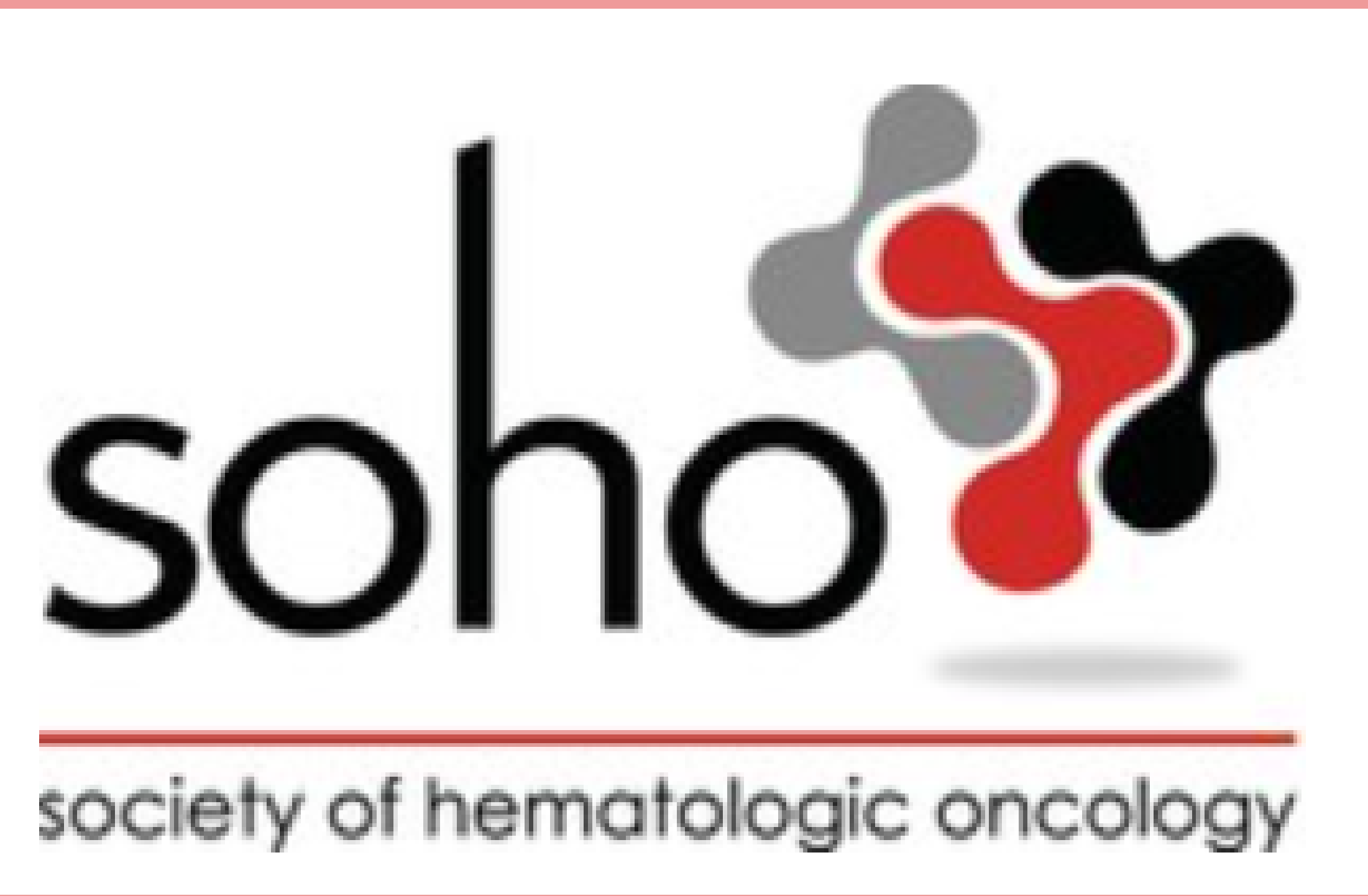




Defining the "Frailty Cliff": A Restricted Cubic Spline Meta-Analysis of AI-Derived Continuous Mesenteric Adiposity and Skeletal Muscle Index on Induction Mortality in Acute Myeloid Leukemia

