Non-Cancer Competing Mortality in Follicular Lymphoma: Cardiovascular, Infectious, and Second Malignancy Deaths in a Population-Based Cohort, SEER 2000–2022

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BACKGROUND

Follicular lymphoma (FL) carries a five-year relative survival exceeding 91%, rendering most patients vulnerable to non-cancer causes of death. No large population-based study has simultaneously quantified cardiovascular, infectious, and second malignancy mortality as competing events in FL, nor examined whether non-cancer mortality rivals lymphoma-specific death among long-term survivors.

METHODS

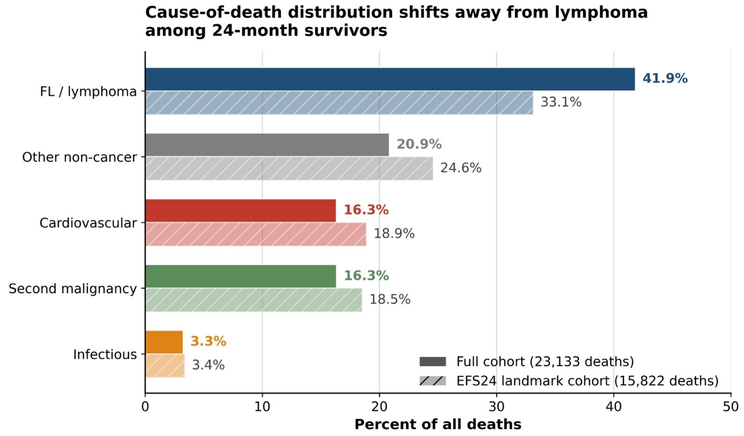
We identified 57,194 adults with FL (ICD-O-3: 9690/3, 9691/3, 9695/3, 9698/3) in the SEER 22-registry database (2000–2022). Cause of death was classified into five mutually exclusive competing events. Cumulative incidence functions were estimated via the Aalen-Johansen method with Gray's test for group comparisons. Fine-Gray subdistribution hazard models were fitted for each non-cancer cause, adjusting for age, sex, race/ethnicity, chemotherapy, radiation, diagnosis era, income, and marital status. A pre-specified 24-month event-free survival (EFS24) landmark analysis characterized competing mortality among patients surviving beyond peak lymphoma-death risk (N = 44,547).

DISCUSSION

Cardiovascular death rivals lymphoma-specific death among elderly EFS24 survivors, and infectious mortality disproportionately burdens Black patients and those with prior chemotherapy exposure. The modern era has reduced cardiovascular and infectious competing mortality, yet second malignancy risk has not declined comparably. These findings support cardio-oncology integration and infectious risk stratification in FL survivorship care, particularly for older patients achieving event-free survival.

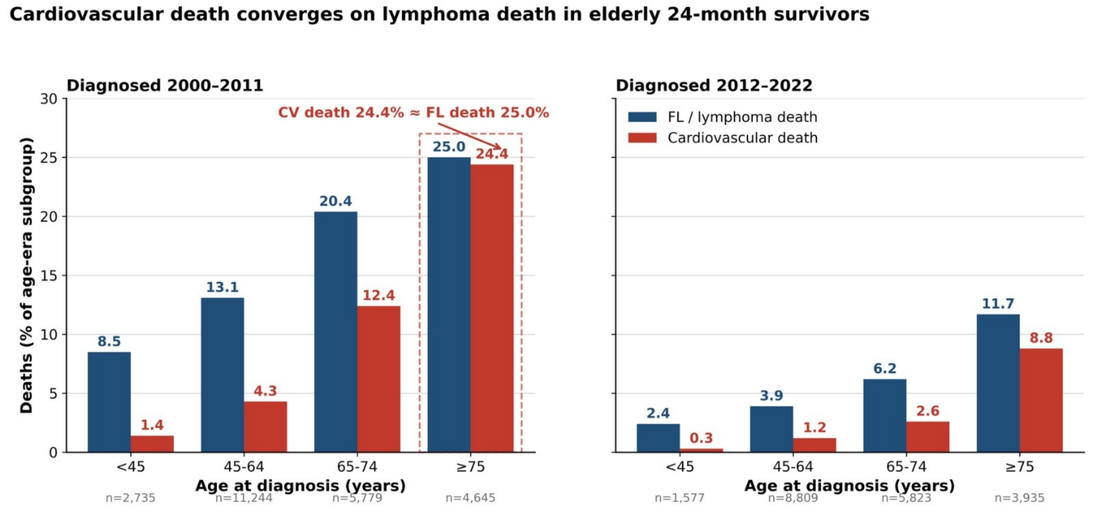
RESULTS

Among 23,133 deaths over a median follow-up of 73 months, FL/lymphoma was the leading cause (n = 9,682; 41.8%), followed by other non-cancer death (20.8%), cardiovascular death (16.3%), second malignancy death (16.3%), and infectious death (3.3%). In the EFS24 cohort, a striking crossover emerged among patients aged ≥75 diagnosed 2000–2011: cardiovascular death (24.4%) was nearly equivalent to FL death (25.0%). Age was the dominant driver of cardiovascular mortality (SHR ≥75 vs. <45: 23.3; 95% CI 17.1–31.8; p<0.001). The modern era (2012–2022) conferred a 37.5% reduction in cardiovascular death risk (SHR 0.625; 95% CI 0.570–0.686; p<0.001) and 37.3% reduction in infectious death risk (SHR 0.627; 95% CI 0.502–0.783; p<0.001), but no comparable reduction in second malignancy death. Non-Hispanic Black patients carried nearly twice the infectious death risk of Non-Hispanic White patients (SHR 1.85; 95% CI 1.29–2.64; p=0.0007). Prior chemotherapy was independently associated with elevated infectious death risk in EFS24 survivors (SHR 1.24; 95% CI 1.03–1.48; p=0.023).



Percentages are of all deaths; unknown cause of death (1.4% full cohort, 1.5% EFS24) not shown.

Figure 2: Cause-of-death distribution shifts away from lymphoma among 24 month survivors



EFS24 landmark cohort. Crude proportions; the lower absolute percentages in 2012–2022 partly reflect shorter follow-up.

Figure 1: Cardiovascular death converges on lymphoma death in elderly 24 month survivors