Serum Ferritin as a Continuous Risk Factor for Major Adverse Cardiovascular Events and Leukemic Transformation in Myelodysplastic Neoplasms: A Restricted Cubic Spline DoseResponse Meta-Analysis and a Methodological Proof-of-Concept Study

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Introduction

Current guidelines recommend iron chelation therapy in MDS at serum ferritin ≥1000 ng/mL; however, emerging evidence suggests iron-driven genotoxicity may begin at lower thresholds. The continuous dose-response relationship between serum ferritin and MACE or LT has not been formally quantified. This analysis serves as a methodological proof-of-concept to demonstrate the RCS dose-response meta-analysis framework.

Methods

We applied RCS dose-response meta-analysis to 12 MDS cohort-level data sets (six for MACE, six for LT), using four knots placed at the 5th, 35th, 65th, and 95th percentiles of the ferritin distribution. Within-study covariance was estimated using an approximation of the Greenland-Longnecker method. Pooling used multivariate Der Simonian Laird random-effects models. Nonlinearity was formally tested via the Wald χ^2 test on the nonlinear spline coefficients.

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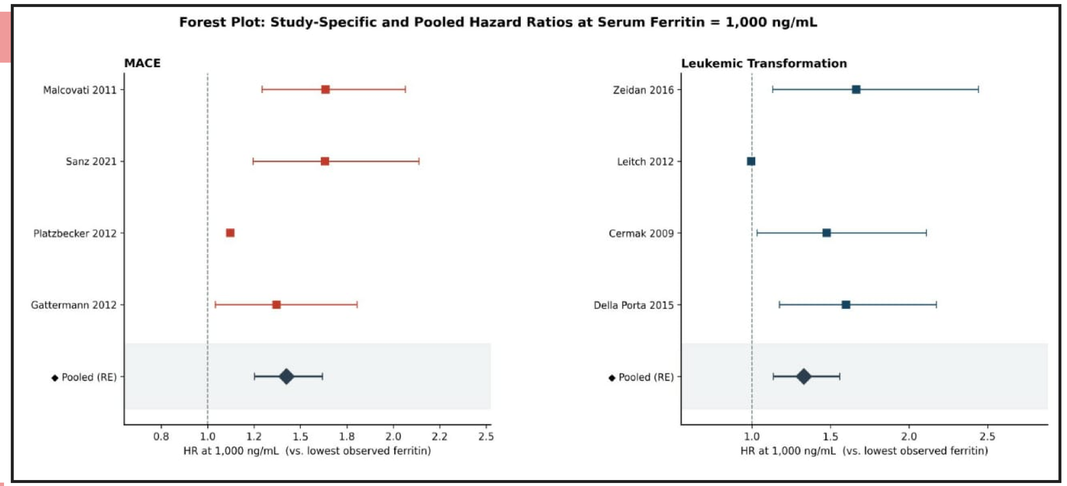

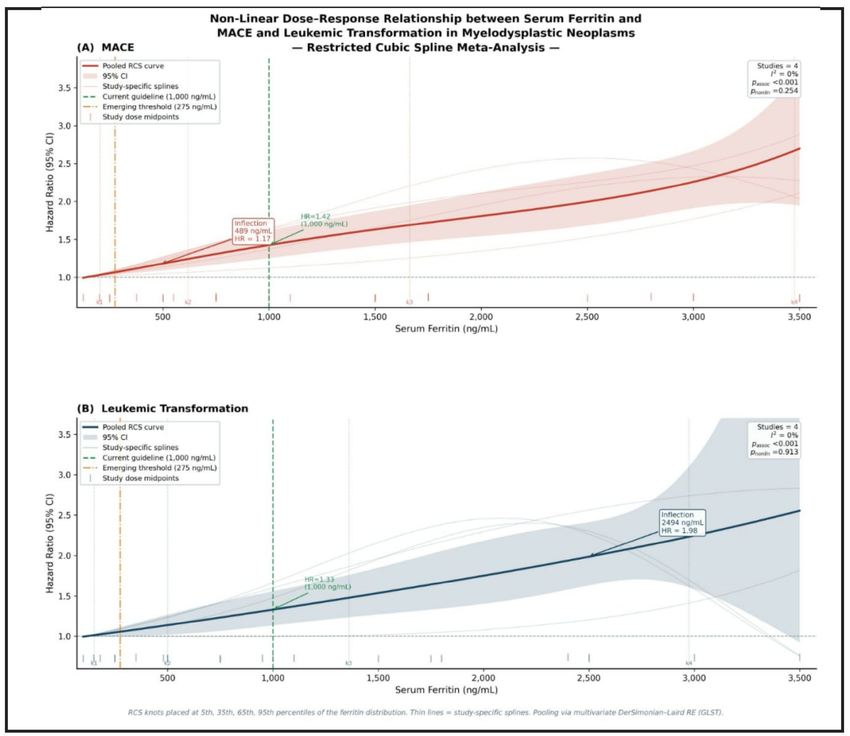

Results

1)MACE: Overall ferritin–outcome association was highly significant ($\chi^2(3)=106.00$, $P<0.001$).
2)Nonlinearity: Not significant ($\chi^2(2)=2.74$, $P=0.254$), indicating an approximately linear log-HR relationship.
3) MACE HRs vs lowest observed ferritin:
275 ng/mL: HR=1.07 (95% CI, 1.03–1.10)
500 ng/mL: HR=1.18 (95% CI, 1.09–1.27)
1000 ng/mL: HR=1.42 (95% CI, 1.25–1.62)
2000 ng/mL: HR=1.81 (95% CI, 1.54–2.12)
3000 ng/mL: HR=2.26 (95% CI, 1.91–2.67)
4)LT: Association was similarly significant. ($\chi^2(3)=55.26$, $P<0.001$).
5)Nonlinearity: Not significant ($\chi^2(2)=0.18$,$P=0.913$).
6)LT HRs vs lowest observed ferritin:
275 ng/mL: HR=1.06 (95% CI, 1.00–1.12),
500 ng/mL: HR=1.14 (95% CI, 1.02–1.27)
1000 ng/mL: HR=1.33 (95% CI, 1.14–1.56)
2000 ng/mL: HR=1.75 (95% CI, 1.40–2.19)
3000 ng/mL: HR=2.25 (95% CI, 1.59–3.18)
7)Between-study heterogeneity: Not estimable for either outcome (Cochran Q<df; $\tau^2=0$), likely due to only 4 datasets/outcome.
Results therefore reflect fixed-effects pooling.

Conclusion

RCS dose-response meta-analysis demonstrated a monotone, approximately linear ferritin–outcome association across the full ferritin range. Both MACE and LT risk increased progressively with ferritin, with significant elevations below the 1,000 ng/mL chelation threshold. Validation requires primary studies with multi-category ferritin data, and findings should not alter clinical guidelines. Future prospective cohorts should report ferritin continuously to enable fully powered dose-response meta-analyses.