Faiza Khalid¹, Haroon Alamy², Raj Nandan Chennuri³, Iman Khan⁴, Laiba Manzoor⁵, Shaiza Maryam⁶, Sravani Bhavanam⁷, Hrishikesh Kommu⁸, Ashesh⁹

- ¹ Sheikh Zayed Medical College, Rahim Yar Khan, Pakistan
- ² Desert Regional Medical Center, Palm Springs, CA, USA
- ³ New York Medical College/St Clares and St Mary’s Hospital, Denville, NJ, USA
- ⁴ Ziauddin Medical University, Karachi, Pakistan
- ⁵ Dow University of Health Sciences, Karachi, Pakistan
- ⁶ Shifa International Hospital, Islamabad, Pakistan
- ⁷ Brookdale University Hospital and Medical Center, New York, NY, USA
- ⁸ JIPMER, Puducherry, India
- ⁹ KPC medical College and hospital Kolkata india

INTRODUCTION

Traditional dichotomous sarcopenia cutoffs inadequately capture the continuous relationship between body composition and treatment-related mortality in acute myeloid leukemia (AML). We hypothesized that restricted cubic spline (RCS) modeling of artificial intelligence (AI)-derived skeletal muscle index (SMI) and visceral fat area (VFA) would identify critical inflection points, “frailty cliffs,” where mortality risk accelerates exponentially, enabling precision risk stratification for induction chemotherapy decisions.

METHODS

We systematically searched PubMed, MEDLINE, EMBASE, and the Cochrane Library from inception to 2026 to identify relevant studies and conducted a dose-response meta-analysis of 12 cohorts (Japan, Brazil, Austria, UK, Italy, Korea, France, USA) published in 2020–2024, encompassing 2,489 AML patients undergoing induction therapy. AI-assisted CT segmentation quantified SMI (cm²/m²) and VFA (cm²) at diagnosis. RCS models with Harrell knots (10th/50th/90th percentiles: SMI 34.8/37.9/41.1 cm²/m²; VFA 88.7/126.0/158.3 cm²) were fitted using generalized least-squares weighting with bootstrap 95% confidence intervals (2,000 iterations). Pooled hazard ratios (HR) employed DerSimonian-Laird random-effects models. Heterogeneity was assessed via Cochran's Q and I², publication bias via Egger's regression

RESULTS

- 1)Pooled HR: Low vs reference SMI: 2.05 (95% CI, 1.83–2.29).
- 2)Heterogeneity: Low (I²=10.6%, τ²=0.0041, Q=12.30, df=11).
- 3)Publication bias: Egger’s test not significant (intercept=4.01, p=0.896).
- 4)Frailty Cliff: SMI=28.9 cm²/m²; below this threshold, mortality HR increased to 5.20.
- 5)Adiposity Cliff: VFA=169 cm², associated with HR 3.25.
- 6)Obesity paradox: VFA <105 cm² showed a protective association.
- 7)Combined effects: Dual-axis heatmap showed synergistic risk amplification when both SMI and VFA thresholds were breached.

CONCLUSION

The Frailty Cliff at SMI=28.9 cm²/m² represents a biologically-grounded, continuous threshold for treatment intensification in AML, superseding arbitrary dichotomous classifications. AI-derived body composition metrics enable precision frailty assessment, potentially guiding personalized induction regimens and improving therapeutic index in vulnerable populations. Prospective validation in randomized trials is warranted.

