Increased risk of axial fractures in patients with untreated chronic lymphocytic leukemia: a population-based analysis

Adam J. Olszewski,[1,2] Roee Gutman[3] and Charles B. Eaton[4,5]

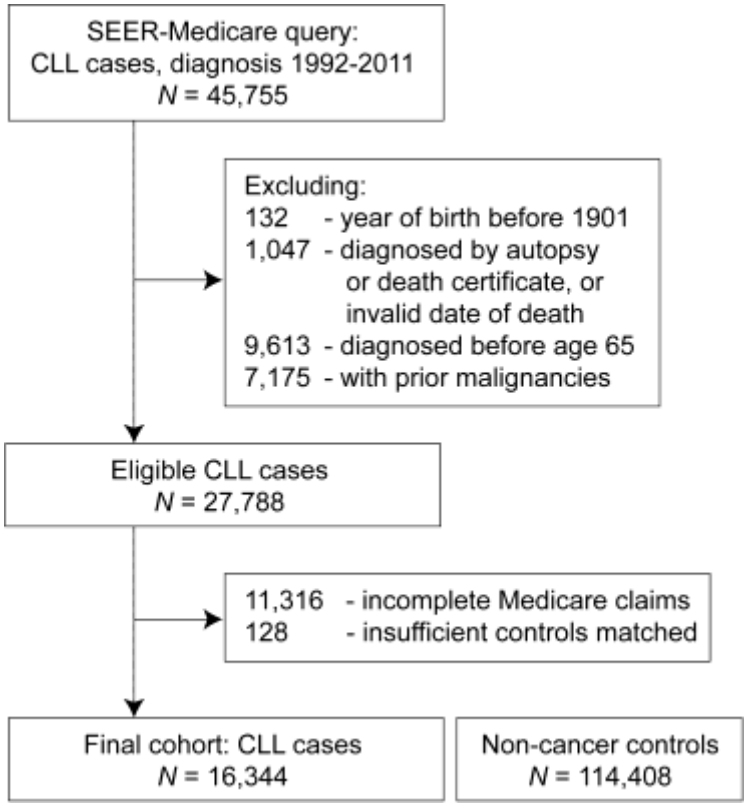
[1]Division of Hematology-Oncology, Alpert Medical School of Brown University; [2]Division of Hematologic Malignancies, Rhode Island Hospital; [3]Department of Biostatistics, Brown University; [4]Department of Epidemiology, School of Public Health of Brown University and [5]Department of Family Medicine, Alpert Medical School of Brown University, Providence, RI, USA

Correspondence: adam_olszewski@brown.edu
doi:10.3324/haematol.2016.148858

Supplemental Methods

Supplemental Figure S1

Selection of subjects from the SEER-Medicare database, including total number of chronic lymphocytic leukemia (CLL) cases and matched controls in the analysis.



The SEER-Medicare dataset links cancer registry records from 18 geographic areas (currently covering about 28% of the US population) with administrative claims for patients covered by Medicare—a government-sponsored health insurance available to all US citizens who are older than 65 years, disabled, or who have end-stage renal disease.[1] CLL cases were identified by morphology code 9823/3 (chronic lymphocytic leukemia/small lymphocytic lymphoma) and primary site codes C42.0 (blood), C42.1 (bone marrow), and C42.4 (hematopoietic, unspecified) according to the World Health Organization classification.[2] We excluded subjects diagnosed before 65 years of age, those diagnosed by autopsy or death certificate, those with prior malignancies as well as those who did not have complete Medicare claims available from 1 year before CLL diagnosis until death or censoring (Figure 1). Cases with incomplete claims primarily include enrollees in managed care insurance plans, whose administrative records are not processed by Medicare. The same exclusion was applied to non-cancer controls, yielding 391,132 control subjects available for potential matching. Medicare claims were available for the period from 1991 to 2013. Survival time was administratively censored on December 31, 2013 for all subjects.

[1] Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Medical care. 2002;40(8 Suppl):IV-3-18.

[2] Swerdlow SH, Campo, E., Harris, N.L., et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon, France: IARC Press, 2008.

Supplemental Table S1

Additional codes according to the International Classification of Diseases, Ninth Revision (ICD-9) and Healthcare Common Procedure Coding System (HCPCS) used in claims-based variable ascertainment for the analysis.

