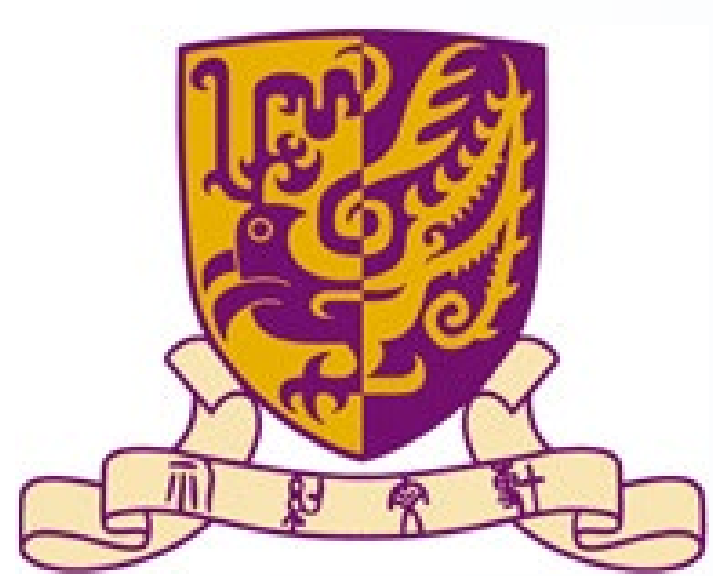




Predicting tissue iron dynamics following intravenous ferric carboxymaltose therapy using a physiologically-based pharmacokinetic model

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Introduction

- Iron deficiency anemia (IDA) is a serious global public health concern. Intravenous (IV) iron therapy, particularly ferric carboxymaltose (FCM), is a cornerstone therapy for IDA treatment. However, its application is hindered by limited understanding of long-term tissue iron distribution post-therapy and the lack of practical clinical methods to assess tissue iron.
- Because the body lacks an active mechanism for iron excretion, excessive IV iron administration can lead to iron overload, which is associated with tissue damage, increased risk of infection, and tumor progression^[1,2].
- There is growing safety concern over suboptimal IV iron dose. Enhancing understanding of iron tissue distribution, improving methods to assess tissue iron levels, and optimizing IV iron dosage have been recognized as critical priorities in anemia management^[3].

Objectives

- To investigate the tissue iron distribution, dynamic response of serum iron biomarkers and their interplay with tissue iron following FCM.
- To develop a PBPK model for predicting tissue iron levels in both rats and humans.