RESULTS

Figure 3 — Publication Bias & Composite Frailty Landscape "Frailty Cliff" Meta-Analysis • AML Induction Cohorts 2020-2024

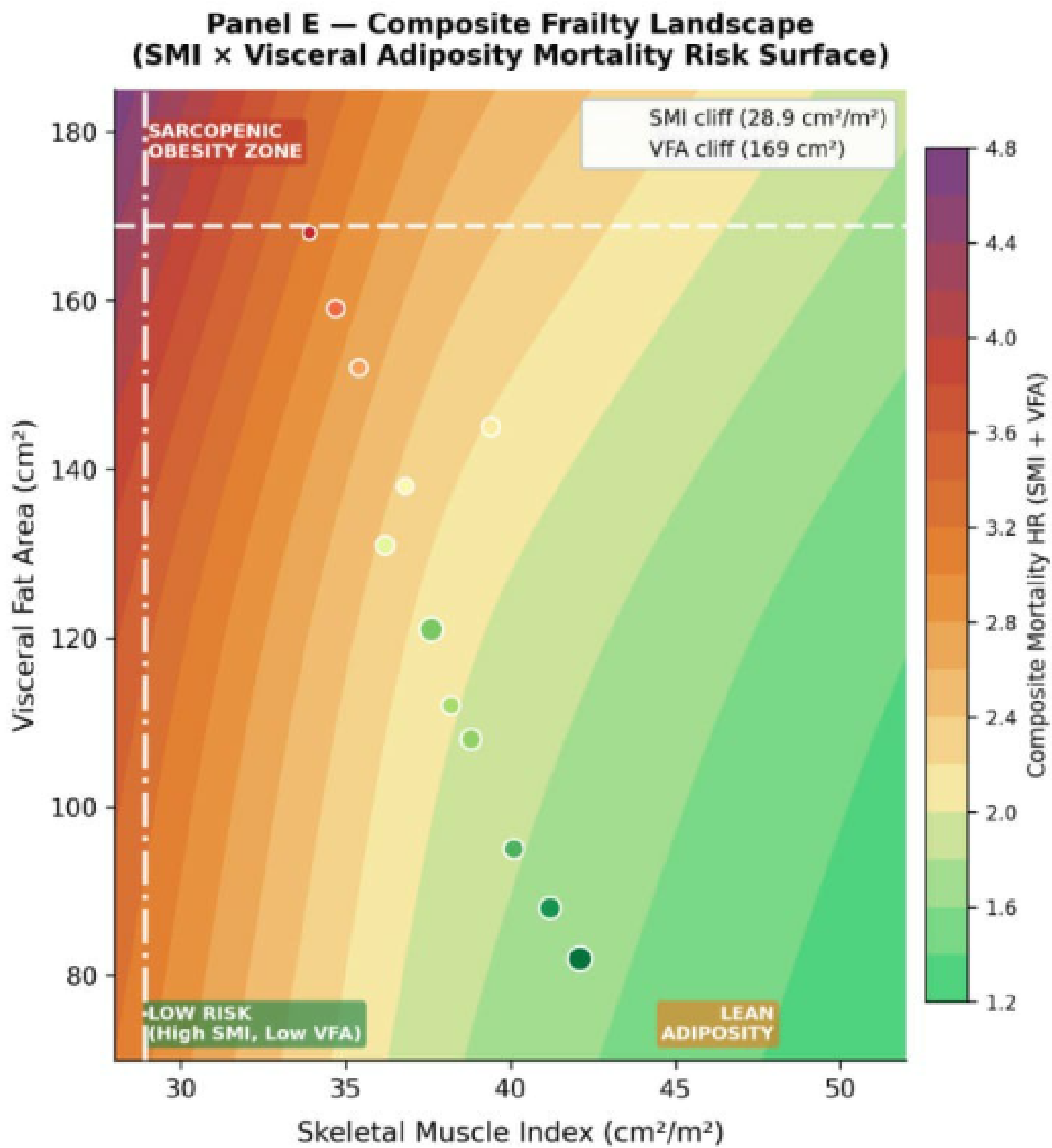
