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Research Article

Longitudinal Ferritin Trends as a Marker of Transfusion Burden in Beta-Thalassemia Major

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Abstract

Background: Serum ferritin has been used to track transfusional iron burden in beta-thalassemia major since cohort studies linked sustained values above roughly 2500 ng/mL to markedly worse cardiac-disease-free survival [1,2].

Objective: This review synthesizes the published evidence on longitudinal ferritin trend as a marker of transfusion burden, its correlation with directly measured liver and cardiac iron, and its role alongside MRI-based monitoring and chelation response assessment.

Methods: We synthesized peer-reviewed cohort studies, randomized chelation trials, and MRI validation studies addressing ferritin, transfusion volume, liver iron concentration, and cardiac T2* in transfusion-dependent thalassemia major.

Findings: Ferritin correlates with liver iron concentration at coefficients around 0.6-0.8 [4], transfusion regimen intensity directly alters iron loading [3], and cardiac T2* below 6 ms carries a roughly 47% one-year heart failure incidence that ferritin trend alone does not resolve with comparable precision [13]; chelation trials show dose-dependent ferritin and liver iron reductions with deferasirox and combination regimens [17,19].

Conclusions: Longitudinal ferritin trend remains a useful, low-cost surveillance tool for transfusion burden when interpreted as a trajectory rather than a single value and combined periodically with organ-specific MRI iron quantification, particularly for the myocardium, where ferritin's predictive value is weakest [16,5].

Keywords: ferritin; beta-thalassemia major; transfusion burden; iron overload; chelation therapy

1. Introduction

Every patient with transfusion-dependent beta-thalassemia major accumulates iron at a rate set almost entirely by the volume of blood transfused, because the human body has no regulated pathway for excreting the iron delivered in packed red cells. A single unit carries roughly 200-250 mg of iron, and a child maintained on a standard high-transfusion regimen from infancy can receive well over 200 mg/kg of transfusional iron by adulthood if chelation is inadequate. Serum ferritin became the default way to track that accumulation not because it is a precise measure of body iron but because it is cheap, fast, and already drawn at most transfusion visits, and because two landmark cohorts in the 1990s tied its trajectory directly to survival. Olivieri and colleagues showed that thalassemia major patients whose serial ferritin values remained persistently above roughly 2500 ng/mL had markedly worse cardiac-disease-free survival than those kept below that threshold [1], and in the companion study from the same Toronto and Montreal collaboration, patients who maintained good compliance with subcutaneous deferoxamine and correspondingly lower ferritin had a 15-year survival free of cardiac disease of roughly 91%, against a much lower figure in poorly compliant patients with sustained high ferritin [2]. Those two papers, published together, are the reason a single laboratory value earned a place at the center of thalassemia management for the following three decades.

The relationship between ferritin and transfusion burden is mechanistically direct but clinically noisy. Ferritin is an acute-phase reactant, its release from hepatocytes and macrophages depends on cell turnover and inflammatory state as much as on total iron stores, and its correlation with directly measured liver iron concentration, while real, is loose enough that a single value can mislead. This review synthesizes what the transfusion-medicine and hematology literature has established about longitudinal ferritin monitoring as a marker of transfusion burden in beta-thalassemia major: where the correlation holds, where it breaks down, how it compares with the MRI-based methods that have partially supplanted it, and how it should be interpreted alongside chelation response over time rather than as an isolated number.

2. Ferritin as a surrogate for total body iron

The pathophysiological chain running from transfusion volume to serum ferritin is well characterized. Each transfused unit delivers iron that is initially sequestered in reticuloendothelial macrophages before redistributing to hepatocytes and, more slowly, to the myocardium and endocrine organs. Cazzola and colleagues demonstrated that even modest changes in transfusion policy alter this loading directly: a moderate transfusion regimen targeting a pretransfusion hemoglobin of 9-10 g/dL produced meaningfully lower iron loading than a more liberal regimen targeting 11-12 g/dL, without provoking the compensatory marrow expansion that undertransfusion causes [3]. That finding established transfusion volume itself, not just chelation intensity, as a controllable determinant of the ferritin trajectory, a point that is easy to lose when ferritin is discussed only in the context of chelator choice.