Methods

Biodistribution study of iron after a single dose of FCM in IDA rats

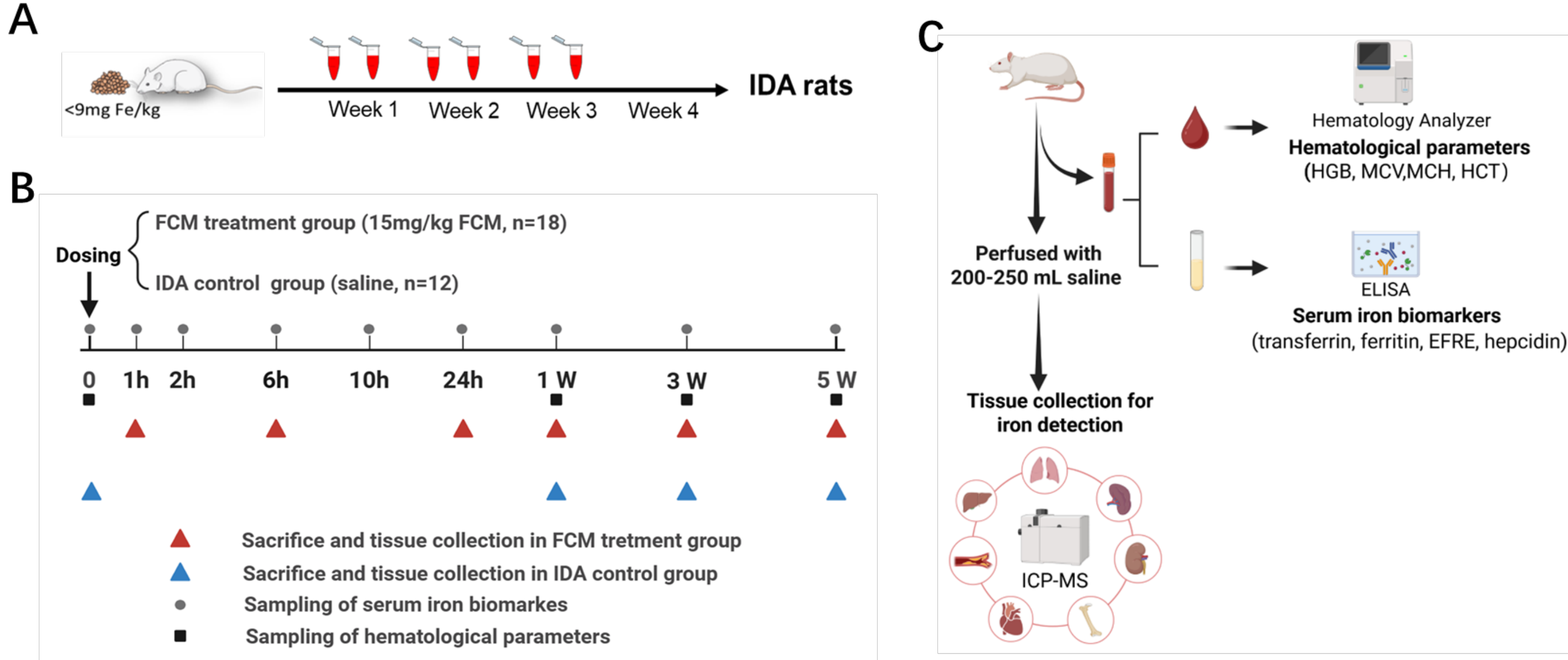


Fig 1. Study design of the biodistribution study. (A) Development of IDA model in rats; (B) Diagram of the time point design; (C) Sample collection and analysis.

Development of a PBPK model in IDA rats

Table 1. Physiological parameters used in the model in 325 g rats*.

Tissue	Plasma flow (mL/h)	Vascular volume (mL)	Extravascular volume (mL)
Plasma	3293	/	/
Heart	169	0.05	1.1
Liver	24	1.56	15.39
Spleen	200	0.39	2.51
Lung	3293	0.27	1.14
Kidney	408	0.15	2.52
BM	69	0.04	1.74
Remainder	2423	2.64	273.69

* Physiological parameters were calculated based on data from 280 g rats in literature^[4] and the actual body weight of rats used in this study.

Software: NONMEM (V7.5., Icon plc, USA)