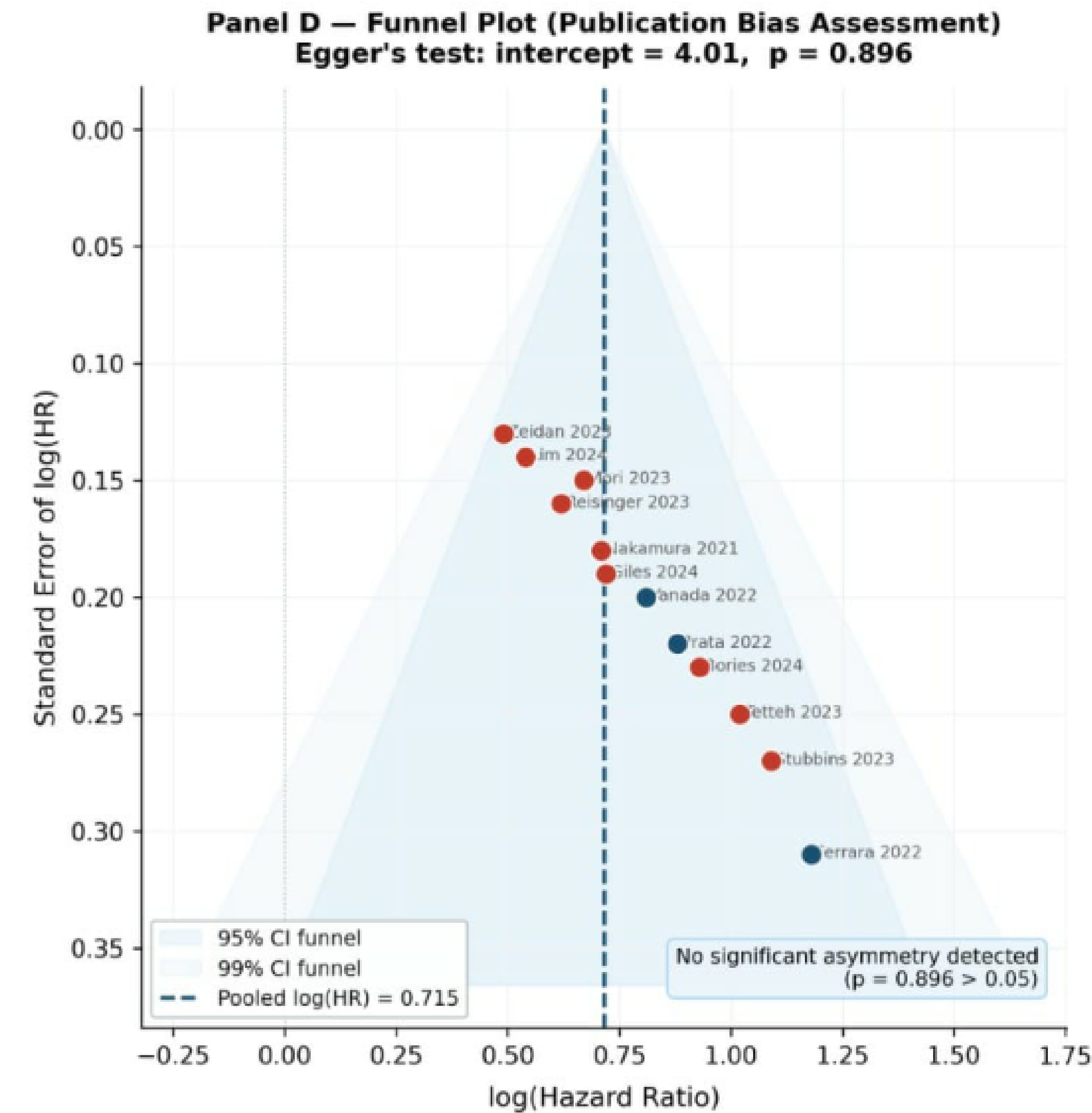
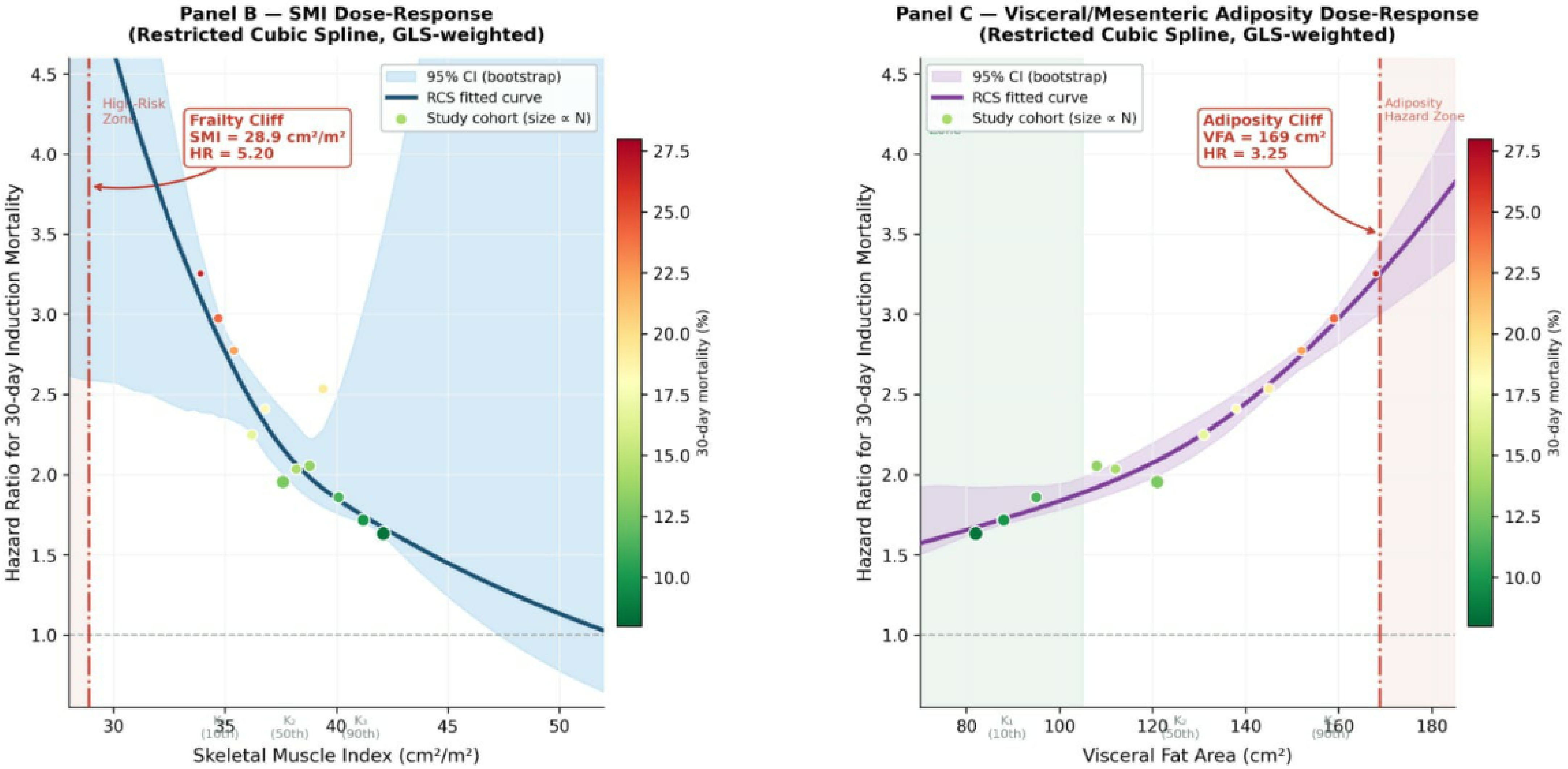


Figure 2 — Restricted Cubic Spline Dose-Response Curves "Frailty Cliff" Inflection Points in AML Induction Mortality



Contact Information: Name: Faiza Khalid
Email: faiza.khalid.173@gmail.com
Contact number: +1 (347) 922-6530