Health service	ICD-9 or HCPCS codes
Encounter for chemotherapy or immunotherapy administration	V58.1 V58.11 99.25 99.28 96400-96549 G0355-G0363
Convalescence or follow-up after chemotherapy	V66.2 V67.2
Specific chemotherapy drugs	J9000-J9999, selected other C, J, and Q codes, and National Drug Codes (NDC) Examples: • Rituximab: J9310 • Fludarabine: J9185, J8562, C9262 • Cyclophosphamide: J9070, J9080, J9090-J9097, C9420-9421, J8530, NDC 0001505*, 0005441*, 0005481*, 1001909* • Bendamustine: J9033, C9432
Osteoporosis	733.00-733.09
Percutaneous vertebroplasty or vertebral augmentation	22510-22515 22520-22525 72291-72292
Kyphoplasty	S2360, S2362, S2363

We identified the date of first chemotherapy administration using diagnostic (International Classification of Diseases, Ninth Revision, ICD-9) codes from hospital admissions, non-specific inpatient or ambulatory ICD-9 codes for chemotherapy administration or follow-up, as well as Healthcare Common Procedure Coding System (HCPCS) codes for chemotherapy drugs. Oral chlorambucil was specifically identified in only a minority of patients who had available prescription records (those diagnosed in 2007-2011 and with Medicare Part D coverage). A significant bias resulting from this weakness is unlikely, because we also used non-specific ICD9 codes for all chemotherapy-related visits or health services. Additionally, we found that in the subgroup of beneficiaries with complete prescription records, only 15% were treated with single-agent chlorambucil. Furthermore, chlorambucil use in CLL has been associated with increased bone density.

Using Medicare claims from 12 months preceding the CLL diagnosis (an inpatient code, or at least 2 outpatient codes ≥30 days apart) we ascertained pre-existing diagnosis of osteoporosis, the National Cancer Institute Comorbidity Index (which

counts comorbid conditions associated with mortality),[3] and Davidoff's disability status indicator, which is a validated measure of patient's self-reported performance status based on utilization of health services. This was established using a proprietary algorithm.[4]

Fractures were ascertained using Medicare claims, according to the algorithm described by Taylor et al.[5] This algorithm improves upon previously validated approaches to claim-based fracture identification, and is optimized to detect new (incident) rather than prevalent fractures. It utilizes inpatient hospital claims with codes corresponding to a specific fracture, outpatient hospital or physician claims with both diagnostic and procedure codes corresponding to fracture repair, and, for vertebral fractures, relevant physician claims within 10 days of spine imaging. The relevant ICD-9/HCPCS codes and details of the algorithm are available at:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767033/bin/NIHMS493044-supplement-1.pdf

[3] Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol. 2007;17(8):584-590.

[4] Davidoff AJ, Zuckerman IH, Pandya N, et al. A novel approach to improve health status measurement in observational claims-based studies of cancer treatment and outcomes. Journal of geriatric oncology. 2013;4(2):157-165.

[5] Taylor AJ, Gary LC, Arora T, Becker DJ, Curtis JR, Kilgore ML, et al. Clinical and demographic factors associated with fractures among older Americans. Osteoporos Int. 2011;22(4):1263-74.

Supplemental Table S2

Clinical characteristics of CLL cases and non-cancer controls (matched by date of birth, sex, race, and reason for Medicare eligibility) included in the study.