Cross-sectional studies quantifying the ferritin-to-liver-iron relationship generally report a positive but imperfect correlation, typically in the range of a Pearson or Spearman coefficient of 0.6-0.8 across cohorts of transfusion-dependent patients, with wide scatter at both the low and high ends of the iron-burden range [4]. The relationship is closer in children and in patients without active inflammation or liver fibrosis, and it degrades in adults with longstanding iron-induced hepatic injury, where fibrotic and cirrhotic livers store iron less efficiently per unit ferritin than healthy liver tissue. Because ferritin is produced predominantly by the liver and reticuloendothelial system, a chronically transfused patient's ferritin reflects a weighted average of recent transfusion load, current chelation efficacy, and the liver's

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own capacity to sequester and release the protein, which is why guideline bodies have consistently recommended trend analysis over single-timepoint interpretation. The Italian Society of Hematology practice guidelines for iron overload in thalassemia major explicitly recommend serial ferritin determinations, typically every one to three months, precisely because a rising or falling trajectory carries more clinical information than any individual value [5].

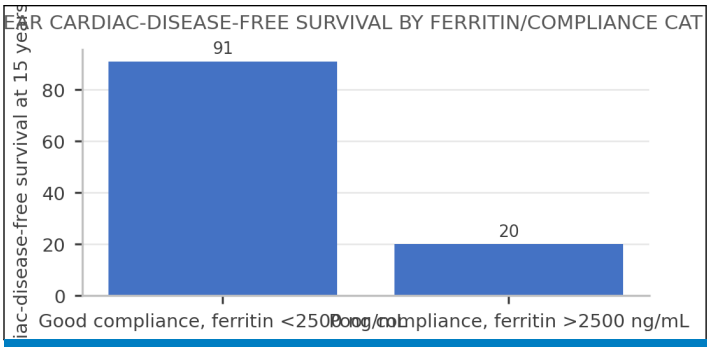

Figure 1: Fifteen-year cardiac-disease-free survival by chelation compliance and sustained serum ferritin category, approximately 91% in patients with good deferoxamine compliance and ferritin maintained below roughly 2500 ng/mL, against a substantially lower figure in poorly compliant patients with persistently elevated ferritin [2,1].

3. Correlation with transfusion volume and frequency

Longitudinal registries that track both transfusion volume and ferritin over years provide the clearest picture of the dose-response relationship. In cohorts followed from early childhood, cumulative units transfused per kilogram correlates with peak and mean ferritin achieved by adolescence, and patients who begin regular transfusion earlier in life, and therefore accumulate a larger total iron burden by a given age, tend to run persistently higher ferritin trajectories despite comparable chelation intensity per unit body weight [6]. This dose relationship is the basis for using ferritin trend, rather than transfusion volume alone, as the practical proxy for cumulative burden in clinic, since actual transfusion volume is rarely tracked with the precision needed for real-time decision-making, while ferritin is drawn routinely.

Table 1: Transfusion regimen and complication risk by sustained ferritin category, drawn from a randomized transfusion-policy comparison and long-term Cyprus and Italy cohort follow-up [3,8,22].