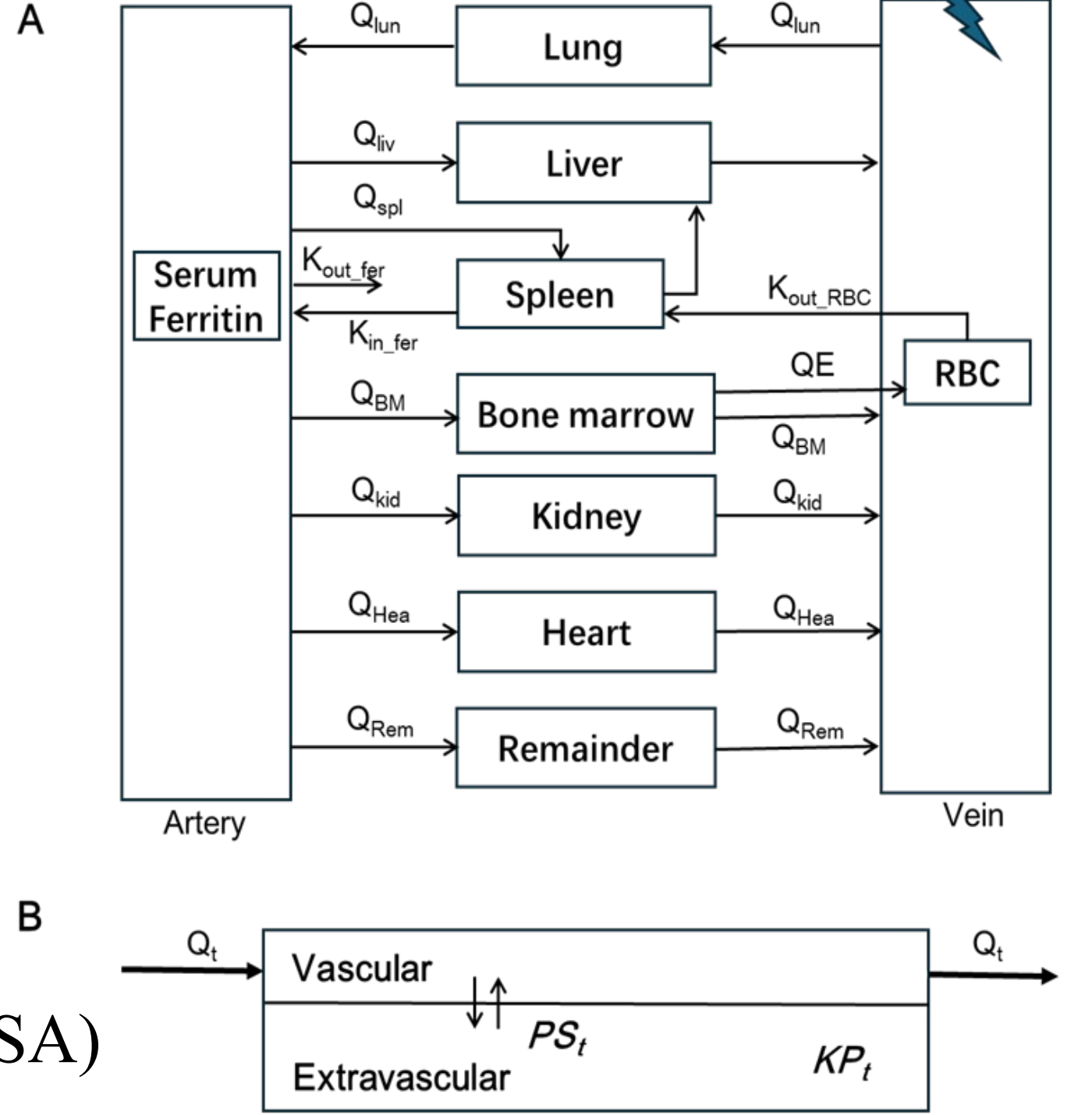


Fig 2. Diagram of the model structure

Extrapolation from rats to humans

- Physiological parameters in humans (70 kg) were obtained from literature^[4].
- K_{out_RBC} was calculated according to the lifespan of RBC (120 days) in humans.
- The Kp_t values were assumed to be identical between rats and humans, while PS_i and QE were scaled to humans using the allometric scaling equation:

$$PS_{t_Human} = PS_{t_Rat} \cdot \left(\frac{BW_{Human}}{BW_{Rat}} \right)^{0.75} \quad QE_{Human} = QE_{Rat} \cdot \left(\frac{BW_{Human}}{BW_{Rat}} \right)^{0.75}$$

Validation of model's capacity to predict tissue iron levels in humans

- Serum iron;
- Tissue iron: Magnetic resonance imaging (MRI)—Established correlation between relaxation time T2 and T2* and liver iron concentrations measured via biopsy in patients with hereditary hemochromatosis and thalassemia.

References

[1]. *Clinical kidney journal*. 2021;14(1):59-69. [2]. *Hematology Am Soc Hematol Educ Program*. 2010;2010:338-47. [3]. *KDIGO Conference*, 2021. [4]. *J Pharmacokinet Pharmacodyn*. 2012;39(1):67-86. [5]. *Arzneimittelforschung*. 2010;60(6a):362-72. [6]. *Eur Heart J*. Nov 8 2024;45(42):4497-4508.

Results

- Serum iron biomarkers including serum iron, ferritin, transferrin saturation (TSAT), hepcidin and erythroferrone do not accurately reflect long-term tissue iron levels or overall body iron storage after FCM administration.
- The proposed PBPK accurately captures tissue iron dynamics following FCM treatment in IDA rats (Fig 3).

