Redefining "Safe" Anthracycline Limits: A Restricted Cubic Spline Meta-Analysis of Continuous Cumulative Dosing and Non-Linear Cardiotoxicity in Hodgkin Lymphoma Survivors

Authors: H.Alamy[1], F.Khalid[2], L.Manzoor[3], S.Maryam[4], R.Chennuri[5], I.Khan[6], H.Kommu[7], S.Bhavanam[8] and A.Das[9]

Affiliations: 1. Desert Regional Medical Center, Palm Springs, California, US 2. Sheikh Zayed Medical College, Rahim Yar Khan, Pak 3. Dow University of Health Sciences, Karachi, Pak
4. Shifa International Hospital, Islamabad, Pak 5. New York Medical College / St. Clare's and St. Mary's Hospital, Denville, USA 6. Ziauddin Medical University, Karachi, Pak
7. JIPMER, Puducherry, India 8. Brookdale University Hospital and Medical Center, Brooklyn, USA 9. Mayo Clinic, Rochester, US

INTRODUCTION

Anthracycline-based chemotherapy remains a cornerstone of curative treatment for Hodgkin lymphoma (HL), yet cumulative dose thresholds for long-term cardiotoxicity remain poorly defined and inconsistently applied. Traditional clinical guidelines cite 250–450 mg/m² as "safe" cumulative limits, but emerging evidence from contemporary cohorts suggests substantial risk accumulation at lower exposures. We conducted a comprehensive dose-response meta-analysis to characterize the continuous, non-linear relationship between anthracycline cumulative dose and heart failure risk in long-term HL survivors.

AIM

To characterize the continuous, non-linear relationship between cumulative anthracycline dose and long-term heart failure risk in Hodgkin lymphoma survivors using restricted cubic spline meta-analysis of pooled contemporary cohorts, and to determine whether a genuinely “safe” cumulative dose threshold truly exists below the traditional 250–450 mg/m² guideline range.

METHOD

Search strategy and data sources

- Systematically searched PubMed, ClinicalTrials.gov, and Google Scholar through March 2026 for cohort studies reporting granular anthracycline dose-response cardiotoxicity data in HL survivors.
- Six landmark cohorts (Aleman, van Nimwegen, Mulrooney/CCSS, Armstrong/CCSS, van Leeuwen, and Goddard, 2009–2025) were included, totaling over 47,000 patients with median follow-up >15 years.