Regimen / ferritin category	Pretransfusion Hb target	Iron loading	Complication signal
Moderate transfusion regimen	9-10 g/dL	Lower	Reduced iron loading without marrow expansion
Liberal transfusion regimen	11-12 g/dL	Higher	Greater cumulative loading
Sustained ferritin <2500 ng/mL	--	Controlled	Lower cardiac/endocrine complication rate
Sustained ferritin >2500 ng/mL	--	Elevated	Substantially higher cardiac/endocrine complication rate

The relationship is not linear across the full clinical range. At the lower end, in well-chelated patients maintained near target ferritin of 500-1000 ng/mL, the marker becomes relatively insensitive to further reductions in transfusion burden because iron is being cleared nearly as fast as it accumulates, so trend slope flattens. At the upper end, above roughly 2500-3000 ng/mL, ferritin rises more steeply per unit of additional iron loading because storage capacity in unsaturated ferritin and hemosiderin pools becomes progressively exhausted, a nonlinearity that clinicians managing serial values need to keep in mind rather than assuming a constant iron-to-ferritin conversion factor throughout follow-up [7]. Registries from Cyprus and Italy that followed cohorts across multiple decades found that patients whose ferritin trend crossed and remained above the 2500 ng/mL threshold for extended periods experienced substantially higher rates of cardiac and endocrine complications than those whose trend stayed below it, reinforcing that it is the duration of elevated ferritin, not a single peak, that predicts organ damage [8].

4. Limits of ferritin: inflammation and confounding

The central limitation of ferritin as a burden marker is that it is not specific to iron. As an acute-phase reactant, its hepatic synthesis rises during infection, inflammation,

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and hepatocellular injury independent of iron status, and thalassemia major patients are chronically exposed to all three: recurrent transfusion-transmitted or immune-mediated inflammatory stimuli, transfusion-acquired viral hepatitis in cohorts transfused before universal screening, and iron-induced hepatocyte injury itself. Vichinsky and colleagues, comparing organ dysfunction in transfused patients with sickle cell disease and thalassemia, found that ferritin values at a given directly measured liver iron concentration differed systematically between the two conditions, attributable in large part to the different inflammatory milieu of the two diseases, which undercuts the assumption that a single ferritin threshold can be applied uniformly across transfused populations [9].

Ascorbate status, splenectomy, and hepatic fibrosis stage each independently shift the ferritin-iron relationship. Splenectomized patients tend to run higher ferritin for a given liver iron concentration because loss of splenic reticuloendothelial iron handling redistributes storage toward the liver and circulation; vitamin C deficiency, common in chronically transfused patients, alters ferritin release kinetics and can transiently depress measured values even as tissue iron continues to climb. These confounders mean that a falling ferritin trend during an intercurrent illness, or a rising trend during a transient inflammatory episode, can be misread as a genuine change in iron burden if the clinician does not account for concurrent clinical status. Neufeld's editorial accompanying the pivotal deferasirox and deferiprone trials made this point directly, cautioning that ferritin decline under a new chelator regimen needs corroboration by a second measure before treatment decisions are finalized on ferritin trend alone [10].

5. MRI T2* and comparison to ferritin-only monitoring

The major methodological advance of the past two decades has been the validation of magnetic resonance relaxometry as a direct, organ-specific alternative to ferritin. St Pierre and colleagues established a calibration curve linking hepatic R2 relaxation rate to biopsy-confirmed liver iron concentration across a wide dynamic range, giving clinicians a noninvasive method to quantify hepatic iron directly rather than infer it from ferritin [11], and Wood and colleagues extended this validation to R2 *mapping, confirming that both R2 and R2* accurately estimate liver iron concentration in transfusion-dependent thalassemia and sickle cell disease across the clinically relevant range [4]. These techniques exposed a critical blind spot in ferritin-only monitoring: cardiac iron loading correlates only weakly with either serum ferritin or liver iron concentration, because the heart takes up and releases iron on a different, slower timescale than the liver.