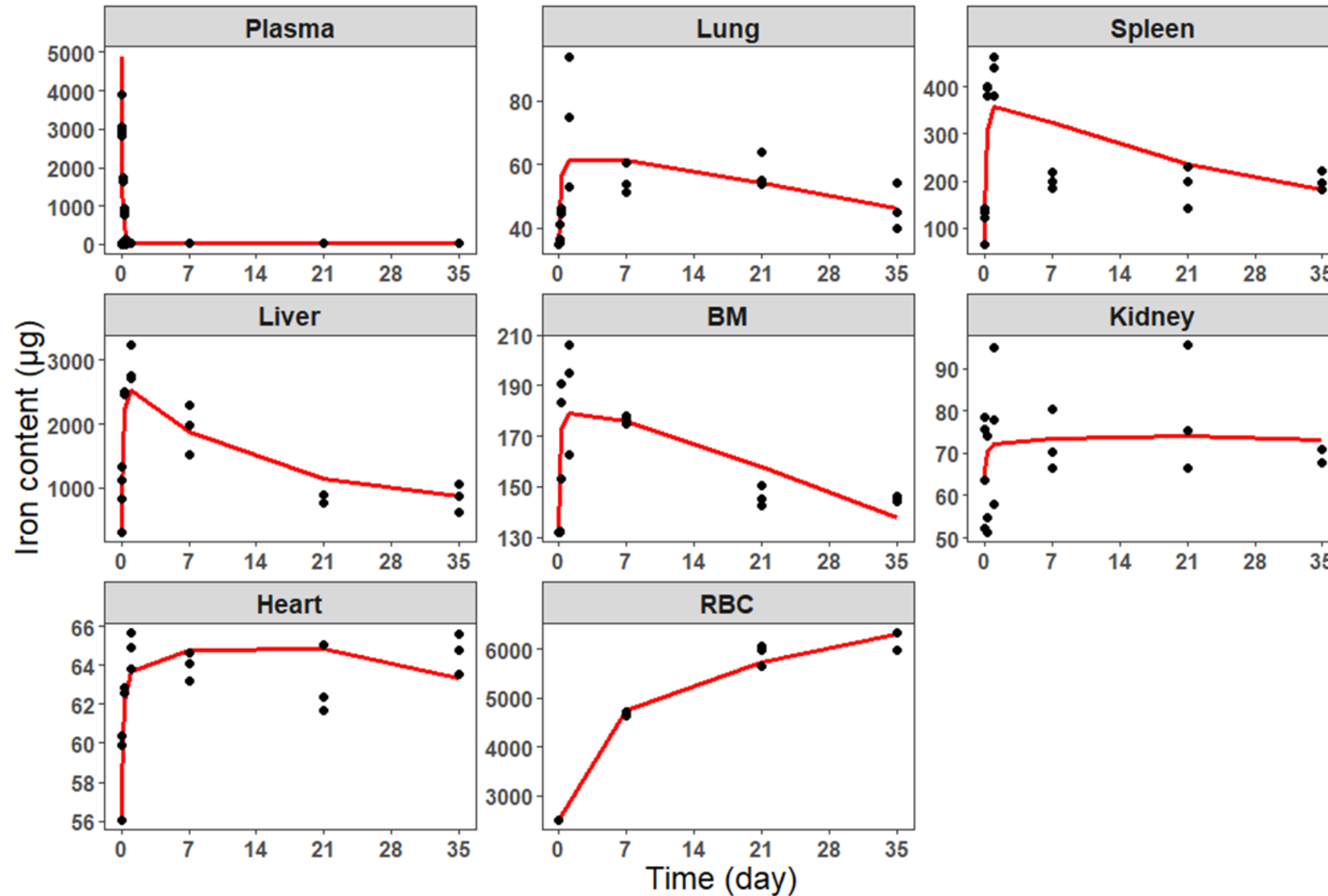


Fig 3. Comparison of the model prediction versus observed data of tissue iron levels in IDA rats. The red lines represent model prediction, while the black dots denote observed experimental values.

Table 2. Parameter estimation of the final model in IDA rats.

Parameters	Description (Units)	Estimates (RSE%)
KP_{hea}	Tissue to plasma partition coefficient in the heart	18 (2)
KP_{liv}	Tissue to plasma partition coefficient in the liver	21.7 (6.7)
KP_{spl}	Tissue to plasma partition coefficient in the spleen	25.9 (7)
KP_{lun}	Tissue to plasma partition coefficient in the lung	12.2 (3.2)
KP_{kid}	Tissue to plasma partition coefficient in the kidney	9.66 (40.6)
KP_{BM}	Tissue to plasma partition coefficient in the BM	21.6 (1.7)
KP_{rem}	Tissue to plasma partition coefficient in the rest of the body	3.07 (2.2)
PS_{hea}	Membrane permeability in the heart (mL/h)	0.00677 (4.4)
PS_{liv}	Membrane permeability in the liver (mL/h)	2.16 (1.8)
PS_{spl}	Membrane permeability in the spleen (mL/h)	0.271 (1.9)
PS_{lun}	Membrane permeability in the lung (mL/h)	0.0239 (18.6)
PS_{kid}	Membrane permeability in the kidney (mL/h)	0.00735 (80.8)
PS_{BM}	Membrane permeability in the BM (mL/h)	0.0436 (13.4)
PS_{rem}	Membrane permeability in the rest of the body (mL/h)	0.571 (17.5)
QE	the production rate of RBC in BM (mL/h)	1.37 (5)
K_{out_RBC}	the clearance rate of RBC ($\times 10^{-4}$ /h)	2.92 (21.5)
K_{in_fer}	the synthesis rate of serum ferritin (1/h)	0.174 (23.9)
K_{out_fer}	the clearance rate of serum ferritin (1/h)	0.178 (21.6)