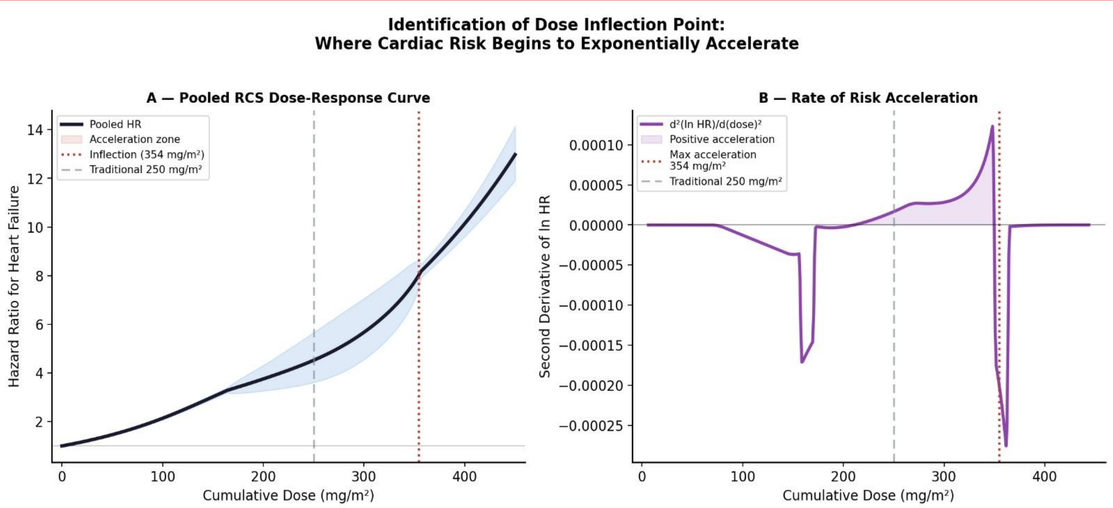
Statistical analysis

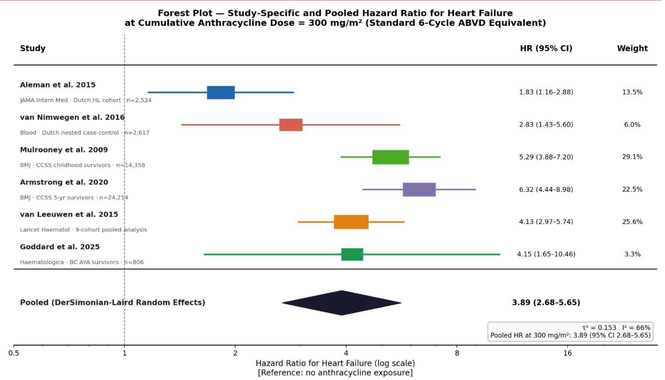
- Two-stage random-effects generalized least squares meta-analysis with restricted cubic splines (knots at 75, 150, 268, 379 mg/m²) modeled the continuous dose-response relationship without arbitrary dose categorization.

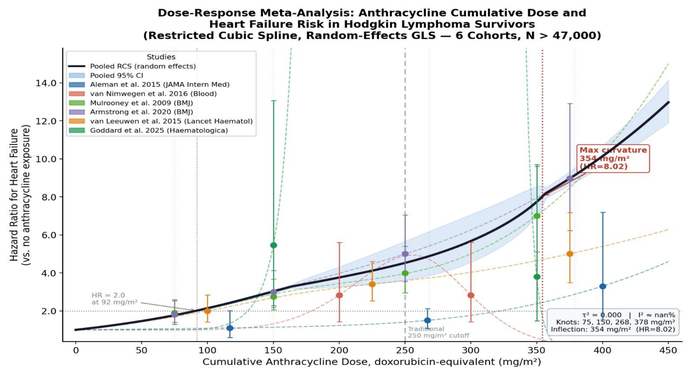
CONCLUSIONS

Current anthracycline dosing paradigms substantially underestimate cardiotoxicity risk in HL survivors. Risk begins accumulating immediately and continuously, fundamentally challenging the notion of "safe" cumulative thresholds. These findings mandate urgent reconsideration of treatment de-escalation strategies in clinical trials, intensified lifelong cardiovascular surveillance protocols for patients receiving even modest cumulative doses, and incorporation of continuous risk modeling into evidence-based cardio-oncology guidelines and survivorship care plans.

GRAPHS & ILLUSTRATIONS







ACKNOWLEDGEMENTS

We thank the investigators of the six cohort studies included in this analysis for their contributions to the field, and the Internal Medicine Residency Program at Desert Regional Medical Centre for supporting this work. No external funding was received; the authors declare no conflicts of interest.

CONTACT INFORMATION

Haroon Alamy MD, PGY-2 IM Resident

Haroon_Alamy@outlook.com

Desert Regional Medical Centre, Palm Springs, CA

REFERENCES

1. **Aleman BMP, et al.** Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. *JAMA Intern Med.* 2015.
2. **van Nimwegen FA, et al.** Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. *Blood.* 2017;129(16):2257–65.
3. **Mulrooney DA, et al.** Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ.* 2009;339:b4606.
4. **Armstrong GT, et al.** Cardiovascular late effects and dose-response analysis in the Childhood Cancer Survivor Study. *BMJ.* 2020.
5. **van Leeuwen FE, et al.** Cardiovascular disease after treatment for Hodgkin’s lymphoma: an analysis of nine collaborative EORTC-LYSA trials. *Lancet Haematol.* 2015.
6. **Goddard ER, et al.** Dose-response analysis of anthracycline-related cardiotoxicity in Hodgkin lymphoma survivors. *Haematologica.* 2025.