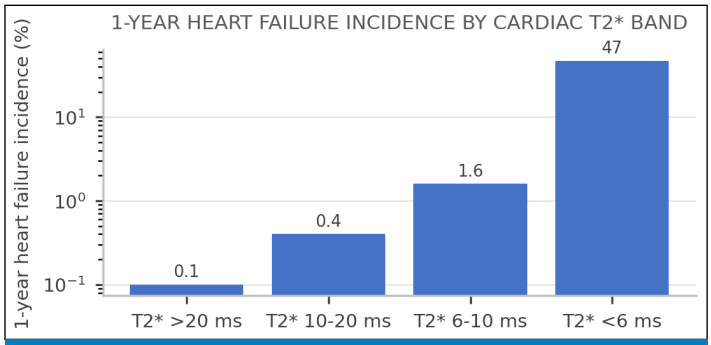

Figure 2: One-year heart failure incidence by cardiac T2 band in a multicenter cohort of 652 thalassemia major patients across 1442 scans, rising sharply once T2 falls below 10 ms and reaching approximately 47% among patients with T2* below 6 ms, a gradient not reproduced with comparable resolution by serum ferritin trend alone [13].

Anderson and colleagues introduced cardiovascular T2 *as a means of quantifying myocardial iron directly, showing that a T2* below approximately 20 ms was associated with measurable left ventricular dysfunction, with the most severely affected patients, those below roughly 8 ms, at the highest risk [12]. Kirk and colleagues subsequently followed 652 thalassemia major patients across 1442 scans in a large multicenter cohort and found that cardiac T2 *below 10 ms carried a relative risk for heart failure roughly two orders of magnitude higher than values above that*

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threshold, with patients whose T2 fell below 6 ms developing heart failure at a rate of approximately 47% within one year, a risk gradient that serum ferritin trend alone failed to capture with comparable precision [13]. Wood and colleagues had earlier shown directly that myocardial iron loading, assessed by cardiac T2, *correlates poorly with contemporaneous ferritin in transfusion-dependent thalassemia and sickle cell disease, meaning patients with reassuring ferritin trends can nonetheless be accumulating dangerous cardiac iron [14]. Davis and colleagues showed that serial left ventricular ejection fraction monitoring, used alongside these iron indices, adds further prognostic information for guiding chelation intensification before overt cardiac failure develops [15]. The clinical consequence is that guideline bodies now recommend periodic cardiac and hepatic T2* or R2* assessment for transfusion-dependent patients rather than relying on ferritin trend as the sole surveillance tool, reserving ferritin as the higher-frequency, lower-cost measure used to flag when imaging should be repeated sooner [16].

6. Chelation response and longitudinal trend interpretation

The most practically useful application of serial ferritin is tracking response to chelation therapy over months to years, where the trend line, rather than any absolute value, indicates whether current chelation intensity is matched to ongoing transfusion burden. The pivotal phase 3 trial of deferasirox by Cappellini and colleagues demonstrated that dose-dependent reductions in liver iron concentration and ferritin trend could be achieved in a dose-stratified fashion: doses of roughly 20 mg/kg/day approximately maintained existing iron burden, while doses of 30 mg/kg/day produced a clear downward ferritin trajectory over 12 months in patients with higher baseline transfusion requirements [17]. Piga and colleagues, in a parallel randomized comparison against deferoxamine, found comparable reductions in both liver iron concentration and serum ferritin trend between the two chelators over the same interval, supporting the use of ferritin trend as a valid efficacy endpoint for chelator comparison trials even though it is an imperfect measure of absolute iron burden [18].

Table 2: Ferritin and liver iron concentration (LIC) trend response by chelation regimen across three randomized trials [17,18,19].

Trial	Regimen compared	Duration	Ferritin / LIC trend
[17]	Deferasirox 20 vs 30 mg/kg/day	12 months	20 mg/kg approximately maintains; 30 mg/kg produces clear downward trend
[18]	Deferasirox vs deferoxamine	12 months	Comparable reductions in LIC and ferritin trend
[19]	Deferiprone + deferoxamine vs deferoxamine alone	12 months	Similar ferritin decline; greater cardiac T2* improvement with combination