- The model well captured the serum iron profiles in IDA patients.
- Model-predicted liver and spleen iron levels exhibited a strong correlation with corresponding MRI-derived T2* and T2 values ($P < 0.001$).

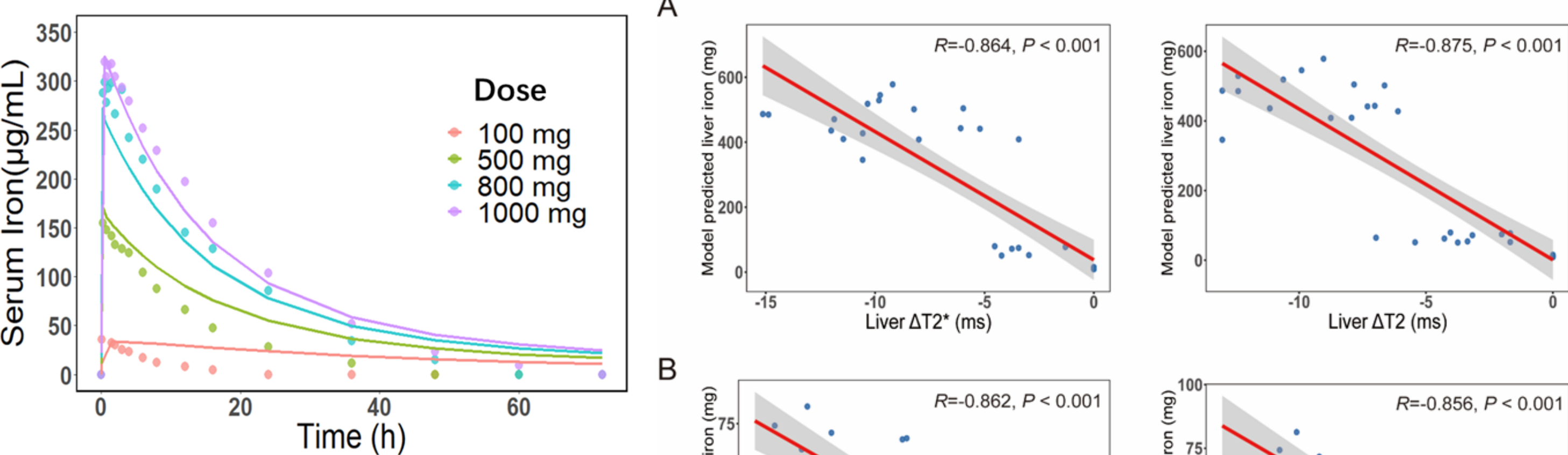


Fig 4. Serum iron after different doses of FCM in patients with IDA. The lines represent model prediction, while the dots are observed data obtained from literature^[5].

Fig 5. Pearson correlation analysis of the model-predicted tissue iron levels and MRI-derived relaxation time parameters ($\Delta T2^*$, $\Delta T2$) in the liver (A) and Spleen (B) ^[6]. The red lines represent the linear regression line and its 95% confidence interval.

Conclusions

- Using an IDA model in rats, we first assessed the tissue-specific distribution of iron and the dynamic changes in serum iron biomarkers over an extended timescale after FCM administration.
- Based on this data, we developed a PBPK model that effectively characterizes tissue iron kinetics in rats.
- This model was scaled to humans and validated with clinical data, demonstrating its capacity to predict tissue iron levels in humans.
- This study provides critical insights into the long-term tissue distribution of iron following FCM and highlights the clinical potential of the computational approach to predict tissue iron levels, optimize dosing strategies, and ultimately enhance the safety and efficacy of iron therapy.

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