JACC: CARDIOONCOLOGY
VOL. 3, NO. 2, 2021
ISSN 2666-0873

RESEARCH LETTER

Long-Term Outcomes Following Myocardial Infarction in Young Adult Survivors of Hodgkin Lymphoma

The YOUNG-MI Registry

Most patients with Hodgkin lymphoma (HL) are diagnosed between the ages of 15 and 30 years and have curable disease (1). However, survivors can develop cardiovascular disease owing to anthracycline-based regimens and mediastinal radiation therapy. In a study that included coronary computed tomography angiography in 79 asymptomatic lymphoma survivors treated with mediastinal irradiation and matched control subjects, 59% of survivors had coronary atherosclerosis, and 24% had 3-vessel/left main coronary artery disease (CAD) (2). Although it is known that survivors of HL can develop premature CAD, their prognosis after a coronary event is not established, particularly compared with individuals without a history of malignancy who develop a myocardial infarction (MI) at a young age. We sought to examine long-term outcomes of HL survivors in a contemporary cohort of young individuals presenting with their first MI at or before the age of 50.

The Mass General Brigham YOUNG-MI registry has been described previously (3). The retrospective cohort study from Brigham and Women's Hospital and Massachusetts General Hospital included all consecutive patients who experienced a first MI at or before the age of 50 years from 2000 to 2016. For the present analysis, only patients with type 1 MI (4) were included. The YOUNG-MI registry was approved by the Institutional Review Board at Mass General Brigham.

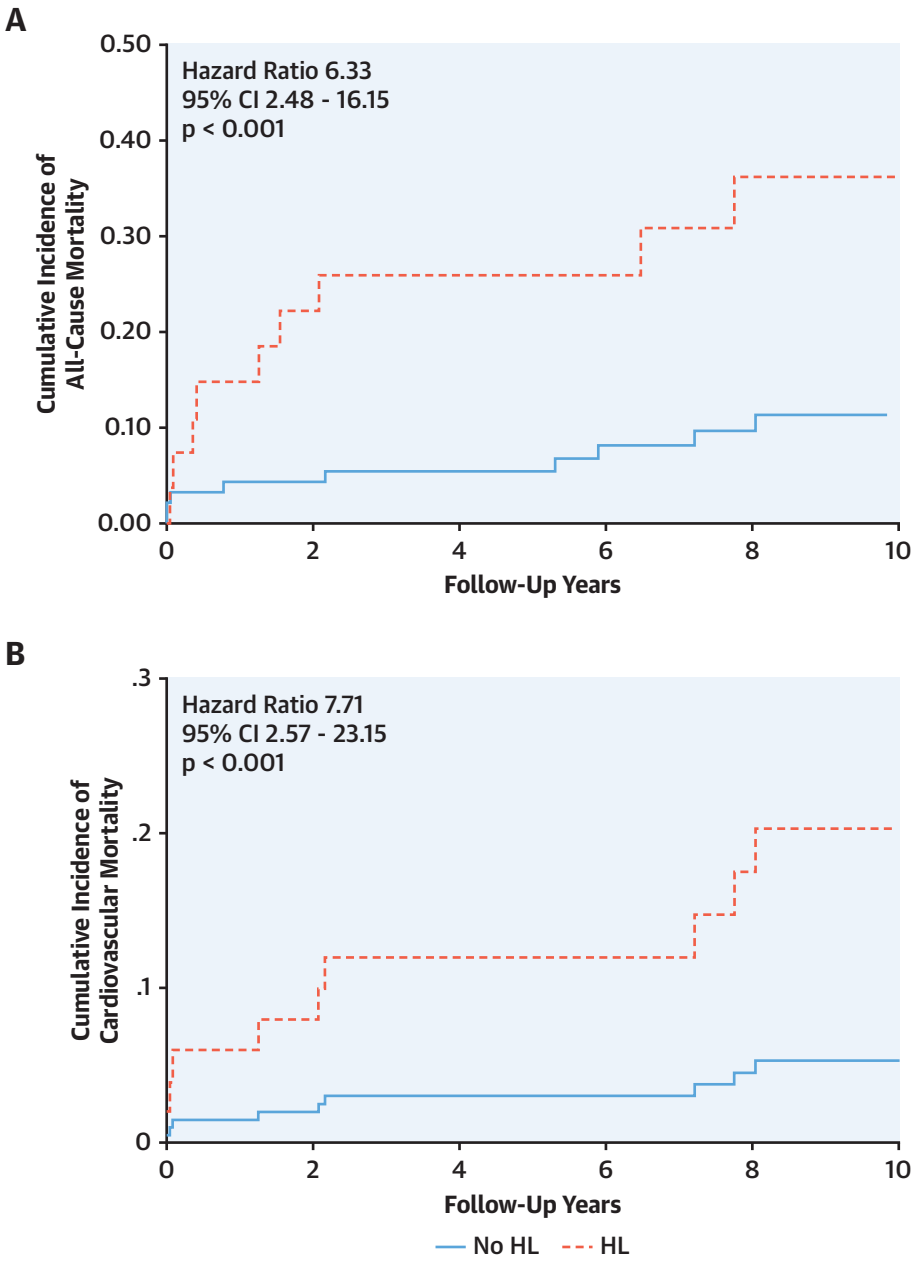
A history of HL and treatment details were ascertained through detailed review of the electronic medical record. A matched cohort (4 for every 1 case) without a history of noncutaneous malignancy was generated from the YOUNG-MI registry with the use of Mahalanobis distance matching on covariates that were unbalanced between patients with and without a history of HL and of clinical significance.