Combination chelation regimens illustrate the same principle from a different angle. Pennell and colleagues randomized patients with asymptomatic myocardial siderosis, defined by cardiac T2 *between 8 and 20 ms, to deferiprone plus deferoxamine or deferoxamine alone, and found that the combination produced significantly greater improvement in cardiac T2* than monotherapy, even though both arms showed comparable reductions in serum ferritin, underscoring that ferritin trend and cardiac iron trend can diverge under different chelation strategies [19]. Real-world adherence data reinforce why trend interpretation matters more than trial-derived averages: Kwiatkowski's review of oral chelator use outside the controlled trial setting found that adherence gaps translate directly into ferritin trajectories that plateau or reverse direction, a pattern rarely captured in efficacy trials with mandated dosing and monitoring schedules [20]. Geographic variation compounds this picture; the CORDELIA study by Aydinok and colleagues found that the prevalence and severity of transfusional iron overload, and the ferritin thresholds at which it is detected, differ meaningfully across regions, reflecting differences in transfusion practice, chelator availability, and monitoring intensity rather than any biological difference in patients

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[21].

Historical cohort data tie these trend patterns to survival outcomes in a way that justifies the ongoing emphasis on serial ferritin despite its imperfections. Borgna-Pignatti and colleagues, following a large Italian cohort across several decades, showed that cardiac disease remained the leading cause of death in thalassemia major and that its incidence declined substantially in birth cohorts who benefited from earlier and more consistent chelation, a shift reflected in improving population-level ferritin trends over the same period [22]. Modell and colleagues, analyzing the UK Thalassaemia Register, reported parallel improvements in survival across successive birth cohorts, attributing much of the gain to earlier initiation and better sustained adherence to chelation therapy, again mirrored in falling median ferritin values across the registry over time [23]. Gabutti and Piga's long-term follow-up of chelated cohorts likewise linked sustained lower ferritin trajectories under deferoxamine to reduced cardiac mortality, an association that predates MRI-based monitoring entirely and that remains part of the rationale for continuing to track ferritin trend even in centers with access to T2* imaging [24]. In patients with thalassemia intermedia or other non-transfusion-dependent phenotypes, the ferritin-to-liver-iron relationship is weaker still, since these patients accumulate iron predominantly through increased intestinal absorption driven by ineffective erythropoiesis rather than through transfusion, and Taher and colleagues found that ferritin systematically underestimates liver iron concentration measured by R2 MRI in this population relative to transfusion-dependent patients, a distinction relevant to this review because it clarifies that the transfusion-driven ferritin relationship discussed throughout is specific to the transfusion-dependent phenotype and does not generalize across the thalassemia spectrum [25].

7. Conclusion

Serum ferritin remains, more than thirty years after the studies that established its prognostic value, the most practical longitudinal marker of transfusion-related iron burden in beta-thalassemia major, precisely because it is inexpensive enough to draw at nearly every transfusion visit and because its trend over time correlates meaningfully with cumulative transfusion load, chelation adequacy, and, ultimately, survival free of cardiac disease [1,2]. Its weaknesses are equally well documented: it is an acute-phase reactant confounded by inflammation, hepatic fibrosis, splenectomy status, and ascorbate deficiency, its correlation with directly measured liver iron concentration is moderate rather than tight, and it tracks cardiac iron loading only loosely, a gap that cardiac and hepatic T2 *or R2* imaging has filled with far greater precision since the mid-2000s [12,13,14]. The evidence supports a layered monitoring strategy rather than a choice between ferritin and imaging: frequent ferritin trend assessment to catch early deviations and flag when imaging is warranted, combined with periodic MRI-based direct organ iron quantification to confirm what the ferritin trend is suggesting, particularly for the myocardium, where ferritin's blind spot is largest and the clinical stakes of missing early siderosis are highest [16,5]. Interpreted this way, as a trend rather than a threshold, and always alongside a second, organ-specific measure when the trajectory is ambiguous or the stakes are high, longitudinal ferritin remains a genuinely useful, if imperfect, window onto the transfusion burden that drives every major complication of thalassemia major.

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