Exploring the Relationship Between Hemochromatosis and Fracture Risk: A Population-Based Matched Cohort Study Stratified on Ferritin Levels

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1 Background

- Patients with iron overload, such as hereditary hemochromatosis, beta-thalassemia, and sickle-cell disease have an elevated risk of fracture.
- The role of high iron levels (iron overload) in this risk is unclear.

2 Objective

- To assess the risk of fractures among patients with iron overload (i.e., serum ferritin values ≥1000ug/L) and among those with a diagnosis of hemochromatosis, beta-thalassemia, or sickle-cell disease without iron overload, compared to matched controls.

3 Methods

Data source and Design

- IQVIA Medical Research Database UK (IMRD-UK), a Cegedim database incorporating anonymized data from The Health Improvement Network (THIN) between 2006 and 2022.
- Population-based matched cohort study.

Exposure

- Cases: Incident diagnosis of hereditary hemochromatosis, beta-thalassemia, or sickle-cell disease OR high ferritin value (>1000ug/L) as per lab results.
- Controls: Cases matched with up to 10 controls on age, sex, practice, and year.

Outcome

- A composite outcome of osteoporotic fractures defined as any vertebral, humerus, hip, or forearm fracture.

Analysis

- Time-varying Cox proportional hazards model adjusted for time-varying confounders confounders.
- Stratified by evidence of iron overload (ferritin value >1000ug/L).

4 Results

Table 1. Patient characteristics and hazard ratio for risk of fracture.

	No Iron Overload		Iron Overload	
	Cases	**Controls**	**Cases**	**Controls**
N	6754	79,256	13,510	113,700
Average Age (SD)	47.0 (17.0)	51.4 (19.9)	63.2 (15.1)	62.1 (15.6)
Women (%)	3292 (48.7)	41,511 (52.4)	4630 (34.3%)	40,034 (35.2%)
Ferritin ug/L at index (mean (SD))	2444 (36.2)	119 (155)	1731 (1440)	153 (249)
Adjusted Hazard Ratio (95% Confidence Interval)	**1.39 (1.18 – 1.64)**		**1.91 (1.73 – 2.10)**	

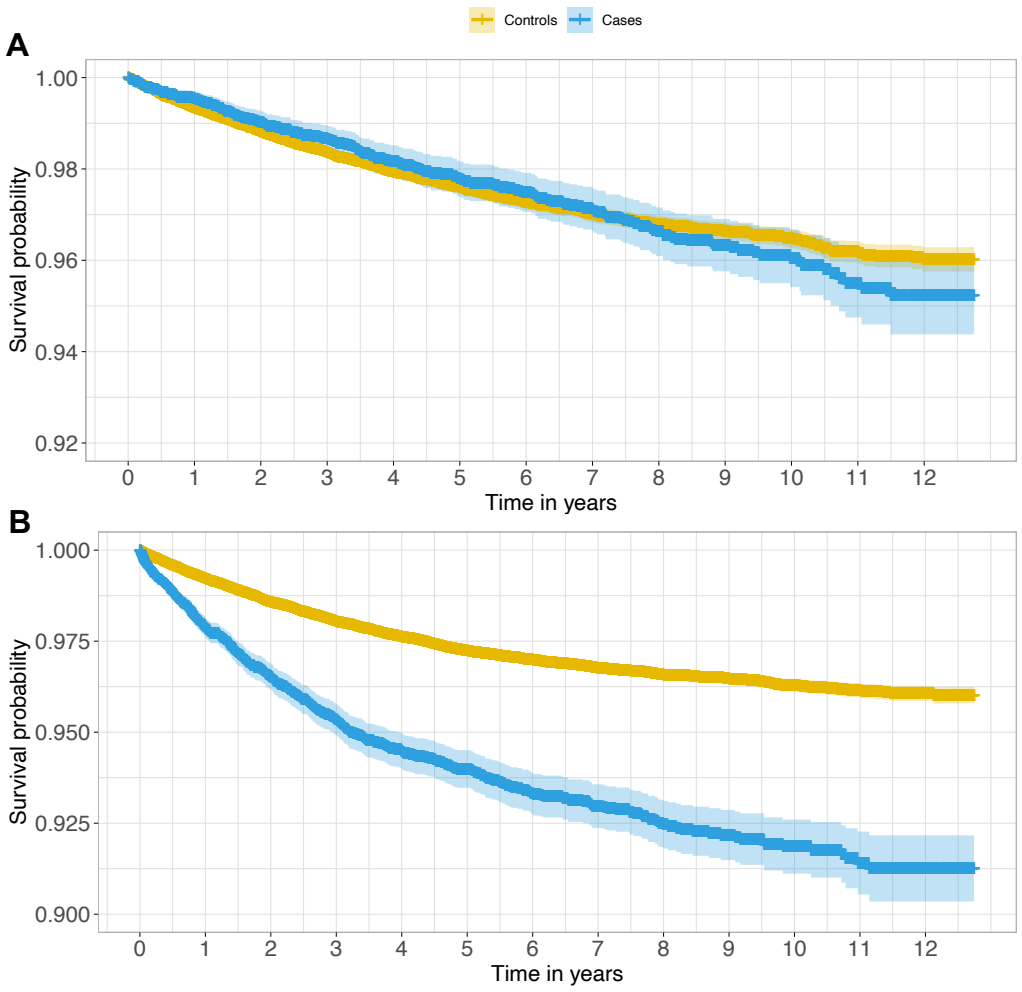

Figure 1. Kaplan-Meier Survival Curves. Figure 1A, presents the survival trends of patients diagnosed with hereditary hemochromatosis, beta-thalassemia, or sickle-cell disease (blue curve) but without iron overload, in contrast to their control groups (yellow curve). Figure 1B illustrates the survival outcomes of patients with elevated ferritin levels (blue curve) in comparison to their respective controls (yellow curve).

- Figure 1 shows the unadjusted survival curves for patients without iron overload (A), and for those with iron overload (B).
- The results after adjusting for confounders are shown in Table 1.
  - Patients without iron overload had a 39% increase in the risk of fractures (HR 1.39, 95% CI: 1.18-1.64).
  - Patients with iron overload had a 91% increased risk of fractures (HR 1.91, 95% CI: 1.73 – 2.10), Table 1.

5 Discussion

- This large population-based cohort study found a 91% increased risk of fracture associated with iron overload.
- Patients without iron overload had a modest 39% increased risk of osteoporotic fractures.
- While iron overload disorders increase the risk of fractures modestly, the risk is significantly increased among those with serum ferritin >1000ug/L.
- It is relevant to measure the actual ferritin levels in order to assess the actual fracture risk.

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