The primary outcomes of interest were all-cause and cardiovascular mortality, including in-hospital deaths. Vital status was assessed through linkage with the Mass General Brigham electronic medical record system, the Social Security Administration's Death Master File, and the National Death Index. The cause of death was adjudicated independently by 2 physicians; in cases of disagreement, consensus was reached by a committee.

All analyses were performed with the use of Stata version 15.1 (StataCorp, College Station, Texas). Categoric variables are reported as frequencies and proportions, and compared by means of chi-square or Fisher's exact test as appropriate. Continuous variables are reported as the mean ± SD or median (interquartile range [IQR]) and compared by means of *t* test or Mann-Whitney *U* test as appropriate. Cumulative incidence curves were constructed to illustrate time to death (all-cause or cardiovascular). Univariable Cox proportional hazards modeling was performed to obtain the hazard ratio (HR) and 95% confidence interval (CI) for survival free from all-cause death, and competing risk analysis was performed to obtain the HR and 95% CI for cardiovascular mortality.

Among 2,097 patients who experienced a type 1 MI, 27 (1.3%) had a history of HL before the index MI. All 27 (100%) were treated with mediastinal radiation, and 16 (59.3%) also received chemotherapy. The year of treatment completion was available for 26 of the 27 patients: 5 completed radiation therapy in the 1970s, 13 in the 1980s, 6 in the 1990s, and 2 in the 2000s.Compared with the rest of the registry, survivors of HL were of similar age at the MI presentation (45.0 [IQR: 40.0 to 47.0] vs. 45.0 [IQR: 42.0 to 48.0]; standardized mean difference [SMD]: 0.16) with a similar female proportion (29.6% vs. 19.1%; SMD: 0.24). Survivors of HL were more likely to be white (96.3% vs. 73.2%; SMD: 0.68), to have a lower prevalence of diabetes (7.4% vs. 20.0%; SMD: 0.37) current tobacco use (14.8% vs. 53.0%; SMD: 0.88), and to have a higher Charlson comorbidity index (CCI) (2.0 [IQR: 1.0 to 3.0] vs. 1.0 [IQR: 1.0 to 2.0]; SMD: 0.38). There were no significant differences in any of these characteristics after matching according to age (SMD: 0.03), race (SMD: 0.03), sex (SMD: 0.04), diabetes (SMD: 0.05), current tobacco use (SMD: 0.07), and CCI (SMD: 0.04). In addition, there was no significant difference between the HL group (n = 27) and the matched cohort (n = 92) in left ventricular ejection fraction (55.5% [IQR: 51.0% to 62.0%] vs. 52.5% [IQR: 41.0% to 60.0%]; p = 0.19), or prevalence of

FIGURE 1 Outcomes According to Diagnosis of a History of Hodgkin Lymphoma



Cumulative incidence curves of **(A)** all-cause and **(B)** cardiovascular mortality among patients with and without a history of Hodgkin lymphoma (HL). CI = confidence interval.

hypertension (37% vs. 50%; p = 0.24) or dyslipidemia (85% vs. 87%; p = 0.81). The matched cohort had a higher prevalence of obesity (body mass index ≥30 kg/m^2) (58% vs. 22%; p = 0.009). At the time of coronary angiography, segment involvement (2 [IQR: 1 to 4] vs. 2 [IQR: 2 to 4]; p = 0.42) and Gensini (32 [IQR: 21 to 48] vs. 39 [IQR: 25 to 61]; p = 0.19) scores were similar in the HL group and the matched cohort. The proportion of patients who presented with an ST-segment elevation MI (37% vs. 52%; p = 0.17), underwent percutaneous coronary intervention (88% vs. 90%; p = 0.71), or were revascularized via coronary artery bypass grafting surgery (11% vs. 11%; p = 0.97) were similar in the 2 groups.