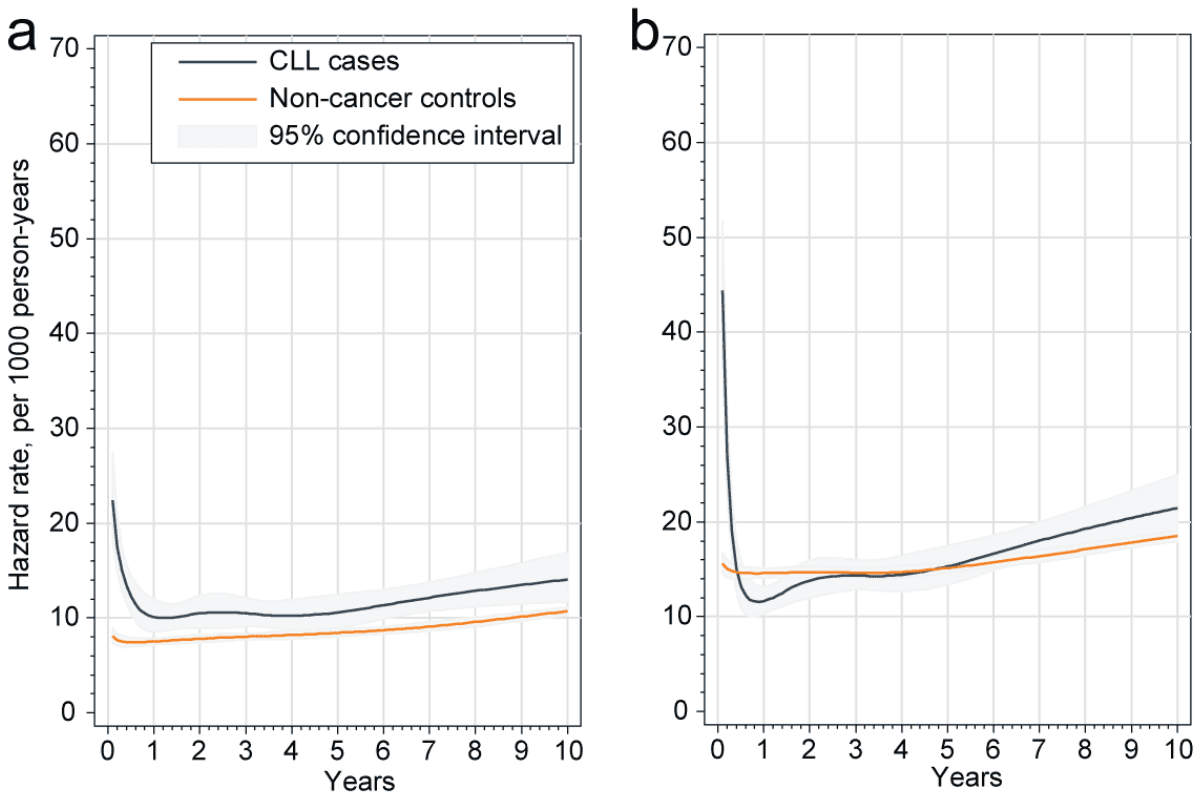
	CLL cases		Controls		*P*
N	16,344		114,408		
Age, median (IQR)	76.9	(71.3-82.9)	76.9	(71.3-82.9)	.74
Age group, *N* (%)					
65-69 years	3,194	(19.5)	22,267	(19.5)	.97
70-74 years	3,564	(21.8)	24,935	(21.8)	
75-79 years	3,617	(22.1)	25,244	(22.1)	
80-84 years	3,004	(18.4)	21,291	(18.6)	
≥85 years	2,965	(18.1)	20,671	(18.1)	
Sex, *N* (%)					1.00
Women	7,585	(46.4)	53,092	(46.4)	
Men	8,759	(53.6)	61,316	(53.6)	
Race, *N* (%)					
White	15,320	(93.7)	107,240	(93.7)	1.00
Black	815	(5.0)	5,705	(5.0)	
Asian/other	209	(1.3)	1,463	(1.3)	
Medicare eligibility, *N* (%)					
Age ≥65 years	15,264	(93.4)	106,848	(93.4)	1.00
Disability or ESRD	1,080	(6.6)	7,560	(6.6)	
Functional status, *N* (%) [a]					
Not poor	14,886	(91.1)	101,885	(89.1)	<.001
Poor	1,458	(8.9)	12,523	(10.9)	
Fracture in prior year, *N* (%) [a]					
No	16,073	(98.3)	112,358	(98.2)	.23
Yes	271	(1.7)	2,050	(1.8)	
Osteoporosis, *N* (%) [a]					
No	15,612	(95.5)	109,241	(95.5)	.83
Yes	732	(4.5)	5,167	(4.5)	
NCI Comorbidity index [a]					
0	10,136	(62.0)	73,023	(63.8)	<.001
1	3,590	(22.0)	23,532	(20.6)	
2	1,514	(9.3)	9,640	(8.4)	
≥3	1,104	(6.8)	8,213	(7.2)	

[a] Based on Medicare claims from the year preceding the CLL diagnosis (cases) or entry into analysis (controls)

CLL: chronic lymphocytic leukemia; ESRD: end-stage renal disease; IQR: interquartile range; NCI, National Cancer Institute

Supplemental Figure S2

Hazard of axial (a) and extremity (b) fracture among patients with chronic lymphocytic leukemia (CLL) and matched non-cancer controls, as a function of time from diagnosis/entry. The hazard was calculated using a flexible parametric survival model with 5 degrees of freedom.[6]



[6] Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002 Aug 15;21(15):2175-97.