46 mg Fe⁺⁺⁺/g | 6.39 mg Fe⁺⁺⁺/g | 5.60 mg Fe⁺⁺⁺/g |
them showing very high SF levels (7000 µg/L up to 14 000 µg/L) and a severe course of GvHD SF was lower in the remaining four patients, revealing lighter courses of GvHD (about the dimension of values from other patients without GvHD). SF levels were measured nearly continuously to be >1000 µg/L when associated with increased CRP SF measurements during these short periods therefore seem not to be very reliable for assessing LIC, which is in agreement with other publications.2,4,12,26–28

MR-Fe values, on the other hand, did not show these peaks associated with CRP, and there was no significant influence of CRP on the three fixed time points. Further, the SF/MR-Fe ratio was decreased during follow-up toward day 365 (see Figure 1D) as were the mean CRP values. As MR-Fe is supposed to reflect LIC correctly,10,11 we attribute these observations to inflammatory reactions. The CRP-related SF peaks in the longitudinal plots support this inference. Lower CRP hence implies more correct estimation of iron levels by SF. Its threshold for iron overload should therefore not be fixed on normal values for this patient population as they are probably less specific and frequently exceeded during inflammation. Defining a specific limit is difficult due to the great data variability. However, the clinically applied limit of SF >1000 µg/L for chronically transfused patients is recommended: The ROC analysis showed high accuracy between SF and MRI of iron overload diagnosis, because the higher threshold of SF >1000 µg/L increased the specificity of SF. Taking elevated CRP values into account increases SF's significance and helps to avoid false-positive decisions during inflammation. Proving the diagnosis of iron overload by comparing MR-Fe from routine MRI with earlier measurements is also an option: The estimation of MR-Fe from T2* is an alternative, especially for patients with ongoing inflammation. When MRIs are scheduled during the course of leukemia and follow-up, T2*-weighted sequences should be included in the standard protocol. Nevertheless, SF remains the method of choice for estimating iron overload qualitatively in routine screening: It is the more economic method, as well as faster and easier to apply.

In the light of these remarks, chelate therapy may still be initiated based on SF also in children after SCT. However, we would recommend a high limit (ie, >1000 µg/L) and additional determination of CRP levels; relying on SF determination within 100 days after SCT is not advisable. Ideally, the indication should be proved by MR relaxometry.

One relevant limitation of our study is that no liver biopsies were performed to confirm LIC histologically. MRI examinations were less frequent than SF determination and not scheduled within 1 month after SCT during preventive isolation of the patients after SCT.

Patients receiving autologous SCT were not included in this study, because the related immune reactions were not expected to be comparable. The study population was homogeneous regarding the myeloablative conditioning, but varies concerning the following immune responses. We assumed that differences between the immune responses and the intensity of complications might also be reflected by different SF levels after SCT. Nevertheless, these effects were independent from MR-Fe at all.

5 | CONCLUSION

The iron intake from transfusions after SCT leads to high liver IL, suggesting chelate therapy to be reasonable even for these pediatric patients. Whereas SF is useful for iron estimation during stable disease, it shows reduced significance during periods of inflammation, as seen after SCT. MRI provides comparable results in iron overload diagnosis; moreover, it is not affected by inflammation.

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CONFLICT OF INTEREST

The authors report no conflicts of interests.

AUTHOR CONTRIBUTIONS

KK and H-JM conceived of the presented idea. K-HH developed the theory in collaboration with JRR, and IK. IK performed the MRI measurements. GW performed the analysis, drafted the manuscript, and designed the figures. KK encouraged GW to investigate the specific effects of inflammation on iron levels and supervised the findings of this work together with H-JM K-HH, JRR, and JFB further aided in writing the manuscript. All authors discussed the results and contributed to the final manuscript.

ETHICAL APPROVAL

The authors assert that all procedures contributing to this work are in accordance with the ethical standards of the institution and with the principles of the 1964 Declaration of Helsinki and its later amendments; a local ethical approval (No. 4130-07/14) was granted. No further registration was realized, as this prospective study was designed only as a local imaging study without therapeutic intervention.

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ENDNOTE

*Neonates: 80-628 µg/L; female adolescents and adults 10-291 µg/L; male adolescents and adults: 22-322 µg/L.
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