Over a median follow-up of 10.9 years (IQR: 6.2-13.4), there were 11 all-cause deaths in the HL group (40.7%) and 11 in the matched cohort (12%), and 6 cardiovascular deaths in the HL group (22%) and 6 in

the matched cohort (7%). After adjusting for obesity, history of HL was associated with higher all-cause (HR: 6.33 [95% CI: 2.48 to 16.15]; $p < 0.001$) and cardiovascular (HR: 7.71 [95% CI: 2.57 to 23.15]; $p < 0.001$) mortality compared with the matched cohort (**Figure 1**). Rates of all-cause (6.02 [95% CI: 3.33 to 10.87] vs. 1.28 [95% CI: 0.71 to 2.30]; $p < 0.001$) and cardiovascular (3.28 [95% CI: 1.47 to 7.31] vs. 0.7 [95% CI: 0.31 to 1.55]; $p = 0.003$) mortality per 100 person-years were also higher among the HL group.

Given the association between mediastinal radiation therapy and the development of CAD (particularly in those with a history of anterior or left-sided chest irradiation and at least one risk factor for radiation-induced heart disease, such as a cumulative dose >30 Gy), screening via stress testing (5) or coronary atherosclerosis imaging 5 to 10 years after therapy in asymptomatic survivors is recommended. The data from our study underscore the importance of such screening to identify opportunities for primary prevention among HL survivors. Our results also reinforce the need for aggressive secondary prevention measures after MI among HL survivors to reduce long-term mortality.

This study is limited by small sample size, retrospective design, and lack of complete treatment details (cumulative radiation dose and cumulative anthracycline dose, among others).

In conclusion, 1.3% of the patients in our registry who experienced a type 1 MI at or before the age of 50 years had a history of HL. Compared with a matched cohort, HL patients had substantially higher all-cause and cardiovascular mortality. These findings underscore the importance of both primary and secondary prevention in this population.

***Sanjay Divakaran, MD**
David W. Biery, AB
Adam N. Berman, MD
Avinainder Singh, MBBS
Jon Hainer, BS
Wanda Y. Wu, BA
Marcelo F. Di Carli, MD
Deepak L. Bhatt, MD, MPH
Anju Nohria, MD, MSc
Ron Blankstein, MD

*Cardiovascular Division and Cardiovascular Imaging Program
Brigham and Women's Hospital
75 Francis Street, 70FR-5-5140
Boston, Massachusetts 02115, USA
E-mail: sdivakaran@bwh.harvard.edu
Twitter: @SanjayDivakaran, @RonBlankstein, @DLBhattMD, @mdicarli, @BrighamWomens

https://dx.doi.org/10.1016/j.jaccao.2021.04.001

Dr. Divakaran is supported by a joint KL2/Catalyst Medical Research Investigator Training (CMeRIT) award from Harvard Catalyst and the Boston Claude D. Pepper Older Americans Independence Center (5P30AG031679-10). Dr. Nohria is supported by the Gelb Master Clinician Scholar Award. Dr. Di Carli has received consulting fees from Bayer and Janssen and research grants from Spectrum Dynamics and Gilead Sciences. Dr. Bhatt discloses the following relationships: advisory boards: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, MyoKardia, PhaseBio, PLx Pharma, and Regado Biosciences; boards of directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; chair: American Heart Association Quality Oversight Committee; data monitoring committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and Population Health Research Institute; honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), and WebMD (CME steering committees); other: *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), and VA CART Research and Publications Committee (Chair); research funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, MyoKardia, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); site co-investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), and Svelte; trustee: American College of Cardiology; unfunded research: FlowCo, Merck, Novo Nordisk, and Takeda. Dr. Nohria has received research support from Amgen and consulting fees from Takeda Oncology and AstraZeneca Pharmaceuticals. Dr. Blankstein has received research grants from Amgen and Astellas. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Hoppe RT, Advani RH, Ai WZ, et al. Hodgkin lymphoma version 1.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2017; 15:608–38.

2. van Rosendael AR, Daniëls LA, Dimitriu-Leen AC, et al. Different manifestation of irradiation induced coronary artery disease detected with coronary computed tomography compared with matched nonirradiated controls. Radiother Oncol 2017;125:55–61.

3. Singh A, Collins B, Qamar A, et al. Study of young patients with myocardial infarction: design and rationale of the YOUNG-MI registry. Clin Cardiol 2017; 40:955–61.

4. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

5. Lancellotti P, Nkomo VT, Badano LP, et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2013;14:721–40.

KEY WORDS cancer survivorship, coronary artery disease, Hodgkin lymphoma, myocardial infarction